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EDITORIAL

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Journal "Clinical Medicine of Kazakhstan" (ISSN 1812-2892) is a multi-field dedicated peer-reviewed medical journal. The main thematic scope – publication of materials on medical science and practice, education and healthcare organization. Joint Stock Company "National Scientific Medical Center" publishes the journal bimonthly in a year (in February, April, June, August, October, and December).

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INTERNAL MEDICINE

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High professionalism of the employees and serious scientific training at the best universities of the Russian Federation, Korea, Austria and Lithuania has provided our team with a leading position in the Republic of Kazakhstan.

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Laura Dybyssova

Executive Secretary, on behalf of editorial team of the Journal of Clinical Medicine of Kazakhstan

On behalf of the Journal of Clinical Medicine of Kazakhstan, we would like to express our appreciation to all editorial and advisory board members, reviewers and authors who contributed to this journal in year 2021.

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Journal of Clinical Medicine of Kazakhstan published 6 regular issues in 2021
- Volume 18, Number 1 (2021) with 17 articles
- Volume 18, Number 2 (2021) with 15 articles
- Volume 18, Number 3 (2021) with 15 articles
- Volume 18, Number 4 (2021) with 17 articles
- Volume 18, Number 5 (2021) with 16 articles
- Volume 18, Number 6 (2021) with 15 articles

During 2021, 84 articles were accepted, 78 articles were rejected, acceptance rate was 52%.

AUTHORS 2021

Authors and coauthors who contributed to this journal in 2021 were from the following countries: Kazakhstan, Turkey, Ukraine, Russia, Kyrgyzstan, India, USA, Indonesia, Nigeria, Malaysia, Moldova, Iran, Iraq, Australia, Azerbaijan, Italy, Macedonia.

The editorial team of the Journal of Clinical Medicine of Kazakhstan would like to express gratitude for your valuable support and being part of our excellent team. We appreciate your continuous efforts and hope to continue receiving your great feedback, valuable ideas, and interesting scientific papers to further improve the quality and impact of the Journal of Clinical Medicine of Kazakhstan.

Sincerely yours,

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Frailty in elderly patients with acute myocardial infarction

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Abstract

In recent years, there has been increasing interest in the frailty as a prognostic factor of acute myocardial infarction in elderly patients. Frailty is an important prognostic marker of frequent complications, readmission to hospital, high hospital mortality and major cardiovascular events in elderly patients with acute myocardial infarction. This category of persons is often not allowed to undergo invasive interventions and are often excluded from the recommended treatment, and they tolerate cardiac surgery worse, recovery from illness is slower, functionality decreases, then disability and death develop.

The present review aims to investigate the impact of frailty on management of elderly patients with acute myocardial infarction (AMI).

To analyze the literature, we searched for information on this issue in PubMed / MEDLINE, PMC, Web of Science, Scopus, The Cochrane Library. The search depth was 15 years: from 2006 to 2021.

One of the important factors in improving clinical outcomes, improving the quality of life in elderly patients with acute myocardial infarction is the early detection of frailty. Frailty assessment is a valuable tool for risk stratification that can be helpful to clinicians in deciding the optimal pathway for management and treatment strategies. Risk prediction is also important for deciding secondary prevention and cardiac rehabilitation measures in the elderly with acute myocardial infarction.

Keywords: acute myocardial infarction, advanced age, frailty, prognosis, risk assessment.

Introduction

Life expectancy of population is increasing globally. According to the report by the United Nations, the share of the population aged 60 years or over is expected to rise from 617 million persons in 2015 to 2,1 billion by 2050 with the highest proportion of elderly persons in Asia [1].

Older individuals comprise a diverse cohort of population. Management of this group of patients must be tailored according to biological age, as patients of the same chronological age might differ in terms of functional status and living conditions. Cohort of aged individuals should be classified into three subgroups: robust, pre-frail (pre-asthenia) and frail (senile asthenia syndrome) [2].

Senile asthenia syndrome or frailty is a state of increased vulnerability to numerous factors resulting from aging-associated decline in function across multiple body systems. This condition leads to high rates of disablement, morbidity, and unfavourable prognoses. However, early detection of frailty allows for regression of this condition and better management of this group of patients [3].

Frailty is a complex clinical syndrome of increased vulnerability to stress factors, caused by multi-systemic functional decline. This in turn results in a mismatch between biological and chronological ages. Patients with low functional status and physiological reserve are at a higher risk of homeostatic imbalance when exposed to a stress factor [4]. Stress factors are classified into two major categories: acute or chronic diseases (acute myocardial infarction) and iatrogenic factors (surgical and

other invasive interventions). The impact of stress contributes to disproportional decompensation in frail patients, they develop unfavourable side effects and complications, have longer periods of recovery after diseases and show lower functional status, this subsequently leads to invalidity and death [5].

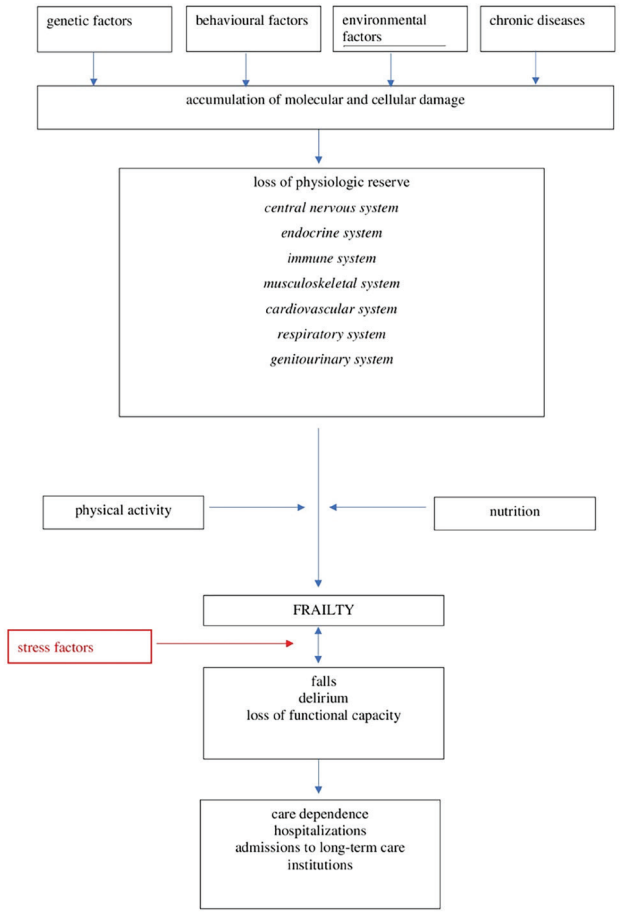
A Call to Action consensus of internationally renowned experts established in 2013 has identified frailty as a multifactorial syndrome (diminished grip strength, endurance and reduced physiologic function) that increases an individual's likelihood of developing dependency and death [6]. According to British Geriatrics Society 2014, frailty is a distinctive health state related to the ageing process in which multiple body systems gradually lose their in-built reserves [7].

In absence of timely interventions such as medical treatment and rehabilitation, pre-frailty deteriorates into frailty. This is a dynamic process that prompts a decline, causing frailty and further worsening of health status, loss of work qualification, frequent falls, recurrent hospitalizations, and mortality.

The present review aims to investigate the impact of frailty on management of elderly patients with acute myocardial infarction (AMI).

To analyze the literature, we searched for information on this issue in PubMed / MEDLINE, PMC, Web of Science, Scopus, The Cochrane Library. Inclusion criteria: original articles, literature reviews, reports of randomized and cohort studies conducted in large populations; meta-analyzes, publications with full text and open access in English and Russian. Exclusion criteria: materials without evidence, abstracts and newspaper articles, conference proceedings, articles describing isolated cases and series of cases. A total of 100 publications were analyzed, of which 81 are included in this review.

Figure 1 - Factors determining frailty



Pathophysiology of frailty

It is generally accepted that ageing is a result of lifelong accumulation of molecular and cellular damage caused by multiple mechanisms (genetic, behavioural, environmental factors, chronic diseases). A certain amount of cellular damage crucial for deterioration of organ function remains unclear. Most body systems make up a physiological reserve that is necessary to compensate age-related changes. Loss of physiologic reserve in these organs leads to frailty which is characterized by higher vulnerability to inadequate rebalancing of homeostasis after stress (acute illness, trauma, changes in treatment, surgery), increasing the risk of unfavourable outcomes such as falls, delirium, loss of functional capacity, disability. These common features of frailty cause higher rates of hospitalization and prompt further deterioration [8,9] (Figure 1).

Frailty is a syndrome of multisystemic dysregulation. Marked inflammation is observed as a reaction of immune system. Pathogenetic mechanisms of frailty include elevation of white blood cells count and levels of inflammatory cytokines IL-6 and C-reactive protein, this has a detrimental effect on body systems. Hyperinflammation plays the key role in pathogenesis of frailty acting directly or through other interim pathophysiological processes.

Yao Xu et al. provided an overview of current understanding of immunological alterations in frail patients describing them as a state of increased inflammation and compromised innate and adaptive components of immune system -immunosenescence. This leads to an increased morbidity and mortality rates in aged patients [10].

Ageing is associated with progressive modifications in T follicular helper cell (TFH) phenotype and function. Other subset of cells namely T-follicular regulatory cells exerts opposing roles to TFH cells in regulating immunity (T FH/T FR cell ratio). Imbalance in T FH/T FR cell ratio is an important component of frailty. Recent studies suggest that dysfunctional T FH play an essential role in the development of cardiovascular, oncological, autoimmune disorders. It is an all-encompassing process that predisposes to unfavourable reactions to vaccination and high infectious morbidity [11].

Risk factors for frailty

To date, numerous studies worldwide are focused on healthy ageing which is achieved by an adequate function of nervous, cardiovascular, and musculoskeletal systems. Lack of physical activity increases risks of developing chronic diseases, geriatric syndromes, and premature mortality [12,13].

Nutrition is another key component of healthy ageing. Lack of protein and overall malnutrition leads to sarcopenia, the loss of muscle mass and function. Poor functional status of musculoskeletal system can potentially lead to permanent disability and premature mortality [14]. The systematic review indicates the importance of adequate nutrition as balanced diet with sufficient intake of micronutrients and macronutrients may delay unfavourable outcomes of frailty [15] and frailty itself in elderly population.

Research suggests that low vitamin D levels correlate with an increased risk of developing frailty and sarcopenia. 25 hydroxy vitamin D deficiency in aged patients leads to low bone mineral density, higher rates of infectious diseases and consequently, frailty [16]. 80-90% of elderly individuals have vitamin D deficiency [17,18].

Polypharmacy (simultaneous administration of multiple medications) is another factor that may increase the risk of developing frailty. M. Gutierrez-Valencia et al. have identified the association between frailty and polypharmacy in aged patients (≥65 years old) in 21 of total 25 reviewed studies. According to the conclusion of the review, drug dose reduction and decreasing the number of administered medications could be a cautious strategy to prevent frailty in patients of advanced age [19]. In meta-analysis of 37 studies Palmer et al. have identified polypharmacy in 59% of frail patients [20]. M. Herr et al. [21] identified a 17% incidence of frailty among studied population, with polypharmacy detected in 54%, among these 14% of patients received more than 10 medications daily. The study has shown direct correlation between frailty and polypharmacy and increased mortality risks in the following years (RR=6,30; 95 % CI 3,09-12,84).

Elderly patients with pre-frailty and frailty should be evaluated for feeling of exhaustion and its causes. Longitudinal Aging Study of Amsterdam (LASA) and Invecchiare in Chianti (InCHIANTI) have identified an exhaustion as the first symptom of frailty [22].

Epidemiology of frailty

According to studies, the prevalence of frailty varies widely and depends on the age, gender, race, physical activity, country of origin, diagnostic criteria, and other factors [23].

Systematic review with over 61 thousand enrolled patients has indicated the prevalence of frailty and pre-frailty as 10,7% and 41,6% respectively. The prevalence of frailty among patients living in nursing homes was 52,3% [24].

Siriwardhana DD et al. evaluated the prevalence of frailty among patients in low-, middle- and high-income countries. Levels of income were evaluated according to World bank classification. The results showed that general prevalence of pre-frailty in low-income countries was 49,3% (95% CI from 46,4% to 52,2%, I 2 = 97,5%), ranging from 13,4% in Tanzania and 40,7%-71,6% in Brazil. The mean prevalence of frailty was 17,4% (95% CI from 14,4% to 20,7%, I 2 = 99,2%), results ranged between 3,9% in China, 26% in India and 51,4% in Cuba. The prevalence of frailty peaked after 75 years of age with higher rates in women. Pre-frailty and frailty rates were higher in middle-income countries compared to high-income countries (Z = -8,86, P <0,001) and (Z = -17,14, P <0,001) respectively [25].

Asian countries with higher income showed lower rates of frailty (Japan, Singapore, Taiwan) compared to middle-income countries [26-28].

Multicenter study has estimated the prevalence of pre-frailty and frailty in Indonesia, results were 66,25% and 18,7% respectively. Main factors of frailty among Indonesian older adults were functional dependency (OR 5,97, 95% CI 4,04–8,80), malnutrition and depression (OR 2,54, 95% CI 1,56–4,12) and (OR 2,56, 95% CI 1,68–3,90) respectively. Falls (OR 1,77, 95% CI 1,16–2,72) and hospital admissions during the period of 12 months (OR 1,46, 95% CI 0,97–2,20) were also associated with frailty. Corelation between frailty and polypharmacy was also identified (OR 2,42, 95% CI 1,50–3,91) [29].

Shinkai S. et al. have identified epidemiologic properties of frailty in 2 decade long prospective study of elderly in Japan. The prevalence of frailty among men and women were 24,3% and 32,4% respectively. Higher incidence of frailty and its progression is observed in adults aged ≥80 years [30].

The prevalence of frailty is higher in individuals with low social and economic status and low level of education [31,32].

Clinical hallmarks of frailty

Higher probability and higher risks of developing frailty in patients of advanced age can be evaluated by several clinical symptoms. Unintentional weight loss over 5 kg in one year, muscle weakness, low physical activity, fatigue, urinary incontinence, falls, delirium, functional dependence, decline in cognitive functions, increased risk of infections are the major signs of frailty [33].

Frailty and COVID-19

At present, COVID-19 pandemic (SARS-CoV-2) has increased mortality in elderly patients according to international reports [34-36]. By August 23 2021, more than 216,3 million cases of COVID-19 and 4,5 million deaths were reported worldwide. 849 557 cases were reported in Kazakhstan, with 12 655 deaths [37]. Mortality from COVID-19 has a linear correlation with age [38].

In this setting age is not the only prognostic predictor. Perhaps frailty and high comorbidity rate cause vulnerability to unfavourable outcomes and mortality in this group of patients.

Thus, numerous studies have stressed the role of frailty evaluation in patients with COVID-19.

European multicenter observational cohort study with 1564 enrolled patients by Jonathan Hewitt et al. has identified that among patients with COVID-19 with mean age of 74 years, frailty prevalence was 49,4% (5-8 according to CFS scale) and mortality was 27,2%. The analysis of study indicated a high mortality risk and prolonged hospitalization in frail elderly patients with COVID-19 (p<0 0001). Reported results are valuable for frailty estimation in combination with factors other than age, such as COVID-19 and other comorbidities [39].

According to a study with 3817 enrolled patients with COVID-19 an increase in reported clinical frailty scale score (CFS) by 1 point corelated with a 12% increase in mortality [40]. Similar results were reported in patients with COVID-19 hospitalized in Madrid, Spain [41]. In this study 30,71% of patients were classified as frail (including pre-frail patients). Comorbidities (cardiovascular diseases, kidney diseases, dementia), residential care homes dwelling, female sex category, advanced age were the predictors of high risk in frail patients. Frailty was a high mortality predictor in COVID-19 patients (RR: 1,39, 95% CI [1,07–1,81]. As it was outlined in other studies, delirium was identified as a common clinical manifestation of COVID-19 and is the main predictor of mortality in frail patients [42-44]. Mentioned studies have shown the association between COVID-19 and frailty, therefore frailty in combination with other comorbidities may indicate high risk of unfavourable outcomes and mortality in aged patients with COVID-19.

Infections cause biological damage and homeostasis imbalance which leads to progressive senescence and development of geriatric syndromes, forming vicious circle [45].

Identification of frailty may assist healthcare practitioners in distinguishing high-risk group of elderly patients requiring special attention and intervention to prevent unfavourable outcomes, improve quality of life and prognosis [46].

Frailty as a prognostic factor of acute myocardial infarction (AMI) in patients of advanced age

Advanced age is a major risk factor for unfavorable outcomes in AMI as this cohort of population has higher rates of comorbidities, functional changes, and low physiological reserve. However, there is a substantial heterogeneity in this

group of patients therefore in certain cases other outcomes might be observed [47].

Stress factors, such as ACS, invasive manipulations and recently, the COVID-19 pandemic, put frail patients at higher risk and may potentially lead to unfavorable outcomes [48]. Frail patients with ACS frequently report complications, high hospital mortality rate, hospital readmissions. This cohort of patients are less likely to receive invasive manipulations, frequently have modified treatment based on their condition, have longer periods of recovery after cardiovascular surgeries [49-51].

Studies have shown the effect of frailty on short- term and long-term outcomes after AMI. In systematic review and meta-analysis of 20 studies including 143 301 participants with mean age of 75 years authors concluded that among patients with AMI frailty was statistically associated with a twofold mortality risk compared with non-frail patients. Analysis also shows statistically higher risks of severe bleeding in frail patients compared with non-frail HR 1,34 (95% CI: 1,12–1,59, P = 0,001, I 2 = 4,7%). The prevalence of frailty in mentioned studies was 5,3%- 53,7% [52].

Uchmanowicz I et al. Identified that frailty occurred in 80% of patients after AMI, and has negative impact on physical, psychological, and social domains of life [53].

TRILOGY ACS trial included patients with non-ST segment elevation acute coronary syndrome. 25% of patients were frail. Frailty was associated with higher cardiovascular mortality [54]. According to CONCORDANCE registry frail patients with ACS had high in-hospital mortality and 6 month all-cause mortality rates (OR: 1,38, 95% CI: 1,05–1,83, p = 0,02) and (OR: 1,74, 95% CI: 1,37–2,22, compared with healthy .<0,001) respectively [55]. Systematic review and meta-analysis including 8,554 patients with ACS investigated corrected mortality odds for patients with STEMI (RR 6,51; 95% CI]). 2.01–21.10]) and NSTEMI (relative risk 2,63; 95% confidence interval [1,51–4,60]). Higher risks of death were observed in pre-frail patients (corrected RR 1,41; 95% CI [1,19–1,66]) [56]. In a study by Kang et al. [57] 40% of total 352 patients were frail. Frailty in patients with ACS is a significant predictive factor of short- term treatment outcomes. The results of mentioned studies emphasize serious health issues in frail adults that should prompt timely evaluation of this condition.

Older individuals have lower food intake which leads to malnutrition. Malnutrition is major a risk factor for developing frailty that can be successfully modified [58]. Malnutrition is widely observed in frail patients with AMI undergoing PCI being a negative prognostic indicator of all-cause mortality. First major cohort study has shown the association between malnutrition and unfavorable outcomes in older patients undergoing PCI. Kaplan Meier analysis showed higher risk of all-cause mortality in malnourished patients [59].

In an observational study aged patients with slow gait speed more frequently sought medical assistance and had higher rates of hospitalization in 1-year period as well as higher mortality in 4-year period (32% with 9%) [60].

Older patients have a high rate of hospital readmission 30 days after hospitalization with AMI and subsequent discharge. Causes are partly associated with the impact of AMI and functional impairment which is frequently observed in frail patients [61]. John A. Dodson et al. studied data from prospective multicenter cohort trial SILVER-AMI. Results showed that in older patients during repeated readmission 30 days after AMI several functional impairments were reported (physical activity, visual function, weak grip strength, disability). The strongest factor that doubled risks of readmissions in patients with AMI was impaired mobility (OR for TUG 15-25 sec = 1,46, 95% CI 0,98-2,17; OR for TUG ≥25 sec = 1,86, 95% CI 1,32-2,61; OR for TUG, unable to finish = 1,49, 95% CI 1,01–2,19) [62].

Cognitive frailty, hearing and vision impairment result in issues with compliance in taking prescribed medications, injuries caused by falls, unintentional weight loss and higher susceptibility to infections. Mentioned functional impairments are associated with hospital readmissions as well.

European Society of Cardiology and American Heart Association underlined the importance of frailty assessment in management of elderly patients with AMI [63] as these efforts will have a major impact on preventive measures and treatment strategies. But to date there is no special tools for mortality risk estimation in frail patients with AMI. Number of other professional cardiac and geriatric associations emphasize the importance of risk stratification tools for aged patients as well [64].

Frailty screening and assessment tools

Aged frail patients experience more prominent exertion on homeostasis in case of AMI compared with healthy individuals. This in turn leads to marked functional disturbances in multiple body systems, increasing risks of hospitalization and death. Considering the increase in proportion of elderly patients with AMI, cardiologists will encounter frail patients with multiple comorbidities more frequently. There is no common opinion on validation of frailty assessment tools. Complex assessment of geriatric patients seems impossible in a routine clinical practice thus adequate adaptation of appropriate tools should be carried out according to particular settings.

Over 20 frailty assessment tools have been introduced [65], most of them focused on 5 phenotypes- slow gait speed, reduced physical activity, exhaustion, and weight loss. Currently, there are two major operational definitions of frailty: frailty phenotype proposed and validated by L.P. Fried et al. and the frailty index by K Rockwood et al. that deems the deficit accumulation as most important factor of frailty.

The definition of frailty phenotype by L.P.Fried at al. [66] is based on Cardiovascular Health Study including over 5 thousand participants, men and women aged 65 years and older. General prevalence of frailty according to the results was 7%, with higher rates in women (14,4%) as opposed to men (7,4%). This definition describes frailty as a decrease in physiological reserves and includes five criteria: unintentional weight loss in past 12 months, self-reported exhaustion, low physical activity, slow gait speed, weakness (grip strength according to dynamometry). The presence of three criteria out of five is sufficient to diagnose frailty. One established criterion out of five is considered pre-frailty. This definition is most reliable and cited.

Another operational definition of frailty is frailty index (FI), or accumulation of deficits across various domains established by K. Rockwood et al. based on Canadian Study of Health and Aging including 10 263 patients, with most patients aged between 75-84 years old. This definition describes the presence of comorbidities, geriatric syndromes and symptoms and includes a count of 70 items. Frailty index is estimated as a ratio of deficits present in given patient to total number of 70 deficits. The closer the result is to 1 the more severe is frailty [67].

The task force of the International Conference of Frailty and Sarcopenia Research (ICFSR) recommends the use of well-studied frailty phenotype by L.P.Fried et al [68].

Frailty assessment scales for patients with AMI

Numerous scales, modified questionaries and tests have been introduced for the assessment of pre-frailty and frailty. Main scales suitable for frailty assessment in AMI patients are listed below.

Frailty assessment scales based on interviewing without objective assessment of physical performance FRAIL scale

This assessment scale consists of five main domains: fatigue, resistance, ambulation, illness, and weight loss. When three or more of these deficits are present, a patient is classified as frail. Advantages of this scale are assessment of multiple domains. Disadvantages are time consuming assessment, lack of data on frail AMI patients, the absence of important laboratory parameters. Prognostic value in AMI: this scale is a predictive tool of 6-month mortality from all causes [69].

Frailty index (FI)

This scale is a 32-item tool based on evaluation of symptoms, signs, disability, illness, and laboratory parameters. The results higher than 0,25 are considered as identifying frailty. Advantages. This scale is a multidimensional assessment tool. Disadvantages.The scale is time consuming. Prognostic value in AMI: association with long term mortality [70].

Clinical frailty scale (CFS)

CFS is a 9-point scale, with 1 point considered as "very fit" and 9 points as "terminally ill". Frailty is assessed with simple questions according to description of each of 9 levels. Advantages. This is practical tool for rapid assessment of frailty. Disadvantages: CFS is subjective, lacks multidimensional approach and clinical and laboratory evaluation. Prognostic value in AMI: this tool is a predictive tool for hospital mortality, 1-month mortality, and prolonged hospitalization [71].

Frailty assessment scales based on physical performance evaluation Fried frailty criteria

This scale is based on 5 criteria: unintentional weight loss > 4,5 kg in less than a year, exhaustion, low physical activity, slow gait speed and grip strength (frailty is diagnosed in presence of 3 to 5 criteria). Advantages. High evidence level in the assessment of frailty, multidomain evaluation. Disadvantages. Introductory course in geriatrics is a prerequisite, time consuming scale. Lack of clinical and laboratory evaluation. Prognostic value in AMI: strong predictive value of mortality from myocardial infarction [72].

Frailty Instrument for Primary Care of the Survey of Health, Ageing and Retirement in Europe or SHARE-FI

SHARE-FI is a 6- point tool that evaluates fatigue, appetite, physical activity, ambulation, resistance and grip strength. Advantages. Multi domain rapid and practical assessment. Disadvantages. The absence of clinical and laboratory evaluation. Prognostic value in AMI: strong association with early complications and survival rates [73].

Edmonton frail scale (EFS)

This is a 17-point questionnaire consisting of questions related to nutrition, symptoms, mood, and physical performance with 0 points indication as "not frail" and 17 points as "severe frailty".

Advantages. Multidimensional assessment of frailty. Disadvantages. Time-consuming process of assessment. Prognostic value in AMI: association with the duration of hospitalization, 1-year mortality and inadequate management [74].

Green score

This is a 12-point (evaluation of following domains: physical activity, serum albumin levels, gait speed, grip strength) scale. Advantages. Multidimensional assessment of frailty including laboratory studies. Disadvantages. This scale does not include comorbidity assessment. Prognostic value in AMI: association with all-cause mortality and recurrent myocardial infarction risks [75].

Assessment of physical performance Grip strength

Grip strength measured using a hand-held dynamometer is a good indicator of upper limb global strength. Advantages. Allows for practical and rapid evaluation. Disadvantages. This is non multidimensional assessment. Absence of relevant clinical and laboratory evaluation. Prognostic value in AMI: predictive factor of cardiovascular mortality, all-cause mortality, and hospitalizations for heart failure [76].

Gait speed

The assessment of usual gait speed on several meters (most used distance is 5-10 meters). Gait speed is considered as "slow" in case if it is ≤ 0,8 meters per second. Advantages. This is practical and rapid assessment tool. Disadvantages. This is non multidimensional assessment. Absence of relevant clinical and laboratory evaluation. Prognostic value in AMI: predictive factor of 1-year mortality and hospital readmissions [77].

Short physical performance battery (SPPB)

SPPB is the functional assessment of lower extremities based on three tests: balance test, gait speed and chair stand. Results range between 0 (worst performance) and 12 (best performance). Physical performance is considered low if SPPB ≤ 9. Advantages. Multi- domain assessment of physical performance. Disadvantages. Geriatric educational course is a prerequisite. Absence of clinical and laboratory studies.

Prognostic value in AMI: the usefulness of this tool is currently being studied [78].

Frailty assessment during an acute phase of acute coronary syndrome

Frailty assessment during an acute phase of ACS has it's characteristic features. During the admission of patients with ACS frailty assessment may be carried out using practical and rapid scales based on interviewing the patient without the evaluation of physical performance. Most suitable scales in this setting are FRAIL scale and clinical frailty scale CFS.

Frailty evaluation after the acute phase of acute coronary syndrome

Accurate assessment of frailty with the analysis of physical performance in patients with ACS is possible to carry out 48

hours after admission. This allows for more precise evaluation of frailty and it's prognosis. Most suitable scales in this setting are Green score, Freid frailty criteria, SHARE-FI, gait speed, Edmonton frail scale. Those scales have the strongest prognostic value. However, data on the most appropriate time period for frailty assessment during hospitalization is scarce [79].

Currently the frailty phenotype proposed and validated by L.P. Fried et al. and the frailty index by K.Rockwood et al. are the two most widely used tools for screening and assessment of frailty. Frailty index is the most appropriate tool for the evaluation of frailty after relevant interventions [80].

Campo et al. have compared seven tools of frailty assessment in patients with AMI. SPPB, EFS and Fried scale were the most precise in terms of corelation with 1-year all-cause mortality. SPPB scale showed the association with higher levels of mortality from serious cardiovascular and cerebrovascular events [81].

Conclusion

Frail population is a constantly growing group of patients with AMI. Early detection of frailty is considered as one of the essential factors in the achievement of better outcomes and the improvement in quality of life of older patients with AMI. Frailty is associated with high in-hospital mortality, hospital readmissions and worse outcomes. Frailty is a key prognostic factor of cardiovascular events in aged patients with AMI.

Frailty assessment provides valuable prognostic information for decision making in management of older patients with AMI who require focused care and early intervention. Thus, early detection of frail patients with AMI has the potential of improving decision making and proper distribution of healthcare costs. Timely evaluation of frailty is useful for healthcare practitioners as it enables the process of early identification of high-risk patients requiring an immediate attention in hospital and ambulatory setting as this group of patients might need more intensive secondary prevention and cardiac rehabilitation.

Discussed tools are widely used in scientific research and are regarded as effective and practical. Choice of a relevant frailty scale depends on personal preferences and its utility. There is no single widely accepted frailty assessment tool.

More research is needed for better management of frail patients with AMI. Tools, scales, and questionnaires discussed in this article can simplify this process and be valuable in clinical practice and further research.

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Experimental study of the pharmacological activity of new azaheterocycles derivatives: A literature review

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Abstract

Diseases associated with the pathology of the cardiovascular system are one of the key causes of death all over the world. In particular, arrhythmia may entail the most severe complications, including unexpected death. With high-tech advances, antiarrhythmic drugs remain an integral part of both therapy and prevention. However, the existing arsenal of drugs often does not provide the necessary clinical effect, and therapy is associated with a high risk of severe adverse events. Another significant problem today is the administration of low-toxic drugs that provide effective anesthesia with a sufficient depth and duration of action. Currently, there is also the problem of the limited effectiveness of many drugs with antitumor, antimicrobial, antiviral, antifungal, anti-inflammatory activity and action on the central nervous system. One of the solutions to address the existing problems in these areas is the search and study of compounds that may serve as a basis for the development of new drugs. Given the membrane-stabilizing action by influencing ion channels, new derivatives of azaheterocycles - compounds of piperidine and piperazine are of particular interest in these areas of medicine. According to domestic studies, new piperidine derivatives during screening and in-depth studies showed pronounced local anesthetic activity during infiltration and conduction anesthesia. The results of a number of studies confirm the presence of antiarrhythmic activity in piperidine derivatives. Experimental data on the synthesis and study of the pharmacological activity of new derivatives of piperidine and piperazine in world practice prove their promise for the creation of drugs in various fields of medicine in the future.

Key words: piperidines, piperazines, preclinical studies, pharmacological activity

Introduction

Cardiac arrhythmia accounts for a significant proportion of cardiovascular diseases and result from numerous complications leading to disability and death all over the world. In modern conditions, with important technological advances in drug-free treatment, the administration of antiarrhythmic drugs remains an integral part of pharmacotherapy and prevention of arrhythmia. Many antiarrhythmics used in clinical practice have not been derived as a result of a systematic development process, taking into account the effect on specific targets and electrophysiological mechanisms of arrhythmia. The appointment of drugs available in the clinic is accompanied by toxic effects from the organs and arrhythmogenic action. Combination therapy with other drugs further increases the risk of adverse events. A comprehensive study of the electrophysiological features of the rhythm disturbances and the discovery of new potential targets did not result in the development of drugs that were superior to the existing ones [1-4].

Local anesthetics are widely used to relieve pain during medical procedures in various areas of medical practice. However, their use in everyday practice is associated with the risk of various adverse reactions, including life-threatening ones. Also, the increase in the number of medical procedures with local anesthesia increases

the hypersensitivity reactions. Despite local administration, increase in serum concentration of drugs may have a toxic effect on the central nervous system and cardiovascular system. In particular, the widespread bupivacaine, in addition to the risk of neurotoxicity inherent for all anesthetics, can also have cardiotoxic effect. One of the solutions to reduce toxicity is to develop micro- or nano-encapsulated forms to provide controlled drug release [5-8]. The results of modern research also show various areas of medicine, where derivatives of piperidine and piperazine are promising compounds for the creation of effective drugs. Thus, in world medical practice, there is an obvious need for safer and more effective antiarrhythmic drugs. In this regard, the search and discovery of new compounds for the development of antiarrhythmics and local anesthetics with high activity and at the same time low toxicity should also become one of the solutions to address the above problems.

Materials and methods

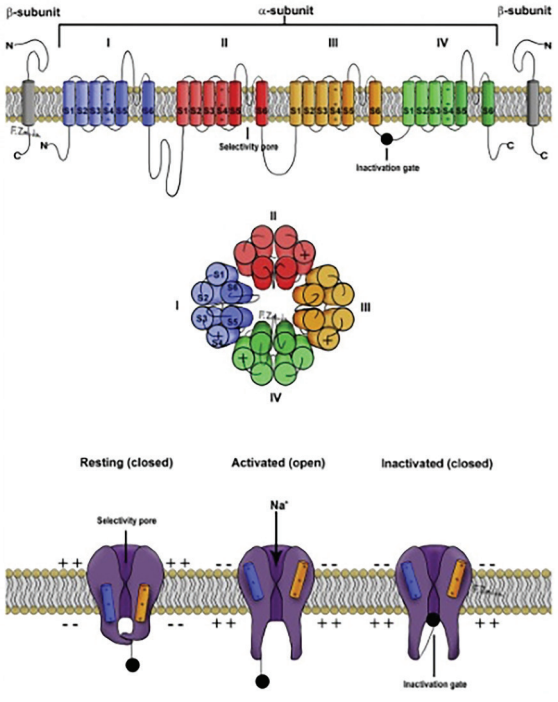
The aim: to study the experience of experimental studies of the pharmacological effects of new derivatives of piperidine and piperazine in domestic and foreign scientific centers. The literature review includes an analysis of foreign scientific publications of scientific electronic databases Elsevier, PubMed, Web of Science, Google Scholar, as well as the results of research presented in domestic publications. The criteria for inclusion in this review were: studies containing experimental data on the study of the pharmacological properties of piperidine and piperazine derivatives in English and Russian over the past 10 years (2010-2021).

Results

Effect on ion channels

Research in recent decades has proven that the local anesthetic effect is achieved by influencing a specifically important target – protein of sodium (Na^+) channels (Figure 1).

Figure 2 - Structure and configurations of the voltage gated Na+ channel. Reprinted from "Basic pharmacology of local anaesthetics" by A. Taylor and G. McLeod, 2020, BJA Education, 20(2), p. 35.



Also at therapeutic concentrations, local anesthetics may affect potassium (K^+) and calcium ($Ca2^+$) channels. It is the effect on these channels causes the certain adverse events. It should be noted that local anesthetic drugs have a lower affinity for potassium channels. Due to the inhibition of K^+ channels, taking into account their contribution to the repolarization process, the action potential is expanded when using this group of drugs. Another type, being ATP-sensitive potassium channels in the heart muscle was found to be sensitive to the action of lidocaine and bupivacaine. This explains the occurrence of toxic and other adverse events from other organs. The effect on voltage-dependent calcium channels is achieved due to the similarity of their structure with sodium channels. In its turn, more than 20 different ion channels are involved in the action potential, which reflects the activity of the heart muscle. In addition, the key factor of the development of arrhythmia is a disorder of the trans-membrane flow of Na^+, $Ca2^+$ и K^+ ions. Most antiarrhythmics are ion-channel blockers by mechanism of action, like local anesthetics. For example, the local anesthetic lidocaine is an effective antiarrhythmic drug for the treatment of ventricular arrhythmia. A study using Rosetta structural computer modeling has shown that both antiarrhythmic and local anesthetics have a common receptor site on the sodium channel of the heart [9-11]. Drugs of other pharmacological groups also influence the sodium channels as targets, but they bind to different sites and differ in the mechanism of action. Many drugs used in clinical practice are blockers of the ion-conducting system. The example is anticonvulsants, antidepressants, neuroprotectors, and other groups of drugs [12]. Ion channels play a central role as drug targets and serve as a key basis for the development of new drugs. From this perspective, the membrane-stabilizing action of piperidine and piperazine derivatives, by influencing the ion channels, determines the presence of not only antiarrhythmic and local anesthetic effects, but also other pharmacological effects, which is of the utmost interest and significance of their study.

Results of domestic studies

Derivatives of piperidine and piperazine have been intensively studied for a long time. The Institute of Chemical Sciences of the Republic of Kazakhstan named after A. B. Bekturov has been actively studying the synthesis of new substituted derivatives. Department of Pharmacology, Kazakh National University named after S.D. Asfendiyarov is conducting research to study the safety and identify the least toxic and most active compounds among new aza-heterocycles. Certain progress has been achieved in the study of local anesthetic and antiarrhythmic effects.

The compound [1- (2-ethoxyethyl)-4-ethynyl-benzoyloxy-piperidine hydrochloride] (laboratory code - Local Anesthetic Substance / LAS-23), named Kazkain is of particular interest for clinical medicine. In the course of screening and in-depth studies of local anesthetic activity during infiltration anesthesia, Kazkain effectively acted in 0.1% solution. The anesthetic effect in terms of the duration of total anesthesia and total duration was also higher than the comparative drugs. But with increase in the studied concentration, a decrease in this difference with reference drugs was observed. The results of in-depth study also showed a pronounced local anesthetic activity during infiltration and conduction anesthesia. The index of Kazkain anesthesia in 0.1% solution definitely exceeded the corresponding indices of trimecaine - 1.5 times, lidocaine - 5.1 and novocaine - 5.3 times. It should be noted that there are advantages in the duration of total anesthesia over all reference drugs: trimecaine (11 times), lidocaine (7.5 times). Both ether groups of the chemical structure

determine the lipoidotropy of the compound, and hence the effect on the local anesthetic activity. In preclinical trials, this compound did not have a significant effect on the central nervous and cardiovascular systems, respiration. No general toxic, allergenic and local irritating effects were observed. Replacement of the radical with the nitrogen atom of the synthesized homologue of Kazkain hydrochloride 1-(-3ethoxypropyl)4 ethynyl-4 benzoyloxypiperidine under the laboratory code LAS-134 allowed to enhance the local anesthetic effect [13].

Research activities to investigate new piperidine derivatives obtained through targeted synthesis as potential local anesthetics continued.

Local anesthetic activity of piperidine derivative (1-(3-n-butoxypropyl)-4-benzoyloxypiperidine hydrochloride) under the code LAS -54, synthesized in the laboratory of chemistry of synthetic and natural drugs of the Institute of Chemical Sciences named after A.B. Bekturov in combination with a vasoconstrictor was studied by G. Pichkhadze et al. (2012). In previous experimental studies, LAS - 54 demonstrated high activity in infiltration, conduction and spinal anesthesia. In terms of toxicity, this compound is comparable to lidocaine. The combination of 0.25% solution of the compound with adrenaline increased the duration of total anesthesia and the duration of general action by almost 2 times with infiltration anesthesia using the tail flick method. However, 0.5% concentration with adrenaline exceeded the anesthesia indices by approximately 1.3 times and 1.4 times, respectively. Analysis of the results of LAS -54 with a vasoconstrictor during infiltration anesthesia using the method of abdominal wall infiltration in rabbits and conduction anesthesia using the "tail flick" method and electrical stimulation of the lower dental nerve in a rabbit also showed an increase in the indices of total anesthesia and total duration of action. In a series of experiments to study the spinal anesthesia, it was determined that in terms of total anesthesia parameter, LAS - 54 with adrenaline exceeded the effect of LAS - 54 by 1.5 times. Thus, the combination with a vasoconstrictor for various types of anesthesia increases the duration of action, which is of particular importance for clinical administration [14].

Other compounds among new synthesized piperidine derivatives showed to a different extent, a pronounced local anesthetic activity during infiltration and conduction anesthesia in the study of G. Pichkhadze et al. (2014, 2015). One of the most promising LAS - 174 caused the deepest anesthesia in 0.25% solution during infiltration anesthesia, and its action was longer than all comparative drugs. The duration of total anesthesia was statistically higher than that of trimecaine by 1.6 times, lidocaine by 2.25 and novocaine by 3.2 times. The compound LAS -166 had a rather pronounced infiltration anesthesia. In 0.25% solutions, LAS - 166 did not differ in the index of anesthesia from trimecaine, it was stronger than lidocaine and novocaine. Compound LAS - 175 during conduction anesthesia in 1% solutions caused a complete block of conduction for 82.5 minutes (duration of total anesthesia), which exceeded the statistically relevant values of other compounds. The total duration of action of LAS - 175 also statistically exceeded that of all tested compounds and comparative drugs. Compounds LAS - 173 had a rather pronounced activity in this type of anesthesia [15, 16].

D. Kadyrova et al. (2017) in a screening study of local anesthetic activity during infiltration anesthesia (in guinea pigs using the Bulbring and Wade method) of a number of new piperidine derivatives identified the most effective compound LAS - 205. According to the results of a preclinical trial of acute toxicity, the substance under study was found to be low toxic when administered subcutaneously to white mice. The lethal dose (LD50) was 625.3±27.2, which is 2.7 times higher than lidocaine and 1.3 times than novocaine. The anesthesia index of 0.25% solution was statistically higher than the relevant value of the comparative drugs. The duration of total anesthesia as an indicator of activity of the LAS -205 compound, lasted 28.3 minutes. Compound LAS - 205 also exceeds all comparative drugs and other studied compounds in this series in terms of the total duration of action. The duration of action of LAS - 205 is 52.1 minutes. For comparison, trimecaine, lidocaine and novocaine act shorter by 1.36; 1.7 and 1.8 times, respectively [17].

According to the results of a study conducted by M. Amirkulova (2017), the most effective of all the studied compounds were LAS - 212, LAS - 213 and LAS - 215. These compounds caused deep anesthesia in 0.25% solutions and showed the maximum effect determined by Bulbring and Wade methods. At the indicated concentration, their anesthesia indices were equal to 36 and exceeded the appropriate indices of trimecaine by 1.2 times, lidocaine by 1.5 times and novocaine by 1.44 times. The study revealed the advantages of LAS -212, LAS - 213 and LAS - 215 over comparative drugs in terms of the duration of total anesthesia and the total duration of action [18].

In a study of the antiarrhythmic activity conducted by K. Esetova et al. (2012) on experimental model of calcium chloride arrhythmia, active compounds were identified under the laboratory code LAS - 100, LAS - 97. The antiarrhythmic effect of LAS - 100 was observed in 100% and was 1.5 times higher than lidocaine in this indicator and 3 times higher than etmozine. LAS - 97 showed the same efficacy as lidocaine, but higher than etmozine. The effective dose (ED50) of the piperidine derivative LAS -100 was 3 and 4 times lower than lidocaine and etmosine, respectively. In experiments on the aconitine model of arrhythmia, high activity was established for the compounds LAS -83 and LAS -100. With this arrhythmia, ED50 of the mentioned compounds also exceeded those of the reference drugs. During the study of acute toxicity after subcutaneous administration, all compounds showed less toxic effect, thus, the relative toxicity of the LAS -100 compound was 0.25 and 0.29 of the toxicity of lidocaine and etmozine. A number of advantages of these compounds indicate their prospects as potential antiarrhythmics and require further in-depth study [19].

The search for low-toxic and highly active antiarrhythmic compounds among the newly synthesized piperidine derivative was continued by K. Esetova et al. (2017). Compounds under laboratory codes LAS - 189, LAS - 190, LAS -191 were studied. Results of the screening study allow us to establish that all compounds are less toxic than lidocaine and etmozine. In the study of antiarrhythmic activity, the compound LAS - 189 had practically no effect. The best results in terms of antiarrhythmic effect were demonstrated by the compound LAS - 190 with calcium chloride arrhythmia 1.25 times higher than the activity of lidocaine and 2.5 times higher than etmozine, with the survival rate of laboratory animals - 83.3% [20].

Thus, the presented results of studies prove the local anesthetic and antiarrhythmic activity in piperidine derivatives. A number of compounds have advantages over the drugs used in clinical practice. In this connection, they are promising compounds for the development of new drugs based on them and require further in-depth study. The study of new synthesized derivatives of piperidine and piperazine will be continued in future studies.

Study of piperidine and piperazine derivatives in world practice

Piperidine has the potential to combine with other molecular fragments, which allows it to be actively used as an effective scaffold. The piperazine matrix also exhibits versatile binding properties that provide selective ligands for a variety of biological targets. Therefore, fragments of piperidine and piperazine are widely used to create new derivatives. It is known that many substituted piperidine and piperazine derivatives exhibit antitumor, antimicrobial, antiviral and antifungal, anti-inflammatory activity and effect on the central nervous system [21-24].

The results of recent studies show various areas of medicine, where derivatives of piperidine and piperazine are promising compounds for the development of effective drugs.

In the treatment of cancers, various groups of chemotherapeutic agents are used, but mortality rates due to oncology prevail all over the world. The current problem is the limited efficacy of many compounds and moderate selectivity against cancer cells. Therefore, the search and development of new drugs continues intensively. According to the results of a number of recent studies, antitumor activity was observed in some derivatives of piperidine and piperazine. Thus, Yanqun Zeng et al. (2015) based on virtual screening of fragments, piperidine derivatives were developed as inhibitors of Heat Shock Protein (HSP70), which is essential in the regulation of apoptosis. Compounds HSP70-36/37/40/43/46 showed antitumor activity by blocking the proliferation of tumor cells in six cell lines of breast cancer. Also, inhibition of the growth of cells resistant to lapatinib was observed, not only in the case of breast tumor, but also in other tumor cell lines. In the study, pyrimidine was found to be more active than thiazole, therefore, R1 of ring A was substituted from thiazole to pyrimidine. The methylthio group at the R1 position was suitable for better functioning of the compound. These substituents showed better antitumor activity than substitutions with chlorine and fluorine. It should be noted that the position of substituent is crucial in the activity of compounds. In the event of replacing 2-substituents with 4-substituents, the degree of inhibition noticeably reduced. Improvement of antitumor activity was observed when placing R3 of C ring in the ortho and/or para position. These findings may facilitate the development of new therapeutic approaches and new drugs successfully used in the treatment of drug-resistant cancer [25].

In another study by Manouchehrizadeh E. et al. (2020), a number of new piperidine and piperazine derivatives of dichloroacetate was developed (antitumor agent - inhibitor of pyruvate dehydrogenase kinases). The synthesized compounds showed better interaction with pyruvate dehydrogenase iso-enzymes. The results showed moderate efficacy and much higher antitumor activity of these compounds than dichloroacetate [26].

The synthesized derivatives of 1-(4-substitutedbenzoyl)-4-(4-chlorobenzhydryl) piperazine demonstrated in one of the studies by Yarim M. et al. (2012), high cytotoxic activity on growing cells of different tumor lines of the liver, large intestine, stomach, breast and endometrium in vitro. After penetration into the cell, 5a compound of this derivative showed a long-term effect, which is evidence of stable in situ activity. The piperazine structure has the universal ability to bind and provide ligands with high efficiency for various potential targets. Therefore, the piperazine scaffold forms the basis of molecule [24].

According to research by the University of Eastern Finland, the compounds Piperazine and Piperidine Triazole Ureas have been developed as monoacylglycerol lipase (MAGL) inhibitors. MAGL releases arachidonic acid as the main substrate of neuroinflammatory prostaglandins. According to the results, the new compounds JJKK-046 and JJKK-048 have shown high in vitro efficacy, exceeding the efficacy of currently existing leading MAGL inhibitors under the same conditions. MAGL inhibition may have great therapeutic potential in the treatment of neurodegenerative diseases and cancer. Promising results can be achieved in the treatment of metabolic disorders, in particular insulin resistance [27].

Also advances were made by Kaya B. et al. (2017) in the synthesis of new derivatives 2-[4-(pyrimidin-2-yl)piperazin-1-yl]-2-oxoethyl 4-substituted piperazine-1-carbodithioate, active in inhibiting monoamine oxidase enzymes (MAO-A and MAO-B). MAO inhibitors are one of the most widely used groups of antidepressants that regulate the metabolism of serotonin and norepinephrine. The basis for their synthesis was (pyrimidin-2-yl)piperazin. 1-(2-Pyrimidinyl)piperazinyl, being an important ligand class of the 5-HT1A receptor and active metabolite of azapirones. Azapirones are widely used in clinical practice (buspirone), have anxiolytic and antidepressant activity. It was also previously known about antidepressant activity of piperazine derivatives. The inhibitory activity of synthesized compounds (2a-n) to monoamine oxidases was determined by in vitro fluorimetric method. The new compounds have shown efficacy and selectivity against MAO-A enzyme. High efficiency was provided by compounds 2j and 2m, carrying 4-nitrophenyl and diphenylmethyl fragments, respectively [28].

There are prospects for the use of piperazine derivatives in the development of anti-tuberculosis drugs. Thus, in a study by Chandran M. et al. (2015) new derivatives of benzothiazinone-piperazine, synthesized by molecular hybridization, exhibited inhibitory activity against DNA gyrase of Mycobacterium tuberculosis with a lower cytotoxic effect. Compounds with a nitro group at the R1 position and chlorine group at the R2 positions manifested effective inhibition [29].

Identified compound 1 (cyclohexyl(4-(isoquinolin-5-ylsulfonyl)piperazin-1-yl)methanone) in a study sponsored by the More Medicines for Tuberculosis consortium is one of several low molecular weight inhibitors of inosine-5′-monophosphate dehydrogenase (IMPDH) of Mycobacterium tuberculosis. Research results in this area show that piperazine and isoquinoline rings are essential in the implementation of anti-tuberculosis activity [30].

As a result of research by Dou D. et al. (2012), two first-generation piperazine derivatives were identified that are active against norovirus infection. In this case, the anti-noroviral activity depended on the nature of substituent in the ring. These results may serve as a starting point for further study of the mechanism of action and molecular targets and will open the way for the development of new drugs against norovirus infection [31].

Antiviral activity among aromatic heterocyclic substituted piperidine and piperazine derivatives was also studied by Zhang X. et al. (2013). These compounds were identified by virtual screening based on the VP1 protein structure of the enterovirus. Their further evaluation showed high efficiency as inhibitors of enterovirus 71 and Coxsackievirus A16. Analysis of the structure-activity relationship revealed the effect of space volume of the 4-electron donating group of substituent in the phenoxyl ring and the length of alkyl linkeran on the activity against enterovirus in vitro. However, these factors did not affect the antiviral activity against Coxsackievirus A16. The study mentioned a weak cytotoxic effect of the most active compounds (9e, 8e) against

Vero cell lines. Thus, these compounds are promising options for optimizing treatment against these viruses [32].

Therapy of Candida albicans infections is difficult due to the rapid development of drug resistance and limited number of antifungal drugs. In a study by Zhao S. et al. (2018), certain compounds among new synthesized derivatives of (1-aryloxy-2-hydroxypropyl)-phenylpiperazine inhibited the morphological transition and virulence of Candida albicans without affecting the growth rate. It was found that some compounds were able to reduce the formation of hyphae in fungal cells by more than 50% and showed inhibitory activity against adhesion and biofilm formation by more than 85%. In addition, the introduction of a group of halogens improves the preventive effect of biofilms. 2,4-dichlorophenol derivatives showed a strong inhibitory activity, while the phenol derivatives showed a weak effect and 4-hydroxybiphenyl derivatives showed moderate activity. It should be noted that the new compound (1-(4-ethoxyphenyl)-4-(1-biphenylol-2-hydroxypropyl)-piperazine) not only showed significant weakening of virulence, but also did not have a cytotoxic effect on human cells even in high concentrations. This group of compounds can be used as a basis for the development of drugs for the treatment of infectious diseases associated with Candida albicans [33].

According to studies by Filipova A. et al. (2020), a range of new substituted derivatives of 1-(2-hydroxyethyl) piperazine were developed and synthesized, exhibiting protection from radioactive emission. Some of the compounds presented for the study exhibited a protective effect on human cells in vitro against radiation-induced apoptosis. The researchers also noted low cytoxicity in vivo. In general, some compounds are subject to further study as potential drugs with radioprotective activity [34].

Marcinkowska M. et al. (2018) synthesized a series of N-arylpiperazine derivatives of 4,4-dimethylisoquinoline-1,3(2H,4H)-dione with antiplatelet activity evaluated on in vitro models. These substances are strong antagonists of alpha 2B receptor. The most active compound 3 demonstrated effective inhibition of platelet aggregation induced by collagen, adenosine diphosphate and adrenaline. In the course of the study, the critical importance of arylpiperazine fragment was determined for the adequate interaction with the required receptors. Also, this fragment provides a charge-enhanced hydrogen bond between the nitrogen atom of piperazine ring and Asp3.32 residue of the alpha 2B receptors. The impact on alpha 2B receptors as a new target opens up the potential for the development of a new therapeutic strategy of antiplatelet therapy, and can be effectively used in the future in patients with resistance or intolerance to aspirin [35].

As a potential antipsychotic, Kaczor AA et al. (2020) investigated N-(2-Hydroxyphenyl)-1-[3-(2-oxo-2,3-dihydro-1H-benzimidazol-1-yl)propyl]piperidine-4 Carboxamide (D2AAK4). This compound is a multipurpose ligand for the aminergic G-protein-coupled receptor. In the study, D2AAK4 at a dosage of 100 mg/kg reduced amphetamine-induced hyperreactivity, thereby implying antipsychotic activity [36]. Another study by Rathore A. et al. (2021) also showed promising effect against dopamine and serotonin receptors of various piperidine and piperazine derivatives. When different heterocyclic groups joint the main rings, antipsychotic activity is significantly enhanced. In this area, new antipsychotics were synthesized in the laboratory, and some drugs (Lu AE58054, PF-04802540, ORG25935, DMXB-A, Bitopertin and ABT-126) are already at the stage of clinical trials [37].

Conclusion

The chemical structure of piperidine and piperazine are versatile in the ability to bind to other molecular fragments and incorporate various substituents and radicals. All this allows to actively use these structures as a scaffold to create new derivatives in various fields of medicine. The focus of domestic research on the study of the pharmacological activity of new compounds is based on the mechanism of action and the presence of membrane stabilizing properties. This gives rise to an active search for new local anesthetic and antiarrhythmic drugs. The sphere of foreign research is aimed at finding solutions to urgent problems in clinical practice associated with the development of new groups of drugs based on piperidine and piperazine derivatives. These are the most pressing problems of modern medicine, such as the search for new antiviral, antibacterial, antifungal agents. Derivatives of piperidine and piperazine have shown promising results in experiments to study other properties that are no less relevant for clinical practice - antiplatelet, antipsychotic and other properties. These data are the rationale for experimental research by domestic scientists and the creation of new directions in the search for promising compounds. The review has shown the effectiveness of many compounds already synthesized, which are of particular interest for the development of new drugs and new therapeutic approaches in the treatment of many diseases.

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Registration procedure of generic drugs in the Republic of Kazakhstan and Europe: Review

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Abstract

Before medicines enter the pharmaceutical market of the Republic of Kazakhstan, the applicant must pass the registration procedure. The process of registration of medicines is necessary to provide the population of Kazakhstan with high-quality, effective and safe medicines, which, in turn, will lead to an improvement in the general health of the population.

The study of the registration process of generic medicines is an urgent problem for practical healthcare, which causes scientific and practical interest in this issue and serves as the basis for this study.

The search for health policy literature was carried out on the official websites: www.who.int, www.ndda.kz, www.ema.europa.eu and the search for scientific publications was carried out in the search engines: PubMed, GoogleAcademia, eLibrary.ru, Cyberleninka.

Further scientific developments in this direction will be of particular relevance and will allow not only to give a comparative description of the registration process of generic medicines, but also to develop recommendations for its improvement.

Key words: drug, generic, medicines, regulatory requirements, registration process, Republic of Kazakhstan

Introduction

One of the most effective measures to reduce the cost of medicines for both healthcare and patients is the use of generics.

Generics have additional social value that exceeds their potential for savings through price reductions. Generics are expanding access to pharmacotherapy, creating an incentive for innovation by both manufacturing and generic companies, and, under certain circumstances, positively impacting adherence to treatment [1].

According to various research low awareness of generic drug characteristics and the reluctance of healthcare providers to prescribe generics have a significant negative impact on the rational use of more affordable generic drugs. It is imperative that doctors and pharmacists correctly understand the characteristics of generics and provide patients with complete and detailed information. An important factor in increasing trust in generic medicines is the provision of complete information about drug regulation, equivalence [2].

Before the medicines enter the pharmaceutical market of the Republic of Kazakhstan, the applicant must pass the registration procedure. The process of registration of medicines is necessary to provide the population of Kazakhstan with high-quality, effective and safe medicines, which, in turn, will lead to an improvement in the general health of the population.

The study of the registration process of Generic drugs is an urgent problem for practical healthcare, which causes scientific and practical interest in this issue and serves as the basis for this study.

The purpose of the study was to compare generic drug registration process in the Republic of Kazakhstan and European Union countries and to find out the differences, lacunae among the regulatory requirements.

Material and methods

The search for health policy literature was carried out on the official websites: www.who.int, www.ndda.kz, www.ema.europa.eu and the search for scientific publications was carried out in the search engines: PubMed, GoogleAcademia, eLibrary.ru, Cyberleninka.

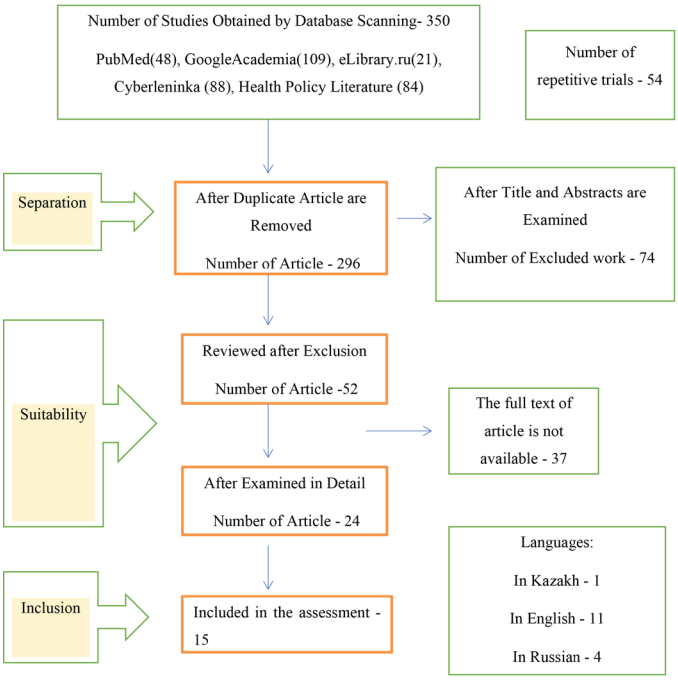
Inclusion criteria: Due to the importance of revealing the historical sequence of the regulation of generics, the search depth was 10 years (1 January, 2011 to 1 December, 2021). Publications in Kazakh, Russian and

English were included, health policy literature and full-text research. Preference was given to high-quality works, such as systematic reviews, meta-analysis. The study was carried out by searching for keywords: Drug, Generic, Medicines, Regulatory Requirements, Registration Process and Republic of Kazakhstan.

Exclusion criteria: publications of low methodological quality that did not reflect the main significance, with unclear and ambiguous conclusions, studies, recurrent publications.

As a result of the search, we identified only 350 foreign and domestic publications. Of these, 15 publications were included in this review, taking into account the inclusion and exclusion criteria. The selection algorithm is shown in Figure 1.

Figure 1 - Algorithm for selecting scientific publications



Results and discussion

Characteristics of Generic Drugs

Medicinal products are conventionally divided according of development into originator medicinal products and generics.

The term "Generic" may have different definitions depending on the country. These definitions are of decisive importance for national agencies of states and determine the scope of requirements for the registration dossier for the state registration of a generic drug. According to the WHO definition: «A pharmaceutical product usually intended to be interchangeable with the originator brand product, manufactured without a license from the originator manufacturer and marketed after the expiry of patent or other exclusivity rights» [3].

Generics are medicinal products, the production of which is possible after the expiration of patent protection for the original drug of the innovator's company. As a rule, pharmaceutical companies have the right of a patent holder for a period of 20 years to justify the resources expended [4].

WHO definition: Originator (innovative) pharmaceutical product - generally the product that was first authorized worldwide for marketing (normally as a patented product) on the basis of the documentation of its efficacy, safety and quality, according to requirements at the time of authorization [5].

Currently, the average cost of generic drugs is about 80% cheaper than the original drugs, have a lower cost due to fewer resources for developing a medicine.

The development of innovative medicine is aggregate, expensive and time-consuming long- term work, the development time can take up to 10 -15 years, and the cost can range from 800 to 2 billion United States (US) dollars higher [6].

The development of innovative medicines includes:

- The discovery of a molecule
- Preclinical development, first in vitro tests, then in vivo laboratory studies on animals, assessment of the pharmacological effect, mutagenicity, toxicity, teratogenicity, etc.
- Clinical trials. Once approved by the appropriate regulatory authority to introduce an innovative medicine, clinical trials can begin.

The clinical trials required to bring a new drug to market usually take place in three phases. In the first phase, the safety profile of the new drug for humans is studied. Typically is performed on healthy volunteers. After the successful completion of the first phase of clinical research, the second phase is started. Studies are conducted in the target population / patients. The main objective of these studies is to determine the effectiveness of a new drug in comparison with existing alternative therapies or placebo. The third phase, as a rule, is large-scale, multicenter studies, comparative studies on a large number of patients. The main goal of these studies is to confirm the safety and efficacy of a new drug. Based on the data obtained in the current of the study, a conclusion is made for the risk- benefit profile of the new medicine [7].

For generics, there is no need for extensive preclinical and clinical development, before entering the pharmaceutical market the generic confirms its equivalence to the original medicine by appropriate bioavailability studies [8].

Comparison Drug Registration Procedures in the Republic of Kazakhstan and Europe

In the Republic of Kazakhstan, medicines are used only if they are registered. The types of drug registration are registration, re-registration and variations. Re-registration and variations are procedures available after registration of a medicine and obtaining a registration certificate. Re-registration is required to confirm authorization upon the expiration of the registration certificate after five years. Variations are made in case of changes that relate to the quality, safety and efficacy of medicines.

The registration procedure is required for the admission of medicines to the pharmaceutical market. The Registration Certificate is issued on the basis of quality, efficacy and safety then the medicine is introduced in the State Register of Medicines and Medical Devices of the Republic of Kazakhstan. The expertise of all pharmaceutical products quality, efficacy and safety is done by Republican State Enterprise with the Right of Economic Management «National Center for Expertise of Medicines and Medical Devices» (National Center). Applicants for registration of medicines submit registration dossier directly to National Center. Upon completion of the examination of the quality, effectiveness and safety of pharmaceutical products at the National Center, expert assessments are submitted to the Committee for medical and pharmaceutical control (Committee) than Committee takes the decision to register the product and issues Registration Certificate [9].

Until recently, two procedures for registration of medicines operated in parallel in the Republic of Kazakhstan: the national procedure for registration of medicines and registration of medicines within the Eurasian Economic Union (EAEU or Union)).

In 2014, the member states of the Eurasian Economic Union signed the Treaty on the Eurasian Economic Union. The member states are five countries: Russia, Kazakhstan, Kyrgyzstan, Armenia and Belarus. The Union also has observers from Uzbekistan, Cuba and Moldova. The Agreement on the Circulation of Medicines of the Union (Agreement) was concluded by the Member States on December 23, 2014. In 2015, the Union began its work, but the common drug market began to function a little later, which was due to the need to adopt a number of rules. The rules provided by the Agreement are requirements, guidelines, procedures and instructions.

The first drug registered in accordance with the rules of the Union, Triumeq (Abacavir + Dolutegravir + Lamivudin), film-coated tablets manufactured by Glaxo Operations UK Limited, United Kingdom, was registered in 2018 in the reference state of the Republic of Kazakhstan. Nowadays, registration within the EAEU is routine.

To date, the only available procedure for registration of medicines in the EAEU member states is registration within the Union. The national procedure for registration of medicines in the Republic of Kazakhstan was completed on July 1, 2021. Total 7,479 medicines (as of November 9, 2021) were registered in the State Register of the Republic of Kazakhstan according to the national procedure [10]. According to the unified rules of the Union, the Unified Register of which included 672 medicines (as of November 13, 2021) [11].

Medicines registered in the EAEU member states must be brought in line with the requirements and rules of the Union by the end of 2025. The transitional period will end on January 1, 2026, and all drug registration certificates issued in accordance with the national legislation of Kazakhstan will be canceled.

In general, the legislation in the field of drug regulation of the Republic of Kazakhstan is harmonized with the Eurasian Economic Union rules. European Union regulatory documents are a prototype of the Union rules [9].

In Europe, marketing authorization is applied for with European medicine agency (EMA). In the European Union, there are three procedures available for authorizing medicines: Centralized procedure (CP), Decentralized procedure (DCP) or Mutual recognition procedure (MRP). In some Member States, a national procedure has been maintained according to which a medicine is registered in accordance with the legislation of that Member State.

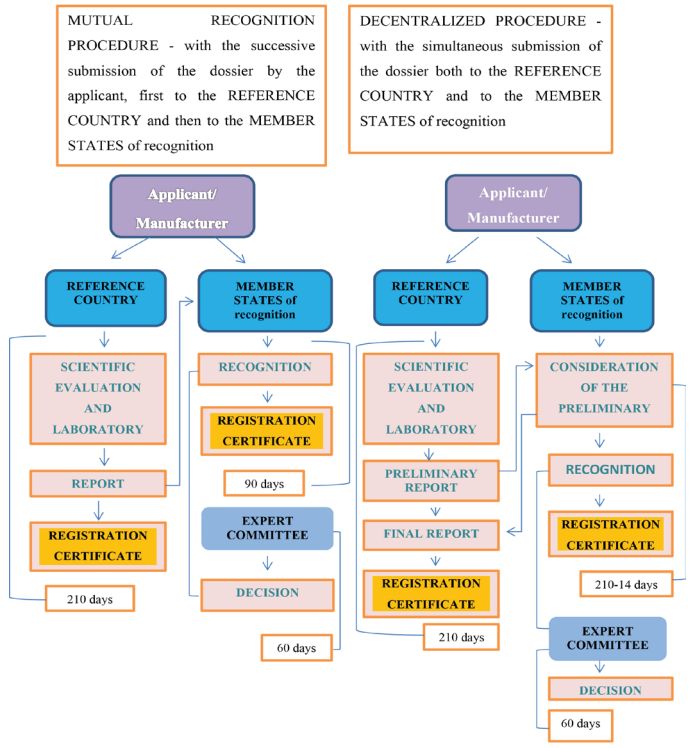
CP is required for innovative drugs, drugs for the treatment of AIDS, neurodegenerative disorders, orphan drugs, drugs for cancer, or diabetes, as well as drugs derived from biotechnological processes. An application for registration of a drug is submitted directly to the EMEA secretariat, if the Eurocomission decides to register a drug, the drug is marketed throughout the EU [12].

The MRP can be initiated if, at the time of application, the drug is already registered in one of the EU countries. The country in which the first registration in the EU is obtained is the reference country. The procedure is based on the principle of mutual recognition of the EU member states. An application for an MRP can be submitted to one or more member states. Registration in the reference country takes 210 days then in case of a positive decision, copies of the report prepared by the experts of the national agency of the reference country are sent to the Member States to which the MRP application was submitted. The decision on registration is made by the national agencies of the EU Member States. Within 90 days, the recognition states make decisions on the basis of the report submitted by the reference state. National marketing authorizations go beyond registration deadlines and take 30 days from [13].

With DCP, an application is submitted simultaneously to several national agencies of the EU countries, one of which is selected as a reference. It is carried out if the drug has not previously been registered in any of the EU countries. The decision on registration is taken by the national agencies of the EU member states [14].

Only two types of registration procedures are available in the Union: the «Mutual Recognition Procedure» and the «Decentralized Procedure». The registration process is shown in Figure 2.

Figure 2 - Registration Procedures for Medicines in the EAEU



Both procedures can be used for registration of original medicines, generic pharmaceuticals, hybrid medicines, medicines with well-studied medical applications, combined medicines, biosimilars, biological medicines, radiopharmaceuticals, homeopathic medicines, herbal medicines, high-tech medicines. The decision of the Council of the Union of November 3, 2016 No. 78 (Decision No. 78) is the legal basis for registration procedures and the life cycle of medicinal products in the Union.

Although the regulatory documents of the European Union are a prototype of the EAEU rules, we see significant differences in the registration procedures of medicines in the Union and the EU, as shown in Table 1.

Table 1 Differences between MRP and DRP in the EU and the Union

EU	UNION
A clear requirement to initiate a MRP or DSP	No clear requirement
Affiliated companies recognize the same the company, therefore, parallel statements are not allowed	There is no restriction on filing applications for one the same drug by affiliated companies
The company and the regulator are discussing the date filing	Discussion not provided, absent time limits for submission of applications
As such, Registration is not provided	The meaning of the Registration procedure is not clear, and the difference from DSP
National stage over the procedure (+30 days)	National stage within the procedure

There is no clear requirement in EAEU to initiate MRP or DCP. It remains unclear what is the fundamental difference between registration according to the MRP and DCP procedure in Union.

In addition, the EAEU does not provide for either national or centralized procedures.

For the registration of medicines, the registration dossier is submitted to the Authorized body (Expert organization) of the Member State, the registration dossier is subject to scientific assessment for quality, safety, efficacy and tolerability. Registration dossier of medicines is provided in the format of a Common technical document in accordance with part I Appendices 1 of Decision № 78. The general Requirements for the Materials of the Registration Dossier are given in Table 2.

Table 2 The General Requirements for the Materials of the Registration Dossier

REFERENCE COUNTRY	MEMBER STATES of recognition
- Completed application form (paper and (or) electronic) - Proof of payment of duties / fees - Modules I-V (electronic) - Samples of the finished product for laboratory testing	- Completed application form (paper and (or) electronic) - Proof of payment of duties / fees - Module I (paper and (or) electronic) - Reference state report - Samples of SmPC, LP, labeling in the official language of the state of recognition (if applicable)

Requirements for Generic Drugs

The registration dossier of the generic medicinal product is submitted in accordance with of Section 6, Part II of Appendix 1 of Decision No. 78.

The bioequivalence of the generic to the original medicinal product must be demonstrated by appropriate comparative bioavailability studies in accordance with the Decision of the EAEU Council of November 3, 2016 No. 85 (Decision No. 85). Differences in the requirements for the Materials of the Registration Dossier for Original Medicines and Generics are shown in Table 3.

Table 3 Differences in the requirements for the Materials of the Registration Dossier for Original Medicines and Generics

Original medicine	Generic
Module I- provided in full	Module I- provided in full - Requires results of user testing of package leaflet (excess requirements for generic) - No clear indication when a Risk Management Plan is required
Module II- provided in full	Module II- provided in full
Module III – provided in full	Module III – provided in full
Module IY- animal studies	Module IY - review of preclinical data
Module V	Module V
- Clinical studies (I, II, III phase)	- Bioavailability/Bioequivalence

As a rule, comparative bioavailability primarily means studies of pharmacokinetic equivalence, that the drug enters the systemic one in an equivalent value, which can be estimated by standard pharmacokinetic parameters AUC, T, Cmax. Generic confirms its equivalence to the original medicine, provided that the Cmax and AUC values do not go beyond 80-125% of the same indicators of the original drug. However, all international documents, including the FDA and EMA, specify that comparative bioavailability, if the drug cannot be measured in the systemic circulation, in this case, pharmacodynamic equivalence studies can be used, and if it is not possible to determine pharmacodynamic points, therapeutic studies (clinical) equivalence (bioequivalence with clinical endpoints). It should be understood that Decision No. 85 refers to an expanded interpretation of comparative bioavailability. Thus, according to the requirements of Decision No. 85, the following research options are possible:

In vivo:

- Studies of pharmacokinetic equivalence (main text of the Decision No. 85)
- Studies of pharmacodynamic equivalence (Appendix 2 to Decision No. 85)
- Studies of clinical equivalence (Appendix 3 to the Decision No. 85)

In vitro:

- According to the dosage form or according to the BCS (Appendix 4 and according to the text of the Decision No. 85).

The definition of the reference medicine in Decision No. 78 is as general as possible, and according to Decision No. 85, clause 18 «When choosing a reference medicine, proceed from the following sequence:

a) An original medicinal product, the quality, safety and efficacy of which were established during registration in the Union (an original drug registered in the Union);

b) An original medicinal product registered in a state where the level of requirements for the regulation of the pharmaceutical market is not lower than the level established in the Union, if it is impossible to comply with subparagraph «a» of this paragraph;

c) A generic medicinal product registered in each of the Member States and confirming its bioequivalence to the original medicinal product (with the approval of the Expert Committee under the Commission) if it is impossible to fulfill subparagraphs «a» and «b» of this paragraph;

d) A medicinal product with at least 25 years of experience in one of the Member States (subject to approval by the Expert Committee on Medicines under the Eurasian Economic Commission) if it is impossible to comply with subparagraphs «a» - «c» of this paragraph» [15].

It is possible to use a non-original drug for equivalence studies only on the recommendation of the Expert Committee.

The definition of the EAEU reference medicine has been tightened, which is an urgent problem for generic manufacturers when choosing a reference drug for equivalence studies.

Many true originators have never been registered in the EAEU or are no longer registered. In some cases, problems arise when tracing the originator to the production site.

Combined drugs, well-studied, drugs registered on the basis of a mixed dossier, cannot be used as a reference drug. The list of reference drugs published by the Expert is not a solution to these problems.

Conclusion

The aim of the study was to compare the registration process of generic medicines and identify differences, gaps in the guidelines. Despite the fact that the prototype of the available registration procedures for medicines, including generics, in the Republic of Kazakhstan are European countries, the registration process is completely different. The rules of registration and examination of the Union establish only the general outlines of the procedure, but do not specify the procedural aspects.

Although the Union adheres to the CTD format, the requirements for module V are different. There are excessive requirements for the registration dossier of a generic drug. In order to eliminate the differences in the guidelines, we need to go for harmonization. Numerous SOPs, reference manuals, templates, etc. are required for the smooth execution of various aspects of the process.

The success of public health programs in improving the health of the entire population in various aspects is due to the effectiveness of generic drug policies. Simplification of the procedure for registration of generics in the Republic of Kazakhstan can become an important tool for increasing savings from the use of generics.

Further research in this direction is important for the rational use of generics by improving access to generics for patients.

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A first approach to identifying cardiotoxic effects of breast cancer chemotherapeutic treatment in Kazakhstan

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Abstract

As known, the clinical efficacy of chemotherapy is limited by the cardiotoxicity of drugs used.

The study aimed to clarify cardiotoxic complications of chemotherapy from the Aktobe Medical Center database for 2018-2019.

Material and methods: We performed a register study on essential parameters of the oncological process, drugs used, duration of chemotherapy, types of complications, and outcomes, including survival.

Results: We found a total of 305 breast cancer cases. Chemotherapy was completed without complications in 65.9% of patients; treatment was interrupted due to complications - 10.5%; 6.2% of cardiovascular complications were identified. The two groups of patients, EchoCG + and EchoCG -, showed significant difference in the number of detected CV complications (p<.001) but no difference in the survival rate (p .814). The survival rate in patients with documented CV complications was 28.1 months vs. 34.3 months in the group without ones (p.005). The survival rate in those who completed the treatment without complications, was 34.9 months vs. 17.6 in individuals whose treatment was interrupted due to complications (p<.001). We performed a detailed review of four cases of cardiotoxicity with fatal outcomes.

Conclusion: The analysis indicates the absence of a systematic approach to recording crucial information regarding cardiotoxicity. There is a lack of concordance in the actions of cardiologists and oncologists in the management of BC patients. The presence of lethal outcomes of chemotherapy with an established cause of cardiac death indicates the need to revise the cancer register management from the standpoint of cardio-oncology. In general, there is a need to develop local protocols for screening and monitoring patients undergoing cardiotoxic chemotherapy and radiation therapy.

Key words: breast cancer, cancer register, chemotherapy, cardiovascular events, cardiotoxicity

Introduction

Breast cancer (BC) consistently ranks first among the causes of death from cancer in women [1,2]. According to the International Agency for Research on Cancer (IARC), in 2020, the proportion of BC worldwide was 10-18% of all new cases of malignant neoplasms [3]. In Kazakhstan, the relative survival rate for BC ranges within 28.7% [4].

The prognosis of BC treatment depends on the tumor tissue's histochemical properties, the tumor's aggressiveness, the cancer process staging, and the cardiotoxicity of chemotherapy [5-7].

As known, the clinical efficacy of chemotherapy is limited by the cardiotoxic (CT) effect on the heart and blood vessels with accelerated development of chronic heart failure (CHF), rhythm and conduction disturbances,

a tendency to thrombosis, etc. [8]. Studies have shown an increase in the relative risk of developing fatal cardiovascular (CV) complications of chemotherapy up to 2.2 times in patients with BC and the risk of developing CHF up to 4.9 times. At the same time, attempts to treat the long-term consequences of CT complications of chemotherapy are not always effective [5].

Chemotherapy in breast cancer patients implies using several groups of pharmaceuticals, mostly Anthracyclines and targeted therapy - monoclonal antibodies, low molecular weight tyrosine kinase inhibitors, proteasome inhibitors, etc.

Currently, researchers identify Anthracycline-mediated irreversible type 1 cardiotoxicity, due to the death of cardiomyocytes (the degree of myocardial damage, in this case, depends on the cumulative dose) and Trastuzumab-mediated reversible type 2 cardiotoxicity due to mitochondrial and protein damage (the effect is not dose-dependent) [9]. In patients treated with Anthracyclines, complications usually develop within the first year after stopping chemotherapy and proceed as progressive CHF, up to the development of dilated cardiomyopathy [10].

Trastuzumab, the mainstay of therapy for human epidermal growth factor receptor-2 (HER2) positive breast cancer, reduced mortality from BC by one-third but did not justify expectancies concerning severe cardiac complications. Up to 3% of BC patients treated with Trastuzumab experience severe CT complications, while the combined uptake of Anthracycline and Trastuzumab leads to a 7-fold increase in CHF risk [11, 12].

Breast cancer chance, like a risk of emerging CV events, increases with age; therefore, most patients with BC will require the close attention of cardiologists and oncologists to balance the antitumor chemotherapy concerning the risk of CT complications [13]. The early detection of chemotherapy cardiotoxicity and timely correction of complications becomes the priority in cancer patients management [6].

Identifying high-risk CT complications can provide a range of additional preventive measures to improve BC patients' outcomes, such as possibly changing the dosage and the grugs administration regimen, applying their new combinations, and/or cardioprotectors with proven efficacy [14,15]. It has been shown that regular echocardiography (EchoCG) reveals significant left ventricular myocardial dysfunction in 98% of patients during the first year of chemotherapy. Cardiac protection using ACE-inhibitors, and beta-blockers can normalize left ventricular ejection fraction (LVEF) in 82% of patients, thus significantly improving the prognosis of the underlying disease [16].

Meanwhile, Cardioncology that studies the cardiotoxic effects of chemotherapy, methods of their detection, and preventive measures, has not yet come into practice in Kazakhstan.

The presented work is the first attempt to scrutinize information from the Cancer register (EROB, electronic register of oncologic patients) on CT effects of Breast cancer chemotherapy.

The study aimed to analyze the overall outcomes of chemotherapy in patients with breast cancer who have undergone treatment at the Aktobe Oncology Center in the period 2018-2019, focusing on the patients' survival and their cardiovascular system condition.

Tasks:

1. To present the overall patients profile, essential parameters of chemotherapy treatment, including the degree and quality of its completion, outcomes, and survival.

2. To select a group of patients with adverse chemotherapy outcomes due to cardiotoxic effects of treatment to analyze the identified complications.

Material and methods

This research performed at Marat Ospanov West Kazakhstan Medical University is a single-center register study presenting the retrospective stage of a joint project of cardiologists and oncologists. The study design and protocol were approved by the University Bioethical Committee (No. 7 dated 09.09.2020). The sample of the retrospective stage was formed by including the medical records of all patients admitted to chemotherapy with a verified diagnosis of C50 and registered in the Cancer register (EROP), with a search depth of two years, 2018-2019. The informed consent was not required due to the register nature of the study. Extracting information from the Cancer register was carried out in pairs - an oncologist and a cardiologist, in several directions:

1) General data: age of patients, IBM, hereditary factor, comorbidity index;

2) Characteristics of the cardiovascular system: baseline intake of cardiac protectors, baseline data on blood pressure, heart rate, ECG, LVEF;

3) Characteristics of the oncological process: staging, clinical classification, and tumor histotype, immunohistochemical data;

4) Characteristics of the treatment performed: class of chemotherapy drugs, type, and duration of chemotherapy, degree of courses completion, and reasons for the interruption;

5) Complications and outcomes of chemotherapy, including death, cardiovascular death, chemotherapy course interruption, and tumor progression.

Statistical analysis

The statistical software packages Statistica.10 (StatSoft - Russia, version 10) and SPSS (IBM, version 25) were used. To determine the normal distribution of quantitative variables, the Kolmogorov-Smirnov method was used. Variables with normal distribution are presented as M (SD). Variables with non-Gaussian distribution are presented as median and 25/75 percentiles, Me (25; 75).Categorical variables are presented as an absolute value and a percentage. Quantitative variables were compared using the nonparametric Mann-Whitney U-test for unrelated samples. The Pearson $\chi 2$ test was used to identify intergroup differences for categorical variables. Event-free survival of Breast cancer patients was determined using the Kaplan-Meier method with a graphical presentation of the results. Differences in survival between groups were determined using the following criteria: log-rank test, Breslow test, Tarone-Ware test. For all tests, a two-sided type I error ($p \leq 0.05$) was assumed statistically significant at a 95% CI.

Results

According to the Cancer register for 2018-2019, in total, 305 patients were admitted to the Chemotherapy department of the Aktobe oncology center in both inpatient and outpatient mode. The average age of patients Me 56.0 (47-64), min-max 24-84 years; BMI min-max 17-53; Charlson comorbidity index min-max 1-15; the duration of chemotherapy was min-max 1-26 months. Echocardiographic monitoring is the most essential in diagnosing cardiotoxicity; therefore, the sample was analyzed from the standpoint of the presence/absence of EchoCG monitoring. The quantitative representation of the sample is shown in Table 1.

The prevailing part of patients are women aged 60+ years (41.6%), in menopause, with metabolic disorders, in the majority with a normal baseline ECG (76.1%), with nodular cancer,

Table 1 Descriptive statistics of patients in the context of EchoCG monitoring, characteristics of the tumor process, and treatment.

Parameter	All, n=305	EchoCG (+), n=60	EchoCG (-), n= 245	p-value
Age, years	55.4±11.4	55.9±12.5	55.3±11.2	0.527
Age groups, n (%) 18-29 30-39 40-49 50-59 60 +	 3 (1.0) 25 (8.2) 72 (23.6) 78 (25.6) 127 (41.6)	 1 (1.7) 7 (11.7) 11 (18.3) 12 (20.0) 29 (48.3)	 2 (0.82) 18 (7.4) 61 (24.9) 66 (26.9) 98 (40.0)	 p= 0.400
Heredity+, n (%)	41 (13.44)	6 (10.0)	35 (14.3)	p= 0.383
Menopause +, n (%)	215 (70.5)	43 (71.7)	172 (70.2)	p=0.824
IBM*, kg/м2	28.4±5.7	28.8±5.6	28.3±5.7	p 0.344
Baseline LVEF*, n 117 (56.1%)	60.7±4,0	61.7±3.4	60.2±4.2	p 0.012
Tumor staging, n (%) I IIA IIB IIIA IIIB IV	 16 (5.3) 127 (41.6) 112 (36.7) 18 (5.9) 24 (7.9) 8 (2.6)	 6 (10.0) 17 (28.3) 24 (40.0) 5 (8.3) 5 (8.3) 3 (5.0)	 10 (4.1) 110 (44.9) 88 (35.9) 13 (5.3) 19 (7.8) 5 (2.0)	 p = 0.109
Tumor histotype, n (%) Invasive carcinoma Intraductal carcinoma Infiltrating ductal Lobular carcinoma Carcinosarcoma	 175 (57.6) 16 (5.3) 107 (35.2) 3 (1.0) 3 (1.0)	 29 (49.2) 5 (8.5) 24 (40.7) 0 (0.00) 1 (1.7)	 146 (59.6) 11 (4.5) 83 (33.9) 3 (1.2) 2 (0.82)	 p=0.399
Immunohistochemical data, n (%) Triple negative Luminal A type Luminal B positive Luminal B negative Her-2 neu negative Not determined	 58 (19.0) 29 (9.5) 35 (11.5) 136 (44.6) 39 (12.8) 8 (2.6)	 9 (15.0) 3 (5.0) 14 (23.3) 20 (33.3) 13 (21.7) 1 (1.7)	 49 (20.0) 26 (10.6) 21 (8.6) 116 (47.4) 26 (10.6) 7 (2.9)	 p=0.003
Tumor's clinical forms, n (%) Nodular Mastitis-like Edematous infiltrative Erysipelas-like Others, without specification	 287 (94.1) 1 (0.33) 9 (3.00) 1 (0.33) 7 (2.3)	 54 (90.0) 0 (0.00) 3 (5.00) 0 (0.00) 3 (5.0)	 233 (95.1) 1 (0.41) 6 (2.5) 1 (0.41) 4 (1.6)	 p=0.397
Charlson comorbidity index, scores Me(25;75)	5[4;7]	5[4;8]	5[4;6]	p 0.169
Cardioprotectors, n (%) Foregoing intake No intake Unknown	 34 (11.15) 120 (39.34) 151 (49.51)	 12 (20.0) 13 (21.7) 35 (58.3)	 21 (8.6) 107 (43.7) 117 (47.8)	 p=0.002
Chemotherapy, n (%) Neoadjuvant Neoadjuvant and adjuvant Adjuvant Due to tumor progression	 11 (3.6) 183 (60.0) 84 (27.5) 27 (8.9)	 2 (3.3) 28 (46.7) 27 (45.0) 3 (5.0)	 9 (3.7) 155 (63.3) 57 (23.3) 24 (9.8)	p = 0.008
Administered treatment, n (%) Anthracyclines Anthracyclines + MCA* Monoclonal antibodies Other	 199 (65.3) 41 (13.4) 30 (9.8) 35 (11.5)	 24 (40.0) 20 (33.3) 9 (15.0) 7 (11.7)	 175 (71.4) 21 (8.6) 21 (8.6) 28 (11.4)	 p<0.001
Chemotherapy duration, months Me(25;75)	5[4;7]	6[4;10]	5[3;7]	p 0.027
Chemotherapy duration before interruption, n (%) 25% 50% 75% 100%	 9 (3.0) 25 (8.2) 41 (13.4) 230 (75.4)	 1 (1.7) 7 (11.7) 7 (11.7) 45 (75.0)	 8 (3.3) 18 (7.4) 34 (13.9) 185 (75.5)	 p=0.639
Quality of completed courses, n (%) Without complications, successfully A correction was required Interrupted due to complications Interrupted for non-medical reasons (refusal, moving)	 201 (65.9) 36 (11.8) 32 (10.5) 36 (11.8)	 36 (60.0) 11 (18.3) 9 (15.0) 4 (6.7)	 165 (67.4) 25 (10.2) 23 (9.4) 32 (13.1)	 p= 0.102
Chemotherapy complications, n (%) Cardiovascular complications Hematological From the gastrointestinal tract A combination of complications (allergic, skin, gastrointestinal, hematol.) Not indicated	 19 (6.2) 20 (6.6) 10 (3.3) 243 (79.7) 13 (4.3)	 11 (18.3) 4 (6.7) 2 (3.3) 40 (66.7) 3 (5.0)	 8 (3.3) 16 (6.5) 8 (3.3) 203 (82.9) 10 (4.1)	 p< 0.001
Chemotherapy outcomes, n (%) Alive, no complications CV* death / interruption of the course due to CT* complications Death, / interruption of the course due to other complications Progression	 258 (84.6) 4 (1.3) 21 (6.9) 22 (7.2)	 49 (81.7) 2 (3.3) 3 (5.0) 6 (10.0)	 209 (85.3) 2 (0.82) 18 (7.4) 16 (6.5)	 p=0.309
Observations, days	657.9±242.3	722.0±260.6	642.3±235.5	p 0.022

*Abbreviations:
CT - cardiotoxic (complications); CV - cardiovascular (death); IBM - index body mass; LVEF - left ventricular ejection fraction; MCA - monoclonal antibodies

Table 2 Kaplan-Meier survival curves indices for the presence of EchoCG monitoring, the presence of recorded CV events, and the quality of chemotherapy courses.

Parameters	%	Months	SE	95% CI	log-rank p
Presence (absence) of EchoCG monitoring					
EchoCG + (1), n 53	90.6	34.0	1.01	32.1;36.1	
EchoCG - (2), n 229	91.3	33.9	0.52	32.9;34.9	.814
Presence (absence) of cardiovascular complications					
Complications not revealed (0), 92.5 33.7 0.44 33.6;35.2 n 266 Recorded (1), n 16 68.8 28.1 3.1 22.0;34.2 .005					
Successfulness of chemotherapy courses completion*					
Without complications (1), n 190	94.5	34.9	0.45	33.9;35.8	
Correction was required (2), n 24	68.6	29.2	1.94	25.4;33.0	<.001
Interrupted due to complications (3), n 11	34.4	17.6	1.63	14.4;20.8	

* Note: individuals who did not complete treatment courses for personal reasons (refusal, relocation) were not included in the statistics.

Figure 1 - Structure of recorded cardiovascular events in Breast cancer patients.

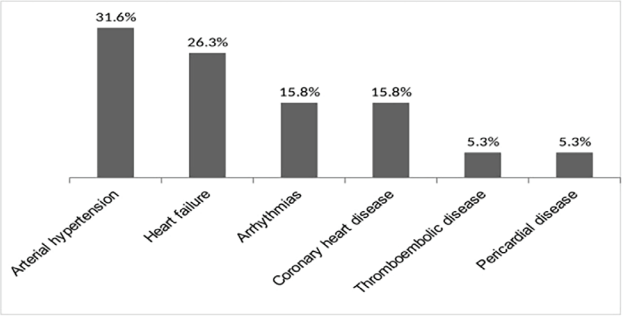
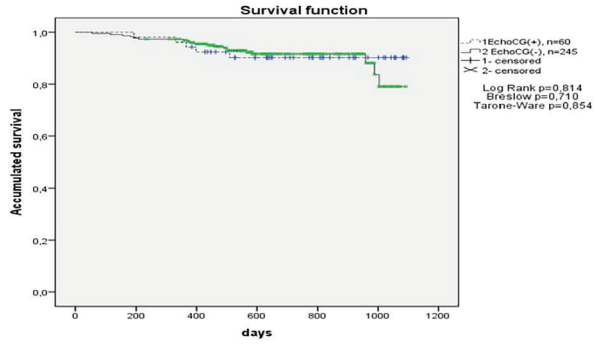


Figure 2 - Kaplan-Meier survival curves for the presence (absence) of EchoCG monitoring.



invasive carcinoma stage IIA, and 7 out of 10 with Her2-neu negative status, cutting off the opportunity for targeted therapy. Information on intaking cardioprotectors before and during treatment is either unknown (49.5% of all patients) or evidencing that no cardioprotectors were prescribed (39.3%). The data of echocardiographic monitoring, the most significant for the early detection of cardiotoxicity, are not entered into the register on a systematic basis: slightly more than half of the patients have baseline LVEF (56.1%, n 117), but only one of five was examined over time (19.7%, n 60). At the same time, a quarter of the total number of patients, 23.9%, shows an abnormal baseline ECG before starting chemotherapy courses. Two-thirds of patients (65.9%) completed chemotherapy without complications, but in every tenth, the treatment was interrupted due to complications (10.5%). In the structure of complications, 6.2% are CV ones. Table 1 also demonstrates a significant difference regarding CV complications between the two groups of patients - EchoCG+ and EchoCG- (p<0.001). One of the explanations for this difference is that in the EchoCG+ group, 33.3% of patients underwent a combined therapy of Anthracyclines + monoclonal antibodies, with a highly increased risk for cardiotoxicity development, vs. 8.6% in the EchoCG- group. Figure 1 shows the structure of CV complications according to Cancer register data (n 19, 6.2%).

Arterial hypertension and heart failure that developed in the course of chemotherapy account for more than half of all cases of CV complications (57.9%). The Kaplan-Meier survival curves were performed for the most significant indicators of the chemotherapy effectiveness in terms of cardiotoxicity - the presence/absence of EchoCG monitoring (LVEF changings during treatment), the presence/absence of recorded CV complications, and the quality of courses completed. The results are presented graphically and in Table 2 (the calculation was performed as event-free).

As follows from Table 2 and Figure 2, there was no difference in the survival of both groups, EchoCG+ and EchoCG- (log-rank p. 814). The analysis of contingency tables indicates a statistically significant difference between these groups in some key parameters. For instance, in the EchoCG+ group, the luminal B positive type predominates (23.3% vs. 8.6%, p.003) in the immunohistochemical structure of tumors, therefore, the proportion of patients in this group undergoing Anthracyclines + targeted therapy is higher (33.3% vs. 8.6%, p<.001) and the course of chemotherapy is longer (p.027).

The survival rate in the group of patients with documented CV complications appeared expectedly lower, 28.1 months. vs. 34.3 months (log-rank p .005), Figure 3.

The overall survival of patients (event-free), depending on the completeness and quality of chemotherapy courses, can be considered demonstrative (Figure 4).

For those who completed the chemotherapy course without complications, the survival rate was 34.9 months. vs. 17.6 in persons whose duration of treatment was interrupted due to complications, and 29.2 months in those with treatment adjusted (log-rank p<.001).

Table 3 presents data from the Cancer register on four identified cases of cardiotoxicity with an unfavorable outcome, but not correctly and timely documented in the register.

Comments on register data:

In Patient 1, death from acute coronary syndrome occurred six months after starting chemotherapy, after an entire course of Anthracyclines and radiation therapy. With that, there was no data on LVEF during chemotherapy in the Cancer register, as well as neither baseline nor prescribed cardiac protection during treatment. The patient died from CV complications detected posthumously, but there was no proper monitoring of probable CT signs during follow-up. There is reason to believe that Patient 1 developed late-onset cardiotoxicity due to the cumulative effect of Anthracyclines.

When an additional searching for information, Patient 2 was found to be developed sinus tachycardia during treatment, heart rate increased from 83 at baseline to 107-115 over five months of follow-up. Still, the register did not contain data on either the baseline ECG and EchoCG or the proceeding ECG, as well as cardiac correction data. The patient took Anthracyclines, Trastuzumab, and antihormonal drugs almost simultaneously, but the register did not reflect proper monitoring of her condition.

During additional information retrieval, we also found

Table 3 Data of patients where cardiotoxicity of chemotherapy was revealed postmortem.

Parameters:	Patient 1	Patient 2	Patient 3	Patient 4
Registration date	19.07.2018	20.02.2019	08.10.2018	27.05.2019
Age (yrs)	55	64	62	61
IBM	25.4	30.0	33.3	36.0
CV risk factors	Arterial hypertension, diabetes mellitus	Arterial hypertension, diabetes mellitus, obesity	Arterial hypertension, diabetes mellitus, obesity	Arterial hypertension, obesity
Baseline ECG	Sinus rhythm, heart rate 88 (normal)	No data	Sinus rhythm, norm	Sinus rhythm,norm
ECG during chemotherapy	Sinus tachycardia, heart rate 100, moderate violations of repolarization	No data	Sinus bradycardia 54, supraventricular extrasystole, moderate violations of repolarization	Sinus rhythm 85, frequent ventricular extrasystoles, unstable ventricular tachycardia, severe violations of repolarization
Baseline BP, HR	120/80; 80	130/70; 68	130/80; 72	110/70; 66
BP, HR during treatment	120/80; 96	120/70; 80	150/80; 68	150/100; 88
Baseline LVEF	55%	No data	58%	69%
LVEF during treatment	No data	56%, hypokinesia zones	No data	56% (in four months)
Baseline cardioprotective treatment	No data	No data	No data	Micardis Plus 80/25 (Telmisartan)
Cardioprotective treatment during chemotherapy	No data	No data	No data	Micardis Plus 80/25 (Telmisartan/ Hydrochlorthiazide)
Charlson comorbidity index	6 scores (diabetes mellitus)	13 scores (moderate or severe liver damage; metastatic tumors; diabetes)	6 scores (diabetes mellitus)	6 scores (moderate liver damage)
TNM diagnosis	St. IIApT2N0M0	St. IIBT2N1M0	St. IIBpT2N1M0	St. I T1NxM0
Tumor histotype	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma	Invasive carcinoma
IHC data	Luminal A subtype	Luminal B subtype	Luminal A subtype	HER-2 positive
Tumor's clinical form	Nodular	Nodular	Nodular	Nodular
Treatment administered	Surgery; adjuvant radiation and chemotherapy	Neoadjuvant chemotherapy; Surgery	Surgery; adjuvant radiation and chemotherapy	Surgery; adjuvant radiation and targeted chemotherapy
Treatment prescribed	Anthracyclines (doxorubicin) 4 courses	Anthracyclines (doxorubicin) Trastuzumab hormone therapy 4 + 4	Other (4 courses) + hormone therapy	Trastuzumab
Duration before interruption (amount of treatment received)	3 months (100%)	5 months (50%)	3 months (100%)	13 courses (75%)
Quality of Chemotherapy courses	No complications	Interrupted	Correction required (not specified which)	Interrupted
Identified cardiotoxic complication (indication in Cancer registry)	I 20.0 Unstable angina (posthumous)	I 42 Cardiomyopathy (posthumous)	I 25.8 Other forms of chronic coronary artery disease (posthumously)	Decreased LVEF> 10%, ventricular extrasystoles, unstable ventricular tachycardia
Chemotherapy outcomes	Death (02.16.2019), after 6 months from the start of treatment.	Interruption of the course due to CT complications; death after 5 months from the start of treatment (08/07/2019).	Death after 6 months from the start of treatment (08.02.2020).	Interruption of the course due to CT complications, admission in the Cardiology division (05/26/2020). Death 31.08.21, after 26 months from the start of treatment, the death cause COVID-19.

Note: CV - cardiovascular; BP - blood pressure; HR - heart rate; LVEF - left ventricular ejection fraction; IHC - immunohistochemistry (conclusion).

Figure 3 - Kaplan-Meier survival curves for the presence (absence) of CV complications.

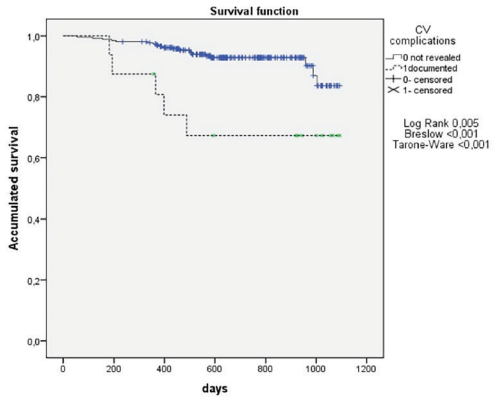
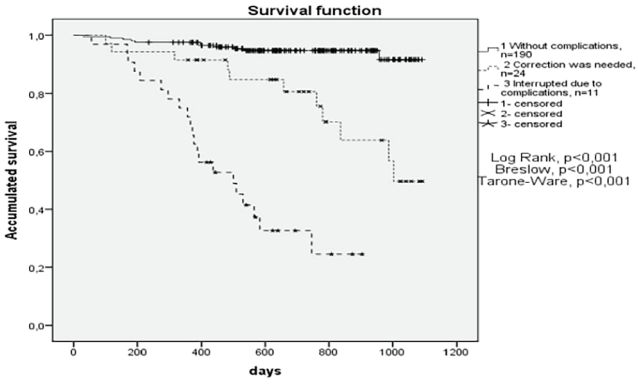


Figure 4 - Kaplan-Meier survival curves on the successfulness of chemotherapy courses completion.



that Patient 3 was administered cardiac protector Valsartan/ Amlodipin 160/10, but there were no data in the register. The register also did not contain data on what kind of chemotherapy correction was required for the patient. Proceeding assessment of LVEF in this patient was also absent.

The death of Patient 4 occurred 26 months after the date of registration, the cause of death recorded as Covid-19. Nonetheless, this case can be attributed to the developed chronic cardiotoxicity.

Discussion

According to a retrospective analysis of data from 305 patients who had undergone breast cancer chemotherapy from 2018 to 2019, the rate of CT complications was 6.2%. Arterial hypertension (31.6%) and CHF (26.3%) prevailed in the structure of CT complications. Transthoracic Echocardiography to detect left ventricular myocardial dysfunction was performed only in 19.7% of patients. The survival rate in the group with documented CT complications was lower (OR = 3.8, 95% CI 1.3; 11.1) than in the group without ones. Baseline assessment of cardiovascular system condition in patients and cardioprotective therapy administered to them were insufficient.

CV diseases can lead to premature disability and the death of cancer survivors. Such events can result from 1) cardiotoxicity, i.e. due to the direct effect of anticancer therapy; 2) accelerating the development of CV diseases in the presence of conventional CV risk factors [17]. It has been established that the risk of left ventricular dysfunction or the development of heart failure in patients with existing CV risk factors increases with the administration tyrosine kinase inhibitors; prescribing Trastuzumab simultaneously with or after Anthracyclines, or even without them; with radiation therapy in combination with chemotherapy, especially with cancer of the left breast; when prescribing VEGF inhibitors [6, 18]. Antineoplastic drugs for the treatment of breast cancer cause both early and delayed (late-onset) cardiotoxic effects. Acute events consist mainly of changes on the ECG, while delayed cardiomyopathy leads to dysfunction of the left ventricle with subsequent development of heart failure [19]. In our sample of unfavorable Chemotherapy outcomes, three of four patients underwent adjuvant radiation and chemotherapy, which deteriorated their condition through the development of severe heart failure signs that resulted in death.

Although the frequency of the chemotherapy cardiotoxic effects depends mainly on the class of drugs prescribed, there are other predisposing factors. Reportedly, the incidence of cardiotoxicity among Anthracyclines ranges from 8.9% (chronic) up to 27.2% (acute); however, the incidence is based on the cumulative dose and other risk factors, such as poor compliance with cardiac monitoring recommendations [20]. According to leading Italian experts (ICOS-ONE Study Investigators), the incidence of Anthracycline-induced cardiac events was 1.1% within the sample of N 273 [21]. The Trastuzumab-induced cardiotoxicity is reversible, unlike the irreversible Anthracycline-induced one, but this combination of drugs being administered together, increases the risk of cardiac events up to 7-fold, despite a relatively favorable safety profile of Trastuzumab [12, 22]. In our Cancer register, we identified 6.2% of documented cases of CV complications in 2 years for all classes of chemotherapy drugs, including 5-FU and other drugs. Regrettably, due to a small sample (n 19) and missed some crucial data in the register, we failed to present a prevalence of cardiotoxicity effects by classes of drugs.

As known, cardiotoxicity can be prevented by screening and modifying existing risk factors, aggressively monitoring for symptoms as chemotherapy is administered, and continuing follow-up after completion of a course or the entire treatment [23]. In this relation, EchoCG is considered a method cost-effective and reliable enough to monitor cardiac function, despite the emerging data on cardiac markers supremacy. Generally, echocardiographic monitoring of the CV system is an integral part of cardiac patient management [22, 24]. LVEF is recognized as a good predictor of CV outcomes, but lacks the sensitivity to detect early subclinical changes in cardiac function. A more sensitive marker for predicting dysfunction of the left ventricle in patients during and after cancer therapy is an assessment of global longitudinal myocardial deformation [25, 26]. Cardiac troponin may also be helpful for early assessment and monitoring of CV events [22, 27]. In our study, we did not find a significant difference in survival between patients of the two groups, where EchoCG monitoring was carried out and where it was none (log rank p.814). Contrary to current guidelines, this situation might have been due to many unaccounted-for confounding factors and incomplete filling of the registry. In particular, we found that in half of the patients (49.5%), cardioprotective treatment was absent in the records, and in 34.3% of them was not prescribed before the treatment. There was no data on baseline cardiac protection or ongoing treatment in three patients with a fatal outcome directly due to the cardiotoxicity of therapy.

Currently, there are no specific medicines to diminish the side effects of chemotherapeutic drugs. The only FDA and EMA-approved cardioprotective drug is Dexrazoxane,

which provides effective primary cardioprotection against Anthracycline-induced cardiotoxicity, in the meantime saving its activity. Under our conditions, Dexrazorane is unavailable so far. Generally, pharmacological treatment of most cardiac events induced by chemotherapy is symptomatic. Various cardioprotectors can be applied to reduce the adverse effects of chemotherapy, depending on symptoms. For instance, compared to placebo, administration of an ACE inhibitor Lisinopril, or the beta-blocker Carvedilol reduces the frequency of interruptions in Trastuzumab treatment and increases survival without CT complications - RR 0.49 (95% CI 0.27; 0.89) for Carvedilol and 0.53 (95% CI 0.30; 0.94) for Lisinopril - in HER2-positive BC patients [28]. In Patient 4, Micardis 80/25 (Telmisartan) was administered at baseline and further, thus providing 13 courses of targeted therapy and relatively long survival comparing to other patients from the sample of unfavorable outcomes.

At least three of our patients out of four who died showed developed chronic or late-onset cardiotoxicity not diagnosed timely due to improper filling in the Cancer register and herein improper cardiac monitoring.

Conclusion

According to Cancer registry data for 2018-2019, CV complications were recorded in 6.2% of patients. The survival rate of these patients is lower than in the group without ones (28.1 months vs. 34.3 months, log-rank p .005).

With that, the database analysis indicates the absence of a systematic approach to the registration of crucial information regarding cardiotoxicity (monitored EchoCG data recorded only in 19.7% of patients, 49.5% of patients had no data on cardioprotective therapy). There is a lack of concordance in the actions of cardiologists and oncologists in the management of Breast cancer patients who need careful monitoring of heart function due to cardiotoxicity of the drugs used.

The lethal outcomes of chemotherapy with an established cardiac death indicate the need to revise the Cancer registry management from the standpoint of cardio-oncology. All Breast cancer patients undergoing chemotherapy require careful cardiac monitoring during treatment and follow-up. In general, there is a need to develop local protocols for screening and monitoring patients undergoing cardiotoxic chemotherapy and radiation therapy.

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Modified checklist for autism in toddlers, revised, with follow-up application in Central Kazakhstan

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Abstract

Objectives: One of the commonly used screening tools (Modified Checklist for Autism in Toddlers, Revised, with Follow-Up, M-CHAT-R/F, 2014) is designed for diagnosis of ASD in children aged 16-30 months. Given the known effectiveness of the M-CHAT-R/F and the need to adjust the tool to the cultural differences of the caregivers, the purpose of this research to test the M-CHAT-R/F test effectiveness and to adapt its Kazakh and Russian versions for the caregivers of Kazakhstan.

Study design: Cross-sectional study

Material and methods: This study was conducted among caregivers of children aged 24-48 months in the period October-November 2020 in Central Kazakhstan. Internal consistency of the Russian and Kazakh versions of the questionnaire was assessed by Cronbach's Alpha. To assess the reliability of the Russian version of M-CHAT-R/F, Guttman's lambda-6 indicator was calculated to consider the variance in each element of the scale explained by linear regression of other elements.

Results: The final size of the analyzed sample was 171 children, among whom the mean age was 30.75 months and 92 (53.8%) were female. The results of the M-CHAT-R/F survey were distributed as follows: the low-risk group included 141 (82.5%) children, the medium-risk group included 23 (13.5%) children, and the high-risk group also included 7 (4.1%) children. The average score for M-CHAT-R and Follow-Up is 1.6 (SD=2.16) and 1.5 (SD=2.3) points, respectively. Both the Russian and Kazakh versions of M-CHAT-R/F demonstrated high internal consistency, with Cronbach's alpha (CI=0.95) calculated as 0.87 and 0.93, respectively. Guttman's lambda-6 also showed an excellent result in the Russian version of the checklist (0.94).

Conclusion: The study findings support the appropriateness of using M-CHAT-R/F in Kazakhstan as an ASD screening tool. The effectiveness of this tool is emphasized by its ease of use and can reduce the average age of diagnosis of ASD in Kazakhstan to two years.

Key words: autism, cross-cultural adaptation, Kazakhstan, M-CHAT-R/F, screening

Introduction

Autism spectrum disorder (ASD) is a developmental disability, associated with significant challenges throughout a person's life and often characterized by repetitive sensorimotor behavior and social communication disorders [1]. The diagnosis of ASD includes several conditions, such as autistic disorder, developmental disorders, and Asperger's syndrome. The Centers for Disease Control and Prevention (CDC) report that in the United States 1 in every 54 children is diagnosed with ASD (https://www.cdc.gov/ncbddd/autism/facts.html). The diagnosis is complicated by the absence of medical tests and the reliance on provider expertise in recognizing the ASD signs and symptoms, which begin in childhood, accompany a person throughout life, and are never cured [2]. While ASD can be detected by experienced professionals in the very early childhood, the final diagnosis is often delayed, subsequently delaying the help a young ASD patient needs (CDC). Early diagnosis and the start of therapeutic interventions are important, because early start of the long-term work on social adaptation and correction with such children may increase their chances of successful adaptation to education requirements, job opportunities, and social life [3].

The risk factors of ASD are commonly listed as environmental and genetic [4]. The epidemiological summary of ASD risk factors includes gender, pregnancy complications, and parental age. For every boy with ASD, there are four girls [5]; low birth weight due to deep prematurity, multiple pregnancies, and short interval between pregnancies are associated with higher risk of ASD [6], the age of both parents over 35 years also significantly increases the risk of child's ASD [7].

According to the Focus on Health portal, the highest prevalence of ASD is observed in Hong Kong, the United States, South Korea, and Japan (1 in 27; 1 in 38; 1 in 45; 1 in 55 children, respectively) [8]. Another source summarized multiple epidemiological studies on the prevalence of ASD worldwide and estimated ASD prevalence as one in every 160 children [9]. However, this is not a generalizable or inferential indicator, because the data is primarily based on studies from high-income countries, while in low-and middle-income countries information on prevalence is limited. In addition, the ASD diagnosis is often grouped with other mental disorders, making accurate estimates impossible.

In Kazakhstan, medical statistics combine ASD with other mental disorders. While the rate of newly diagnosed mental disorders reported in Kazakhstan in 2018 was 54.9 per 100,000 people, with the highest incidence rate reported in Central Kazakhstan (85.1 per 100,000 population [10]), actual incidence rate of the ASD is not known.

Currently, the ASD diagnosis can be assigned to children aged four years and older, preventing early start of correction of existing developmental disorders in younger children. The Kazakhstan Ministry of Health identified three stages for childhood psychophysical development screening (MoH, September 9, 2010 №704), with the third stage of screening called "early childhood screening assessment". The assessment is aimed at children aged 0-6 years with a risk of lagging in the physical, mental and social development. Based on the assessment results, a medical provider prescribes a psychological, medical and pedagogical consultation by a multidisciplinary team, which may refer the child to medical specialists or may recommend the use of special educational settings.

A qualitative study of families with ASD-diagnosed children in Kazakhstan reported on the struggles of caregivers. Many caregivers noticed worrying symptoms in their child at an early age, however, they did not seek medical help immediately and delayed contact with medical specialists. The study also found that many caregivers believed that psychiatric institutions were "unfriendly", "not suitable for their children", and "do not understand the specific needs of children with ASD" [11]. The reluctance to record the diagnosis and general dissatisfaction with available care emphasizes the need for timely detection of ASD in Kazakhstan, both in primary health care and in community settings. A recent study found that only four out of 21 cases of ASD were detected in primary health care settings [12], indicating the need for further use of appropriate screening methods [13]. An early ASD screening approach usually requires minimal training for health professionals, and some screening tools can be used by caregivers themselves.

One of the commonly used screening tools is the Modified Checklist for Autism in Toddlers, Revised, with Follow-Up (M-CHAT-R/F), developed and tested in 2014 for early detection of ASD in children aged 16-30 months. The tool uses a two-step approach with the questionnaire (M-CHAT-R) completed by the caregivers or healthcare providers followed by a set of clarifying questions or demonstration of skills (Follow-Up) to confirm the accuracy of the responses. Using this tool may reduce the age at the diagnosis to two years, thereby increasing the time available for early interventions [14]. In addition, M-CHAT-R/F has also been shown to be effective when used by primary care providers to screen low-risk young children in a large, geographically distributed population [15] with minimal costs. The effectiveness of the tool is partly due to its ability to focus on the caregivers' concerns about their child's development in a timely and independent manner. At the same time, this focus on caregivers relies on their opinion about the typical actions of their children, and the effectiveness of this screening method may vary, which indicates the need for appropriate cultural adaptation of the questionnaire [16]. Given the known effectiveness of the M-CHAT-R/F and the need to adjust the tool to the cultural differences of the caregivers, the purpose of this research to test the M-CHAT-R/F test effectiveness and to adapt its Kazakh and Russian versions for the ASD caregivers of Kazakhstan.

In this study, the authors will try for the first time to assess the effectiveness of the M-CHAT-R / F screening tool in a Kazakhstani sample. Currently, there are very few epidemiological studies of autism spectrum disorders in Kazakhstan. More research on autism spectrum disorders in all countries will improve understanding of the epidemiology of these disorders.

Material and methods

This cross-sectional study was conducted in the period October-November 2020 in an area of high mental and behavioral disorders prevalence (Central Kazakhstan). Today, in Kazakhstan, there are no official statistics from the Ministry of Health of the Republic of Kazakhstan on the number of children with autism. Due to the lack of medical reporting such a column reflecting a given diagnosis. Autism is included in the summary statistics of mental retardation, so the prevalence and morbidity rates are not specifically taken into account. At the moment, Central Kazakhstan is leading in the number of cases of mental and behavioral disorders among children under 14 years of age (107.8 per 100,000 population), in Kazakhstan in general, this number is 66.2 per 100,000 population.

Study was conducted in an online format due to the conditions of the pandemic. The study Modified Checklist for Autism in Toddlers, Revised, with Follow-Up 14 was employed as a screening tool. After receiving permission from the developers, a Russian/English bilingual team performed a critical analysis of the Russian version of M-CHAT-R/F, obtained from the official website (www.mchatscreen.com). Subsequently, a Kazakh/English bilingual team translated the questionnaire into the Kazakh language. Both teams were based in Karaganda Medical University and included a psychiatrist to represent the specialty responsible for assigning the ASD diagnosis. The translation was limited to question text and did not include changes in scoring responses or using quantitative score to evaluate the risk of ASD, as 0-2 – low risk, 3-7 points - medium risk, and 8-20 points – high risk group. The questionnaire was translated to Russian and Kazakh languages, then back-translated to English, and reconciled by a bilingual Russian-English and Kazakh-English psychiatrist and researcher.

After completion of the translation process by the research team in October, participants were recruited through use of social media. The study focused on the most popular social medial outlet in Kazakhstan (Instagram) where information about the study was offered on a number of thematic forums about child raising. The forums explained the study goals and

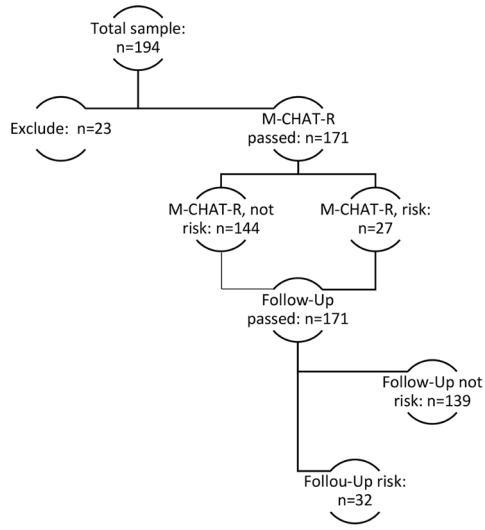
provided a link to be followed for those who were interested in participation. Interested participants who followed the link were screened for the inclusion criterion and were provided details of the study. Informed consent was obtained in an online format. The single inclusion criterion of participants was the child's age in the range of 16-48 months. Eligible participants were forwarded the link to the anonymous M-CHAT-R/F questionnaire. In addition to questionnaire, the study collected data on the child's and parents age and gender, city of residence, ethnic background, and presence of diagnosed developmental delays. Parental ages were grouped into categories: 21-25 years, 26-30, 31-45 years for the mother, and 21-30 years, 31-40 years, 41-48 years for the father. Due to the multiethnic composition of Kazakhstan, additional information was collected on the participant's ethnic background. The participants were given the choice to respond to either a Kazakh or a Russian language questionnaire. To control for the previous diagnosis of ASD, the survey collected responses to question "Has you child been diagnosed with developmental delays?". No reimbursement, reward, or any incentive was offered to participants.

This study protocol was approved by the Ethical committee of the Karaganda Medical University to ensure the protection of participants. The number of Ethical Approval is №26 dated October 10, 2020. Based on the study protocol, the participants signed an online Informed consent. R-studio software was used for statistical analysis. Internal consistency of the Russian and Kazakh versions of the questionnaire was assessed by Cronbach's Alpha. To assess the reliability of the Russian version of M-CHAT-R/F, Guttman's lambda-6 indicator was calculated to consider the variance in each element of the scale explained by linear regression of other elements. Chi-square test of association was used to analyze categorical variables.

Results

The study received 194 completed surveys; after removal of 23 surveys that did not meet the inclusion criterion, the final size of the analyzed sample was 171 children (n=171). One caregiver completed the questionnaire for each of the 171 children. The number of participants at each stage of the M-CHAT-R/F study is shown in Figure 1. Based on the results of the M-CHAT-R screening stage, the low-risk group included 144 (84.2%) children, the medium-risk group included 20 (11.7%) children, and the high-risk group included 7 (4.1%) children.

Figure 1 - The number of participants at each stage of the M-CHAT-R/F screening, as well as the number of children at risk



The results of the Follow-Up survey were distributed as follows: the low-risk group included 141 (82.5%) children, the medium-risk group included 23 (13.5%) children, and the high-risk group also included 7 (4.1%) children. The average score for M-CHAT-R and Follow-Up is 1.6 (SD=2.16) and 1.5 (SD=2.3) points, respectively. After scoring the responses, the scores of 3-7 points (medium risk) and 8-20 points (high risk) were recoded as a binary variable of a single risk group.

Demographic characteristics of the total sample and the risk group are presented in Table 1. The average age of the assessed children was 2.5 years (30 months); the majority of participants were identified as ethnic Kazakhs (n=102, 59.6%), followed by ethnic Russians (n=23, 13.5%). Due to the small number of participants identified as other ethnic groups, they were combined as "Other" (n=46, 26.9%) for the purpose of analysis. Despite the sample having a higher proportion of ethnic Kazakhs, the majority of participants selected Russian language version of the questionnaire (n=149, 87.1%).

Based on the results of M-CHAT-R, 15.8% of participants were at risk of ASD; the percentage increased to 18.7% in the Follow-Up scoring. Although the ratio of boys and girls in the sample was similar (46.2% and 53.8%, respectively), proportion of boys was significantly higher in the risk group for ASD according to the results of M-CHAT-R/F ($\chi 2(1, N=171)=12.7$, $p<0.05$). Also, a significant relationship ($p<0.05$) was observed between the father's age category and the ASD risk group on the results of the M-CHAT-R/F. A similar relationship between maternal age and child's risk group ($p>0.05$) was not observed. No significant difference in risk level was detected among ethnic groups or based on the survey language preference ($p>0.05$). Overall, 8 participants disclosed an early ASD diagnosis (Childhood autism, Atypical autism, Asperger's Syndrome, and pervasive disorder unspecified) which represents 6.6% of the sample. Statistical analysis revealed a significant difference in the distribution of ASD diagnosis based on both the M-CHAT-R and M-CHAT-R/F results ($p<0.05$). Both the Russian and Kazakh versions of M-CHAT-R/F demonstrated high internal consistency, with Cronbach's alpha (CI=0.95) calculated as 0.87 and 0.93, respectively. Guttman's lambda-6 also showed an excellent result in the Russian version of the checklist (0.94).

Table 2 compares the responses that matched the risk ("Failed" questions) based on M-CHAT-R/F and the risk ("Failed" questions) based on Follow-Up results between the children from the medium/high-risk and low-risk groups. The highest number of "Failed" responses was observed for the M-CHAT-R questions 7 *(Using one finger to point at objects of interest)* and 16 *(Follows the eyes parents),* both at 17 responses (9.94%). Same questions were identified as most common for M-CHAT-R/F, with 18 and 20 "Failed" responses respectively, with additional high-frequency "Failed" response to question 18 *(Follows verbal directions, n=19, 11.1%)*. Questions 3 *(Plays pretend or make-believe games, n=13, 7.6%),* 9 *(Shows objects to share, not for help, n=12, 7.02%),* 17 *(Attempts to attract the attention of parent, n=12, 7.02%),* and 18 *(Follows verbal directions, n=12, 7.02%)* represented second group of high frequency of "Failed" responses.

Table 2 also shows some discrepancy in the results between M-CHAT-R and Follow-up in identifying children at risk. For example, in the M-CHAT-R questionnaire among children in the risk group, 13 (7.6%) "failed" the question 3 (Plays pretend or make-believe games), and 9 (5.26%) "failed" the question in the low-risk group; however, the Follow-Up did not confirm any "failed" responses. In other cases, such as in question 10 *(Responds to their name),* M-CHAT-R identified a lower number

Table 1 M-CHAT-R and Follow-Up (FU) results and demographic characteristics of the sample

Variables	Total Sample (n=171)	M-CHAT-R risk group	M-CHAT-R, not at-risk group	p-value	FU risk	FU, not at-risk	p-value
Gender							
Male, N (%)	79 (46.2)	23 (13.5)	69 (40.4)	<0.001	23 (13.5)	69 (40.4)	<0.05
Female, N (%)	92 (53.8)	4 (2.3)	75 (43.9)		9 (5.3)	70 (40.9)	
Age							
Mean age in months (SD)	30.75 (7.2)	31.5	30.75		30.77	30.75	
Mean mother's age (SD)	28.68 (4.2)			0.54			0.57
21-25 years	32 (18.7)	3 (1.8)	29 (17.0)		5 (2.9)	27 (15.8)	
26-30 years	98 (57.3)	17 (9.9)	81 (47.4)		21 (12.3)	77 (45.0)	
31-45 years	41 (24.0)	7 (4.1)	34 (19.9)		6 (3.5)	35 (20.5)	
Mean father's age (SD)	31.39 (5.7)			<0.05			<0.05
21-30 years	88 (51.5)	7 (4.1)	81 (47.4)		11 (6.4)	51 (29.8)	
31-40 years	71 (41.5)	18 (10.5)	53 (31.0)		20 (11.7)	77 (45.0)	
41-48years	12 (7.0)	2 (1.2)	11 (6.4)		1 (0.6)	11 (6.4)	
Ethnicity (%)							
Kazakh	102 (59.6)	13 (7.6)	89 (52.0)	0.11	18 (10.5)	84 (49.1)	0.62
Russian	23 (13.5)	7 (4.1)	16 (9.4)		6 (3.5)	17 (9.9)	
Other	46 (26.9)	7 (4.1)	39 (22.8)		8 (4.7)	38 (22.2)	
Screening language							
Russian	149 (87.1)	24 (14.0)	125 (73.1)	1	27 (15.8)	122 (71.3)	0.82
Kazakh	22 (12.9)	3 (1.8)	19 (11.1)		5 (2.9)	17 (9.9)	
Diagnosis							
Previous diagnosis	8 (4.7)	6 (3.5)	2 (1.2)	<0.05	5 (2.9)	3 (1.8)	<0.05
No previous diagnosis	163 (95.3)	21 (12.3)	142 (83.0)		27 (1.2)	136 (79.5)	

Table 2 Prevalence of the «failed» items across risk groups

№ Child's behavior, questions were shortened for clarity	M-CHAT-R "failed" items frequency (%)		Follow-Up "failed" items frequency (%)	
	Risk	Not Risk	Risk	Not risk
1 Looks at the pointed objects	9 (5.26)	1 (0.58)	11 (6.43)	0
2 Doubts about hearing	7 (4.09)	8 (4.68)	7 (4.09)	3 (1.75)
3 Plays pretend or make-believe games	13 (7.6)	9 (5.26)	0	0
4 Climbs various structures and objects	2 (1.17)	2 (1.17)	0	2
5 Unusual finger movements in front of the eyes	8 (4.68)	22 (12.87)	14 (8.19)	24 (14.04)
6 Using one finger to point at objects for help	5 (2.92)	2 (1.17)	11 (6.43)	1 (0.58)
7 Using one finger to point at objects of interest	17 (9.94)	10 (5.85)	18 (10.53)	16 (9.36)
8 Interests in other children	6 (3.51)	4 (2.34)	10 (5.85)	4 (2.34)
9 Shows objects to share, not for help	12 (7.02)	1 (0.58)	10 (5.85)	2 (1.17)
10 Responds to their name	4 (2.34)	3 (1.75)	11 (6.43)	6 (3.51)
11 Smiles in response to a smile	1 (0.58)	1 (0.58)	5 (2.92)	6 (3.51)
12 Upset by household sounds	7 (4.09)	31 (18.13)	10 (5.85)	7 (4.09)
13 Able to walk	0	0	0	1 (0.58)
14 Direct eye contact in communication	3 (1.75)	3 (1.75)	0	1 (0.58)
15 Copies the actions of adults	5 (2.92)	0	0	3 (1.75)
16 Follows the eyes parents	17 (9.94)	16 (9.36)	20 (11.7)	15 (8.77)
17 Attempts to attract the attention of parent	12 (7.02)	5 (2.92)	3 (1.75)	0
18 Follows verbal directions	12 (7.02)	1 (0.58)	19 (11.11)	1 (0.58)
19 Seeks reaction of parents to an unusual situation	9 (5.26)	9 (5.26)	8 (4.68)	3 (1.75)
20 Likes movement activities or games	0	0	0	0

of fails in both high-risk and low-risk children (n=4 and 3), but the frequency increased in the Follow-Up (n=11 and 6 children). In some cases, such as in question 3 *(Plays pretend or make-believe games)*, M-CHAT-R identified 22 "failed" responses, while Follow-up did not confirm any as "failed". A similar tendency was observed for question 17 *(Attempts to attract the attention of parent)* with a decline in "failed" responses from 17 to 3. Overall, this difference may suggest that caregivers may have not fully understood the meaning of the wording in questions despite the accurate translation.

Discussion

This study is the first epidemiological study of ASD in Kazakhstan, introducing the M-CHAT-R/F screening tool for early detection of ASD. The M-CHAT-R/F showed an acceptable internal consistency index and lambda Guttman-6, indirectly confirming correct translation of the questionnaire into Kazakh and Russian. At the same time, the study found a difference in the identification of at-risk children with the first (M-CHAT-R) and second (Follow-Up) stages of the screening. Special attention should be requested to question with high

discrepancy between the stages, such as a child's ability to play pretend games (question 3) or attempts to attract parent's attention (question 17), where the first stage questionnaire detects more failures than the follow up. Utilization of the Follow-up may reduce the frequency of false-positive responses. Similarly, a child's behavior that was not detected as "failed" at the first stage, but failed the follow-up, such as smiling in response to a smile (question 11), may need special attention from the providers. In some cases, additional research is needed to explore the high frequency of failure for some questions (e.g., unusual finger movements in front of the eyes, question 5) to exclude the possibility of caregiver misunderstanding or cultural expectations and to take into account the possibility of ethnically traditional childhood games that may induce similar behavior.

In previous studies on cross-cultural adaptation of the non-English version, M-CHAT-R/F shows high accuracy and efficiency [18, 19–24], and this study also supported its ability to successfully screen for ASD with high specificity and sensitivity levels. The appropriateness of the M-CHAT-R/F for use in Kazakhstan was indirectly supported by the study findings. Higher ASD prevalence among boys was also established in previous studies, and was supported by the [24] findings of this study. Similarly, the study confirmed previously reported [25] influence of the child's father's age on the risk of developing ASD, while there was no such relationship found in this study between the mother's age and the risk of ASD.

Being the first M-CHAT-R/F tool validation study in Kazakhstan, aimed at an increase in early ASD diagnosis, the research is also relevant to Kazakhstan's healthcare policy guidelines. According to the Rules of Emergency Medical Care in the Republic of Kazakhstan, approved by order of the Minister of Health of the Republic of Kazakhstan dated July 3, 2017, No. 450, a primary care provider must identify a patient with possible mental and behavioral disorders. Utilization of the Kazakh and Russian versions of the M-CHAT-R/F by primary care providers can be beneficial for early diagnostic and referral to specialists. Offering the tool for caregivers through primary care settings allows parents to monitor a child's development and seek advice and care at the earlier stages of the child's growth.

The study, however, has a number of limitations. The main limitation of the study is the absence of confirmed ASD diagnosis by medical specialists; therefore, the study findings are limited to the data from the self-screening tool. However, the goal of introducing the screening tool is to attract caregiver's attention and request an early specialist assessment to allow for early diagnosis if appropriate.

Another major limitation is a small sample size of 171 volunteers within a relatively small geographical region of Kazakhstan. The study deliberately did not offer any incentives for participation to avoid false responses. An even smaller proportion of caregivers selected the Kazakh-language version of the questionnaire. Participants' preference for the Russian version can be explained by the high prevalence of ethnic Kazakhs who identify themselves as primarily Russian-speaking; this limitation is also related to the study region having been predominantly Russian-speaking. Follow-up studies in Kazakhstan should select a geographically broader sample, both in household and in primary health care settings. The same small sample issue led to the grouping of medium and high-risk children into a single "at-risk" category; however, this regrouping does not bias the overall proportion of children at risk.

Conclusion

The Kazakh and Russian versions of the M-CHAT-R/F show acceptable validity and are recommended for use in Kazakhstan. The effectiveness of this screening tool is emphasized by its ease of use, both for caregivers and medical professionals and can reduce the average age of diagnosis of ASD in Kazakhstan to two years. Easy availability of the M-CHAT-R/F will lead to early diagnosis and start of timely intervention, which is commonly associated with the most favorable forecasts for the development of children with ASD.

M-CHAT / R-F screening procedure should be used in daily practice, as it is already a standard procedure in many countries. In the United States, this tool has proven to be an effective tool for screening low-risk toddlers, and the American Academy of Child and Adolescent Psychiatry (AACAP) supports screening ASD in young children. Screening information should be carefully communicated to parents, and in addition to training on how to use the M-CHAT-R / F, the health workers should gain knowledge of caregivers motivational tactic for follow-up diagnosis and treatment.

The implementation of the M-CHAT / R-F should begin with a pediatrician and / or a member of a development team at a primary health care center. They should educate parents about the characteristics of this screening tool.

The introduction of a standardized screening procedure can significantly reduce the time it takes for children and their parents to be referred to centers where they can receive appropriate diagnosis and suggested treatment. In addition, when designing early development policies, it is important to have standardized screening tools in order to be able to identify children at risk and to facilitate the further development of early intervention centers.

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Semi-refined carrageenan induces eryptosis in a Ca2+-dependent manner

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Abstract

Background: Semi-refined carrageenan (food additive E407a) is a widely used thickener, which has been reported to exert toxic and pro-inflammatory effects. In particular, there is accumulating evidence that it induces eryptosis, i.e. a programmed cell death of eryptocytes, via ROS-mediated pathways. However, the role of Ca^{2+}-dependent mechanisms in E407a-induced eryptosis is not elucidated.

Material and methods: Semi-refined carrageenan at concentrations of 0 mg/ml, 1 mg/ml, 5 mg/ml and 10 mg/ml was incubated with blood of intact female WAG rats (n=9) for 24 h in RPMI and fetal bovine serum. After 24 h, the samples were used to obtain erythrocyte suspensions. The obtained suspensions were stained with a Ca^{2+}-sensitive FLUO4 AM probe (30 min, 2.5 μM). The fluorescence of FLUO4 in erythrocytes was detected by a BD FACSCanto II flow cytometer.

Results: The intracellular Ca^{2+} levels are proportional to the fluorescence of FLUO4. The mean fluorescence intensities (MFI) were compared. Low levels (1 mg/ml) of E407a had no impact on Ca^{2+} concentrations in erythrocytes ($p>0.05$). On the contrary, high concentrations (5 mg/ml and 10 mg/ml) of this food additive promoted an increase in the intracellular Ca^{2+} levels. The MFI values were 2.3- and 2.5-fold higher, respectively ($p<0.0001$). In addition, the exposure to E407a at concentrations of 5 mg/ml and 10 mg/ml ($p<0.0001$) increased the percentage of cells with high FLUO4 fluorescence.

Conclusion: Food additive E407a induces eryptosis in a Ca^{2+}-dependent manner.

Key words: calcium ion, erythrocytes, food additives, FLUO4

Introduction

The lifespan of erythrocytes is approximately 120 days. After that period, they are eliminated from the bloodstream by the fixed macrophages. However, in response to unfavorable factors, including lack of energy, hyperosmolarity, accumulation of reactive oxygen species (ROS), they undergo cell death referred to as eryptosis [1, 2]. In some ways, it resembles apoptosis of nucleus-containing cells and is characterized by blebbing, shrinkage and plasma phospholipid membrane scrambling [3]. The activation of eryptosis is mediated by oxidative stress (ROS overproduction), elevation of intracellular calcium ions, ceramide formation, etc. [4]. The physiological aim of eryptosis is to prevent destruction of damaged cells by hemolysis, which is associated with membrane rupture and release of alarmins or damage-associated molecular patterns (DAMPs). Erythrocyte-derived DAMPs such as hemoglobin, ATP, interleukin-33 and heat shock protein 70 are strongly pro-inflammatory [5]. In addition to endogenous factors, eryptosis is induced by a plethora of xenobiotics, including drugs [6, 7].

Eryptosis contributes significantly to the pathophysiology of many diseases, since its activation is associated with the reduced lifespan of red blood cells and impaired blood clotting, which alters microcirculation [8]. Accelerated erythrocyte removal from the bloodstream via eryptosis favors the development of anemia in thalassemia [4], end stage renal disease [9], malaria [10], sickle cell anemia [2], etc. This suggests that the approaches used to manipulate eryptosis can be applied as therapeutic strategies in diseases associated with anemia [11].

It is important to note that nowadays eryptosis parameters are considered to be markers of biocompatibility and cytotoxicity [12-14]. In particular, eryptosis indices can be used to assess the cytotoxicity of food additives [15]. The safety of one of the numerous food additives available in the market called carrageenan, which is registered in EU countries as either E407 (refined or native carrageenan) or E407a (semi-refined carrageenan), is debating. Carragenans are thickeners and gelling agents whose share in the global food market has been increasing for decades. Their content in food

and daily intake may vary significantly. In some dairy products, the content of carrageenan can reach up to 0.5% of weight [16]. According to some estimates, the amount of daily ingested carrageenan can be up to 7.2 g and this amount has been growing for years due to the prevalence of carrageenan-containing processed foods in Western diet [17]. However, carrageenans have been suggested to induce inflammation [16, 18-24]. The pro-inflammatory effects attributed to them contributed to setting up a programme for re-evaluating carrageenan safety for consumers (EFSA-Q-2018-00771). Controversial data on the findings of toxicity studies indicate that novel models for assessing the carrageenan safety are required. Semi-refined carrageenan has been shown to induce eryptosis in a dose-dependent way with the involvement of ROS-mediated pathways in activation of this cell death mode [15]. However, it is not clear whether this food additive can promote eryptosis via calcium-mediated pathways.

The aim of this study was to analyze the role of Ca^{2+}-dependent mechanisms in eryptosis induced by the common food additive E407a.

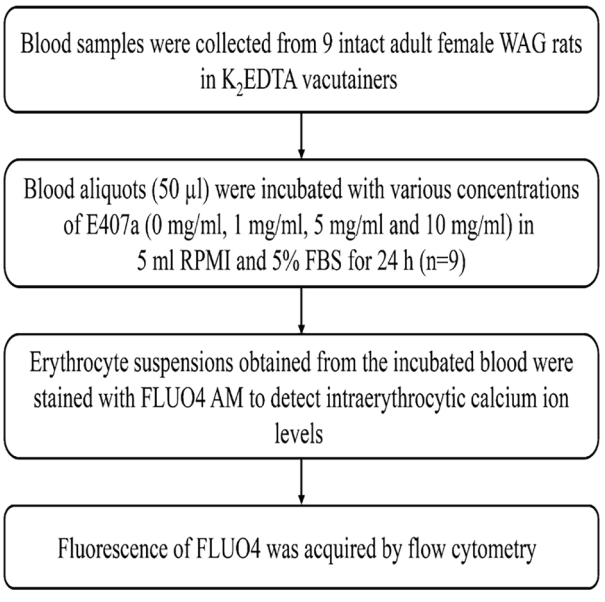
Materials and methods

Incubation of E407a with blood

Blood specimens were taken from nine intact adult female WAG rats weighing up to 200 g. To ensure prevention of blood clotting, K2EDTA Vacutainers (IMPROVACUTER Evacuated EDTA K2 Spray Dried PET Tubes, Guangzhou, China) were used. Then blood samples (50 µl) were incubated horizontally with 5 ml RPMI-1640 medium with stable glutamine (Biowest, France) and 5% fetal bovine serum (BioWhittaker®, Lonza, Belgium) during 24h in sterile SPL 15 ml conical tubes. Four tubes were used per rat (E407a concentrations: 0 mg/ml, 1 mg/ml, 5 mg/ml and 10 mg/ml). After incubation, blood samples were centrifuged. Supernatants were discarded. Cell pellets were used to obtain erythrocyte suspensions, which was performed by double washing using phosphate buffer saline (PBS). Thereafter, 2 µl of red blood cell mass was used for FLUO4 AM loading. The study design is demonstrated in Figure 1.

The study was carried out in conformity with the Directive 2010/63/EU for the Protection of Animals Used for Scientific Purposes and the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (EST 123). The Commission on Ethics and Bioethics (Kharkiv National Medical University, Kharkiv, Ukraine; minutes #5 dated September 17, 2019) approved of the study.

Figure 1 - Diagram of the study design



FLUO4 AM staining

FLUO4 AM staining was used to assess intraerythrocytic Ca^{2+} levels by flow cytometry. FLUO4 AM dye powder purchased from Becton Dickinson (USA) was stored at - 20 °C. Prior to the experiment, it was warmed up to room temperature and dissolved in anhydrous dimethyl sulfoxide (Sigma Aldrich, USA) to obtain 5 mM stock solution. The stock solution was used to stain erythrocyte suspensions containing 2 µl of erythrocytes incubated with various concentrations of E407a and 98 µl PBS. The final concentration of Ca^{2+}-sensitive probe in working solutions was 2.5 µM. The FLUO4-loaded erythrocyte suspensions were incubated in the dark for 30 min. Then 400 µl PBS was added to each tube. Fluorescence was acquired by BD FACSCanto™ II system. In each sample, 300 000 events were collected. The fluorescence of FLUO4 was analyzed (FL1 = 530/30 BP). Erythrocyte suspensions with no added FLUO4 were used as negative controls. Hydrogen peroxide-treated (0.1 mM) erythrocytes were used as positive controls.

Statistical analysis

The Shapiro-Wilk test allowed assessing the distribution normality. Four independent invariables were compared using the Kruskal-Wallis and *post-hoc* Dunn's tests. The mean fluorescence intensities (MFI) of FLUO4 were represented as the median (Me) and interquartile range (IQR; 25%–75%) with p values below 0.05 considered statistically significant. All statistical calculations were performed with Graph Pad Prism 5.0 (USA).

Results

Since calcium release into the cytosol of erythrocytes plays a pivotal role in induction of eryptosis, its concentration in red blood cells exposed to E407a was determined by FLUO4 staining. Quantitatively, intracellular Ca^{2+} levels were estimated by comparing MFI values of FLUO4, which depend on Ca^{2+} concentrations, and the percentage of erythrocytes with the increased FLUO4 fluorescence.

Representative histograms and MFI values of FLUO4 in all the studies groups of samples are shown in Figures 2 and 3.

Figure 2 - Representative side scatter (SSC) & green fluorescence (FL1) histograms demonstrate a more intense fluorescence of FLUO4 in erythrocytes exposed to the highest concentrations of semi-refined carrageenan (E407a)

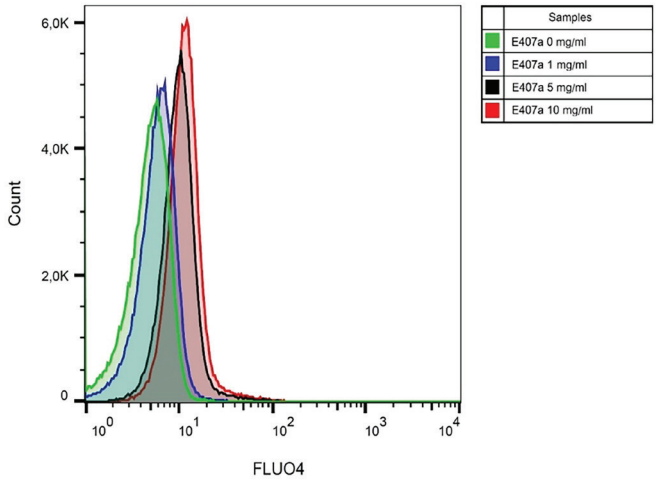


Figure 3 - Mean fluorescence intensity (MFI) values of FLUO4 in red blood cells treated with semi-refined carrageenan (E407a) reflect the intracellular calcium ion levels

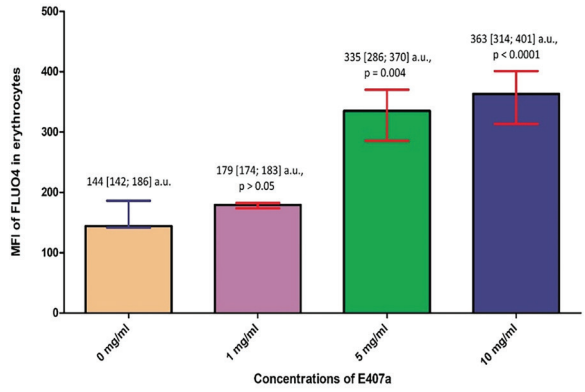
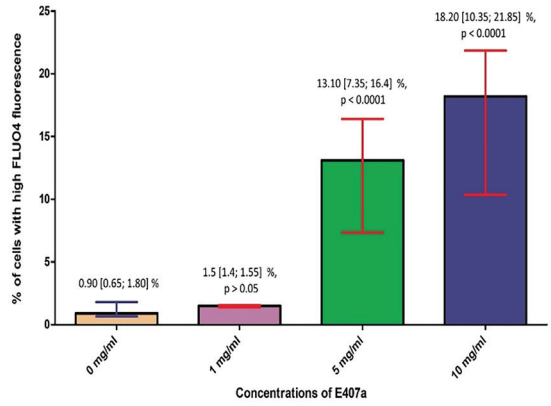


Figure 4 - The amount of cells with enhanced FLUO4 fluorescence after exposure to semi-refined carrageenan (E407a)



The lowest concentration of semi-refined carrageenan, i.e. 1 mg/ml did not promote the elevated FLUO4 fluorescence, evidenced by no statistically significant changes in MFI values of FLUO4 ($p=0.25$). At the same time, a 2.3-fold elevation of this index was observed in response to 5 mg/ml ($p=0.004$). The highest amount of semi-refined carrageenan used in this study (10 mg/ml) increased FLUO4 fluorescence over 2.5 times, $p<0.0001$ (Figure 3).

In addition to the MFI values of FLUO4, we analyzed the amount of erythrocytes with high FLUO4 fluorescence. Low levels of E407a (1 mg/ml) were revealed to have no effects on this parameter ($p>0.05$), whereas an increase in the concentration of this food additive promoted the increase in the percentage of such cells either 14.6-fold (5 mg/ml) or 20.2-fold (10 mg/ml). These data are represented in Figure 4. It should be noted that the difference is statistically significant ($p<.0001$). Thus, changes in both parameters of FLUO4 fluorescence indicate an increase in the intracellular Ca^{2+} levels in erythrocytes exposed to over 5 mg/ml E407a.

Discussion

Reports on the mechanism of carrageenan toxicity are multiple, but controversial. There is accumulating evidence that pro-inflammatory effects of E407a are mediated by TLR4 (toll-like receptor 4) signaling, NF-kB (nuclear factor kappa light chain enhancer of activated B cells) transcription factor, ROS-activated pathways and NLRP3 (NOD-, LRR- and pyrin domain-containing protein 3) inflammasome activation [25-27]. All these pathways eventually result in the upregulation of pro-inflammatory cytokines. However, in red blood cells the pathways outlined above are either absent or their role differs. These facts make erythrocytes a useful tool for evaluating the toxicity of xenobiotics.

It has been recently reported that carrageenans have pro-eryptotic activities, evidenced by phosphatidylserine exposure on the surface of cells and excessive ROS production [15]. However, no data on the ability of dietary high-molecular-weight carrageenans to activate Ca^{2+}-mediated pathways in red blood cells or other types of host cells are available. This is especially interesting given the crucial role of calcium ions in eryptosis. In particular, increased intraerythrocytic calcium concentration promotes phosphatidylserine translocation to the outer leaflet of cell membrane influencing the activity of scramblases [28].

Eryptosis indices estimated in this study indicate that semi-refined carrageenan significantly increased intracellular Ca^{2+} concentrations, which leads to activation of eryptosis. When comparing with the data on ROS overproduction in erythrocytes exposed to the same concentrations of E407a, the ability of E407a to increase Ca^{2+} levels in red blood cells is more pronounced [15]. Thus, pro-eryprotic effects of carrageenans can be primarily ascribed to Ca^{2+}-mediated damage. This conclusion is quite unexpected due to the multiple reports on pro-oxidant activities of carrageenans, their ability to induce ROS production and oxidative stress [18, 25, 27, 29, 30]. In addition, it is important to note that our findings are consistent with other data that suggest the dose-dependent cytotoxicity of carrageenans. In particular, the same semi-refined carrageenan is demonstrated to increase the metabolic activity and reduce the motility of fibroblasts at concentrations of over 5 mg/ml [31].

Thus, this study contributes to revealing the molecular mechanisms for carrageenan-mediated toxicity by demonstrating the ability of E407a to induce intracellular Ca^{2+} levels. However, more research efforts should be made to close the knowledge gap on the molecular targets and pro-inflammatory pathways activated by carrageenans.

The study has several strengths. Firstly, FLUO4 AM staining with data acquisition via flow cytometry is a widely recognized and modern technique to assess intracellular Ca^{2+} levels. Secondly, two parameters for FLUO4 fluorescence were used. Thirdly, simple experimental design can be easily replicated. The study limitations include: application of only one method to assess intracellular Ca^{2+} levels; human erythrocytes were not used.

Conclusion

Semi-refined carrageenan (E407a) promotes eryptosis in a Ca^{2+}-dependent manner.

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The predictive value of the prognostic nutritional index for contrast-induced nephropathy

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Abstract

Aim: This study aims to evaluate the association between prognostic nutritional index (PNI) and contrast-induced nephropathy (CIN).

Material and methods: A total of 251 patients who were at high risk for contrast nephropathy were included in the study. The patients were grouped according to their PNI score (PNI score <45 or PNI score ≥45). CIN was defined as a 25% relative increase, or 0.5 mg/dL absolute increase in serum creatinine level above baseline within 72 hours of contrast exposure, in the absence of an alternative explanation.

Results: Two groups were assigned according to the PNI score. The first group consists of 111 patients (PNI<45) and the second group has 140 patients (PNI≥45). CIN developed in 162 (%64.8) patients. C-reactive protein was higher in the low-PNI group. Also, the patients with the low-PNI group had lower ejection fraction, lower serum albumin levels, and lower hemoglobin levels. CIN, postprocedure renal replacement therapy requirement and in-hospital mortality were higher in the low PNI group. Multivariable logistic regression analysis revealed that advanced age (p=0.012, [OR] = 1.044 [1.009-1.079]), low baseline GFR (p=0.033, [OR]= 1.022 [1.002-1.043]), high amount of contrast media (p=0.022, [OR]= 1.017 [1.002-1.031]), and low PNI score (p=0.033 , [OR]= 2.069 [1.060-4.039]) were independent predictors of CIN.

Conclusion: Our study demonstrated that the PNI score was an independent risk factor for the development of CIN.

Key words: prognostic nutritional index, contrast induced nephropathy, coronary angiography, percutaneous coronary intervention

Introduction

Contrast-induced nephropathy (CIN) is a potentially benign form of acute kidney injury (AKI) that occurs following contrast media administration. In most cases, the glomerular filtration rate (GFR) mildly decreases within three to seven days and then returns to baseline or close to baseline values. CIN is a common cause of AKI in hospitalized patients, and the incidence of it varies from 3% to 30% in different studies due to the contrast volume, accompanying risk factors, and route of administration [1]. Although it is generally reversible, CIN development is associated with increased prolonged hospitalization and mortality [2]. Once it occurs, there are no spesific treatment options for CIN yet [3]. Therefore, it is very important to identify the population at risk and take measures to prevent AKI progression [3].

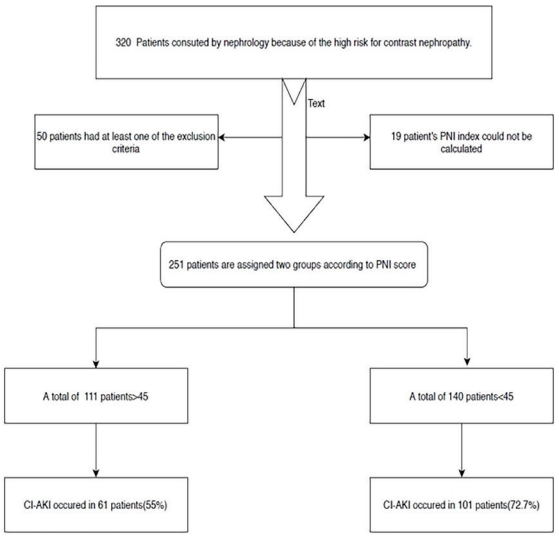
Prognostic nutritional index (PNI) has been introduced as a simple indicator of nutritional and inflammatory status in cancer patients [4,5]. It is calculated by using serum albumin concentration and total lymphocyte count. PNI has also been proposed to indicate the prognosis of heart failure and ST-segment elevated myocardial infarction (STEMI) [6,7]. The aim of this study is to explore the predictive effect of PNI on CIN in patients that underwent coronary angiography (CAG) or percutaneous coronary intervention (PCI).

Materials and methods

Between October 2016 and March 2018, patients requiring nephrology consultation before CAG or PCI because of the high risk for CIN were included in this study. The exclusion criteria were; 1) exposure to contrast media less than one week before the procedure, 2) exposure to nephrotoxic drug less than ten days before the procedure, 3) severe hepatic disease, 4) active malignancy, 5) active infectious disease, 6) recent major surgical procedure or trauma, 7) being presented with other causes of AKI, 8) being treated with hemodialysis.

A total of 69 patients were excluded from the study. Fifty patients were excluded because of having at least one exclusion criterion and 19 patients for missing data on serum albumin or total lymphocyte count. Finally, 251 patients were eligible for the study. The study flow chart was demonstrated in Figure 1. PNI was calculated with the formula: 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (per mm3). The PNI cut-off score of 45 points has been used in previous studies and has been confirmed as optimal [6,8]. Based on those results, we chose a score of 45 points as an optimal cut-off value. Two groups were assigned according to the PNI score. The first group was 111 patients (PNI<45) and the second group was 140 patients (PNI≥45).

Figure 1 - Study flow-chart



Samples for hemogram and biochemical parameters were taken from the patients at the time of admission and the serum creatinine (SCr) level was measured daily postprocedure until the discharge. All enrolled cases were received hydration (0.9% normal saline at 0.5–1.0 mL/kg/h) for 3–12 h before CAG or PCI and it was continued for up to 12 h after CAG depending on the patient's volume status. N-acetylcysteine (> 1200 mg/day) treatment was started 1 day before CAG or PCI and ceased up 2 days after the procedure. The contrast medium (iohexol) used for the procedure was nonionic, iso-osmolar. Within the 72 hours following intravascular contrast media administration; an absolute rise of 0.5 mg/dL (44 μmol/L), or a relative 25% rise from the baseline, in serum creatinine value, in the absence of other causes was defined as CIN [9]. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation was used for GFR calculation [10].

Statistical analysis

Descriptive statistics were presented as percentage of the total (%) for categorical variables and mean ± standard deviation for continuous variables. Mann-Whitney U test or Student's t-test was used for comparing the differences in continuous variables between the two groups. The Kolmogorov-Smirnov test was used to evaluate the distribution of continuous variables. Categorical variables compared with the Chi-square test or Fisher's exact test. Binary logistic regression analysis was employed to determine the independent predictors of CIN. Data were analyzed using the Statistical Package for Social Sciences Software (SPSS 17.0 Chicago, Illinois). The statistical significance was considered when a p-value ≤0.05.

Results

A total of 251 high-risk patients were enrolled in the present study (mean age 68.4±9,8, 68.10% male). The basal creatinine level was 1.76 (0.63-4.17) mg/dl, hemoglobin level was 11.6 (7.6-18.3) g/dl, ejection fraction was 50% (20%-65%), C-reactive protein (CRP) value was 2,86±3.85 mg/dl. The amount of contrast media used during the procedure was 52.75 ± 28.63 ml, and CIN developed in 162 (64.8%) patients. Baseline demographic and clinical characteristics of the patients categorized according to PNI value is given in Table 1.

Gender, history of diabetes mellitus, and pre-procedure SCr levels were similar in both groups. The values of CRP were higher in the low-PNI group. Whereas the patients with the low-PNI group had lower ejection fraction, lower serum albumin levels, and lower hemoglobin levels. The occurrence of CIN, post procedure renal replacement therapy requirement and in-hospital mortality were higher in the low PNI group.

The variables that are thought to be associated with CIN were conducted in a univariable model to investigate risk factors for CIN. PNI (p=0.004, odds ratio[OR] = 2.179 [95% CI: [1.285-3.694]), female gender (p=0.002, [OR] = 2.5 [1.385-4.513]), diabetes mellitus (p=0.007, [OR] = 2.019 [1.210-3.366]), age (p = 0.018, [OR]= 1.032 [1.006-1.059]), amount of contrast media (p=0.023, [OR] = 1.012 [1.002-1.023]), and hemoglobin levels (p < 0.001, [OR] = 0.768 [0.672-0.878]) were associated with the development of CIN. In multivariable logistic regression analysis, advanced age (p=0.012, [OR] = 1.044 [1.009-1.079]), low baseline GFR (p=0.033, [OR] = 1.022 [1.002-1.043]), high amount of contrast media (p = 0.022, [OR] = 1.017 [1.002-1.031]), and low PNI score (p=0.033 , [OR] = 2.069 [1.060-4.039]) were found as independent predictors of CIN (Table 2).

Discussion

With this study, the association between PNI and CIN following CAG or PCI was evaluated, and it is shown that PIN was a strong predictor of CIN. Besides, PNI was associated with an increased rate of mortality, and renal replacement therapy requirements.

PNI is a unified nutritional-inflammatory score, based on serum albumin levels and the lymphocyte count, reflecting the immunological and nutritional status of patients. Initially, it had been used to indicate postoperative outcomes of malnourished cancer patients undergoing gastrointestinal surgery [11]. Subsequently, it has been stated that PNI was a simple and useful predictor of prognosis in end-stage liver disease, heart failure, and STEMI [6,7,12].

The pathogenesis of CIN is not entirely understood. However, hemodynamic injury, systemic inflammation, and toxic injury are accused mechanisms for the development of CIN. Especially, multiple inflammation-related factors, such as endothelial dysfunction, oxidative stress, and renal vasoconstriction are thought to influence the development of

Table 1 Demographic, clinical and biological characteristics of the patients according to their PNI score

	PNI<45	PNI≥45	P value
Age	69.6±9.3	66.9±10.3	0.030
Gender (Female)	46 (32.9%)	34(30.6%)	0.707
Diabetes Mellitus(%)	88(62.9%)	59(%53.2)	0.121
Ejection Fraction(%)	47,5(20-60)	50(20-65)	0.045
Preprocedure Cr(mg/dl)	1.845(0.63-4,17)	1.6(0.65-3.5)	0.321
Preprocedure e-GFR (ml/min/1.73m^2)	38(3.37-108)	40.4(14-147)	0.049
CRP(mg/L)	1.38(0,34-23.2)	0.79(0.2-17.5)	0.002
Albumin(g/L)	3.29(2.18-4.10)	3.97(2.57-5.4)	<0.001
WBC(10^3/ml)	8.5(1,7-24)	8.5(3.9-20)	0.671
Hemoglobin(g/dl)	10.9(7.7-18.3)	12(7.6-16.9)	<0.001
LDL cholesterol(mg/dl)	120.6±41.3	130.7±44.3	0.136
Triglycerides(mg/dl)	191±91	157.7±88.6	0.019
Postprocedure e-GFR(ml/min/1.73m^2)	22.75(8.0-70.7)	30(6-154)	0.002
CI-AKI(%)	101(72.8%)	61(55%)	0.04
RRT (%)	37(26.40%)	10(9%)	<0.001
İn-hospital mortality(%)	13(9.3%)	2(1.8%)	0.013

Abbreviations: Cr-creatinine; e-GFR-estimated glomerular filtration rate; CRP-C-reaktive protein; WBC-white blood cell; CI-AKI-contrast induced acute kidney injury; RRT-renal replacement theraphy

Table 2 Univariable and multivariable predictors of contrast nephropathy in the study population

	Univariable		Multivariable	
	OR(%95 CI of OR)	p value	OR(%95 CI of OR)	p value
PNI	2.179[1.285-3.694]	0.004	2.069[1.060-4.039]	0.033
Gender(female)	2.5[1.385-4.513]	0.002	2.087[0.977-4.457]	0.057
Age(years)	1.032[1.006-1.059]	0.018	1.044[1.009-1.079]	0.012
DM	2.019[1.210-3.366]	0.007	1.609[0.834-3.106]	0.156
Hemoglobın	0.768[0.672-0.878]	<0.001	0.861[0.721-1.028]	0.98
CRP	1.087[0.996-1.187]	0.06	1.034[0.941-1.136]	0.488
Pre-procedural e-GFR	1.014[0.999-1.03]	0.06	1.022[1.002-1.043]	0.033
Contrast Media	1.012[1.002-1.023]	0.023	1.017[1.002-1.031]	0.022

Abbreviations: PNI-prognostic nutritional index; DM-diabetes mellitus; CRP-C-reaktive protein; e-GFR-estimated glomerular filtration rate

CIN [13]. Moreover, recent studies have indicated a strong association between inflammatory markers and CIN [14]. Kaya et al. stated that the neutrophil-lymphocyte ratio (NLR) was an independent predictor of CIN in STEMI patients undergoing coronary intervention [15]. Sun et al. demonstrated that a higher platelet-lymphocyte ratio (PLR) was an independent risk factor for CIN development in patients with STEMI who underwent PCI [9]. Also, Yuan et al. evaluated the predictive value of relevant inflammatory factors on CIN development including; white blood cell count, NLR, CRP level, hs-CRP level, and endothelin-1 level on CIN development, in patients undergoing an emergency PCI and the results had shown that inflammatory factors were all associated with an increased risk of CIN development in patient group [14]. Additionally, recent studies have suggested that malnutrition, like inflammation, may play an important role in the development of CIN [16,17]. Chen and colleagues showed that malnutrition is associated with a twofold increased risk of CIN in patients with chronic artery disease undergoing coronary angiography [17]. Therefore, we thought that PNI, which contains information about both inflammation and nutritional status, may be useful in predicting CIN.

In the present study, the patients that developed CIN had significantly lower PNI scores than those that not developed CIN, and lower PLR was an independent risk factor for CIN development in patients with coronary artery disease undergoing PCI. We thought that the connection between PNI and CIN is not based on a cause-effect relationship. Both of these conditions are probably clinical manifestations of the same physiological impairments, particularly inflammation. As mentioned before, PNI is based on serum albumin levels and the lymphocyte count. Both serum albumin levels and lymphocyte count are related to inflammation. Therefore, a high frequency of CIN development in the low PNI score group can be an expected situation. Besides, the CRP level, a biomarker that reflects inflammation, was higher in the low PNI score group, which supports that idea.

PNI scores in chronic kidney disease patients were evaluated only in a few studies. Two of these studies were conducted in peritoneal dialysis patients [18,19]. Low PNI scores were associated with cardiovascular mortality, comorbidities, and impaired immuno-nutritional status in peritoneal dialysis patients. In another study, lower PNI scores were associated with decreased GFR in patients with acute heart failure [7]. Only one study explored the relationship between the PNI score and AKI [20]. Dolapoglu et al. investigated the predictive value of PNI regarding the development of AKI after elective coronary artery bypass grafting (CABG) surgery. They demonstrated that PNI was an independent predictor of AKI in patients undergoing on-pump CABG surgery [20]. In this study, we showed the relationship between low PNI scores and CIN.

The present study has several limitations. Firstly, this was a single-center, retrospective observational study. Second, the present study was conducted in high-risk group patients so the

rate of CIN development was very high. We believe that PNI is a reliable indicator of CIN. However, it should be validated in the ordinary population. Third, inflammation-associated markers other than WBC counts and CRP were not analyzed or not compared with the PNI score.

Conclusion

This study demonstrated that PNI, a novel immune-nutritional index, was an independent predictor of CIN development in patients undergoing CAG or PCI. Since PNI is simple and easy to be applied, it has the potential to become a convenient tool to stratify the risk of CIN development.

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The effect of personality traits on pain perception and maternal self-confidence in the postpartum period: A cross-sectional study

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Abstract

Aim: This research was conducted to determine the effect of personality traits of postpartum women on pain perception and maternal self-confidence.

Material and methods: The population of this study, which was designed as a descriptive cross-sectional study, was determined as 202 with a confidence interval of 0.95 and a power of 0.95 to represent the universe, according to the power analysis. The study was completed with 258 puerperant women. Data were collected with the "Personal Description Form", "Ten-Item Personality Scale (TIPS)", "Visual Analog Scale (VAS)" and "Pharis Self-Confidence Scale (PSCS)". In the statistical evaluation, descriptive statistics (percentage, mean, standard deviation), Pearson's correlation and multiple linear regression analysis were used.

Results: According to VAS, 25.2% of the participants had severe pain in the legs, 27.1 % in the abdomen, 46.4% in the waist, 17.4% in the chest, 30.3% in the head, 9.4% in the knee, 25.5% in the hips and 43% in the perineum region. The total mean score of the PSCS was 43.72±11.8. It was found that there was a significant correlation between TIPS sub-dimensions and pain regions and total PSCS score averages ($p<0.001$, $p<0.05$). As a result of multiple linear regression analysis, it was determined that the personality traits of women predicted pain and maternal self-confidence negatively and the models were statistically significant ($p<0.05$).

Conclusions: It has been determined that personality traits have an effect on pain perception and maternal self-confidence. In line with the results obtained, midwifery interventions should be planned to reduce the perception of pain and increase maternal self-confidence.

Key words: postpartum, personality traits, pain, maternal confidence

Introduction

The postpartum period, covering the first 42 days [first 6 weeks] postpartum period, is of great importance in terms of maternal and newborn health, as it is a period in which maternal-neonatal mortality and morbidity occur most frequently as a result of physiological and psychological changes [1]. However, in the postpartum period, many women try to cope with the physiological and psychosocial changes that occur during pregnancy and childbirth [2]. In the postpartum period, women experience vaginal bleeding, cramping, bladder and intestine problems, pain in the head, perineum, back and incision site [3, 4]. The vast majority of women perceive the experience of pain as mild or severe [5], which differs from person to person and culture to culture. It is reported that the experience of pain perception is a personal experience depending on individual psychological factors, and pain that can be easily tolerated by a person may be intolerable in another person [6]. It is stated that body perception is related to pain severity and pain duration, and women with high body perception awareness experience lower back pain in both pain severity and pain duration [7]. Appropriate evaluation and management of pain complaints occurring in the postpartum period, timely identification of complications and delivery of care are very important for health professionals and midwives [8]. During this period, pain and other complications in women can lead to inability to manage their own and their baby's

care, causing them to have self-confidence problems [9, 10]. In order to overcome these problems, women need strong self-confidence and self-efficacy [8]. It was stated that self-confidence is one of the most important features required for a person to lead a happy and successful life, to fulfill the responsibilities and roles she undertakes in a healthy way, and to cope with the problems she may encounter in life more easily [8]. Studies showed that those who delivered by cesarean section experience more pain [10], and vaginal delivery is more disadvantageous on postpartum chronic pain than cesarean section [11]. However, it is stated that the baby's weight, mother's age, education level and mood during pregnancy are effective factors on the postpartum pain perception experience [12], and that physical activity has a positive effect on the postpartum pain perception experience [13]. It is stated that maternal self-confidence is affected by factors such as being educated about baby care, having experience in baby care, and feeling ready for the role of motherhood, and that mothers need information in this special period [8,14]. Considering that there are insufficient studies on this subject in the literature it was aimed to determine the effect of personality traits on pain perception and maternal self-confidence in the postpartum period and to improve midwifery care in line with the results obtained. Thus, it is predicted that by determining the effect of the mother's personality traits on the postpartum period pain perception experience, the management of pain by non-pharmacological methods by midwives, and this situation may pave the way for attempts to improve maternal self-confidence.

Material and methods

Type of the study

The study was conducted as cross-sectional.

Population and sample of the study

Whether the data fit the normal distribution or not was checked with the Kolmogorov Smirnov test. Since the skewness value of the model is between -2 and +2, it has been observed that it provides a normal distribution [15]. Participants were determined by the virtual snowball chain sampling method, one of the purposive sampling methods. According to the sample calculation made using the G*power 3.1 program, the sample size was determined as at least 202 with an effect size of 0.25, a margin of error of 0.05, a confidence level of 0.95, a population representation of 0.95, and the study was completed with 258 puerperal women.

Inclusion criteria

- Having given birth at term (38 weeks and above),
- Being in the first 7 days after birth,
- Ability to read and write,
- Having an electronic device with internet connection.

Exclusion criteria

- Filling in the form incompletely.

Data collection tool

Study data were obtained with the tools of “Personal Presentation Form”, “Ten-Item Personality Scale”, “Visual Analog Scale” and “Pharis Self-Confidence Scale”.

Personal introduction form

The personal introduction form [8, 13, 16] created in line with the literature reviews made by the researchers consists of a total of 17 questions including socio-demographic and obstetric characteristics.

Ten-item personality scale (TIPS)

The Ten-Item Personality Inventory, developed by Gosling et al. (2003) [17], was adapted to Turkish culture by Atak (2013) [18]. The language validity of the scale (correlations ranging between 0.92 - 0.97), exploratory (5 factors and 10 items; explained variance 65.21 %) and confirmatory (X2 /sd: 2.20, GFI (Goodness-Of-Fit İndex) .95, AGFI (Adjusted Goodness-Of-Fit İndex) .92, CFI (Comparative Fit İndex) .93, NNFI (nonnormed fit index) .91, RMR (Root Mean Square Residual) .04 and RMSEA (Root Mean Square Error Of Approximation) .03) factor analysis results, item analysis and criterion-resilient validity results support the suitability of the proposed five-factor model in Turkish youth. The results of reliability analysis (n=54; Openness to Experience 0.89, Compassion 0.87, Emotional Stability 0.89, Conscientiousness 0.87, and Extraversion 0.88) based on internal consistency (Openness to Experience 0.83, Amenability 0.81, Emotional Stability 0.83, Responsibility 0.84, and Extraversion 0.86) and test-retest method reported that the scale was acceptable and reliable [18]. It was calculated as 0.657 in this study.

Visual analog scale (VAS)

Developed by Bond and Pilowsky in 1966, the VAS is a 10 cm ruler scale defined as "no pain" at one end and "worst pain" at the other [19]. In the evaluation of VAS, 0 cm is defined as no pain, 1-3 cm mild pain, 4-6 moderately severe pain, and 7-10 severe pain [20, 21, 3]. This scale was adapted to Turkish by Aslan and Öztürk [22].

Pharis self-confidence scale (PSCS)

The scale was first developed by Pharis (1978). It was adapted into Turkish by Çalışır [23]. The Pharis Self-Confidence Scale, which is a 13-item five-point measurement tool, measures a parent's feelings of self-confidence about daily baby care. Each infant care item is rated from 1 to 5 (not at all, very little, moderately, very much, completely). The increase in the total score obtained from the scale indicates that the self-confidence levels of the mothers increase in baby care. The lowest score on the "Pharis Self-Confidence" scale is 13, the highest score is 65. In his study, Cronbach's alpha reliability coefficient was found to be 0.85. In this study, it was calculated as 0.95.

Data collection

The data were collected by the researchers via google form. Postpartum women were contacted separately via the mobile network system and the informed consent form was approved before the scale questions using the google forms method. Again, using the google forms method, data collection forms were sent to the participants via WhatsApp and the answers were digitally archived. It took approximately 10 minutes to fill out this form.

Ethical aspect of research

Approval was obtained from the Inonu University Health Sciences Non-Interventional Clinical Research Ethics Committee (Decision No:2021/2264) to conduct the study. Participants were informed about the study and postpartum women who volunteered were included in the study.

Evaluation of data

The data were evaluated by creating a data set in the IBM SPSS Statistics for Windows, Version 25.0 package program on the computer, descriptive statistical analyzes (frequency distribution, mean, standard deviation), correlation and linear regression analysis were used. Statistical significance was accepted as $p<0.05$, $p<0.01$.

Results

It was determined that the mean age of the puerperant women participating in the study was 28.75±5.57, 39.1% of them were high school graduates, 70.2% of them were not working and 82.9% of them had a planned pregnancy. It was determined that 46.1% of the participants had problems during pregnancy, 85.3% received social support, 25.8% went to nine or more controls, and 55.4% performed these controls in a state hospital (Table 1).

Table 1 Some Socio-demographic and Obstetric Characteristics of the Participants (n=258)

Variables	n	%
Education Level		
Primary School	44	17.1
Middle School	51	19.8
High School	101	39.1
University and Above	62	24.0
Working Status		
Working	77	29.8
Not Working	181	70.2
Income State		
Low	21	8.1
Middle	205	79.5
High	32	12.4
Living Place		
City Center	131	50.8
District	82	31.8
Village	45	17.4
Planned Pregnancy		
Yes	214	82.9
No	44	17.1
Having Problems During Pregnancy		
Yes	119	46.1
No	139	53.9
Type Of Problem Experienced		
Pyhsically	83	32.2
Psychosocial	25	9.7
Other	150	58.1
Getting Support During Pregnancy		
Yes	220	85.3
No	38	14.7
Control Frequency During Pregnancy		
1-2 times	18	7
3-4 times	45	17.4
5-6 times	67	26
7-8 times	62	24
9 and above	66	25.6
Preferred Organization For Control		
Family Health Center	36	14
Public Hospital	143	55.4
University Hospital	21	8.1
Private Hospital	58	22.5
Total	258	100
	Mean±SD	
Age (years)	28.75 ± 5.57	
Size (cm)	163.7 ± 11.0	
Weight (kg)	71.28 ± 11.3	
Marriage Duration	6.58 ± 5.21	
Number Of Pregnancies	2.28 ± 1.1	
Number Of Living Children	1.9 ± 1.02	

TIPS sub-dimensions and total PSCS mean scores were given in Table 2. The extroversion sub-dimension mean score of the postpartum women was 7.89±2.02, the emotional stability sub-dimension mean score was 7.74±1.91, the openness to experiences sub-dimension mean score was 6.94±2.16, and the conscientiousness sub-dimension mean score was 7.86±1.95, the mean score of the sub-dimension of agreeableness was 8.20±1.59, and the total mean score of PSCS was 43.72±11.8 (Table 2).

Table 2 TIPI Sub-Dimensions and PSCS Total Score Averages (n=258)

Variable	Mean ± SD
Extraversion	7.89 ± 2 .02
Emotional Stability	7.74 ± 1.91
Openness To Experiences	6.94 ± 2.16
Conscientiousness	7.86 ± 1.95
Agreeableness	8.20 ± 1.59
Total Score Average	43.72 ± 11.8

SD= Standard Deviation, TIPI; Ten-İtem Personality İnventory, PSCS; Pharis Self-confidence Scale

The distribution of visual analog scale scores according to the regions where postpartum women experience pain was given in Table 3. In the study, 25.2% of the participants stated that they experienced severe pain in the leg region, 27.1% in the abdomen, 46.4% in the lumbar region, 17.4% in the chest region 30.3 % in the head region, 9.4% in the knee region, 25.5% in the hip region and 43% in the perineum region (Table 3).

Table 3 Distribution of Participants' Visual Analogue Scale Scores by Regions Where They Experience Pain (n=258)

Variables Extraversion	VAS Pain Scores (n %)				
	No Pain (0)	**Mild Severe Pain (1-3)**	**Moderate Pain (4-6)**	**Severe Pain (7-10)**	**Total**
Leg	70 (27.1)	79 (30.6)	44 (17.1)	65 (25.2)	258 (100)
Abdominal	40 (15.5)	106 (41.1)	42 (16.3)	70 (27.1)	
Waist	43 (16.7)	66 (25.6)	29 (11.3)	120 (46.4)	
Chest	100 (38.8)	69 (26.7)	44 (17.1)	45 (17.4)	
Head	88 (34.1)	65 (25.2)	27 (10.4)	78 (30.3)	
Knee	116 (45)	91 (35.2)	27 (10.4)	24 (9.4)	
Hip	83 (32.2)	66 (25.6)	43 (16.7)	66 (25.5)	
Perineum	47 (18.2)	66 (25.6)	34 (13.2)	111 (43)	

VAS: Visuel Analog Skala, n; numbers; %; percent.

The relationship between TIPS sub-dimensions, pain regions, and total PSCS score averages were given in Table 4. A statistically significant negative correlation was found between the extraversion sub-dimension and leg pain, headache, knee pain, hip and perineal pain. A statistically significant correlation was found between the emotional stability sub-dimension and all pain regions, and a statistically significant relationship was found between the PSCS total score and positively. A statistically significant negative correlation was found between the sub-dimension of openness to experiences and headache and perineal pain, between the responsibility sub-dimension and leg, low back pain, chest pain, headache, hip and perineal pain, and between the mildness sub-dimension and head, hip and perineal pain (Table 4).

Table 4 TIPI Sub-Dimensions and PSCS Relationship Between Total Mean Scores Averages (n=258)

Variable	Extraversion		Emotional Stability		Openness to Experiences		Conscientiousness		Agreeableness		PCSC total	
	r	p	r	p	r	p	r	p	r	p	r	p
Leg area	-.131	.036	-.140	.024	.035	.581	-.189	.002	-.113	.071	-.365	.000
Abdominal Area	-.076	.223	-.132	.034	-.040	.523	-.119	.056	-.048	.440	-.273	.000
Waist Area	-.063	.316	-.187	.003	.065	.297	-.184	.003	-.020	.745	-.327	.000
Chest Area	-.058	.350	-.186	.003	-.033	.593	-.182	.003	-.103	.099	-.322	.000
Head Area	-.156	.012	-.324	.000	-.161	.010	-.313	.000	-.205	.001	-.451	.000
Knee Area	-.147	.018	-.135	.030	-.003	.964	-.091	.147	-.095	.130	-.307	.000
Hip Area	-.162	.009	-.215	.000	-.010	.869	-.155	.013	-.160	.010	-.330	.000
Perineum Area	-.231	.000	-.337	.000	-.126	.043	-.290	.000	-.265	.000	-.304	.000
PSCS	-.031	.623	.251	.000	.079	.205	.099	.113	.099	.111		

TIPI; Ten-İtem Personality İnventory, PSCS; Pharis Self-confidence Scale, r; Pearson correlation analysis, The correlation is significant at the p<0.01 level. The correlation is significant at the p<0.05 level.

Table 5 TIPI Multiple Linear Regression Analysis Results on the Predictions of Pain and PSCS by Sub-Dimensions

Variables Extraversion	Leg	Abdominal	Waist	Chest	Head	Knee	Hip	Perineum	PSCS Total
B	-.131	-.076	-.063	-.058	-.156	-.147	-.162	-.231	.627
t	-2.108	-1.220	-1.004	-.936	-2.520	-2.376	-2.629	-3.802	12.890
β	-.065	-.038	-.031	-.029	-.077	-.073	-.081	-.115	Oca.99
R2	.017	.006	.004	.003	.024	.022	.026	.053	.394
F	4.443	1.490	1.009	.876	6.353	5.645	6.911	14.456	166.55
p	**.036**	.223	.316	.350	**.002**	**.018**	**.009**	**.000**	**.000**
Emotional Stability									
B	-.140	-.132	-.063	-.186	-.031	.135	-.215	-.337	.651
t	-2.264	-2.134	-3.046	-3.030	-5.481	-2.187	-3.529	-5.724	13.713
β	-.075	-.070	-.099	-.099	-.172	-.072	-.115	-.179	2.214
R2	.020	.017	.035	.035	.105	.018	.046	.113	.423
F	5.149	4.555	9.277	9.179	30.037	4.785	12.453	32.761	188.043
p	**.024**	**.034**	**.003**	**.003**	**.000**	**.030**	**.000**	**.000**	**.000**
Openness To Experiences									
B	.029	.040	.065	-.033	-.161	-.003	-.029	-.126	.582
t	.553	-.640	1.046	-.535	-2.606	-.045	-.165	-2.029	11.464
β	-.016	-.018	.030	-.015	-.074	-.001	.005	-.058	2.106
R2	.001	.002	.004	.001	.026	.000	.000	.016	.339
F	.306	.410	1.094	.286	6.791	.002	.027	.027	131.417
p	.591	.523	.297	.593	**.010**	.964	.869	.869	**.000**
Conscientiousness									
B	-.189	-.119	-.184	-.182	-.313	-.091	-.155	-.290	.701
t	-3.086	-1.918	-2.995	-2.958	-5.279	-1.455	-2.505	-4.841	15.713
β	-.091	-.057	-.088	-.087	-.150	-.043	-.074	-.139	2.151
R2	.036	.014	.034	.033	.098	.008	.024	.084	.491
F	.9.523	3.677	8.970	8.749	27.868	2.116	6.276	24.433	246.902
p	**.002**	.056	**.003**	**.003**	**.000**	.147	**.013**	**.000**	**.000**
Agreeableness									
B	.035	-.048	-.020	-.103	-.205	.035	-.160	-.265	.582
t	-1.814	-.774	-.326	-1.657	-3.344	-1.519	-2.599	-4.406	11.464
β	-.064	-.027	-.012	.058	-.116	-.053	-.091	-.150	2.106
R2	.013	.002	.000	.011	.042	.009	.026	.070	.339
F	3.292	.599	.106	2.747	11.181	2.308	6.754	19.410	131.417
p	.071	.440	.745	.099	**.001**	.130	**.010**	**.000**	**.000**

TIPI; Ten-İtem Personality İnventory, PSCS; Pharis Self-confidence Scale, B;unstandardized coefficient of regression, β, standardized coefficient of regression, R^2: coefficient of determination, , p1<0.05; F test result for the significance of the model, p2<0.05; t test result for the significance of the regression coefficients

As a result of the analyzes, it was determined that personality traits in the postpartum period predicted pain and maternal self-confidence in a negative way and the established models were statistically significant. When the R^2 values of the models were examined, 1% of the pain in the leg area, 2% of the headache, 2% of the pain in the hip area, 5% of the pain in the perineum and 39% of the maternal self-confidence were explained by the extraversion sub-dimension of the ten-item personality traits scale.

In the study, 2% of the pain in the leg area, 1.7% of the pain in the abdomen, 3.5% of the pain in the chest area, 10.5% of the headache, 1.8% of the pain in the knee area, 4.6% of the pain in the hip area, 11.3% of pain in the perineum and 42.3% of maternal self-confidence were explained by the emotional stability sub-dimension of the ten-item personality traits scale.

2.6% of headache and 33.9% of maternal self-confidence were explained by the openness to experiences sub-dimension of the ten-item personality traits scale.

According to the results, 3.6% of pain in the leg region, 3.4% of pain in the lumbar region, 3.3% of headache, 2.4% of pain in the hip region, 8.4% of pain in the perineum and 49.1% of maternal self-confidence were explained by the responsibility sub-dimension of the ten-item personality traits scale.

4.2% of headache, 2.6% of hip pain, 7% of perineal pain and 33.9% of maternal self-confidence were explained by the ten-item personality traits scale's agreeableness sub-dimension.

Starting from the equations that can be established regarding the regression models, a 1-unit increase in the extraversion sub-dimension score causes a decrease of -.065 in the leg area, -.077 in the head region, -.073 in the knee region, -.081 in the hip region, -.115 in the perineum region, and an increase of 1.99 units in maternal self-confidence. A 1-unit increase in the emotional stability sub-dimension score causes an increase of -.075 in the leg region, -.070 in the abdomen, -.099 in the waist region, -.099 in the chest region, -.172 in the head region, -.072 in the knee region, -.115 in the hip region, -.179 in the perineum region, and 2,214 units on maternal self-confidence. A 1-unit increase in the openness to experiences sub-dimension score causes a -.074-unit decrease in the head area and an increase of 2.106-unit on maternal self-confidence. A 1-unit increase causes a decrease of in the Responsibility sub-dimension score -.091 in the leg region, -.088 in the waist region, -.087 in the chest region, -.150 in the head region, -.074 in the hip region, -.139 in the perineum region, and an increase of 2.151 in the maternal self-confidence. A 1-unit increase in the Compassion sub-dimension score causes a -.116-unit decrease in the head region, -.091-unit decrease in the hip region, -.150-unit decrease in the perineum region, and an increase of 2.106-unit in maternal self-confidence (Table 5). Consequently, it can be said that the personality traits of extraversion, emotional stability, openness to experiences, responsibility and agreeableness accompany low levels of pain and high maternal self-confidence in the postpartum period.

Discussion

After pregnancy, which is the most special stage of a woman's life, in the postpartum period, the mother transitions to a new process socially and psychologically. In this process, being able to carry out and manage social and psychological processes in a healthy way is closely related to the personality traits of the mother [24]. Considering the studies on personality traits in the postpartum period, studies on postpartum depression and breastfeeding [25-28] were found.

In this study, personality traits sub-dimensions mean scores were found to be extroversion 7.89±2.02, emotional stability 7.74±1.91, openness to experience 6.94±2.16, conscientiousness 7.86±1.95, and agreeableness 8.20±1.59. In Brown's study, personality traits sub-dimensions score averages were determined as 8.41±2.42 for extraversion, 7.50±2.63 for emotional stability, 6.94±2.57 for openness to experience, 8.75±2.47 for conscientiousness, and 8.47±2.47 for agreeableness [26]. In the study conducted by Sunay et al., the mean scores of personality traits sub-dimensions were found to be 8.92±3.33 for extraversion, 8.90±3.09 for emotional stability, 9.00±3.25 for openness to experience, 10.51±3.16 for conscientiousness, and 11.14±3.16 for agreeableness [25]. In this study, it was seen that the average score of personality traits sub-dimensions was slightly lower than the literature. The reason for this may be that the data was obtained online. More realistic results may have been obtained since postpartum women answered questions more comfortably in online interviews than in face-to-face interviews.

Pain is a condition that can cause negative consequences in many areas of life, both physically and psychologically. It is known that pain affects people's quality of life. The negative effect of pain on dynamic physiological and psychological processes in the postpartum period is inevitable [29]. Therefore, examining pain, considering the role of women in mental and physical health, is necessary for improved health and treatment process [5]. In this study, it was found that pain was felt in the leg, abdomen, waist, chest, knee, hip and perineum region in the postpartum period, and that the majority of puerperal women experienced severe pain in the low back, perineum and head region. It was stated that 25-68 % of women experience low back pain in the postpartum period [13]. In this study, it was determined that 46.4 % of puerperant women had severe low back pain and 29 % had moderate low back pain. People who experience similar levels of pain intensity may react differently. The most important factors affecting the perception of pain and enduring pain are individual characteristics, including psychological and personality traits [5]. In this study, it was determined that postpartum women with extrovert personality traits experienced less leg, head, knee, hip and perineal pain, that puerperant women, who had more emotionally balanced personality traits, experienced less leg, abdomen, waist, chest, knee, hip and perineal pain, that puerperant women who had personality traits that were open to experiences experienced less headache and perineal pain, that puerperant women with higher level of responsible personality traits experienced less leg, waist, chest, head, hip and perineal pain, and puerperal women with mildness personality traits experienced less head, hip and perineal pain. In a study, it was determined that there is a strong relationship between personality traits and headaches [30, 31]. In the study of Yadolahi et al., a relationship was found between personality traits and pain [5]. In the studies conducted by Özsoy et al. (2018) and Jalali and Ghaleban (2005), no significant relationship was found between personality traits and pain perception [6, 32]. According to the results of the literature, our research finding was similar to the studies that found a relationship between personality traits and pain, but differs from the studies that did not.

Looking at the relationship between maternal self-confidence and areas of pain, a statistically significant negative correlation was found between self-confidence and pain perception. It was observed that as maternal self-confidence increased, perceived pain decreased in each region. Self-confidence is the psychological prerequisite for meaningful, happy, satisfying, loving and balanced moments [33]. In this context, every effort of midwives to increase self-confidence will contribute to the realization of this prerequisite and contribute to less perception of pain.

Self-confidence is defined as a dynamic cognitive process that explains a personal belief to successfully perform a necessary behavior in a given situation. Self-confidence is an important prerequisite for behavior change and self-control [33, 34]. It has a vital role for the mother and baby in the postpartum period [26]. Women's low self-confidence creates a negative self-perception that increases guilt, shame, feelings of worthlessness, helplessness, and ultimately frustration, depression, and motivational impairment of problem-solving ability [35]. High maternal self-confidence is needed for the positive development of children [36]. In studies conducted in the postpartum period in Turkey, the mean PSCS score was 50.2±9.5 [9]. It was determined as 42.6±6.2 [2]. In this study, the mean total score of maternal self-confidence was determined as 43.72±11.88. Considering the maximum score that can be obtained from the scale 65, we can say that there was a medium level of maternal self-confidence. For this reason, midwives should aim to develop self-confidence by constantly supporting mothers in the postpartum period.

Moreover, a 1-unit change in the extraversion sub-dimension score causes a decrease of .077 in the perception of headache, .081 in the hip region, .115-unit in the perineum, and an increase of 1.99 units in the total maternal self-confidence score. A 1-unit change in emotional stability sub-dimension score causes an increase of -.075 units in the leg region, -.070, in the abdomen region, -.099 in the waist region, -.099 in the chest region, -.172 in the head region, -.072 in the knee region, -.115 in the hip region, -.179 in the perineum, and an increase of 2.214 in maternal self-confidence. A 1-unit increase in the openness to experiences sub-dimension score causes a -.074-unit decrease in the head area and an increase of 2.106-unit on maternal self-confidence. A 1-unit increase in the Responsibility sub-dimension score causes a decrease of -.091 in the leg region, -.088 in the waist region, -.087 in the chest region, -.150 in the head region, -.074 in the hip region, -.139 in the perineum region, and an increase of 2.151 in the maternal self-confidence. A1-unit increase in the agreeableness sub-dimension score causes a decrease of -.116 in the head area, -.091 in the hip region, -.150 in the perineum, and an increase of 2.106 units in maternal self-confidence. These findings showed that personality traits were an effective variable in reducing pain perception and increasing maternal self-confidence in postpartum women. Since there is no study supporting this finding, it is thought that our study result will contribute to the literature.

Conclusion

As a result, it was determined that personality traits have a significant effect on pain perception and maternal self-confidence in the postpartum period. In the postpartum period, it is important to eliminate the perception of pain with pharmacological or non-pharmacological methods in accordance with the personality characteristics and preferences of women and to establish self-confidence communication with mothers. In this context, we think that maternal self-confidence can increase as puerperant women are informed about pain, baby care, psychological processes and parental identity by midwives and nurses during the early postpartum period that they stay in the hospital.

Limitation of the study

The limitation of this study is that puerperant women who did not have internet on their phones and did not know how to use mobile devices could not be included in the study because google forms were used in the study. Our findings cannot be generalized to all pregnant women since the research was carried out on google forms, and a certain population could be reached, and more studies are needed in this area.

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Is fetal CTG a reliable indicator of fetal distress? A prospective study on relationship between CTG suspected fetal distress and immediate postpartum umbilical cord blood pH

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Abstract

Introduction: Perinatal asphyxia is one of the major causes of neonatal morbidity and mortality. Fetal Cardiotocography (CTG) has been used for long to predict fetal asphyxia. Despite its popularity, it has not been proved to be an ideal tool for monitoring as, although a normal trace is indicative of a normal acid-base status at birth, in about 98% of cases, an abnormal trace has a low positive predictive value in term of fetal acidosis (pH less than 7.25) .An undisputed evidence of perinatal asphyxia is metabolic acidosis on arterial cord blood or very early neonatal samples: pH< 7 and base deficit >12 mmol/L

Aim: To see the correlation between suspicious/pathological CTG and umbilical cord blood pH at birth in term pregnancies.

Material and methods: This was a hospital based prospective randomized observational study over a period of 1 year. It was conducted on 165 pregnant women with singleton term pregnancy admitted to labour ward for delivery and having suspicious / pathological CTG trace or meconium stained liquor with normal CTG trace. Immediately after the birth of the neonate, umbilical cord was clamped, cut and umbilical artery cord blood was collected in a pre - heparinized syringe and sent for pH analysis. Cord blood pH of less than 7.2 was interpreted as acidosis.

Results: The number of acidotic cases (as determined by cord blood pH less than 7.2) was 2(5.6%) in normal traces whereas 34 cases (94.4%) of normal traces were non acidotic. In the suspicious traces, 2 cases (3.2%) were acidotic and 59 cases (96.8%) were non acidotic. In the pathological category, 13 cases (19.1%) were acidotic and 55 cases (80.9%) were non acidotic. There was no significant association of CTG category with cord blood pH, acidosis, pO2 or pCo2 values but that with presence of MSL and grade of MSL was statistically significant.

Conclusion: Abnormal CTG while being a good predictor of the presence of MSL and also the grade of MSL, is a poor predictor of the presence of fetal acidosis and neonatal status after birth. Fetal monitoring using cardiotocography was associated with considerable false positive results. Thus, using fetal heart rate abnormalities alone as a measure of diagnosis of fetal distress during labour is a contributing factor of increasing rate of cesarean sections.

Key words: CTG, fetal cardiotocography, fetal distress, cord blood pH

Introduction

Labour is a stressful event for the fetus. Fetal distress is defined as a condition in which fetal physiology is so altered to make death/ permanent injury a probability within a relatively short period of time and usually considered to denote disruption of normal fetal oxygenation, ranging from mild hypoxia to prolonged fetal asphyxia [1].

Perinatal asphyxia is one of the major causes of neonatal and childhood morbidity and mortality. WHO states that about nine million neonates develop birth

asphyxia every year and out of these, around one million die, while the same number develop severe consequences like cerebral palsy, epilepsy and delayed developmental milestones.

There are various methods to recognize perinatal asphyxia. The easiest method is intermittent auscultation of fetal heart rate (FHR); but it focuses only on the determination of basal heart rate. Another method is Cardiotocography (CTG). Cardiotocography (sometimes known as electronic fetal monitoring), records changes in the fetal heart rate and their temporal relationship to uterine contractions. In addition to estimating the basal heart rate, it also assesses other parameters like variability, accelerations and decelerations of fetal heart rate [2]. CTG has now become a very popular tool in labour wards. Despite its popularity, it has not been proved to be an ideal tool for monitoring as, although a normal trace is indicative of a normal acid-base status at birth, in about 98% of cases, an abnormal trace has a low positive predictive value in term of fetal acidosis (pH less than 7.25) [3].

Fetal scalp blood sampling gives an accurate intrapartum fetal oxygenation status, but it is invasive, requires expertise, needs relatively large amount of blood, often require to be repeated and is associated with a sampling failure rate of 11-12% making it relatively less popular [4-6]. One more method is ST analysis (STAN) that involves a combination of the fetal electrocardiogram interpretation and analysis of the fetal electrocardiogram. This analysis requires special machines that are not available widely.

An undisputed evidence of perinatal asphyxia is metabolic acidosis on arterial cord blood or very early neonatal samples: pH< 7 and base deficit >12 mmol/L [7]. Acute fetal distress induces asphyxia, leading to hypoxia of most of the organs which causes increase in lactic acid level along with alteration in pH and HCO3.

Cardiotocography is the most commonly used method to suspect perinatal asphyxia. CTG monitoring is a modern and non-invasive method for assessing both antepartum and intrapartum fetal status. Intrapartum CTG tracings are classified into Normal (category I trace), Suspicious and Pathological trace according to the NICE 2017 guideline [8]:

1. Normal-All features are reassuring
2. Suspicious- 1 non-reassuring AND 2 reassuring features.
3. Pathological-1 abnormal feature OR 2 non-reassuring features.

Aim: To see the correlation between suspicious/pathological CTG and umbilical cord blood pH at birth in term pregnancies.

Objectives: Primary: Correlation of suspicious/pathological CTG or those with a normal CTG but having meconium stained liquor with cord blood pH.

Secondary:

1. Correlation of suspicious/pathological CTG with Apgar at 1 minute and 5 minutes
2. Correlation of suspicious/pathological CTG with meconium stained liquor (MSL)
3. Correlation of suspicious/pathological CTG with cord blood acidosis in Meconium stained liquor cases.
4. Correlation of suspicious/pathological CTG with Neonatal ICU admission, need for resuscitation and convulsions in the first 24 hours after birth.

Material and methods

The present study included women with term singleton pregnancies in labour with suspicious/pathological CTG tracings or those with a normal CTG but having meconium stained liquor, who were admitted for delivery in the labour ward at a tertiary care hospital and this was correlated with the cord blood pH immediately at birth. This hospital based prospective randomized observational study was conducted over a period of 1 year (from September 2019 to September 2020)

Intrapartum CTG tracings were taken and classified into Normal (category I trace), Suspicious (category II trace) and Pathological trace (category III trace) according to the NICE 2017 guidelines [8].

Umbilical cord arterial blood was taken immediately after birth, in a pre-heparinized syringe and was sent to the laboratory for pH study to detect acidosis. A cord blood pH of less than 7.2 was interpreted as acidosis and a cord blood pH equal to or more than 7.2 as normal, as described by Saling [9].

Statistical Analysis

Sample size for the study was calculated as:

$n = Z2\times (p) \times (1-p)/\Delta 2$

Where n is the sample size,

Z is confidence interval i.e., 1.96 for 95%

Δ is confidence level i.e., 0.05 for ±5%

p=prevalence of the event in the population as determined by previous studies.

Taking incidence of fetal acidosis in term singleton pregnancies as per previous studies as 12.2% [10] sample size for my study is calculated to be:

$n = (1.96)2\times (0.122) \times (1-0.122)/ (0.05)2 = 165$

Data was analyzed and statistically evaluated using SPSS-PC-20 version.

Inclusion Criteria

All term (> 37 weeks) singleton pregnancies with vertex presentation in labour with documented suspicious/pathological CTG or Normal CTG with MSL.

Exclusion criteria

All high-risk pregnancies (anemia, hypertension, thyroid disorders, diabetes, epilepsy, asthma, teenage, elderly)

Intrauterine growth restriction, oligohydramnios, preterm deliveries

Multiple gestation, malpresentations

Abruptio placenta

Fetus with congenital anomalies

Maternal infections and Premature rupture of membranes (PROM)

Patients not giving consent.

Baseline data recording

All women with term singleton pregnancies in labour with suspicious/pathological CTG and women who may be having a normal CTG but had MSL ,fulfilling the inclusion criteria and admitted to our labour ward, were enrolled in the study, after taking an informed consent. On admission, all patients underwent general, systemic and obstetrical examination to rule out any fetal compromise. Labour was monitored by 4-hourly CTG when the cervix was less than 6cm dilated and thereafter, continuous CTG monitoring was done. Details were recorded including gestational age at onset of labour, mode of onset of labour (spontaneous or induced), cervical dilatation on admission, membranes status, time of rupture of membranes (spontaneous or artificial), nature/color of liquor after rupture of membranes, CTG tracings, mode of delivery, Apgar score at 1 and 5 minutes, nursery stay, cord blood pH values, need for resuscitation, occurrence of neonatal seizures were all recorded

in study proforma sheets. Intrapartum cardiotocography was recorded using Philips Avalon FM20 EF Monitor machine. Tracings were taken by the machine at a speed of 1 cm/min for 20 minutes 4 hourly till 6 cm dilation. Continuous CTG tracings were taken when the patient was in active labour i.e.>6cm dilation. Fetal heart rate patterns were interpreted using the NICE guidelines 2017 [8].

Cord blood collection

Immediately at birth, possibly before the baby's first breath and before delivery of the placenta, the umbilical cord was clamped at two points, 10 cm apart, with Kocher's clamps and cut. The umbilical artery was immediately identified in the cord and 5 ml of blood was aspirated with a pre-heparinized syringe. In order to prevent air contact, the syringe tip was sealed with a plastic cover. Cord blood was analyzed by Radiometer ABL800 Basic Machine used at our institute within 30 minutes of collection. Fetal acidosis was assessed using umbilical cord blood pH. An umbilical artery pH <7.20 was defined as fetal acidosis.

Results

The study included 165 term labouring women who had been admitted in a tertiary care hospital who had either MSL or abnormal CTG and had cord blood ABG taken immediately after delivery of the fetus. 21.8% (n=36) cases had a normal CTG but with MSL, 41.2% (n=68) had a pathological CTG and 37 % (n=61) had a suspicious CTG (Table 1).

Table 1 CTG Category

CTG Category	Frequency	Percentage
Normal (but having MSL)	36	21.80%
Pathological	68	41.20%
Suspicious	61	37.00%
Total	165	100%

There was no statistically significant association between maternal age and CTG category (Table 2).

There were 106 primigravidas and 59 multigravidas. The frequency of pathological trace was higher in primigravidas than in multigravidas (44.3% vs 35.6%, i.e. 47 cases and 21 cases respectively). However, it was not statistically significant (Table 3).

Similarly, there was no statistically significant association between period of gestation and CTG category (Table 4).

In our study, 21.2 % (35 cases) were induced and 78.8 % (130 cases) had a spontaneous onset of labour. Frequency of pathological trace was similar in both induced and spontaneous labour, 40% (14 cases) and 41.5% (54 cases) respectively, making it statistically insignificant (p value- 0.981) (Table 5). There was no statistical association between the mode of onset of labour and CTG category (Table 5).

In our study, 79 (47.9%) cases had MSL while 86 (52.1%) cases did not. Out of the 79 cases with MSL, 36 (45.6%) cases had a normal trace, 21 (26.6%) cases had a pathological trace and 22 (27.8%) cases had a suspicious trace. Out of the 86 cases without MSL, 47 cases (54.7%) had a Pathological trace and 39 cases (45.3%) had a suspicious trace. The p value for this association between presence of MSL and abnormal CTG category was <0.001 for both suspicious and pathological traces, making it statistically significant (Table 6).

Of the 79 (47.9%) cases that had MSL, 19 (24%) cases had Grade 1 MSL, 32 (40.5%) cases had Grade 2 MSL and 26 (35.5%) cases had Grade 3 MSL. 10 (52.6%) cases of Grade 1 MSL had a normal trace, 3 (15.8%) cases had a pathological trace and 6 (31.6%) cases had a suspicious trace. In cases with Grade 2 MSL, 15 (46.9%) cases had a normal trace, 6 (18.8%) cases had a pathological trace and 11 (34.4%) cases had a suspicious trace. Amongst the cases with Grade 3 MSL, 11 (39.3%) cases had a normal trace, 12 (42.9%) cases had a pathological trace and 5 (17.9%) cases had a suspicious trace. The p value for this association between grade of MSL and abnormal CTG category was <0.001 for both suspicious and pathological cases and was statistically significant (Table 7).

There was no statistical association between the Apgar scores at 1 and 5 minutes and abnormal CTG category (Table 8).

The mean pH for a normal CTG but having MSL was found to be 7.35 with a standard deviation of 0.08, the mean pO_2 was 91.56 with a standard deviation of 12.46 and mean pCO_2 was 43.51 with a standard deviation of 9.53. The mean pH for a pathological CTG was found to be 7.34 with a standard deviation of 0.1, the mean pO_2 was 88.09 with a standard deviation of 15.29 and mean pCO_2 was 45.22 with a standard deviation of 10.15. The mean pH for a suspicious CTG was found to be 7.36 with a standard deviation of 0.07, the mean pO_2 was 91.43 with a standard deviation of 11.45 and mean pCO_2 was 42.89 with a standard deviation of 7.11. All p values are not significant (Table 9).

The number of acidotic cases (as determined by cord blood pH less than 7.2) was 2 (5.6%) in normal traces whereas 34 cases (94.4%) of normal traces were non acidotic. In the suspicious traces, 2 cases (3.2%) were acidotic and 59 cases (96.8%) were non acidotic. In the pathological category, 13 cases (19.1%) were acidotic and 55 cases (80.9%) were non acidotic. There was no significant association of CTG category with cord blood pH, acidosis, and pO_2 or pCO_2 values (Table 9, Table 10).

Only 5.4% (9 cases) cases required NICU stay. All of these had acidosis on ABG. In patients who had a normal CTG but had meconium stained liquor 91.7% (33 cases) did not require any NICU care. Only 8.3% (3 cases) were admitted to NICU. In patients who had a pathological CTG 92.6% (63 cases) did not require any NICU care. Only 7.4% (5 cases) were admitted to NICU. In patients who had a suspicious CTG, 98.4% (60 cases) did not require any NICU care. Only 1.6% (1 case) were admitted to NICU. The p-value came out to be 0.25, making the strength of association statistically insignificant (Table 11).

7.8% (12 cases) required resuscitation. Only 8.3% cases (3 cases) with a normal trace along with MSL required resuscitation and the rest 91.7% (33 cases) did not. In the pathological trace category, 11.8% cases (8 cases) required resuscitation while the rest 88.2% (60 cases) did not. Interestingly, only 1 case (1.6%) of suspicious trace cases required resuscitation while the rest 60 cases (98.4%) did not. The p value was 0.084, making the association statistically insignificant (Table 12).

In our study, 3 cases (1.8%) had convulsions within the first 24 hours after birth. All of these had acidosis on ABG. Of these, 2 cases had a pathological trace (2.9% of pathological cases) and 1 case had a suspicious trace (1.6% of suspicious traces). None of the normal CTG cases with MSL had convulsions within the first 24 hours after birth. The p value of 0.56 was statistically insignificant (Table 13).

The sensitivity and specificity of a pathological trace was 86.6% and 38.2% respectively while that of a suspicious trace was 50% and 36.5% respectively. The positive predictive value and negative predictive value of a pathological trace was 19.2% and 94.5%, while that of a suspicious trace was 3.27% and 94.5% respectively.

Table 2 Maternal Age

Maternal Age	Total Cases	CTG Category			p value
		Normal (with MSL)	Pathological	Suspicious	
		Frequency (%)	Frequency (%)	Frequency (%)	
20-25 years	48	07 (14.6%)	27 (56.2%)	14 (29.1%)	0.572- not significant
26-30 years	63	18 (28.6%)	16 (25.4%)	29 (46%)	
31-35 years	46	08(17.4%)	23(50%)	15(32.6%)	
36-40 years	8	03(37.5%)	2(25%)	3(37.5%)	
Total	165	36 (21.8%)	68 (41.2%)	61 (37.0%)	

Table 3 Parity

Obstetric History	Total Cases	CTG Category			p value
		Normal (with MSL)	Pathological	Suspicious	
		Frequency (%)	Frequency (%)	Frequency (%)	
Primigravida	106	20 (18.9%)	47 (44.3%)	39 (36.8%)	0.389- not significant
Multigravida	59	16 (27.1%)	21 (35.6%)	22 (37.3%)	
Total	165	36 (21.8%)	68 (41.2%)	61 (37.0%)	

Table 4 Gestational Age

Period of Gestation	Total Cases	CTG Category			p value
		Normal (with MSL)	Pathological	Suspicious	
		Frequency (%)	Frequency (%)	Frequency (%)	
37 - 37+6 wks	21	8 (38.1%)	6 (28.6%)	7 (33.3%)	0.254 -not significant
38 - 38+6 wks	48	6 (12.5%)	23 (47.9%)	19 (39.6%)	
39 - 39+6 wks	57	11 (19.3%)	26 (45.6%)	20 (35.1%)	
40 - 40+6 wks	39	11 (28.2%)	13 (33.3%)	15 (38.5%)	
Total	165	36 (21.8%)	68 (41.2%)	61 (37.0%)	

Table 5 Mode of Onset of Labour

Labour type	Total Cases	CTG Category			p value
		Normal (with MSL)	Pathological	Suspicious	
		Frequency (%)	Frequency (%)	Frequency (%)	
Induced	35	8 (22.9%)	14 (40.0%)	13 (37.1%)	0.981-not significant
Spontaneous	130	28 (21.5%)	54 (41.5%)	48 (36.9%)	
Total	165	36 (21.8%)	68 (41.2%)	61 (37.0%)	

Table 6 Presence of Meconium Stained Liquor

Meconium	Total Cases	CTG Category			p value
		Normal (with MSL)	Pathological	Suspicious	
		Frequency (%)	Frequency (%)	Frequency (%)	
Absent	86	0 (0.0%) Not included in the study	47 (54.7%)	39 (45.3%)	<0.001 -significant
Present	79	36 (45.6%)	21 (26.6%)	22 (27.8%)	
Total	165	36 (21.8%)	68 (41.2%)	61 (37.0%)	

Table 7 Grade of Meconium Stained Liquor

Grade	Total Cases	CTG Category			p value
		Normal (with MSL)	Pathological	Suspicious	
		Frequency (%)	Frequency (%)	Frequency (%)	
-	86	0 (0.0%)	47 (54.7%)	39 (45.3%)	<0.001- significant
1	19	10 (52.6%)	3 (15.8%)	6 (31.6%)	
2	32	15 (46.9%)	6 (18.8%)	11 (34.4%)	
3	28	11 (39.3%)	12 (42.9%)	5 (17.9%)	
Total	165	36 (21.8%)	68 (41.2%)	61 (37.0%)	

Table 8 Apgar score

	CTG Category			P Value
	Normal (with MSL)	Pathological	Suspicious	
	Mean ± SD	Mean ± SD	Mean ± SD	
APGAR 1 MIN	8.03 ± 1.03	7.78 ± 1.29	8.10 ± 0.87	0.231
APGAR 5 MIN	8.75 ± 0.60	8.60 ± 0.98	8.85 ± 0.57	0.187

Table 9 ABG Characteristics

	CTG Category			p value
	Normal (with MSL)	Pathological	Suspicious	
	Mean ± SD	Mean ± SD	Mean ± SD	
pH	7.35 ± 0.08	7.34 ± 0.1	7.36 ± 0.07	0.609
pO2	91.56 ± 12.46	88.09 ± 15.29	91.43 ± 11.45	0.28
pCO2	43.51 ± 9.53	45.22 ± 10.15	42.89 ± 7.11	0.321

Table 10 Presence of Acidosis

	Total Cases	CTG Category			p value
		Normal (with MSL)	Pathological	Suspicious	
		Frequency (%)	Frequency (%)	Frequency (%)	
Acidotic	17	2 (05.6%)	13 (19.1%)	2 (3.2%)	0.0904 – not significant
Non acidotic	148	34 (94.4%)	55 (80.9%)	59 (96.8%)	
Total	165	36 (21.8%)	68 (41.2%)	61 (37.0%)	

Table 11 NICU Stay

NICU Stay	Total Cases	CTG Category			p value
		Normal (with MSL)	Pathological	Suspicious	
		Frequency (%)	Frequency (%)	Frequency (%)	
No	156	33 (91.7%)	63 (92.6%)	60 (98.4%)	0.25- not significant
Yes	9	3 (8.3%)	5 (7.4%)	1 (1.6%)	
Total	165	36 (21.8%)	68 (41.2%)	61 (37.0%)	

Table 12 Need for Fetal Resuscitation

Resuscitation	Total Cases	CTG Category			p value
		Normal (with MSL)	Pathological	Suspicious	
		Frequency (%)	Frequency (%)	Frequency (%)	
No	153	33 (91.7%)	60 (88.2%)	60 (98.4%)	0.084- not significant
Yes	12	3 (8.3%)	8 (11.8%)	1 (1.6%)	
Total	165	36 (21.8%)	68 (41.2%)	61 (37.0%)	

Table 13 Occurrence of Convulsions within the first 24 hours after Birth

Convulsions	Total Cases	CTG Category			p value
		Normal (with MSL)	Pathological	Suspicious	
		Frequency (%)	Frequency (%)	Frequency (%)	
No	162	36 (100%)	66 (97.1%)	60 (98.4%)	0.56- not significant
Yes	3	0 (0.0%)	2 (2.9%)	1 (1.6%)	
Total	165	36 (21.8%)	68 (41.2%)	61 (37.0%)	

Table 14 Sensitivity, Specificity, Positive and Negative predictive value of pathological and suspicious trace

	Pathological	Suspicious
Sensitivity	86.6%	50%
Specificity	38.2%	36.5%
Positive predictive value	19.2%	3.27%
Negative predictive value	94.5%	94.5%

Discussion

The foetus undergoes physiological stress during labour. Fetal morbidity and mortality may occur as a consequence of labour even in low risk patients. Cardiotocography is a simple, non-invasive recordable method of intrapartum fetal monitoring which can be used as a tool to detect hypoxemic events in the foetus-in utero during labour, enabling initiation of appropriate management. We studied the correlation between intrapartum

CTG in term labouring women with cord blood pH in their neonates in order to predict acidosis in the foetus and thus to detect the number of cases with actual distress in cases with abnormal CTG traces.

We recruited 165 labouring women who had either a suspicious or pathological CTG, or had a normal CTG but having meconium stained liquor. The study recruited women in the age group of 20 to 40 years. In our study, maximum number of cases were between the ages of 26 to 30 years while the least were between 36 to 40 years. This correlates well with the normal pattern of maximum fertility between 20-30 years of age.

Most cases were between 38 to 38 weeks 6 days of gestation with a decline on either side of this interval. The least number of cases were in the 40 weeks to 40 weeks 6 days period of gestation due to higher rate of spontaneous labour before 40 weeks and also due to most cases that reach 40 weeks of gestation being induced for postdatism in our centre.

The number of cases that went into spontaneous labour were almost four times those that were induced as most cases that were induced due to some medical comorbidity were excluded from our study. Frequency of pathological trace was similar in both induced and spontaneous labour (40% and 41.5% respectively), making it statistically insignificant (p value-0.981).

79 cases were associated with MSL. Out of these, 36 cases (45.6%) had a normal CTG, 21 cases (26.6%) had a pathological CTG and 22 cases (27.8%) had a suspicious CTG. We also had 86 cases without MSL. A pathological trace was seen in 47 (54.7%) cases of these 86 cases and a suspicious CTG was seen in 39 (45.3%) cases. The association of CTG category with presence of MSL was statistically significant (p-value <0.001). This showed that in the presence of a pathological/suspicious trace, there was a strong possibility of the presence of MSL.

MSL was strongly associated with a pathological trace. It also correlated well with the Grade of MSL. Hence, Grade 1 had more normal traces than Grade 2 and 3 where pathological or suspicious were more. In a study performed by Sunitha C et al. [11] on 100 women, 4% of normal traces had the presence of meconium stained liquor and 44% of abnormal traces had the presence of meconium stained liquor. Similar to our study, they found a positive correlation between the presence of MSL with CTG category. Similar result was obtained in the study conducted Kumar N et al. [12] in which, out of 30 cases, 5 (16.7%) had a normal CTG while 10 (33.4%) had an abnormal CTG, with a positive correlation between CTG category and the presence and grade of MSL.

The mean Apgar score at 1 minute was similar for normal and suspicious traces with slightly lower Apgar for a pathological case. However, the mean Apgar at 5 minutes was similar for all categories of CTG traces. CTG traces did not correlate well with the Apgar score and was a poor predictor of neonatal outcome. This was in contrast to the study by W M Aboulghar et al. [13], where there was a positive correlation between the Apgar score at 1 and the CTG category, but not with the 5 minute Apgar score. The 1 minute Apgar was less than 4 in 29.2 % cases of pathological traces and 9.6% of suspicious cases. The 5 minute Apgar score was less than 6 in 8.3% of pathological and 3.6% of suspicious traces. In the study by Agrawal SK et al. [14], the mean Apgar scores at 1 minute were 7.5± 0.6 for normal category CTG and 7.6± 0.3 for abnormal category CTG. The 5-min Apgar score was 8.8± 0.2 and 8.7± 0.2 respectively. Their result was similar to our study with no significant correlation between CTG category and Apgar score. In the study by van den Berg P et al. [15] on 2659 women, the proportion of infants who had low modified Apgar scores (less than 7) in the group with normal CTG was 8% (19 of 236) and 0.9% (22 of 2433) for those with abnormal CTG. Similar to our study, there was no statistical correlation with Apgar score and CTG category. In a study by Sowmya D et al. [16], 100 women with either suspicious or pathological traces were recruited. In their study, 25% of cases in the suspicious category and 38.46% in the pathological category had 1-minute Apgar less than 7. The 5-minute Apgar was less than 7 in 75% pathological cases and in 61.53% suspicious cases. Unlike our study, they showed a positive association between CTG category and Apgar score.

When cord blood ABG characteristics were compared, there was not much difference in pH for all 3 categories. The pO2 and pCO2 for normal and suspicious category were similar. The pO2 was lower and pCO2 was higher for the pathological category, but this difference was not statistically significant.

The number of acidotic cases were similar for normal and suspicious CTGs. Of all the cases that had a pathological trace, 13 cases (19.1%) had acidosis (pH less than 7.2). Acidosis was present in 2 cases (3.2%) of suspicious and 2 cases (5.6%) of normal CTG category. There was no statistical significance between CTG category (suspicious/pathological) and presence of acidosis.

The total percentage of acidotic cases was 10.3 % (17 cases) while 89.7% (148 cases) were non acidotic which is comparable to the study by Kaban et al. [17] (13.26%) who studied 101 term pregnant women admitted for delivery. In their study 85 neonates had normal cord arterial pH and 13 had fetal acidosis as diagnosed by cord arterial pH values less than 7.2. Of the 13 neonates with acidosis, 5 had non-reactive CTG tracings intrapartum. A similar study was performed by Aboulghar et al. [13]. The mean cord blood pH was 7.24 ± 0.07 (range: 7.05 – 7.39). The acidosis group comprised only 34% of their neonates, while the rest 66% had normal cord blood pH. This difference from our study could be attributed to the fact that they included only abnormal CTG cases and did not include any normal cases. Similar to our study, there was no significant association of CTG category with cord blood pH, acidosis, and pO2 or pCo2 values. In a study conducted by Kumar N et al. [12] on 30 women, 13 had abnormal CTG. Out of the 13 women having abnormal CTG results, only 3 (23.07%) showed acidosis (fetal distress in true sense) and required NICU admission. They observed that CTG wasn't a very effective tool for fetal assessment and correlation between cord blood pH and CTG was not significant.

The sensitivity of a pathological trace for acidosis was good (86.6%) but the specificity was poor as it was only 38.2%. The positive predictive value was poor at 19.2%. However, the negative predictive value was good at 94.5%. The sensitivity of a suspicious trace for acidosis was poor at 50%, with an equally poor specificity of 36.5%.The positive predictive value was poor at 3.27%, but the negative predictive value was good at 94.5%. A pathological trace is highly sensitive for detecting fetal acidosis but the specificity for detecting it is poor in our study. However, the presence of a normal trace rules out the presence of fetal acidosis due to a good negative predictive value. A suspicious trace had a poor sensitivity, specificity and positive predictive value, but it had a high negative predictive value like a pathological trace.

These findings are comparable with those found by Parveen et al. [18] who concluded that a normal CTG trace correlates highly with absence of fetal acidosis. Parveen studied 122 cord blood samples using umbilical cord arterial base excess (more than 12mmol/l) at birth to diagnose fetal acidemia. From their study they found that cardiotocography has a sensitivity of

15.38%, specificity of 86%, positive predictive value 11.76% and a negative predictive value 89%. This difference may be because of the fact that they took umbilical artery base excess at birth to diagnose fetal acidosis, while in the present study, umbilical cord arterial pH value of less than 7.2 was taken to diagnose fetal acidosis.

Steer PJ et al. [19] conducted a prospective study to find correlation among FHR patterns, MSL, umbilical cord arterial blood pH and Apgar score in 698 cases and found that sensitivity of an abnormal CTG at any time for fetal acidosis (cord arterial pH less than 7.17) was 80% and for severe acidosis (pH less than7.08) was 83%. However positive predictive value was low: 32% foetuses had abnormal CTG but no acidosis. If only CTG abnormality in I stage labour was considered sensitivity was 47% for acidosis & 67% for severe acidosis and false positive was 14%. These results were comparable to those found in our study. In a study by Tasnim et al. [1], positive predictive value of CTG was 18% for fetal hypoxia, 21% for fetal hypercarbia, 26% for fetal acidosis and 37% for base excess. Predictive value of suspicious trace for similar blood indices was 13%, 13%, 17% and 35% respectively. For pathological trace, predictive value was 50%, 83 %, 100% and 66% and respectively. From the findings of this study, although the sensitivity of CTG was found to be low, its high negative predictive value, low cost and ease of carrying out the monitoring supported its use in intrapartum fetal monitoring and in alerting the obstetrician regarding an intrauterine hypoxic event.

CTG abnormality did not correlate well with the need for resuscitation or NICU stay. Again, this showed that it was a poor predictor of adverse fetal outcome.

The presence of a normal CTG ruled out the occurrence of seizures in the first 24 hours after birth but the presence of a suspicious or pathological trace did not necessarily mean that the fetus will have seizures after birth as that was a rare occurrence even with a suspicious or a pathological trace. Similar to our study, the study by W M Aboulghar et al. [13] showed no statistical association between the CTG category and need for NICU stay. In their study, 33.3% of cases with pathological traces required NICU admission and 23.1% of those with a suspicious trace required NICU admission.

In a study by Patil SS et al. [20] who performed a similar study on 295 women, there was no association between need for NICU stay, acidosis at birth and CTG category.

In a study by Sowmya D et al. [16], out of 100 women with either suspicious or pathological traces, 34.6 % cases with pathological CTG and 27.08% with suspicious CTG required NICU admission. This was in contrast to our study and they showed a significant association between the need for NICU stay and CTG category.

In our study, 7.8% (12 cases) required resuscitation. Only 8.3% cases (3 cases) with a normal trace along with MSL required resuscitation and the rest 91.7% (33 cases) did not. In the pathological trace category, 11.8% cases (8 cases) required resuscitation while the rest 88.2% (60 cases) did not. Interestingly, only 1 case (1.6%) of suspicious trace cases required resuscitation while the rest 60 cases (98.4%) did not. The p value was 0.084, making the association statistically insignificant.

In a study by Patil SS et al. [20] who performed a similar study on 295 women, 24 babies required resuscitation and all 24 of these had severe metabolic acidosis. Like our study, their study showed poor correlation with need for resuscitation.

In our study, 3 cases (1.8%) had convulsions within the first 24 hours after birth. All of these had acidosis on ABG. Of these, 2 cases had a pathological trace (2.9% of pathological cases) and 1 case had a suspicious trace (1.6% of suspicious traces). None of the normal CTG cases with MSL had convulsions within the first 24 hrs after birth. The p value of 0.56 was statistically insignificant.

In the study by Patil SS et al. [20], 1.7% cases had convulsions within the first 24 hours after birth. Similar to our study, this was statistically insignificant.

In a large multicentre study on more than 37000 women by Alfirevic et al. [21], there was a significant association between CTG category and neonatal seizures within the first 24 hours of birth.

Conclusion

Abnormal CTG is worrisome from both obstetrician's and pediatrician's point of view. Abnormal CTG while being a good predictor of the presence of MSL and also the grade of MSL, is a poor predictor of the presence of fetal acidosis and neonatal status after birth.

Fetal monitoring using cardiotocography was associated with considerable false positive results and subsequent surgical intervention that may have not been necessary. Thus, using fetal heart rate abnormalities alone as a measure of diagnosis of fetal distress during labour is a contributing factor of increasing rate of cesarean sections.

Recommendations

All patients in active labour should undergo CTG monitoring as although it is not a very specific tool for detecting fetal distress, it's high sensitivity, ease of use and low cost make it a good tool for monitoring.

Decisions for cesarean section based on abnormal CTG findings should be made with caution. Maternal corrective measures as recommended by NICE guidelines should be undertaken first before deciding upon abandoning trial of labour.

In case of an abnormal CTG finding, decision for artificial rupture of membranes should be made wherever feasible to check for the status of liquor and further plan of management should be made accordingly.

Better training in CTG interpretation and its correct interpretation is required to identify, understand and take appropriate corrective measures in those patients that are at a high risk of adverse fetal outcome.

The pediatrician should be kept in the loop in case of any abnormal CTG, as, although the incidence of hypoxia and acidosis is less, the presence of a skilled pediatrician coupled with good resuscitative measures can reduce neonatal morbidity and NICU admissions significantly even in the occasional occurrence of acidosis with abnormal CTG.

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Use of a device for bone allograft channeling in an experiment with rabbits: Narrative review

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Abstract

Aim: to investigate the method of antibiotic impregnation of the femoral bone head (prepared according to the Marburg bone bank system) using a patented device designed for uniform channeling followed by deep soaking of the bone graft spongy tissue with drug solutions.

Materials and methods: Femoral bone heads prepared according to the Marburg bone bank system and impregnated with gentamicin were used in the experiment. Four groups were formed depending on the impregnation method. A whole femoral head was used in groups I and II, a perforated femoral head – in groups III and IV. In groups I and III, antibiotic impregnation was carried out simultaneously with heat treatment of the femoral heads, in groups II and IV – after heat treatment. The perforated, treated, gentamicin-soaked femoral bone head was compared to the "PerOssal" beads soaked in gentamicin. The degree of influence on the S. aureus strains was determined using the agar diffusion method.

Results and conclusion: The results indicate the presence of antimicrobial activity in the antibiotic-impregnated allograft in all groups. However, the growth inhibition zone was lower in groups I and III. The antimicrobial activity of gentamicin in the I and III was lower than in the groups II and IV. An increase in the diffusion of the antibiotic is facilitated by the perforation of the bone allograft according to the developed method using a patented device. It has been established that perforation and soaking of the bone allograft in an antibiotic solution increases the antibiotic impregnation of the bone graft.

Key words: antibiotic prophylaxis, arthroplasty, implant, osteomyelitis

Introduction

Currently, infectious complications after chronic osteomyelitis are an important problem in traumatology and orthopedics, which should be paid attention to [1]. The use of bone allograft avoids fractures and chronic pain syndromes at the area of donor material collection. The literature often describes the impregnation of a bone graft by manual stirring, shaking, placing the bone graft into antibiotic-containing solutions for a certain period, as well as physical methods (iontophoresis) [2-4]. A number of researchers describe the use of bone allografts as carriers for antibiotics. Thus, E. Wits et al. found that ground bone grafts impregnated with antibiotics are effective for a variety of clinical situations – they store and release large amounts of aminoglycosides and vancomycin [5].

It is known that, grafts in the form of allo-, auto-, or heterotransplants are used in osteoplastic operations [6, 7]. When filling defects in bone tissue, a backbone from an organic matrix is required, on which new bone tissue is formed. The use of bone chips or whole massive bone grafts to fill large bone defects showed that partial resorption occurs, and the bone defect does not completely heal [8]. Therefore, the allograft must be created in the form of a maximally porous spongy skeleton, along which the restoration of bone tissue will be more favorable, and the penetration of liquid with antiseptic substances (antibiotic solutions) will provide better graft impregnation [9].

Orthopedic awl, described in the manual of G. Ye. Ostroverkhov, is a known device [10]. The device consists of an oblong handle and a stylet with a tapered point. This device can form channels in the graft in order to improve

the penetration of drugs into the graft depth. However, the use of this device has the following disadvantages:

1. Irrationality of the oblong shape of the orthopedic awl handle, continuing along the vector of its stylet. The tight grip of the instrument during the formation of the bone canal causes bending and overstraining of the muscles of the surgeon's hand with dulling of his "muscular feeling". This leads to an uneven distribution of canals over the allograft mass, which implies impregnation of the spongy bone allograft with liquid solutions of different saturation [11]. As a result, zones are formed with the absence of the drug, or with the drug content less than the required level. Also, in the place of possible intersection of the canals, a cavity is formed, which will create a defect in the neoplasm of bone tissue.

2. The absence of indicative marks on the awl stylet causes insufficient visual control over the depth of the canals.

3. Long time of channel formation.

4. A "cleaver effect" is possible, in which wedging and cracking of the bone occurs.

For this study, a device was created with which it is possible to quickly and conveniently form uniformly distributed canals in the bone allograft array. The channels are designed for uniform impregnation of bone allograft spongiosa with solutions, as well as for increasing the allograft surface area for bone tissue neoplasm.

Figure 1 - Utility model patent "Device for bone allograft perforation"


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PATENT
№ 3980
ПАЙДАЛЫ МОДЕЛЬГЕ / НА ПОЛЕЗНУЮ МОДЕЛЬ / FOR UTILITY MODEL

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Устройство для перфорирования костного аллографта
Device for perforating bone allograft

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The utility model relates to medical technology, namely to traumatology and orthopedics, and is intended for uniform channeling with subsequent deep soaking of the spongy tissue of the bone graft with solutions of medicinal substances. The device is patented, utility model patent No. 3980 [12] (Figure 1).

Materials and methods

The new device was used for bone allograft channeling, followed by the impregnation of medicinal substances into the bone tissue. The device consists of a rectangular structure made of metal, 50 mm wide, 50 mm high and 100 mm long. Threaded holes for brackets are available on two side walls, which is necessary for stable fixation of the bone allograft inside the base. The other two walls have through channels located at the same distance from each other over the entire surface of the wall. Channels 10 mm thick are required to prevent drill deflection. Multiple through channels at the same distance from each other are formed on two perpendicular sides in the bone allograft, they are intended for subsequent uniform bone tissue impregnation (Figures 2-4).

Figure 2 - General view of a device for bone allograft channeling with subsequent impregnation of drugs into bone tissue

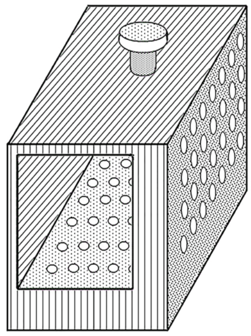


Figure 3 - Side view of a device for bone allograft channeling with subsequent impregnation of drugs into the bone tissue

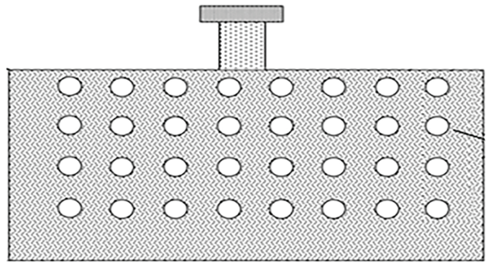
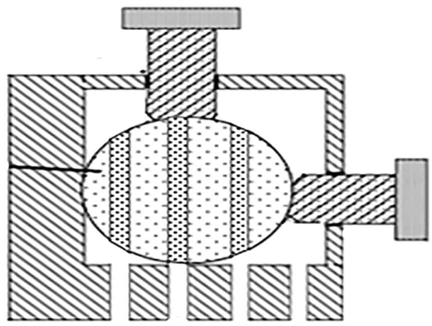


Figure 4 - Sectional view of a device for bone allograft channeling with subsequent impregnation of drugs into the bone tissue with a fixed graft



Removed femoral bone head is used after hip arthroplasty for the manufacture of an allograft matrix. The formation of channels using a drill is carried out in the head after appropriate mechanical treatment and boiling in order to deeply impregnate with drugs and create a skeleton. The optimal conditions for the formation of bone tissue and scaffold are combined if the distance between adjacent canals is the same. After the formation of canals in the allograft, further processing is carried out in the Lobator device according to the Marburg system (EP0584484A1. 02.03.1994. Verfahren und Einrichtung zum Desinfizieren von Knochentransplantaten, insbesondere von humanen Spongiosa-Transplantaten Harald Priv. Dozent Dr. KnaeplerGarrel Thomas Dr. Von.). Then the allograft is placed in a sterile bag with an antiseptic liquid and sealed.

The method of device using is as follows. The bone graft is fixed with two bolt brackets in the device. Channels are formed by the drill according to a template (channels for a drill, located

at the same distance from each other over the entire surface of the two perpendicular walls of the device). Then the graft is washed in saline to clean the canals from bone chips. Next, the antibiotic is impregnated by boiling and soaking with the antibiotic in a Lobator device according to the Marburg system.

Figure 5 - Top view of a device for bone allograft channeling with subsequent impregnation of drugs into the bone tissue with femoral bone head fixed in it

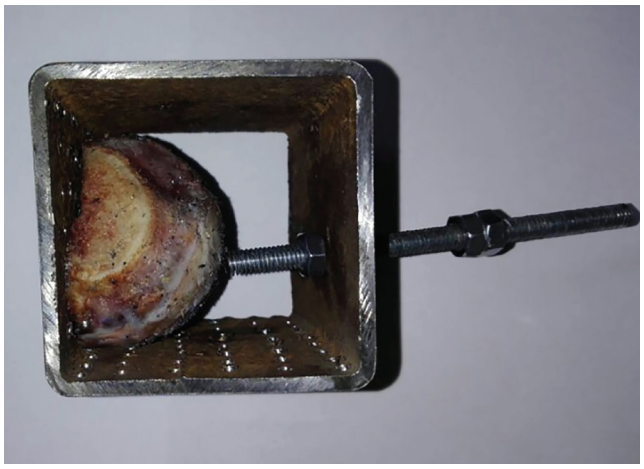
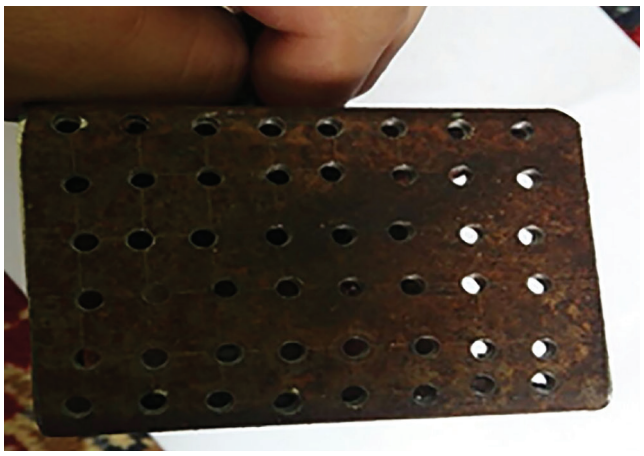


Figure 7 - Side view of a device for bone allograft channeling. The holes with a diameter of 3.2 mm for perforation are visible on the side wall



The criteria for excluding heads from the experiment: the presence of severe sclerosis and damage. There were various damages of the femoral bone head. Basically, these were focal lesions of the cartilaginous tissue typical for cocarthrosis of the III-IV degree. The average diameter of the femoral bone heads was 53 mm. The treated head was placed in a special cartridge with 330 ml of saline solution. The entire surface of the graft was placed in saline solution. The head cartridge was processed for 94 minutes on a Lobator apparatus (Figure 8).

The temperature in the center of the allograft was 82.5 °C. After processing the grafts on the Lobator apparatus, the femoral bone heads were sterile and completely ready for further work. Gentomycin was chosen as an antibiotic for impregnation because it showed good thermal stability properties.

Bone grafts were divided into 4 groups depending on the impregnation method:

Group I: whole head, treated on the Lobator sd-2 apparatus with the addition of gentamicin;

The bone graft was taking in patients after hip arthroplasty using a special instrument, namely electrocutter. The femoral bone heads were cleaned of cartilaginous tissue. Femoral bone head perforation was performed using an original bone allograft perforation device (Figures 5-7).

Figure 6 - Side view of a device for bone allograft channeling with subsequent impregnation of drugs into the bone tissue with femoral bone head fixed in it

Figure 8 - Antibiotic treatment of the whole femoral bone head in the Lobator sd-2 system

Group II: after treatment on the Lobator sd-2 apparatus, the graft was placed in a gentamicin solution with an exposure time of 60 minutes;

Group III: the graft was perforated according to the developed technique, then treatment was carried out on the Lobator sd-2 apparatus with the addition of gentamicin;

Group VI: the graft was perforated according to the developed technique, then treatment was carried out on the Lobator sd-2 apparatus, and then the head was placed into gentamicin solution with an exposure time of 60 minutes (Figure 8).

Results and discussion

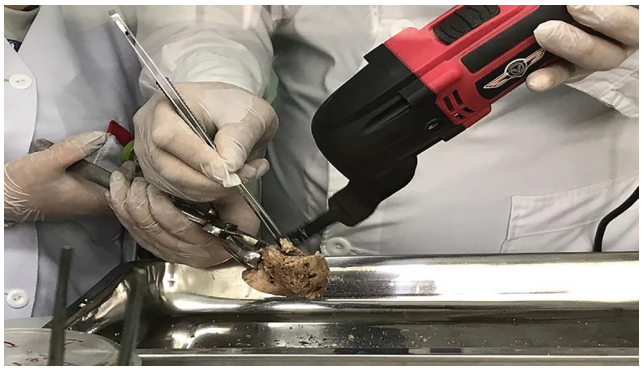
Comparison of four types of treatment of the femoral bone heads is carried out. It was revealed that the perforated femoral bone head, treated on the Lobator apparatus and soaked in gentamicin for 60 minutes, had the greatest influence on S. aureus activity.

The perforated, treated, gentamicin-soaked femoral bone head was compared with the gentamicin-soaked "PerOssal" beads in terms of the effect on S. aureus strains using the agar diffusion method.

The antibiotic release was assessed by the agar diffusion method. We used 3 bone fragments of perforated, treated, soaked in gentamicin bone head from a certain depth level (cortical, subcortical and central) with dimensions of 1 cm x 0.5 cm.

All selected allografts were placed in sterile Petri dishes 9 cm in diameter (1 bone plate per dish). The figure shows the process of femoral bone head crushing with use of oscillator saw (Figure 9).

Figure 9 - Femoral bone head crushing with use of oscillator saw



The study results indicate the presence of antimicrobial activity in all groups [13]. However, allografts perforated according to the developed technique showed a higher zone of bacteria growth inhibition in comparison with whole femoral bone heads. This fact testifies to the effectiveness of the developed device. The device contributes to the efficient formation of evenly distributed channels in the bone allograft array. The channels are intended for uniform impregnation of bone allograft spongiosis with solutions, as well as for increasing the allograft surface area for bone tissue new grow [14]. Uniform channeling facilitates deep soaking of bone graft spongy tissue with solutions of medicinal substances [15].

Conclusion

A device for bone allograft channeling with the subsequent impregnation of medicinal substances into the bone tissue is effective. The device is a rectangular metal structure, on two side walls of which there are threaded holes for brackets. They are necessary for firm fixation of the bone allograft inside the base. The other two walls have through channels located at the same distance from each other over the entire surface of the wall. The channels are 10 mm thick to prevent drill deflection. In the bone allograft, multiple through channels oriented from two perpendicular sides are formed, intended for subsequent uniform bone tissue impregnation.

1) The device has through channels that fix the drill direction, which eliminates the "cleaver effect" with the danger of bone wedging and cracking.

2) Wall thickness with 10 mm guide channels avoids the smallest deviations of the drill during channel formation.

3) The bone graft is securely fixed in the device, which avoids displacement of the bone during the bone canal formation.

4) The use of the device makes it possible to neglect the bone unevenness due to the graft fixation.

5) The presence of the guide channels of the device ensures the evenness, parallelism of the channels at the same distance, as well as the absence of intersection of the channels drawn from both sides. This has a positive effect on the strength of the allograft and on the impossibility of cavity forming, in the place of which a void defect can form during the new grows of bone tissue.

Thus, the proposed device makes it possible to improve the quality of the bone graft channeling by forming multiple non-intersecting through channels precisely oriented from two perpendicular sides at the same distance, intended for subsequent uniform impregnation of bone allograft spongy tissue with drug solutions.

Ethical aspects: The study was conducted in accordance with Directive 2010/65/EC of the European Parliament and of the Council of the European Union from September 22, 2010 on the protection of animals used for scientific purposes. All procedures are approved by the Ethical committee of the Karaganda State Medical University (Protocol No. 13 from 25/09/2017). Anesthesia was done by inhalation and intravenous. The object of the study were 150 rabbits, 6-8 months old with weight 3000.0-3500.0 grams. The used rabbits were from the vivarium of Karaganda medical university.

Disclosures: There is no confict of interest for all authors.

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Evaluation of nursing care requirements in mechanically ventilated patients

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Abstract

Objective: This study aims to plan and carry out the determination of daily living activities, nursing care needs and to what extent these needs are met in patients who have been undergoing mechanical ventilation and then weaned from mechanical ventilation.

Material and methods: This research is a descriptive study planned to determine the daily living activities, nursing care needs and to what extent these needs are met in patients who have been weaned from mechanical ventilation. In this study, "What is the level of meeting the daily living activities of the patients who have been undergoing mechanical ventilation and then weaned from mechanical ventilation?", "Is there a difference between the socio-demographic characteristics of the activities of daily living?", "What are the opinions of the patients who have been undergoing mechanical ventilation and then weaned from mechanical ventilation about the nursing care needs?" sought answers to questions.

Results: The patients who participated the research were determined including into the half-dependent group cause of being the point average 11,63±3,314 of the KATZ scale of the daily life routines. It was found statistically significant difference (p<0,05) between the answer of the questions which were asked by the participating patients who needed to know about suppling with nursing care requirement. According to this: It was determined that people trust nursing care, are moderately affected by medical treatment, nutritional problems are reduced with nursing care, they receive moderate information from nurses, and they receive help from nurses for symptoms such as nausea-vomiting and pain due to illness.

In addition, it was determined that they needed to be supported in complying with care, giving explanatory information about care, being honest and communicating effectively during the therapies, paying attention to the protection of privacy, and families' participation in nursing care therapies.

Conclusion: There is a need to increase nurses' levels of knowledge about determining the care needs of patients receiving undergoing mechanical ventilation and then weaned from mechanical ventilation and meeting these needs. According to this, the knowledge of intensive care nurses should be strengthened by using visual learning techniques and simulation application methods, in addition to relevant theoretical trainings.

Key words: mechanical ventilation, patient, nursing, care, need

Introduction

Mechanical ventilation [MV] is a frequently used method to relieve respiratory muscles in patients with acute respiratory failure and to reduce the workload, especially in intensive care units [1, 2].

The general purposes of Mechanical Ventilation are to provide oxygen transfer to body organs and tissues until respiratory function improves, to improve hypoxia and acute respiratory acidosis, to prevent or eliminate atelectasis, to eliminate the fatigue and weakness of respiratory muscles, to reduce systemic or myocardial oxygen consumption, to decrease intracranial pressure and to stabilize the chest wall [3-5].

The patients undergoing MV who are treated in intensive care units more frequently face complications because of their critical condition. Most of these

complications may be directly related to the application of MV, while the application of MV is an important risk factor in some of them [6].

The patients receiving treatment on the ventilator in intensive care units are fully dependent on nurses in terms of the level of care since they cannot meet self-care needs on their own. Therefore, all systems should be evaluated in detail every hour to ensure the full care of patients, eliminate physiological needs, and avoid complications due to lack of care.

As a result of the care performed by nurses by taking into account evidence-based practices, potential complications will be avoided, it will be easy for patients to wean from the ventilator, and the duration of mechanical ventilation will be reduced [7, 8].

Detailed determination of the care needs of the patients on mechanical ventilation is quite important and life-saving so that their bio-psycho-social needs are not ignored.

This study plan and carry out the determination of daily living activities, nursing care needs and to what extent these needs are met in patients who have been undergoing mechanical ventilation and then weaned from mechanical ventilation.

In the study, answers to the following questions were sought:

1. What is the level of meeting the daily living activities of the patients who have been undergoing mechanical ventilation and then weaned from mechanical ventilation?

2. Is there a difference between the socio-demographic characteristics of the activities of daily living?"

3. What are the opinions of the patients who have been undergoing mechanical ventilation and then weaned from mechanical ventilation about the nursing care needs?

Materials and methods

Design

This study was designed as a descriptive-sectional.

Participants and setting

This study was conducted to determine the daily living activities and nursing care needs of patients weaned from mechanical ventilation and to determine to what extent these needs are met.

This descriptive study was carried out in the intensive care unit of a research and training hospital affiliated with a foundation university in Istanbul province.

All patients hospitalized in the intensive care unit between the specified dates constituted the population of the study.

The sample of the study consisted of patients over 18 years of age, who were separated from the mechanical ventilator, who agreed to participate in the study, and who had no communication problems. The score of the selected patients on the Glasgow coma scale is 15.

The sample was determined by the convenience sampling method, which is one of the improbable sampling methods. In this context, the study was completed with 71 patients who met the inclusion criteria between May October 2017.

Data collection tools

1. Patient information form: This form includes the questions about the socio-demographic data of the patients.

2. KATZ activities of daily living scale: The permission to use the scale was obtained from Prof. Dr. It was taken from Mustafa Cankurtaran. The scale, which was developed by Katz et al. and adapted into Turkish by Arık et al. under the supervision of Cankurtaran, measures the degree of addiction in self-care activities such as feeding, dressing, bathing, mobility, continence, and going to the toilet [8].

This scale is widely used both abroad and in our country, and it is a scale with high validity and reliability. This scale is a tool used to define functional status by measuring the patient's ability to independently perform activities of daily living. The scale, which is a Likert type, is scored between 1-3.

The individual is evaluated by giving 3 points if he/she does the activities of daily living independently, 2 points if he/she does it with help, and 1 point if he/she cannot do it at all. According to the ADL scale, 0-6 points are evaluated as a dependent, 7-12 points as semi-dependent, and 13-18 points as an independent [9].

3. Care needs questionnaire: The questionnaire developed by the researcher by using the literature data [1, 6-8] was prepared to examine the care needs of the patients. It consisted of 17 questions answered as "Yes" and "No". The questions answered as Yes were arranged in the 'Very, Moderate and Low' 3 points Likert form.

Data collection

Data were collected by the researcher by face-to-face interview method in six months [May-October 2017]. Information about the disease and treatment was obtained from the patient's medical records. Data were collected using the "Patient Information Form", the "KATZ Activities of Daily Living Scale" and the" Care Needs Questionnaire".

Ethical approach

Approval [29.11.2016/55-10] was obtained from the Istanbul Bilim University Institute of Health Sciences Ethics Committee before starting the study. Institution permission was obtained for the application from the administration of the hospital where the study would be carried out. Patients whose mechanical ventilation treatment was terminated and who did not have a disability to communicate (without tracheostomy) were included in the study. The patients who volunteered to participate in the study were informed about the aim of the study and that information would not be shared with anyone, and their informed consents were obtained.

Data analysis

Data were analyzed using the statistical analysis program. Data were evaluated using descriptive statistics such as frequency distribution, arithmetic mean, standard deviation and percentage, and nonparametric tests [Kruskal-Wallis test, Mann-Whitney U test, Spearman correlation analysis]. The results were evaluated at a confidence interval of 95% and a significance level of $p<0.05$.

Results

Results on the KATZ activities of daily living scale

While 50.7% of the patients stated that they had baths by standing, sitting, or wiping, 12.7% stated that they needed help to wash more than one area of their body, and 14.1% stated that they could not take a bath at all. While 46.5% of the patients stated that they completely needed help in getting and wearing their clothes, 32.4% of them stated that they needed help in going to the toilet, cleaning and preparing their belongings, 31%

of them stated that they used a walking stick and walking tool for support while walking, 38% of them stated that they needed observation for urinary and intestinal emptying, and 25.4% of them stated that they received support on nutrition.

It was determined that the mean score of the KATZ scale was 11.63±3.314, and accordingly, the patients were semi-dependent in meeting their activities of daily living.

It was determined that there was a statistically significant, positive, and low-level relationship between the ages of the patients and the KATZ activities of daily living scale scores [*rs:* 0.459; p<0.05] (Table 1). The KATZ Activities of Daily Living Scale scores of the patients who were civil servants were found to be statistically significantly high [p<0.05] (Table 1).

Table 1 Comparison of KATZ Activities of Daily Living Scale Scores with the Patients' Socio-Demographic Characteristics

Socio-Demographic Characteristics		N	KADL S Score		Z_{mwu} / X^2_{kw} / r_s p
			$\bar{x}$	±sd	
Age					r_s = .459** **P= .000**
Gender	Male	43	13.81	3.581	Z_{mwu} = - .759 p = .448
	Female	28	13.32	2.894	
Educational Status	Primary school	20	13.20	3.318	X^2_{kw} = 7.049 p = .133
	Secondary school	11	12.82	2.960	
	High school	18	13.67	3.531	
	University	16	13.44	3.405	
	Postgraduate	6	16.83	1.602	
Profession	aHousewife	18	11.61	2.789	X^2_{kw} = 19.486 **p = .001**
	bCivil Servant	7	17.00(a)	1.826	
	cWorker	6	16.33(a)	1.633	
	dSelf-employment	12	14.33	3.447	
	eOther	28	13.18	3.128	
Marital status	Married	60	13.60	3.284	Z_{mwu} = -0.168 p = .866
	Single	11	13.73	3.636	
Place lived	City	60	13.27	3.394	X^2_{kw} = 4.358 p = .113
	Town	5	15.40	2.408	
	Village	6	15.67	1.862	
Family Income Status	Income less than expense	7	14.86	1.864	X^2_{kw} = 3.026 p = .220
	Income equal to expense	46	13.11	3.274	
	Income higher than expense	18	14.44	3.682	
Smoking	Yes	28	14.07	3.288	Z_{mwu} = - .966 p = .334
	No	43	13.33	3.336	
Duration of smoking	0-5 years	7	13.71	3.817	X^2_{kw} = 1.750 p = .417
	6-10 years	6	15.50	3.017	
	10 years and above	20	13.45	3.284	
Alcohol Use	Yes	51	13.35	3.180	Z_{mwu} = -1.256 p = .209
	No	20	14.30	3.629	
Presence of Chronic Disease	Yes	37	13.16	3.176	Z_{mwu} = -1.363 p = .173
	No	34	14.12	3.436	
Continuous Drug Use	Yes	43	13.28	3.210	Z_{mwu} = -1.210 p = .226
	No	28	14.14	3.461	

Zmwu: Mann-Whitney U Test X2kw: Kruskal-Wallis Test
rs: Spearman's correlation coefficient ** p< .01

Results on the care need questionnaire

It was determined that 97.2% of the patients answered yes to the question "Can you get information about nursing care practices related to your disease from nurses?" while 95.4% of them answered yes to the question "Do you rely on the nursing care provided?".

When the distribution of the positive responses of the patients participating in the study towards nursing care as 'Very, Moderate and Low' was examined, a statistically significant difference was found between the groups. Accordingly, it was determined that the patients highly relied on nursing care, the nursing care provided moderately affected receiving medical treatment and moderately reduced the problems related to nutrition, they could moderately obtain from nurses during these practices, nursing practices were very helpful in eliminating the complaints of pain and nausea-vomiting due to disease, intraoral problems further decreased and disappeared with drug applications, nurses acted quite properly for the opinions and values while performing care practices, provided explanatory information about care, were very sincere during the practices and moderately established effective communication, was very attentive to protect the privacy and ensured families' participation in nursing care practices [p<0.05] (Table 2).

Table 2 Distribution of Patients' Views on the Grading of Care in the Questions Positively Answered by Them

Item	Very		Moderate		Low		x^2	p
	N	%	n	%	n	%		
1. Do you rely on the nursing care provided?	48	67.6	20	28.2	-	-	11.529	**.001**
2. Did the nursing care provided ensure a decrease in adverse effects you experienced due to disease, treatment?	34	47.9	31	43.7	-	-	.138	**.710**
3. Did the nursing care provided make it easier for you to receive medical treatment?	36	50.7	28	39.4	1	1.4	31.046	**.000**
4. Did the nursing care provided reduce your problems related to nutrition?	18	25.4	29	40.8	5	7.0	16.654	**.000**
5. Can you get information about nursing care practices related to your disease from nurses?	31	43.7	33	46.5	5	7.0	21.217	**.000**
6. Were nursing practices helpful in relieving the pain you experienced due to your illness?	31	43.7	30	42.3	3	4.2	23.656	**.000**
6A. Did your pain complaint decrease or disappear with drug applications?	34	47.9	21	29.6	1	1.4	29.607	**.000**
6B. Did your pain complaint decrease or disappear with non-pharmacological interventions?	14	19.7	24	33.8	8	11.3	8.522	**.014**
7. Were nursing practices helpful in relieving nausea and vomiting you experienced due to disease?	23	32.4	18	25.4	2	2.8	16.791	**.000**
7A. Did your nausea-vomiting complaint decrease or disappear with drug applications?	24	33.8	12	16.9	-	-	4.000	**.046**
7B. Did your nausea-vomiting complaint decrease or disappear with non-pharmacological interventions?	12	16.9	13	18.3	4	5.6	5.034	.081
8. Were nursing practices helpful in overcoming oral problems you had due to your illness?	18	25.4	18	25.4	-	-	.000	1.000
8A. Did oral problems decrease or disappear with drug applications?	14	21.1	10	14.1	3	4.2	7.786	**0.020**
8B. Did oral problems decrease or disappear with non-pharmacological interventions?	15	21.1	10	14.1	-	-	1.000	0.317
9. Does the nurse act properly for your views and values when performing care practices?	36	50.7	29	40.8	1	1.4	31.182	**.000**
10. Are you provided explanatory information about care by nurses?	36	50.7	27	38.0	2	2.8	28.646	**.000**
11. Do you think that you have been informed by the nurse about the examinations to be performed about the disease?	33	46.5	31	43.7	2	2.8	27.364	**.000**
12. Is information provided by the nurse before and after the drug applications performed?	33	46.5	30	42.3	2	2.8	26.985	**.000**
13. Do you think nurses are sincere to you in care practices?	32	45.1	22	31.0	6	8.5	17.200	**.000**
14. Do you think that nurses communicate effectively with you during their care practices?	29	40.8	32	45.1	6	8.5	18.119	**.000**
15. Are nurses attentive to protect privacy during care practices?	35	49.3	29	40.8	2	2.8	28.091	**.000**
16. Can you talk to nurses when you feel psychologically distressed?	21	29.6	19	26.8	18	25.4	.241	.886
17. Is the participation of your family in nursing care practices ensured?	22	31.0	22	31.0	5	7.0	11.796	**.003**

x^2: Chi-square test

Discussion

Intensive care units and the mechanical ventilation support treatment applied to cause some physiological changes in patients. Due to the negative effects of these health problems experienced, individuals become dependent on activities of daily living [ADL] and need someone else's help. Inadequacy in activities of daily living is evaluated by the criteria such as respiration, nutrition, excretion, movement, performing self-care, bathing, dressing, using phone, shopping, doing household chores, and taking own medicine. To be connected to a ventilator causes patients to be unable to meet these needs on their own. The patients with this condition are considered to be semi-dependent or fully dependent within the scope of their needs. The care needs of the dependent, semi-dependent, and independent patients are different from each other, and their levels of dependence should be first determined while planning nursing care [10]. In this study, it was determined that the levels of dependency of the patients were semi-dependent and that they needed support for personal needs such as bathing and toilet needs. In a similar study carried out by Yazıcı and Kalaycı [10], it was determined that 26.5% and 36.3% of the patients were fully dependent and semi-dependent, respectively, on bathing; and when the distinction was made by gender, it was determined that 33.3% of female patients and 22.2% male patients were dependent in meeting the need for bathing. In the same study, concerning meeting the need for a toilet, it was determined that 28.4% of the patients were fully dependent, and 33.3% of women and 25.4% of men were dependent according to gender. Similarly, in the study carried out by Akca et al. [11], it was determined that 6.3% of the patients were fully dependent and 15.7% of them were semi-dependent in activities of daily living. In the study carried out by Tasdelen and Ates [12], it was

determined that four out of ten patients were fully dependent on bathing while four of them were fully dependent on performing excretion activity. According to these results, the vast majority of patients receiving ventilator support treatment need help in meeting the need for bathing. Help levels vary at full or semi-dependent levels according to the prognosis of patients. High levels of dependence of women than men are thought to be because female patients fear falling during bathing. Similarly, research results indicated that the patients were semi-dependent or fully dependent on meeting their toilet needs. The fact that the levels of dependence of women are high and they need more help is due to the difference in the anatomic structure.

Along with the physiological changes observed in intensive care units, invasive procedures such as mechanical ventilators and catheters may lead to physical limitations and psychological problems in patients. Patients may experience loneliness and isolation because they cannot be with family members and friends and cannot maintain their daily life habits. Furthermore, they also have anxiety due to the sounds of monitor systems, ventilators, fluid and/or drug infusion pumps in the intensive care setting and require psychological support at varying degrees. Therefore, establishing effective communication with patients and informing them before each application will comfort both the patient and their relatives. Indeed, it was determined that the patients participating in this study received sufficient information about their diseases and the practices performed by the nurses who provided care. In the questions related to the rating of care, it was determined that the item "Do you think that nurses communicate effectively with you during their care practices?" was answered as "moderately". In the study carried out by Kumcagız et al. [13], it was indicated that communication was an important care tool in treatment in the periods of disease during which people are dependent, and it was determined that nurses' effective communication with the individual for whom they provided care, and with their family increased the quality of care positively. Similarly, Avsar and Kasıkcı [14] also indicated that effective communication with the patient and his/her family increased the quality of nursing care. In the same study, significant differences were found in the communication skills with the patients and their families of the nurses who were working in clinics such as outpatient clinics where there is less care, had high education level and average age, were married, had children and a working period of 20 years and more. In the study carried out by Dunsford [15], effective communication positively affected patient care in emergency and intensive care units where information flow between the medical team and the patient-family is active. According to the study carried out by Dilek et al. [16], the patients with mechanical ventilator support are the group experiencing communication difficulties. It is observed that these patients experience anxiety, fear, stress, loss of consciousness and control due to their inability to communicate. In the same study, it was indicated that eye contact, yes/no questions, facial expressions, paper-pencil, various signs, and shapes should be used in communication with the patients with mechanical ventilation support. In the study of Tosun et al. [17], communication with lip movements was reported to be a form of communication commonly used by patients on ventilation support. In the study carried out by Patak et al., it was determined that the communication board developed to minimize communication barriers in patients whose mechanical ventilation support terminated contributed to establishing communication in 69% of the patients.

According to the study, it was determined that the patients relied on the nursing care provided. In a similar study carried out by Soyuk et al. [18], it was determined that the patients generally relied on physicians, nurses, and staff working in intensive care units, found the treatment and care sufficient, could ask questions to them, and were satisfied with the intensive care setting and healthcare workers. In the study carried out by Hindistan et al. [19], care satisfactions were evaluated and patients were reported to be moderately satisfied. In the study carried out by Sekmen and Hatipoglu [20], it was determined that the sense of trust of 63.4% of the patients treated in intensive care units was due to the importance that the health team attached to care services. In the study carried out by Stein-Parbury and McKinley [21], the patients receiving treatment in intensive care units described nurses as the individuals who provide care, constantly monitor the patient, support while performing their self-care and reduce their fear and anxiety, and they stated that they relied on nurses.

It was determined that the item "Can you talk to nurses when you feel psychologically distressed?" was mostly answered as "Low", concerning the grading of care of patients participating in the study. The patients receiving mechanical ventilation support treatment in intensive care units frequently have communication problems. However, in the study carried out by Korhan et al. [22], it was determined that there was no numerical similarity between the patients who had communication problems and the patients receiving mechanical ventilation treatment. In the same study, it was determined that nurses did not pay attention to the communication problems experienced with the patients, did not provide sufficient communication, and ignored the communication efforts of the patients. Following these studies, nurses should give time to non-sedated or extubated patients receiving mechanical ventilation support treatment to express themselves, and they should support them for communication.

It was determined that the patients participating in the study largely answered "Yes" to the question "Were nursing practices helpful in relieving the pain you experienced due to your illness?". According to the study carried out by Simsek et al. [23], the catheters used, drains, invasive-noninvasive ventilation methods, aspiration, dressing changes, treatment, and care applications, position changes, pressure sores, and infections due to lying in the same position for a long time, in addition to the illnesses of the patients receiving treatment in intensive care units, cause pain. Furthermore, in the same study, it was indicated that the changes in consciousness due to the use of sedation prevented the evaluation of pain. The presence of pain in patients restricts the activities of daily living and causes them to remain inactive. On the other hand, in the study carried out by Payen et al. [24], it was determined that the behavioral pain scale including the parameters of facial expression, upper extremity movements, and compliance with mechanical ventilation were effective in patients under sedation undergoing mechanical ventilation support treatment was effective in evaluating the effectiveness of analgesia applied to patients, and it was adopted by nurses. In the study carried out by Aslan and Karadag [25], pain caused nurses in intensive care units to feel the responsibility for thinking and feeling instead of the patient and prolonged the healing process by negatively affecting the quality of care. Intensive care nurses have important roles in identifying and relieving pain by closely monitoring the patients since they are the team members who spend the most time with the patients. In the study carried out by Woo et al. [26], it was determined that pain was associated with the socio-economic condition of the patient. It was determined that people with poor

socio-economic conditions and low educational levels had more pain in advanced age. In the study carried out by Simsek et al. [23], it was determined that the incidence of pain was higher in patients with high educational levels and more chronic diseases. In the same study, being a woman, advanced age, and chronic diseases were determined as important risk factors for pain. In the study carried out by Jakobsson et al. [27], it was determined that the incidence of pain was higher in the patients who were dependent on activities of daily living. In the study carried out by Reyes-Gibby et al. [28], it was indicated that pain affected the activities of daily living and caused activity limitation. The presence of pain in intensive care units is questioned by pain scales, and these studies show parallelism with the results of the research.

It was determined that the patients participating in the study answered positively to the question "Is the participation of your family in nursing care practices ensured?". Hill indicated that the vast majority of nurses included the family of patients while providing care. In the study carried out by Gurkan [29], it was determined that the most needed issue of patient relatives was to be with their patients and to participate in their care. These studies support the research results.

Nurses play an active role in the selection of correct care tools and products and the determination of the frequency of oral care by evaluating oral mucosa daily in patients receiving mechanical ventilation support treatment. Effective oral care provided significantly decreases the formation of ventilator-associated pneumonia [VAP] in the patient. It was determined that the patients participating in the study answered positively to the question "Were nursing practices helpful in overcoming oral problems you had due to your illness?". In the study carried out by Aygin et al. [30], continuous opening mouth due to endotracheal tube used during mechanical ventilation treatment, inability to receive drugs and nutrients orally, disruption of tissue integrity caused by ligaments, plasters used for fixation of endotracheal tube led to the formation of dental plaque, periodontal diseases, bad breath and stomatitis in patients. In the study carried out by Li et al. [31], it was determined that the oral care provided with antiseptics such as chlorhexidine and povidone-iodine significantly reduced the formation of VAP in patients. In the study carried out by Par et al. [32], it was determined that VAP occurred as a result of aspiration of colonized bacteria in the oral cavity and dental plaques of the patients receiving mechanical ventilation support treatment, and therefore, the oral care provided with chlorhexidine significantly decreased the incidence of VAP. In addition, it was stated that the care given by the nurses regarding oral care significantly reduced the VAP formation. The results obtained from the studies support this study.

Conclusion

According to the study, there is a need to increase nurses' levels of knowledge about determining the care needs of patients receiving mechanical ventilation support treatment and meeting these needs. For this purpose, the knowledge of intensive care nurses should be strengthened by using visual learning techniques and simulation application methods, in addition to relevant theoretical training.

Limitations

There is a need to increase nurses' levels of knowledge about determining the care needs of patients receiving mechanical ventilation support treatment and meeting these needs.

Nurses should be informed about the importance of communicating with family members and patients during care practices.

Semi-dependent patients should be explained how to perform the care needs for which they need support.

Nurses should be supported in the development and implementation of care practices and the importance of care practices should be emphasized with frequent training.

The latest technological developments for care should be followed and cooperation should be ensured with the hospital administration to use these innovations in the field.

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A case of pediatric perioperative anaphylaxis to neuromuscular agents and its management

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Abstract

Background: Perioperative anaphylaxis is one of the most challenging complications in anesthesiology. The key role is to determine the causative agent of the reaction. Neuromuscular agents are ones of the most common causes of anaphylaxis. Skin tests including prick and intradermal reaction tests are gold standard for definite diagnosis.

Case presentation: We present a case of a child undergone several operations due to congenital esophageal atresia. Later on, attempts to perform a definitive repair failed because of perioperative anaphylaxis. Allergic skin tests were performed and rocuronium was found to be positive and atracurium – negative. The operation was successfully performed with atracurium.

Conclusion: In patients who have gone through multiple surgeries the risk of anaphylaxis development is higher. The most common cause is considered to be neuromuscular blocking agents. In our case, after thorough examination of the anesthesiology cards, rocuronium and pipecuronium were defined as causes of anaphylaxis in our patient, so the surgery was done with atracurium which had been seen negative on a skin prick test. Eventually, the surgical procedure was performed successfully.

Key words: peroperative anaphylaxis, NMBA, atracurium

Introduction

Perioperative anaphylaxis is one of the most challenging complications in anesthesiology. The key role is to determine the causative agent of the reaction. Neuromuscular blocking agents (NMBA) are ones of the most common causes of anaphylaxis. Skin tests including prick and intradermal reaction tests are gold standard to define the allergen. We present a case of a child with a congenital esophageal atresia, in which several attempts to repair failed because of perioperative anaphylaxis. Allergic skin tests were performed and rocuronium was found to be positive and atracurium – negative. Eventually, the surgery was successfully performed with atracurium.

Case presentation

An infant was born on 24.11.2016 with esophageal atresia with trachea-esophageal fistula. On the second day of life the right thoracotomy with lower trachea-esophageal fistula ligation was done, however, primary repair was not feasible. Because of this feeding gastrostomy and esophagostomy was created.

Due to gastrostomy and esophagostomy dysfunction their reconstruction was done on the second year of life without any perioperative complications in UMC NRMCC Astana city.

2 attempts to perform esophageal reconstruction with a modified colonic interposition graft as definitive treatment failed because of perioperative anaphylactic shock developed during the procedures.

Both surgical procedures were performed under general anesthesia induced with 50 mg of propofol, 30 µg of fentanyl and 10 mg of Suxamethonium chloride. Tracheal intubation was performed uneventfully. Sevoflurane was used for general anesthesia.

In the first procedure on the 40th minute after anesthesia induction 10 mg of Rocuronium was administered for myorelaxation. In 15 minutes increase in airway pressure up to 40 cm H2O, reduction in blood pressure, skin flushing, and edema on his face and groin

were confirmed. Heart rate was 90 bpm or more and systolic arterial blood pressure fell to less than 60 mmHg. Anaphylaxis was suspected, and after appropriate treatment signs of allergic reaction resolved. Decision was made to postpone the surgery in order to define the cause of the reaction.

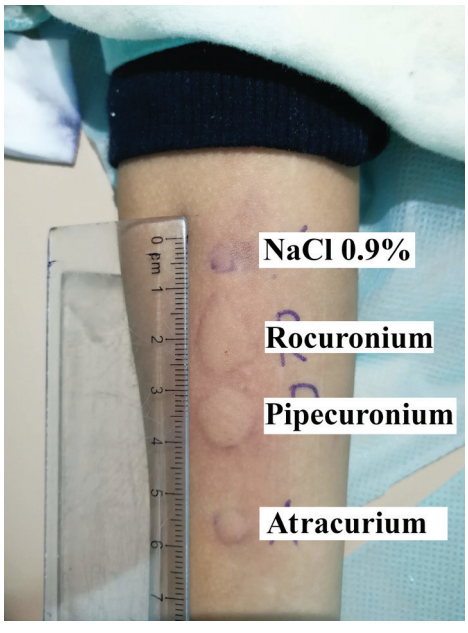
In the second procedure based on the results of skin prick tests the tactic of anesthesia induction and maintenance had been changed. However, in 30 minutes after Pipecuronium administration signs of anaphylactic shock were observed again. Of note, fentanyl was continuously infused during the both procedures.

In November 2020 the child was admitted to the National Research Center for Maternal and Child Health for elective surgery. Considering previous reactions, skin prick tests were performed to check all the drugs which would be used during the surgery (Table 1) (Figure 1).

Table 1 Results of skin prick tests.

Agent	Positive/negative result.
Rocuronium	+
Pipecuronium	+
Atracurium	-
Suxamethonium chloride	-
Propofol	-
Fentanyl	+/-
Ceftriaxon	-
Iodine	-
Morphine	+/- (was considered as false positive due to local irritating reaction).
Tramadol	-
Trimeperidine	-
Ketamine	-

Figure 1 - Skin prick tests



Based on these results the decision was made to perform the procedure using atracurium for myorelaxation. Also adequate premedication with corticosteroids and H1 blockers was done.

The operation - Esophageal reconstruction with a modified colonic interposition graft - was started under general anesthesia with propofol, fentanyl, and atracurium and was maintained with sevoflurane, atracurium (continuous infusion), ketamine and intermittent fentanyl. 2 central venous catheters, 1 peripheral venous catheter and 1 central arterial catheter were placed. Invasive arterial pressure measurement with intra-arterial catheter was established and central venous pressure was measured through the central venous line. The procedure was started in 1 hour after the induction of general anesthesia. The duration of the general anesthesia was 6 hours 9 minutes, surgery itself - 5 hours 10 minutes. The vital signs were in normal range during the general anesthesia. Surgery was completed uneventfully.

No further anaphylactic reaction or other complications occurred, and the child was extubated the next day.

Discussion

The perioperative anaphylaxis is a rare yet life-threatening situation leading to multisystem failure which may happen during any surgical procedure. The incidence rate is 1:10 000 to 1:20 000 cases [1]. The mechanism is typically an IgE-mediated (type 1) hypersensitivity reaction which involves release of mast cell- and basophil-derived mediators into the circulation after re-exposure to a specific antigen [2].

The anaphylactic reaction may occur after administration of any drug. Therefore, because during surgery multiple drugs are administered it can be difficult to define the exact cause of this reaction. In order to define the trigger of hypersensitivity reaction thorough analysis of the preceding anesthesiology cards is crucial. Since it was not an emergency surgery, it was suspended until definite identification of the antigen for anaphylaxis.

Among various methods for diagnostic investigation, in vivo skin tests including prick and intradermal reaction tests remain the gold standard for detection of IgE-dependent allergies [3]; these tests are best done after a delay of 4 to 6 weeks. According to the Kazakhstan clinical guideline [4] the evaluation includes a clinical history, review of the records, analysis of laboratory tests obtained at the time, skin testing or in vitro serum-specific IgE testing, and provocation test, which are useful in the case when other methods failed.

Generally, NMBAs are considered to be one of the main causes of perioperative anaphylaxis [5]. An IgE-mediated response is due to the quaternary ammonium (NH4+) structures that represents the main antigenic epitope of NMBAs [6]. We detected rocuronium and pipecuronium to be positive on skin prick tests 8 months after the onset of anaphylaxis, therefore, we were able to recognize them as possible causes of the reaction. Also we suspected fentanyl as a causative agent of the anaphylaxis, however, fentanyl is rarely a cause of true anaphylaxis [7] and our skin tests excluded fentanyl from the list.

Among NMBAs atracurium, cis-atracurium, and pancuronium are associated with a lower allergic risk [8]. During our evaluation, atracurium was confirmed negative after performing the skin prick tests. The surgery was successfully performed using atracurium for myorelaxation.

In the case of perioperative anaphylaxis NMBAs should be considered one of the first causative agents. If an allergic test to NMBA is positive other low allergy risk NMBAs may be considered. Furthermore, it is important to evaluate all cases of perioperative anaphylaxis with a multidisciplinary approach.

During our work-up regarding causative agents of anaphylaxis other potential causes were excluded. Antibiotics are often administered prior or during anesthesia and they are an increasing cause of perioperative anaphylaxis. Based on negative skin allergic tests, ceftriaxon was used. Another

common cause of allergic reaction is latex. However, we used latex-free equipment during the surgery. Povidone-iodine, said to be a much rarer cause of anaphylaxis, had also been excluded as a causative agent. Less common causes of perioperative anaphylaxis such as opioids and hypnotic agents were shown to be negative after the skin prick test.

Conclusion

In patients who have gone through multiple surgeries the risk of anaphylaxis development is higher. The most common cause is considered to be neuromuscular blocking agents. In our case, after thorough examination of the anesthesiology cards, rocuronium and pipecuronium were defined as causes of anaphylaxis in our patient, so the surgery was done with atracurium which had been seen negative on a skin prick test. Eventually, the surgical procedure was performed successfully.

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The case of determining the species, gender, age and race of the skull with congenital multiple developmental anomalies

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Abstract

In forensic medicine, a reconstructive victim profile is a widely used procedure for providing individual data in cases of complex identification of a person. The most valuable data such as gender, age, origin and height are obtained from skeletal and dental analyses. Deformed skulls require special expert attention during the forensic examination of bone remains. Unusual skull shapes are usually formed with certain diseases (hydrocephalus, craniostenosis, rickets), various kinds of injuries or as a result of artificial (intentional) changes in the shape of the head. The detection of cranial deformity has a great forensic importance in identifying a person, allowing you to further outline the range of diseases that an unknown person could have suffered during his lifetime. The article describes a rare forensic case of identification of a human skull with congenital multiple developmental anomalies. During the forensic medical and forensic examination, the deceased had a history of signs of a rare disease characterized by the formation of a specific deformation of the skull. A comprehensive assessment of the data is very important when conducting forensic medical studies aimed at helping investigative authorities to identify human remains.

Key words: forensic medical examination, skull, deformity, developmental anomalies, identification

Introduction

In the research, forensic identification of a person of bone remains can present significant difficulties for forensic experts [1,2]. Difficulties in identifying bones arise during the destruction of bone tissue as a result of exposure to high temperatures, chemical and other factors, as well as when several corpses are found in one burial [3,4]. The skull and long tubular bones remain the most informative for determining gender, age and individual anthropometric data [5,6]. For the present, a number of problems remain in identifying a person's identity, despite the improvement of biometric identification and DNA analysis methods [4,7]. This is primarily due to the processes of race mixing, a characteristic trend of modern humanity, which leads to a change in the main craniometric parameters of the skull [1,5,8]. On the territory of the Republic of Kazakhstan, the mestization of the population is directly related to migration processes. In this region, the formation of a contact zone (the zone of fusion of Caucasians and Mongoloids) [2] is clearly traced, which is caused by many factors, including the deportation of the people of the former USSR during the repressions, the evacuation of the population during the Second World War and the subsequent processes of globalization. As a result, the number of Mestizos living in this territory is steadily increasing, creating certain difficulties in the racial identification of bone remains. The digital indicators existing in the methods for identifying a person by bone remains are somewhat outdated, in addition, in most cases they are adapted exclusively for the identification of the Caucasian population of central Russia. The use of these data for the multinational ethnic composition of the Republic of Kazakhstan is poorly justified, since they can be interpreted incorrectly due to the processes

of acceleration and urbanization of the local population. At the same time, individual innate and acquired bone features has a particular importance [9, 10]. However, the differential diagnosis of gender, age and race in congenital anomalies of the development of the skull bones in forensic medical practice is difficult, because anomalies of the development of the skull lead to changes in metric, anatomical, morphological and radiological signs [5,11,12]. At the same time, situations when it is necessary to identify the identity of skeletonized human remains continue to be very popular. In this regard, an interesting example of a medical and forensic examination of bone remains found in the Almaty region.

Case presentation

Not far from the farm "Zhylkibayev", located near the village of Shengeldy, Almaty region, skeletal fragments were found, presumably belonging to a missing person who became a victim of murder. For identification of the person, the material was transferred for medical and forensic examination to the Institute of Forensic Examinations in Almaty, RSME "Center for Forensic Examination of the Ministry of Justice of the Republic of Kazakhstan". The skull, four cervical, three thoracic and two lumbar vertebrae, five ribs, left femur, left and right tibia were presented for the research. The bones presented for examination are white with a yellowish tinge, dry, light, completely devoid of soft tissues. A comparative analysis of the morphology of the skull bones revealed a pronounced deformation in the occipital bone, forming a hemispherical protrusion (Figure 1, Figure 2).

Figure 1 - Skull, front view (no visible changes)

Figure 2 - Skull, left view (the arrow indicates the deformity in the occipital bone)

The interparietal suture is deformed and deviates to the left in its apical and bregmatic parts (Figure 3). The occipital suture is represented by significantly overgrown teeth, has a width of up to 35 mm (Figure 4).

Figure 3 - Skull, top view (the arrow indicates the described changes)

Figure 4 - Skull, back view (the arrow indicates the described changes)

For further investigation, the cranial cavity was opened with the help of an angular saw passing through the frontal and parietal bones. When measuring the base of the skull using anthropological craniometric instruments and subsequent comparison of anatomical characteristics, it was revealed: a decrease in the size of the anterior and middle cranial pits, an increase in the size of the posterior cranial fossa, a decrease in the length of the Blumenbach slope and a flattening of the base of the skull (Figure 5). The mastoid processes are reduced, the awl-shaped processes are reduced, one horizontal abnormal suture of the occipital bone departs from the occipital-mastoid sutures (Figure 6). The circumference of the skull is 555 mm, the longitudinal diameter is 195 mm, the transverse is 148 mm. The thickness of the frontal and parietal bones corresponds to the norm, the occipital bone is somewhat thinned.

When establishing the race of the investigated skull, out of 28 craniometric indicators of the external structure of the skull [1], 21 indicators were identified, confirming the Mongoloid origin. 3 indicators were identified as probable Caucasoid signs. The remaining 4 craniometric indicators of the examined human skull could not be identified due to the absence of a part of the dental apparatus. Additionally, a comparative analysis of the cranioscopic parameters of the examined skull was carried out with similar indicators of 10 skulls of men of the Mongoloid race taken from the regional database (there are no female skulls of the Mongoloid race in the regional database). It should be particularly noted that from 25 generally accepted cranioscopic indicators, 3 indicators (forehead width, condylar and bigonal width) were not studied. This is due to the fact that on some skulls the frontal bone and lower jaw were missing.

Figure 5 - View of the base of the skull from the inside (the arrow indicates the described changes)

Figure 6- View of the base of the skull from below (the arrow indicates the abnormal seams of the occipital bone)

Figure 7 - X-ray picture of the skull in Hajdu-Cheney syndrome (there is an underdevelopment of the bones of the facial skull, protruding frontal and occipital tubercles, wide cranial sutures)

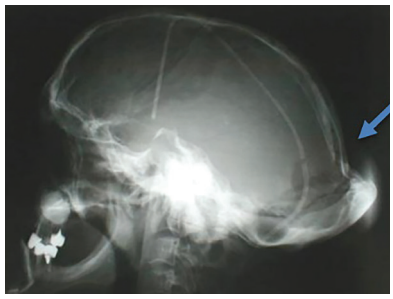
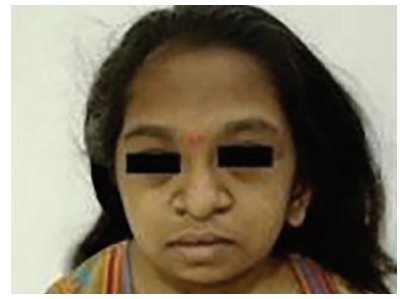


Figure 8 - Appearance of a patient with Hajdu-Cheney syndrome (hypertelorism, bushy eyebrows, micrognathia, low set ears and short neck present)



For the convenience of comparison, for each of the studied 22 signs, the smallest, average, the largest indicators were used, which are respectively designated as uncertain (U), probably male (PM), reliably male (RM) and probably female (PF). The results of the comparative research are presented in Table 1.

It was found that from 22 signs, 14 exceed the average indicators, while 7 of them exceed the largest values. The analysis of the results showed that the skull provided for the research has metric characteristics that differ from most indicators characteristic of the skulls of the Mongoloid race.

Table 1 Cranioscopic signs of the examined skull

No	Indicator	Measures of examined skull	Indicator			Indication
			the smallest	average	the largest	
1.	Longitudinal diameter	195,0	145,0	142,8	187,0	RM
2.	Transverse diameter	148,0	115,0	139,1	148,0	PM
3.	High altitude diameter	130,0	87,0	123,0	138,0	U
4.	Length of the base of the skull	101,0	95,0	109,8	155,0	PM
5.	Width of the base of the skull	137,0	116,0	128,5	136,0	RM
6.	Nape width	139,0	113,8	116,1	121,0	RM
7.	Mastoid width	115,0	101,0	108,8	119,4	PM
8.	Skull circumference	555,0	520,0	534.3	560,0	RM
9.	Sagittal chord	140,0	135,0	144,7	175,0	PM
10.	Frontal chord	112,0	111,0	117,5	119,0	PM
11.	Parietal chord	111,0	112,3	114,6	117,0	PM
12.	Length of the large occipital foramen	37,0	33,0	35,2	37,0	PM
13.	Width of the large occipital foramen	33,0	26,0	29,5	32,0	PM
14.	Bizygomatic diameter	141,0	140,0	142,0	144,0	RM
15.	Face base length	102,0	63,0	91,6	106,0	PM
16.	Upper face height	67,0	63,0	69,0	74,0	U
17.	Full face height	114,0	114,0	115,0	116,0	U
18.	Upper face width	109,0	98,0	86,3	125,0	PM
19.	Average face width	103,0	91,0	100,0	106,0	PM
20.	Nose height	56,0	42,0	52,2	57,0	RM
21.	Width of the orbit (left)	41,8	38,0	40,0	42,0	PF
22.	The height of the lower jaw body	34,0	32,0	33,0	34,0	PM

Notes:
PF - probably female
PM - probably male
RM - reliable male
U – uncertain

When examining the skull to establish somatic gender, only 23 parameters out of 25 parameters accepted in forensic medical practice were identified. It was not possible to determine 2 parameters, due to the complete absence of the left branch of the lower jaw. There were 6 reliably male signs, probably male – 12, uncertain – 4 and probably female – 1.

When determining the age, it was found that: the teeth on the examined skull of the coronal suture were smoothed in the temporal and bregmatic parts, which corresponds to the age of about 30-40 years. At the same time, the interparietal suture is partially smoothed in the back, which corresponds to 20-30 years. The degree of occipital suture overgrowth was not evaluated due to the presence of anomalies in the development of the skull. The wedge-frontal, wedge-parietal and wedge-temporal sutures are smoothed, but not overgrown throughout, which corresponds to an age of less than 40 years. On the inside of the skull sutures, the coronal suture is overgrown, the rest of the sutures are smoothed, which corresponds to an age of less than 40 years. A comprehensive analysis of the data obtained showed that the degree of overgrowth of the skull sutures corresponds to the age of 20 to 40 years, however, taking into account the presence of anomalies in the development of the skull, the result of the study may have relative significance.

Discussion

The results obtained convincingly indicate that the anatomical and physiological features of the bones of the skull under study are characteristic of basilar impression, in which the base of the skull is flattened, the dimensions of the anterior and middle cranial pits at the level of the Turkish saddle are reduced, and the length of the Blumenbach slope is also reduced [13,14]. According to some authors, basilar impression is rarely isolated and often occurs in such genetic diseases as Hajdu-Cheney syndrome, Gorham syndrome and others [12,14,15]. Hajdu-Cheney syndrome is a rare autosomal dominant congenital connective tissue disorder characterized by severe and excessive bone resorption, leading to osteoporosis and a wide range of other possible symptoms [12]. Patients may have a peculiar phenotype, which characterized by a small lower jaw, a thick depression in the back of the head, osteoporosis, low height, dislocations of bones, a short neck, thick eyebrows, thick hair, high or low palate and low-lying ears (Figure 7, Figure 8) [16].

Gorham-Staut disease is an extremely rare disease characterized by osteolysis due to anomalous proliferation of blood vessels. In the case of the onset of the disease in childhood, skeletal deformities develop. Bone loss can occur both in one bone and in several, involving soft tissues in this process [13]. The course of the disease is variable and unpredictable. Involvement of the bones of the skull and spine in the process is unfavorable in prognostic terms. However, there are cases when people with this nosological form lived up to 70 years [11,13]. In our case, the bones of the arch and the base of the skull also had pronounced finger-like indentations (Figure 5), which indicates the presence of pronounced intracranial hypertension in the during his lifetime.

The racial affinity of the examined skull was carried out solely for the purpose of identifying human remains. However, one of the main problems of human identification is that the emergence of racial hybridity is not taken into account [7]. According to a number of authors, skeletons currently show features "typical" of two or more racial groups and it is very problematic to attribute them to one specific racial group [3,17]. World migration has further strengthened categorical ideas about biological variations, and some authors emphasize the important influence of socio-geographical environmental factors on the shape of the human skeleton [18]. At the same time, some authors emphasize that when conducting a forensic medical examination, one should be fully aware of the presence of many biological inaccuracies when identifying human remains [3,7]. However, there is also a point of view according to which it is necessary to form databases characterizing specific craniometric indicators of populations for each region separately, since the geographical movement of people occurs on a very large scale and leads to an increase in populations of mixed individuals [1,7,19,20].

The solution of the issue of the gender of bones has the greatest practical importance in forensic medical examination, because, in the identification process, it allows to reduce the number of wanted persons by half. However, in human populations, the degree of difference in size characteristics between men and women may be small [17,19]. The size range within each gender is widely superimposed so that only the smallest women and very large men are outside the overlap range of indicators of the opposite gender, in addition, it is necessary to take into account the racial and ethnic characteristics of the population [2,10,20]. Diagnosis of gender by the skull can be complicated by various factors, including environmental, occupational, as well as nutritional characteristics and pathological changes due to diseases [4,21,22]. The craniometric approach allows to unify the degree of human identification, however, the craniometric method of determining the gender of V.I. Pashkova used in the CIS countries requires certain additions and changes, since it was originally based on the research of skulls belonging exclusively to people of Russian nationality aged 22 years and older who lived in the north-west of Russia. In addition, this technique is not recommended for use in the study of deformed, fragmented skulls and remains exposed to high temperature, as well as the skulls of children [10]. According to many researchers, the significance of various signs is not the same, and therefore, the use of a combined application of craniometric and cranioscopic approaches is recommended [2,7,19].

The solution of the tasks is impossible without an integrated approach to the research of the totality of all diagnostic and identification features of the human skeleton. Based on the conducted research, it was found that the skull most likely belonged to a man of the Mongoloid race with the presence of separate Caucasoid features. The age of the unknown ranged from 20 to 40 years, but at the same time had only relative significance due to multiple congenital anomalies of the skull, the formation of which is due to the presence of a rare genetic disease during the life of the deceased, most likely the Hajdu-Cheney or Gorham syndrome. The detection of such a developmental anomaly has a great forensic importance, since the appearance of such people during their lifetime is very specific and contributes to rapid identification of the individual. Thus, it can be argued that a forensic medical research characterized by variability of results, cannot be used in isolation from auxiliary data indicating the presence during life of certain diseases affecting the structure of the skeleton when identifying a person. The expansion of the competence of a forensic medical expert is due to the demands of time, the expansion of the tasks of expertise and methods of their solution. The technologies applied within the framework of the conducted medical and forensic examination made it possible to successfully solve the issues of interest to the investigator and to work out all possible investigative versions of criminal events as objectively as possible.

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Prevalence of COVID-19 related factors among medical and emergency and critical care nursing students during COVID-19 pandemic outbreak

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Abstract

Background: COVID-19 pandemic outbreak has become an unprecedented threat for global mental health. Medical and nursing healthcare profession is among the most effected due to both COVID-19 and COVID-19 related measures.

Material and methods: This cross-sectional study aimed to examine undergraduate medical and emergency and critical care nursing students' mental health through attitudes, perception, anxiety, and coping strategies during COVID-19 outbreak.

Results: The study was conducted using online questionnaire. COVID-19 has led to instigate strong reactions amongst medical and emergency and critical care nursing student population (N=330). Results have indicated that medical and nursing students had adequate knowledge and high risk perception. Participants expressed un-satisfaction with the state sanctioned preventive strategies to curtail COVID-19. Participants showed unwillingness towards public and private academic institutions' introduced learning programs. Moreover, participants utilized a wide range of coping strategies to manage mental health problems during the COVID-19 related lockdown period.

Conclusion: It is highly imperative to address medical and emergency and critical care nursing students' mental health needs during and post-COVID-19 period.

Key words: COVID-19, coping strategies, medical and emergency and critical care nursing students, mental health

Introduction

COVID-19 (Coronavirus Disease – 2019) has spread across the 213 countries and territories across the world. COVID-19 has drastic impacts on physical and psychological mental health, apart from the devastating impact on all systems around the globe, among the general population [1,2]. Government of Pakistan closed down all academic institutes from March 11, 2020 to May 31, 2020. Later, the lockdown period was extended to April 7, 2020, which keeping in view of the condition across the country has been extended again. Despite the proactive and immediate preparedness at the initial stage of COVID-19 pandemic outbreak, latest relaxation in the lockdown has brought overwhelming surge in cases across all regions in Pakistan – 226 thousand cases as of the date. National Institute of Health (NIH) has implemented health care initiatives in the wake of COVID-19 outbreak in Pakistan [3,4]. Although, global health organizations stated earlier in the pandemic outbreak that the mental health impact on general population could become a secondary crisis, yet Pakistan is lagging behind in terms of mental health policy and psychological crisis intervention implementation [5].

COVID-19 pandemic outbreak, in itself, and the associated emergency measures of COVID-19, in addition, are creating mental health impacts and psychosocial issues among general public [6,7]. But the mental health

of youth has drastic impacts from the social distancing to closed academic institutes. Classes are postponed, students are being promoted based on previous results, and board examinations will be held accordingly and a mass online classes system are being introduced in Pakistan, for the first time. Majority of the academic intuitions are facing challenges with virtual learning from faculty to students. Pakistan's higher education commissions are striving to establish online management approaches and to promote virtual learning environment among students. Previous studies have highlighted the academic and mental health challenges on multifaceted and multifarious levels [8].

Youth's mental health from constant (mis)infodemics about the pandemic and its effects; self-isolation and social distancing; home confinement; closed socializing institutions and agents; and the anxiety (uncertainty and unpredictability) revolving around the emergency situation as a product of COVID-19 are having adverse impact on the psychosocial health of students. Symptoms such as general attitudinal change, anxiety, depression, fear, stress, and unhelpful coping strategies are some of the frequently occurring mental health concerns during COVID-19 pandemic outbreak [9,10]. One extensive study explored that 0.9% students exhibited severe symptoms of anxiety, 2.7% moderate symptoms and 21.3% mild symptoms. Anxiety and coping strategies are multifaceted phenomenon, varying from increased to decreased response based on the actual and perceived situations. Attitudes, anxiety and coping strategies could help determine help-seeking or help-denying; adherence towards lockdown policies or civil disobedience; behavioral modification or resistance; compliance with changed lifestyle or reluctance; adjustment or maladjustment; and wellbeing or mental health issues among the young population segment. To the best of our knowledge, this is the first study of prevalence of medical and emergency and critical care nursing students' mental health examined through attitudes, perception, anxiety and coping strategies during the COVID-19 pandemic. Considering the relevance of these conditions, this study aimed at assessing COVID-19 related factors amongst students such as attitudes, perception, anxiety and coping strategies of students during the COVID-19 pandemic in Pakistan. This study investigated and analyzed the mental health status of students during the COVID-19 pandemic outbreak in Pakistan: a) to evaluate the psychological situation of medical and emergency and critical care nursing students; b) to provide a theoretical framework for psychological intervention with medical and emergency and critical care nursing students; c) and provide a ground for the promulgation of local and global medical and emergency and critical care nursing student mental health policies.

Material and methods

This was a cross-sectional study conducted during the period of April 20 – May 20, 2020. The targeted sample was composed of undergraduate medical and emergency and critical care nursing students of local academic institutes. The participants in the study were sampled through cluster sampling. The sample consisted of 330 students from the undergraduate enrolled medical and emergency and critical care nursing. The mental health of students was assessed during the COVID-19 outbreak by using structured questionnaires. Self-structured questionnaires were used to collect the data. The instrument demonstrated high correlation, validity, reliability and Cronbach's alpha. Items included were "my constant thoughts about coronavirus", "my frustration towards people's lack of compliance" etc. Student participants were determined using the snowball sampling techniques. Participants who answered the online survey developed through Google forms with an appended consent form. The survey link was sent to the participants through social media platforms (Facebook, WhatsApp and Twitter). The research population consisted of individuals above 18 years in various academic institutes across the country. Statistical analyses were carried out using SPSS IBM-21 software. The institutional review board of the author's practicing medical college and hospital approved this study. All participants were provided with the informed consent appended with the study.

Results and Discussion

A total of 330 participants who completed the questionnaires, 212 (64.24%) were female participants, 100 (30.30 %) were male and 18 (5.45%) were members of the LGBTQI+ community. Participants belong to the age group of 20-25 years (176 or 53%) and single in terms of relationship status (313 or 94%) with family income less than a ten thousand Pakistani rupee per month (218 or 66%). And the majority of the participants' major subject was emergency nursing (75 or 22%). Majority of the participants (243 or 73%) were well aware of the epidemiology and transmission of COVID-19 including the modes of transmission through physical contact, touching, kissing, coughing and sneezing. Participants were aware of the primary symptomology of COVID-19 is fever and coughing (322 or 97.55%). And majority of the participants (303 or 91%) were well aware of the importance of preventive and precautionary strategies including staying at home, maintaining social distancing and self-isolation to curtail the spread of coronavirus among family, friends and community. Studies conducted so far have provided evidence of epidemiology and symptomology of COVID-19 through social contact as mainly transmission mode [11] with mild to severe symptoms [12] through symptomatic and asymptomatic transmission [13].

Participants' perception (206 or 62%) on the risks of COVID-19 and the importance of COVID-19 related precautionary measures showed the understanding of high risk level of COVID-19. Furthermore, participants' perceived following precautionary and preventive measures as highly effective in controlling coronavirus spread: staying at home, social distancing, sanitizing and washing hands, screening and testing, and the implementation of nationwide lockdown. Additionally, Rana et al (2020) and Mukhtar (2020) from Pakistan stressed upon the implementation of the lockdown measures as an effective tool to prevent the transmission of coronavirus in addition to the prevalence of mental health and psychological issues among general public. Participants' attitudes toward COVID-19 screening, treatment and vaccination indicate that the majority of the participants (268 or 81%) were willing to be vaccinated against coronavirus, while only a few number of participants (62 or 18%) rejected the possibility of vaccination. Those participants who were not willing to be vaccinated (150 or 45.45%) reported distrust in science and apprehension towards health risks and side effects. This is similar in line with the earlier studies' findings which indicated that the main concern of students' during the pandemic influenza H1N1 was related to the vaccinations' safety [14].

Study participants' reported dissatisfaction and distrust (135 or 40.9%) with the state's mitigation and actions to curtail the spread of the coronavirus in the community. Many participants (137 or 41.51%) reported less satisfaction with the information dissemination process ordained by the government, however, reported (184 or 55%) high satisfaction with the services of

medical health practitioners (doctors, nurses, and paramedical staff) of the frontline workers. This is divergent with the results of the study conducted at Australia (developed country) whose respondents reported satisfaction with the government's actions in handling of COVID-19 in Australia [15] (Table 1).

Table 1 Medical and emergency and Critical Care Nursing students' attitudes towards online programs during COVID-19 (n=330)

Reasons for saying 'yes'	%
To finish academic requirements	81.07
Misses academic environment	80.47
Online classes are convenient	54.44
Timely managed studies	53.25
Does not want to quit studies	42.01
Reasons for saying 'no':	
Unavailability of internet connection	75.48
Unavailability of computer	72.29
Unavailability of smartphones	61.78
Boring online modules	57.01
Difficulty in learning through online classes	41.40
Lack of contact with tutors	39.49

Further, attitude of medical and emergency and critical care nursing students' towards their education during the COVID-19 pandemic outbreak (as shown in table 1) indicated their affirmative reaction towards academic institutions' closing amidst COVID-19 (265 or 80%), and many participants (217 or 65.85%) approved with the extension of the classes to the next semester until the end of COVID-19 pandemic outbreak. However, many participants (196 or 59%) displayed apprehension with the online learning program. These participants further reported the reasons of dissatisfaction due to unavailable or unstable internet connection (238 or 72%). These findings are parallel with the results of Ja'ashan (2015) which indicated that the majority of the students expressed dissatisfaction with the online learning program due to internet connection problem [16] (Table 2).

Furthermore, the majority of the participants exhibited anxiety during the period of COVID-19 lockdown as shown in table 2. Majority of the medical and emergency and critical care nursing students (206 or 62.42%) were concerned about financial resources and food availability and other participants (54%) reported limited social contact, large gatherings and social distancing. These findings are parallel with the research which showed individuals were concerned about their families and acquaintances for coronavirus transmission during the on-going peak-time COVID-19 pandemic outbreak [17]. Studies moreover affirmed the impact of COVID-19 on the mental health of students [18] (Table 3).

In order to cope with the anxiety of the COVID-19 pandemic outbreak, participants responded a range of coping strategies and techniques as shown in. During the peak time of COVID-19 pandemic outbreak, participants reported following rigorous standardized infection control measures (297 or 90.19%) and 80% reported limited social contact and public mass gatherings to minimize public COVID-19 exposure. This study's findings are similar with the study of other studies which indicated that during disease outbreaks, individuals tend to follow strict precautionary infection personal protective measures [19-21].

The current study aimed at assessing attitudes, perceptions, anxiety and coping strategies of students indicated that medical and emergency and critical care nursing undergraduate students

Table 2 Medical and emergency and Critical Care Nursing students' anxiety (Impact of COVID-19 Scale ICVS) (Mukhtar et al., 2020) related to COVID-19 pandemic outbreak (n=330)

Sr. No	Items (I am worried about)	(%)
1	Getting infected from coronavirus.	62.64
2	My acquaintances getting infected of coronavirus	56.04
3	Our country's healthcare system is insufficient	54.15
4	Violation of coronavirus quarantine	51.70
5	That coronavirus health instructions is not followed	50.75
6	About feeling lonely	62.64
7	About the coronavirus-related death news	48.30
8	About the lack of funeral arrangement after coronavirus-related death	48.30
9	Limited scientific knowledge about coronavirus	45.85
10	My constant thoughts about coronavirus	44.15
11	My frustration towards people's lack of compliance	37.36
12	If someone coughed or sneeze near me, I feel conscious of getting infected of coronavirus	35.66
13	Thinking or hearing about coronavirus caused aches and pains in my body	34.91
14	I have difficulty in breathing because of coronavirus	34.31
15	I have troubled sleep because I worry about the coronavirus	33.58
16	Feeling bored	62.64
17	I regularly search internet for coronavirus related news	48.30
18	I spend more time on social media coronavirus related reports	45.85
19	I daily watch coronavirus related news on television	44.15
20	About restricted daily routine	50.75
21	Coronavirus affects my social relationships	62.64
22	Travelling spreads coronavirus	50.75
23	Visiting non-native's shops will make me affected	23.21
24	In-direct contact with foreigners can make me affected of coronavirus	22.25
25	Native traveler can make me infected of coronavirus	19.06
26	Foreigner can make me infected of coronavirus	19.06
27	Foreigners are more susceptible of coronavirus because of their lifestyle	18.68
28	Foreigners are more susceptible of coronavirus because of their faith	18.49
29	Foreigners are more susceptible of coronavirus because of their country origin	18.45
30	Visiting any other country will spread coronavirus	12.64
31	Food shortage due to coronavirus	12.30
32	My family's starvation due to coronavirus	11.21
33	My family will not survive of poverty after coronavirus lockdown	8.87

Table 3 Medical and emergency and Critical Care Nursing students' personal coping mechanisms related to COVID-19 pandemic outbreak (n=330)

Sr. No.	During the lockdown period	%
1.	To follow strict protective measures	90.19
2.	To research about COVID-19 mechanism and prevention	80.38
3.	Avoid public mass gatherings	78.87
4.	Praying and worship	68.87
5.	Chat with family and friends	58.87
6.	Using social media accounts	48.87
7.	Avoid COVID-19 related news	29.06
8.	Reschedule daily activities	22.45
9.	Seeking help and support	15.09
10.	Emotional catharsis	8.87

were aware of the COVID-19 pandemic related information even though there were gaps in the knowledge. Medical and emergency and critical care nursing students responded generally positive attitudes, perceptive understanding, anxiety towards governmental actions and various coping strategies to manage COVID-19 related factors. However a considerable number of medical and emergency and critical care nursing students displayed distrust and reluctance towards the COVID-19 vaccination. In the academic and educational context, medical and emergency and critical care nursing students were apprehensive towards online learning programs due to technology's unavailability and financial reasons. Participants further respond dissatisfaction with the government's role in curtailing COVID-19. Although medical and emergency and critical care nursing students expressed anxiety towards COVID-19 related factors yet they were well equipped with the coping strategies to manage the anxieties of COVID-19 related factors.

Conclusion

The COVID-19 pandemic outbreak posed significant threat for general population students, however, medical and emergency and critical care nursing students' are impacted on multiple levels especially among communities of low and middle income countries (LMICs). Government should strengthen their approaches to manage, disseminate information, timely assess, effectively test and vaccinate concerning any future outbreaks of epidemics or pandemics. Institutions should introduce innovative and helpful strategies to promote and address the mental health issues of students during and post the COVID-19 pandemic outbreak. Pakistan is still developing online learning and class modules and paradigm shift in pedagogical delivery. State should ensure the availability of educational support and develop policies considering the health emergences in the future.

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