Clinics in Oncology

Research Article
Published: 10 May, 2021

Protocolized Management of Pain, Sedation, and Delirium in the Mechanically Ventilated Oncology Population

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Abstract

Purpose: To test the hypothesis that a protocolized approach to Pain, Agitation, Delirium (PAD) management in mechanically ventilated (MV) oncology patients would reduce the initiation and doses of sedatives used during intubation without increasing analgesic requirements.

Materials and Methods: PAD was managed using a protocol focusing on analgesia-first sedation, executed by a multi-disciplinary team. Data was obtained on interventions from routine assessments for PAD and treatment was based on protocol recommendations.

Results: 204 patients were identified with 68 patients pre- and 91 patients post-protocol meeting inclusion criteria in the final analysis. Patients initiated on benzodiazepine infusions decreased from 31% to 5% ($p<0.05$). Total average Fentanyl Equivalent (FE) received during intubation remained significantly less post-protocol. No statistically significant difference was observed in FE requirements during intubation for opioid tolerant patients. A non-significant decrease in duration of MV was observed in patients not terminally extubated (6 ± 7 *vs*. 4 ± 4, $p=0.17$).

Conclusion: Pain and agitation can be successfully managed in the oncology population by using a protocolized, multi-disciplinary approach that applies the recommendations in Society of Critical Care Medicine© guidelines. This approach may lead to decrease use of sedatives and analgesics, preventing harmful long-term effects in an opioid-tolerant population.

Keywords: Pain; Agitation; Delirium; Sedation; Oncology; Mechanical ventilation

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Received Date: *13 Apr 2021*
Accepted Date: *07 May 2021*
Published Date: *10 May 2021*

Citation:
Patel T, McGovern E, McGovern JK, Mack KL, Hoag JB. Protocolized Management of Pain, Sedation, and Delirium in the Mechanically Ventilated Oncology Population. Clin Oncol. 2021; 6: 1805.

Introduction

Appropriate management of Pain, Agitation, and Delirium (PAD) in an oncology critical care setting optimizes timely recovery and prevents long-term complications but is distinctively challenging. Exposure to surgery, chemotherapy, and radiation augmented by characteristics of malignancy including boney metastases, spinal cord compression, and chemotherapy-induced peripheral neuropathy place the oncology population at increased risk of underlying pain prior to critical illness [1]. Therefore, pain associated with the critical care setting is often additive and treatment must address all sources. As pain is an individualized experience, accurate reporting is complex and can be confounded in an Intensive Care Unit (ICU) by altered mental status, Mechanical Ventilation (MV), sleep disruption, and mobility issues [2]. Effective analgesia while avoiding over sedation can decrease long-term complications including delirium and other physical impairments [3]. With adequate pain control, sedation can be required for management of agitation; however, the use of non-benzodiazepine sedatives has been proven to improve short-term outcomes [3-5]. In order to optimize the management of PAD_1 a standardized, protocolized approach to guideline adherence supports ideal clinical and economic outcomes [6-9]. Unfortunately, existing PAD_1 guidelines provide minimal guidance for the oncology population, which overall remains understudied within critical care [4]. The aim of this study was to evaluate a protocolized approach to PAD_1 management that focused on analgesia-first sedation by applying a stepwise approach in dose escalation of analgesics and sedatives. It was hypothesized that by implementing this strategy to manage PAD_1, the overall initiation and doses of sedatives used during the intubation course could be reduced [10,11].

Materials and Methods

This protocol was approved by the Institutional Review Board (IRB) of Cancer Treatment Centers of America® with a waiver of consent.

Patient population

This study was conducted at a mixed medical-surgical ICU_2 of a single subspecialty cancer hospital. All patients mechanically ventilated >1 day and ≥ 18 years of age were included. Those receiving neuromuscular blockade were excluded. Additionally, patients terminally extubated were excluded from the analysis of MV_3 duration. Baseline data obtained on the patients is provided in Table 1.

Protocol development and implementation

Prior to this initiative, patients received a continuous infusion of an analgesic and a sedative upon intubation. No protocolized approach was used for bolus dosing and assessment of pain and agitation was inconsistent. All intubated patients meeting inclusion and exclusion criteria between November 2013 and December 2014 comprised the control group. A comprehensive protocol incorporating multi-modal interventions while diminishing long-term consequences, aimed to identify methods for optimally assessing and managing PAD_1. Extensive education, consisting of lecture, printed references, and on-going discussions during daily medical rounds, was delivered by the ICU_2 pharmacist to nurses, physicians, physical/occupational therapists, speech therapists, and respiratory therapists. Binders containing assessment tools (Confusion Assessment Method in the ICU-CAM-ICU, Critical Pain Observation Tool-CPOT, Glasgow Coma Scale, Richmond Agitation Sedation Scale-RASS) were also created and placed in each ICU_2 patient room for ease of access by nursing [12-15]. After this focused education, the protocol was adapted into our institution's electronic health record (Allscripts Sunrise Clinical Manager™ Version 15.1, Chicago, IL) for order entry, monitoring, data capture, and clinical documentation. An order-set containing options for bolus and continuous infusion sedatives and analgesics as well as tasks for each discipline involved was created. Tasks were automatically and appropriately timed to ensure holding of sedation to perform spontaneous awakening and spontaneous breathing trials (SATs and SBTs) in a consistent, safe manner. The intervention group included all intubated patients meeting inclusion/exclusion between October 2015 and March 2017. The duration of each phase was selected to match sample sizes.

Endpoints

The primary endpoint was compliance to the analgesia-first sedation method by which patients' pain was treated with bolus dosing and appropriately escalated to reduce use of excessive analgesia and sedation. This was measured by the number of patients who received bolus dosing, the day of intubation patients were initiated on continuous analgesia, and number of patients initiated on benzodiazepine *vs.* non-benzodiazepine sedatives. Table 3 provides secondary endpoints included in the study.

Statistical analysis

Data is presented as means (± standard deviation) unless otherwise specified. Descriptive statistics are provided for groups. Pre-protocol (control) and post-protocol (intervention) data points are compared using two-sample t-tests assuming unequal variance to determine statistical significance. Results were declared statistically significant with a p-value <0.05.

Pain, agitation, and delirium

Pain was assessed every 4 hours using the pain scale of 1 to 10 in all patients physically or verbally able to express a pain score. The Critical Care Pain Observation Tool (CPOT) was used if the patient was not able to express a pain score [16]. The analgesic agents included fentanyl, morphine, and hydromorphone with usage expressed in Fentanyl Equivalents (FE). FE_5 was calculated using the following ratio: Fentanyl 0.1 mg intravenous to morphine 10 mg intravenous to hydromorphone 1.5 mg intravenous: hydromorphone 7.5 mg oral: Oxycodone 20 mg oral [17]. Methadone was converted to morphine equivalents and then converted to FE_5. The specific analgesic agent initiated was at the discretion of the treating physician with consideration of the patient's home regimen if such agents were used prior to admission. Upon intubation, the patient was initiated on a scaled, escalating dose, and "as needed" analgesia regimen. If the patient was on long-acting analgesia or patient-controlled analgesia prior to admission, a continuous analgesic infusion was immediately initiated in addition to the bolus regimen. Initial management and acute episodes of pain were treated with boluses rather than increasing the rate of continuous infusion. If the patient required a specific amount of analgesia *via* boluses within a short time frame, then a continuous infusion was initiated, or the rate was increased.

Agitation and sedation were assessed every four hours using the Richmond Agitation and Sedation Scale (RASS) [12,13]. Dexmedetomidine was the first-line anxiolytic followed by propofol for refractory agitation. Benzodiazepines were avoided when possible. The Bispectral Index and Glasgow Coma Scale were utilized hourly and every four hours [18], for assessment of mental status and level of sedation during intubation. Each morning, patients were screened for a Spontaneous Awakening Trial (SAT). If the screen failed, infusions were reduced until a RASS6 score of >-2 was achieved if clinically appropriate. If the SAT_7 was successful, a Spontaneous Breathing Trial (SBT) was performed.

The Confusion Assessment Method in the Intensive Care Unit (CAM-ICU) was performed three times daily on patients during waking hours [14]. The Barthel Index and Cognistat tests were employed to assess functional outcomes. Results were recorded on the earliest day of intubation that each test could be performed, then the subsequent three, six, and 12 months following extubation. If >2 assessments were performed, the first and last score were compared to determine a change in cognitive function or physical dependence. Changes in Cognistat scores were reviewed for three areas: Memory, orientation, and attention. Rehabilitation activities were performed when appropriate throughout intubation period. All patients received cognitive/speech therapy interventions regardless of level of cognitive function to achieve improvement in or maintain level of function and prevent decline. Furthermore, the interventions were customized to degree of cognitive severity and patient participation.

Respiratory parameters collected were SBT_8 screen and post-assessments, Rapid Shallow Breathing Index (RSBI), Negative Inspiratory Force (NIF), leak tests on the day of extubation, and the number of times a patient was placed on Continuous Positive Airway Pressure (CPAP) or Pressure Support (PS) daily [19]. An SBT_8 screen was required prior to initiating an SBT_8 to ensure safety. The screening criteria mimicked the criteria required by nursing for the post-SAT_7 assessment, ensuring cooperative, safe continuity of care. If the patient was placed on an SBT_8, the respiratory therapist was responsible for documenting a post-assessment to describe pass or failure.

The Barthel Index is used to evaluate ten various assessments of daily living and mobility activities in the following categories: Feeding, bathing, grooming, dressing, bowel control, bladder

Table 1: Patient characteristics.

Characteristic	PRE-protocol (n=68)	POST-protocol (n=91)
Male, n (%)	30 (44%)	33 (36%) [NS]
Age (yrs), mean ± SD[a]	55 ± 11	59 ± 10 [NS]
Medical *vs.* surgical patient	40 Medical (59%)	41 Medical (45%)
	28 (41%)	50 surgical (55%) [NS]
Cancer type or stage		
Colorectal, Hepatobiliary, Pancreatic, Liver, Endocrine, Adrenal	23	31 [NS]
Lung	18	24 [NS]
Head/neck, Adenocarcinoma, Brain, Neuroendocrine, Unknown primary	9	9 [NS]
Breast, prostate, GYN	8	19 [NS]
Renal, bladder	6	2 [NS]
Sarcoma, myeloma, lymphoma, hematologic, melanoma, mediastinal, squamous cell	4	6 [NS]
APACHE[b] IV upon ICU admission, mean ± SD	79 ± 23	81 ± 28 [NS]
Actual mortality upon ICU discharge, n (%)	9 (13%)	35 (39%) *
Patient on home analgesics (short & long-acting), n (%)	58 (85%)	56 (62%) [NS]
Patient on home opioid analgesic (%)	55 (81%)	52 (93%) [¥]
Patients on at least one home long-acting opioid analgesic, n (%)	34 (62%)	20 (38%) [¥]
Home anti-anxiety and/or anti- depressant, n (%)	22 (32%)	36 (40%) [NS]

[a]SD: Standard Deviation; [b]APACHE: Acute Physiology and Chronic Health Evaluation
* p<0.05; [¥] p<0.001; [NS]: Not Significant

control, toileting, chair transfer, ambulation, and stair climbing. The calculated score can then be used to determine the patient's degree of dependence and predict the level of assistance needed post-discharge. The assessment tool was actively being used by the rehabilitation department prior to the protocol implementation and therefore, was incorporated into the methods of this study to determine if it would provide any meaningful conclusions about the change in the patients' level of physical function due to mechanical ventilation.

The assessment tool has been validated primarily in stroke patients with no current studies evaluating its use in cancer patients. However, with lack of any such tool available specific to this population, it was determined it would be appropriate to incorporate the assessment and determine its value upon completion of the study. Based on observations during this study another assessment tool may be considered in the future.

Barthel total score ranges from 0 to 100

0-20 Total Dependence

21-60 Severe Dependence

61-90 Moderate Dependence

91-99 Slight dependence

100 Independence

The Cognistat test is a seven-point scale that measures mild cognitive dysfunction in adult patients with dementia. It has been studied in numerous patient groups with various neurological deficits. However, there are currently no studies performed in the mechanically ventilated oncology population. This test was included in the protocol and performed by the speech therapists to detect if there was improvement, decline or no change in cognitive function during and after mechanical ventilation. Although Cognistat is not validated in cancer patients, it has been studied extensively in a wide range of neurological injuries and diseases. It was instituted as a part of this protocol to provide data on the degree of cognitive impairment, which is not obtained from the CAM-ICU_9 delirium assessment currently supported by national guidelines. Validation of the Cognistat test will need to be performed in the future to make any direct correlations between results of the assessment and the patients' true levels of cognitive function.

Cognistat assessment interventions

Alertness, Orientation, Attention:

- Delirium reduction strategies via environmental clues such as having lights on/natural light during the day
- Visual aids such as calendars

Memory:

- Visual aids such as reminder board and daily memory journal
- Memory strategy training

Language:

- If intubated, establishing a reliable means of expressive communication for the patient.
- Thought organization
- Word finding strategies
- Reading comprehension strategies

Executive functions:

- Reason strategies
- Problem solving- safety awareness strategies
- Functional planning and self-monitoring

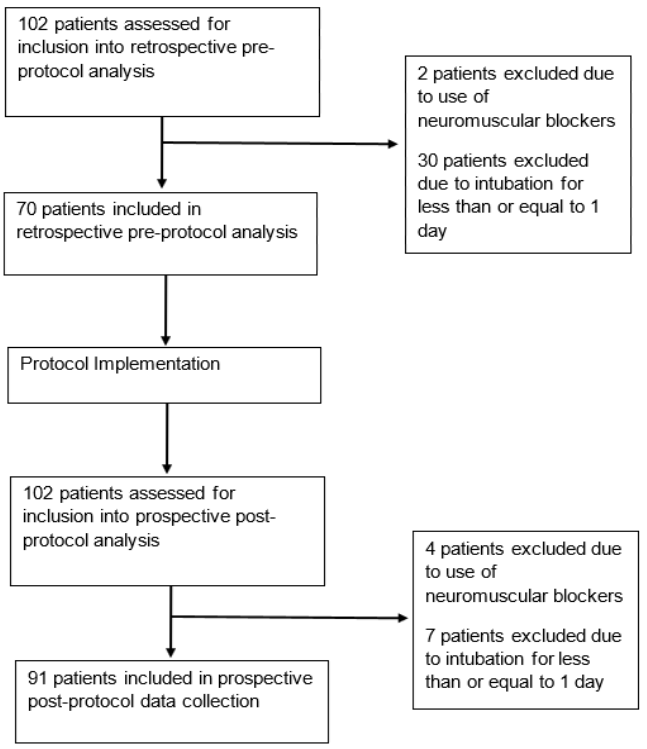

Figure 1: Patients included in and excluded from pre- and post-protocol analysis.

Results

Data was collected on 204 patients (102 pre- and 102 post-protocol implementation). Sixty-eight patients' pre-protocol and 91 post-protocol met criteria and were included in the final analysis (Table 1). The duration of MV_3 was analyzed in 61 pre-protocol and 81 post-protocol. There were no statistically significant differences between groups, except the control group was younger (p=0.03) and had greater use of long-acting home analgesia (p=0.0001) (Figure 1).

Pain, agitation, and delirium

Comparisons of the primary outcome pre- and post-protocol implementation are displayed in Table 2. Post-protocol implementation, less patients were initiated on continuous analgesic infusions (59% *vs.* 40%,) and if initiated, were started later in the patient's intubation course (day 1.0 ± 0.7 *vs.* 2.0 ± 2.0, p<0.05). More patients post-protocol were also initiated on bolus as needed opioid analgesia (63% *vs.* 90%, p<0.05). However, the average total FE_5 received during intubation still remained significantly less (14,446 ± 26,967 mcg *vs.* 5,738 ± 9,816 mcg, p=0.02). The number of patients initiated on a benzodiazepine infusion as the initial sedative decreased from 31% to 5% (p<0.05). Furthermore, the infrequent use of continuous infusions post-protocol did not increase the number of patients receiving bolus benzodiazepines but remained low (60% *vs.* 34%, p<0.05). Despite less use of analgesia, post-protocol pain assessments resulted in 86% of patients with a pain score of <5 or a $CPOT_4$ score ≤ 3. The number of patients initiated on continuous sedation on day one of intubation did not demonstrate a substantial difference, (43 (63%) *vs.* 54 (65%), p=0.62) likely due to more patients receiving non-benzodiazepine sedatives post-protocol. Table 3 summarizes the key secondary outcomes observed in this study. The average rate for dexmedetomidine (0.4 ± 0.2 *vs.* 0.6 ± 1.5, p=0.6), propofol (26 ± 15 *vs.* 22 ± 10, p=0.09), and midazolam (3 ± 1 *vs.* 4 ± 2, p=0.25) did not significantly differ between both groups. Given that the cancer population is more often administered opioids and anti-anxiety/anti-depressants at home, it was crucial to determine if such prior use had any influence on the amounts of analgesics and sedatives required during intubation. Less FE_5 were administered to patients that did not use opioids at home, but this was not statically significant (PRE: 8,440 ± 16,556 *vs.* 13,760 ± 27,487, p=0.37; POST: 3,925 ± 8,467 *vs.* 6.655 ± 10,405, p=0.17). The difference in the total FE administered to medical versus surgical patients was also not disparate.

Due to the low number of accurate $CAM\text{-}ICU_9$ assessments performed, no meaningful conclusion or data could be reported for incidences of delirium. However, a single full Cognistat assessment was performed on 8 patients (9%) (Table 4). A total of 40 patients (44%) received at least one assessment in memory, orientation, and attention. Decline in cognitive function in these areas occurred in only 4 comparisons (7%), and all other assessments showed stability or improvement. However, due to small sample size, statistical comparisons were not performed. A Barthel Index score was calculated for 30 patients (33%) post-protocol (Table 3). Most patients had single assessments; however, >2 assessments were performed in 17 (19%) patients. Nine patients (53%) had improvement in category of dependence, 7 (41%) remained within the same category, and 1 (6%) patient declined in dependency. There was clinically significant decrease in the duration of intubation (6 ± 7 *vs.* 4 ± 4, p=0.17) (Table 3), and no direct correlation was revealed between the duration of intubation and duration of benzodiazepine use (r=0.42).

Discussion

This study sought to determine if the recommendations of the Society of Critical Care Medicine© PAD_1 guidelines could be effectively applied to an oncology population and how PAD_1 management differs in non-cancer ICU_2 patients. Our findings emphasize the importance of accurate, consistent pain assessments to individualize pain management after initial protocol orders are employed. Although fewer analgesic medications were utilized post-protocol, 86% of patients' average pain scores remained below 5 ($CPOT_4$ ≤ 3), suggesting that pain remained adequately controlled on less analgesics. To represent adequate pain control, on a pain scale of 1 to 10, a score of <5 was chosen, as <4 represents "mild" pain. A $CPOT_4$ score of ≤ 3 was selected because scores >3 suggest pain sources should be evaluated and treatment enhanced [16]. It was presumed that less use of continuous opioid infusions would result in a trend towards lower risk of delirium; unfortunately, this could not be confirmed in this study due to inconsistency of $CAM\text{-}ICU_9$ assessments. On average, post-protocol continuous analgesic infusions were started one day later than pre-protocol, with significantly more patients receiving bolus dosing, allowing for less continuous analgesic requirements. Bolus doses given prior to each increase in continuous analgesic infusion rate cannot be confirmed. However, the decrease in analgesic administered post-protocol may be due to the strategic use of bolus dosing prior to initiating or increasing continuous forms of analgesia.

One unique characteristic of the cancer population is higher opioid tolerance due to frequent use of pain medications prior to critical illness. This study sought to determine if patients who use opioids at home would require a greater amount of FE_5 during intubation. A trend towards greater total usage of FE_5 was observed

Table 2: Primary outcomes.

Outcome	PRE-protocol (n=68)	POST-protocol (n=91)
Patients initiated on continuous analgesic infusion, n (%)	40 (59%)	36 (40%)¥
Day of intubation continuous analgesic initiated, mean ± SD	1 ± 0.4	2 ± 2*
Percent of intubation course on continuous analgesic infusion (% mean ± SD)	69 ± 43	39±43¥
Patients initiated on bolus as needed opioid analgesia (oral and IV) (%)	43 (63%)	82 (90%)¥
Patients initiated on bolus as needed non-opioid analgesia (%)	32 (47%)	27 (30%)*
Average total fentanyl equivalent received during intubation (continuous plus bolus) mcg, mean ± SD	14,446 ± 26,967	5,738 ± 9,816*
Patients initiated on intermittent benzodiazepines (oral and IV) (%)	41 (60%)	60 (66%) [NS]
Patients initiated on continuous benzodiazepine as initial sedative agent (%)	21 (31%)	5 (5%)¥
Patients initiated on a non-benzodiazepine anxiolytic as initial sedative (%)	20 (29%)	61 (67%)¥

[c]CPOT: Critical Care Pain Observation Tool
* p<0.05; ¥ p<0.001; [NS]: Not Significant

Table 3: Secondary outcomes.

Outcome	PRE-protocol (n=68)	POST-protocol (n=91)
Sedation		
Percent of intubation course on continuous infusion benzodiazepine, mean ± SD	68.8 ± 28	61.8 ± 36.7 [NS]
Average total daily dose of midazolam received (infusion plus bolus medication)	89 ± 126	41 ± 113 *
Average total daily additional benzodiazepine doses received (mg)	Alprazolam: 3	Alprazolam: 2 [NA]
	Clonazepam: 1	Clonazepam: 2 [NA] Diazepam: 90 [NA]
	Lorazepam: 6	Lorazepam: 3 [NA]
Analgesia		
Average total fentanyl equivalent in medical *vs.* surgical patients (mcg)	13,622 ± 28,198 *vs.* 11,487 ± 22,195	4,553 ± 8,8819 [NS] *vs.* 7,129 ± 10,542 NS
Average total fentanyl equivalent in patients previously on home opioids *vs.* not on home opioids (mcg)	13,760 ± 27,487 *vs.* 8,440 ± 16,556	6,655 ± 10,405 [NS] *vs.* 3,925 ± 8,467 [NS]
Delirium		
Patients on anti-psychotic during intubation (not taken prior to admission)	4 (6%)	4 (4%) [NS]
Patients on anti-depressant and/or anti-convulsant/manic medication during intubation (%)	6 (9%)	8 (9%) [NS]
Respiratory		
Duration of mechanical ventilation (days), mean ± SD	6 ± 7	4 ± 4 [NS]
Rehabilitation		
Cognistat score changes	N/A	See Table 4 [NA]
Average day of intubation Cognistat test performed	N/A	(3 ± 2) [NA]

[d] RASS: Richmond Agitation Sedation Scale; [e] CAM-ICU: Confusion Assessment Method for Intensive Care Unit
* p<0.05; ¥ p<0.001

Table 4: Post-protocol Cognistat assessment score changes.

Assessment	Performance Measure (total patients per category)			Total per category of change
	Memory	Orientation	Attention	
Improvement	5/20 (8.3%)	7/20 (35%)	10/20 (50%)	22/60 (37%)
No change	12/20 (60%)	13/20 (65%)	9/20 (45%)	34/60 (57%)
Decline	3/20 (15%)	0/20 (0%)	1/20 (5%)	4/60 (7%)
Total Assessments per category	20	20	20	60

*Assessment performed 2 or more times in total of 20 patients; 6 patients demonstrated improvement in more than one area

in patients taking opioids prior to admission pre- and post-protocol, but no statistically significant difference was observed. Analgesia usage in medical versus surgical patients was also included to determine if a difference was observed to assist in predicting requirements for future patients in order to improve post-operative pain management. No significance was observed between these two patient groups. As over sedation may mask undertreated pain, light levels of sedation are preferable for improved long-term outcomes, an ability to perform more frequent neurocognitive assessments, early mobilization, and earlier rehabilitation minimize negative long-term outcomes including mortality, cognitive decline, and psychological complications [20]. Furthermore, benzodiazepine-based sedative regimens have been associated with delirium and over-sedation, with an increase in ICU_2 length of stay [4,21]. As a result of protocol implementation, a significant decrease in benzodiazepines was observed, allowing the primary management to be focused on pain control. With less benzodiazepine, it was expected that patients would exhibit alertness and lower $RASS_6$ scores; however, no difference was

able to be evaluated due to inconsistent documentation of $RASS_6$ scores in the pre-protocol group.

Depression in the cancer population is common, as evidenced by one study demonstrating 47% of cancer patients exhibit psychiatric disorders, and nearly 68% of those patients were depressed or anxious [22]. Therefore, it was unsurprising that 34% and 40% of pre- and post-protocol patients in this study were on anti-anxiety or anti-depressants. Despite this prevalence, this study demonstrated that patients with such pre-existing conditions could still be safely managed with minimal to no use of benzodiazepines. Additional studies suggest non-benzodiazepine-based regimens are associated with a 1.9-day shorter duration of intubation [21]. Unfortunately, our study did not include a large enough population and was not intended to detect a difference in duration of MV_3. It is possible that the trend towards shorter intubation duration was due to a combination of strategies used in the protocol. A weak correlation between the number of days a patient had a $RASS_6$ >-2 and duration of intubation (r=0.7) was discovered, suggesting patients being more awake may not always result in sooner extubation. Despite that the RASS6 scores did not reflect lighter levels of sedation, the team was able to extubate patients on average two days sooner than pre-protocol.

With evidence of long-term physical and cognitive deficits observed after intubation, we sought to incorporate assessment scales that could evaluate function early in the intubation course and post-extubation to identify any negative consequences of intubation or positive influences from distinct interventions. The Barthel Index assesses functional independence. Although it has not been validated in ICU_2 oncology population, our institutional experience suggests benefit (unpublished data), and therefore was applied to our study group. The goal was to detect deterioration in patients' physical abilities following extubation and after ICU_2 discharge. Cognistat is a neurocognitive function test extensively studied in multiple neuropsychiatric conditions and was employed routinely by the speech therapists. Cognistat test was incorporated in the protocol to provide insight on the patients' degree of cognitive dysfunction and areas of cognitive ability that were affected by intubation. Unfortunately, a Barthel Index and Cognistat assessment could only be performed on a small number of patients, thus effects on these outcome measures remains hypothetical and an area for future investigation. Nevertheless, most patients that received rehabilitation intervention either maintained or improved their functional status during the intubation course.

There were several limitations that made it challenging to confirm the true impact of the protocol and strategies implemented. Because this study was performed in a "real world environment," we suffered from the effects in several areas of incomplete or undocumented data. Due to the protocol introducing the use of $CPOT_4$ for pain assessments in addition to a pain scale, the documented pain scores pre- and post-protocol could not be compared. Therefore, it cannot be concluded if the patient's pain was better treated using the strategies employed in the protocol. Similarly, pre-protocol $RASS_6$ scores were inconsistently documented with the same frequency per day as they were post-protocol; therefore, days on which a patient's $RASS_6$ was <-2 may have been missed pre-protocol, skewing the results. Although consistently performed during the trial, SAT_7 and SBT_8 checklists were inconsistently completed in the electronic health record, making analysis of reasons for failure difficult to assess. The measured level of delirium suffered similarly from documentation inconsistencies, not allowing for appreciation of the effects of this protocol on delirium. Despite missing data from the $CAM\text{-}ICU_9$, the Cognistat test provided insight on other areas of cognitive dysfunction. After the first day of intubation, a total of 159 assessments in memory (n=30), orientation (n=53), and attention (n=34) were performed and 65%, 83%, 69% of memory, orientation, and attention assessments, were better than or equal to a level of mild dysfunction. Although this data does not confirm delirium was not experienced during intubation, it could suggest the majority had less than moderate cognitive dysfunction.

The Barthel assessment was introduced to assist in identifying physical deterioration. Unfortunately, as the assessment was being performed throughout the study, the physical and occupational therapists noticed the score may not have always been reflective of the patient's true level of dependence. Furthermore, many patients were lost to follow up or expired before assessments could be performed after ICU_2 discharge. Therefore, data was limited to a short period of time and no reasonable conclusions could be drawn about long-term quality of life and physical function. Future research should consider investigating implementation of strategies identified in the Society of Critical Care Medicine updated guidelines, such as the ICU_2 Liberation Bundle, in the oncology critical care setting not only during intubation, but also post-discharge when patients resume anticancer therapy. With the limitations identified, several steps will be taken to improve the protocol interventions, including re-education to ensure patients receive the maximum impact from such interventions.

Conclusion

Based on the outcomes of this study, it is important that clinicians recognize the Society of Critical Care Medicine PAD_1 goals should be the same for cancer patients. The oncology patients differ from those included in prior similar studies in that the majority have underlying sources of pain, anxiety, and depression that must carefully be considered upon selecting the most appropriate therapy during intubation. If preexisting levels of tolerance or chronic use of opioids prior to admission are reviewed, less potential harm and risk of uncontrolled pain can be avoided, increasing the likelihood for successful outcomes. This study demonstrated that PAD_1 can be successfully managed in the oncology population by using a protocolized, multi-disciplinary approach. Despite a higher opioid exposure in this population, analgesics can still be used at lower doses to achieve acceptable levels of pain control while reducing use of potentially harmful sedatives. Implementation of a protocol as the one employed in this study paves the way for other components of the ICU_2 Liberation Bundle to be incorporated into the routine care of ICU_2 cancer patients and positively impact their recovery and quality of life.

Abbreviations

$_1$ Pain, Agitation, and Delirium

$_2$ Intensive Care Unit

$_3$ Mechanical Ventilation

$_4$ Critical Care Pain Observation Tool

$_5$ Fentanyl Equivalent

$_6$ Richmond Agitation and Sedation Scale

$_7$ Spontaneous Awakening Trial

$_8$ Spontaneous Breathing Trial

$_9$ Confusion Assessment Method-Intensive Care Unit

Acknowledgement

The following individuals were instrumental in the success of this project: Dana Wright, Sharon Barniak, Sarah Fulcher, Meredith Grigsby, Joseph Domanico, Kellie Joseph, Dean Howarth, and Stacie Gaige.

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