ORIGINAL ARTICLE

Beta-blockers for the treatment of problematic hemangiomas

Vishal K Sharma BSc MD[1], Frankie OG Fraulin MD FRCSC[1,2], Danielle O Dumestre[3], Lori Walker MD FRCPC[4], A Robertson Harrop MD MSc FRCSC[1,2]

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OBJECTIVE: To examine treatment indications, efficacy and side effects of oral beta-blockers for the treatment of problematic hemangiomas.

METHODS: A retrospective review of patients with hemangiomas presenting to the Alberta Children's Hospital Vascular Birthmark Clinic (Calgary, Alberta) between 2009 and 2011 was conducted. The subset of patients treated with oral beta-blockers was further characterized, investigating indication for treatment, response to treatment, time to resolution of indication, duration of treatment, occurrence of rebound growth and side effects of therapy.

RESULTS: Between 2009 and 2011, 311 new patients with hemangiomas were seen, of whom 105 were treated with oral beta-blockers. Forty-five patients completed beta-blocker treatment while the remainder continue to receive therapy. Indications for treatment were either functional concerns (68.6%) or disfigurement (31.4%). Functional concerns included ulceration (29.5%), periocular location with potential for visual interference (28.6%), airway interference (4.8%), PHACES syndrome (3.8%), auditory interference (0.95%) and visceral location with congestive heart failure (0.95%). The median age at beta-blocker initiation was 3.3 months; median duration of therapy was 10.6 months; and median maximal treatment dose was 1.5 mg/kg/day for propranolol and 1.6 mg/kg/day for atenolol. Ninety-nine patients (94.3%) responded to therapy with size reduction, colour changes, softened texture and/or healing of ulceration. Rebound growth requiring an additional course of therapy was observed in 23 patients. Side effects from beta-blockers included cool extremities (26.7%), irritability (17.1%), lower gastrointestinal upset (14.3%), emesis (11.4%), hypotension (10.5%), poor feeding (7.6%), lethargy (4.8%), bronchospasm (0.95%) and rash (0.95%). Side effects did not result in complete discontinuation of beta-blocker treatment in any case; however, they prompted a switch to a different beta-blocker preparation in some cases. Resolution of the primary indication, requiring a median time of three months, occurred in 87 individuals (82.9%).

CONCLUSIONS: Treatment of infantile hemangiomas with oral beta-blocker therapy is highly effective and well tolerated, with more than 94% of patients demonstrating a response to treatment and 90% showing resolution of the primary functional indication for treatment.

Key Words: *Beta-blocker; Hemangioma; Indications; Propranolol; Side effects; Treatment efficacy*

Les bêtabloquants pour traiter les hémangiomes problématiques

OBJECTIF : Examiner les indications thérapeutiques, l'efficacité et les effets secondaires des bêtabloquants par voie orale pour traiter les hémangiomes problématiques.

MÉTHODOLOGIE : Les chercheurs ont procédé à une analyse rétrospective des patients ayant des hémangiomes qui ont consulté à la clinique des angiomes vasculaires de l'*Alberta Children's Hospital* de Calgary, en Alberta, entre 2009 et 2011. Le sous-groupe de patients traités à l'aide de bêtabloquants par voie orale était caractérisé de manière plus détaillée, puisqu'on examinait l'indication thérapeutique, la réponse au traitement, le délai jusqu'à la résolution de l'indication, la durée du traitement, l'occurrence d'une excroissance de rebond et les effets secondaires du traitement.

RÉSULTATS : Entre 2009 et 2011, 311 nouveaux patients ayant des hémangiomes ont consulté, dont 105 ont été traités à l'aide de bêtabloquants par voie orale. Quarante-cinq patients ont terminé le traitement, tandis que les autres continuent d'être traités. Les indications thérapeutiques étaient des préoccupations d'ordre fonctionnel (68,6 %) ou le préjudice esthétique (31,4 %). Les préoccupations d'ordre fonctionnel incluaient une ulcération (29,5 %), un foyer périoculaire avec un potentiel d'interférence visuelle (28,6 %), une interférence avec les voies aériennes (4,8 %), un syndrome PHACES (3,8 %), une interférence auditive (0,95 %) et un foyer viscéral avec une insuffisance cardiaque congestive (0,95 %). Les patients avaient un âge médian de 3,3 mois au début du traitement aux bêtabloquants, et le traitement avait une durée médiane de 10,6 mois. La dose maximale médiane du traitement était de 1,5 mg/kg/jour s'ils prenaient du propranolol et de 1,6 mg/kg/jour s'ils prenaient de l'aténolol. Quatre-vingt-dix-neuf patients (94,3 %) ont répondu au traitement par une diminution de la dimension, un changement de la couleur, une amélioration de la texture ou une guérison de l'ulcération. Chez 23 patients, une excroissance de rebond a exigé une cure supplémentaire. Les effets secondaires des bêtabloquants incluaient des membres froids (26,7 %), l'irritabilité (17,1 %), des troubles du bas de l'intestin (14,3 %), des vomissements (11,4 %), une hypotension (10,5 %), une alimentation insuffisante (7,6 %), une léthargie (4,8 %), un bronchospasme (0,95 %) et une éruption (0,95 %). Les effets secondaires n'ont jamais suscité l'interruption complète du traitement aux bêtabloquants, mais ont parfois donné lieu à un transfert vers une nouvelle préparation de bêtabloquants. Chez 87 patients (82,9 %), les chercheurs ont constaté la résolution de l'indication primaire, dans un délai médian de trois mois.

CONCLUSIONS : Le traitement des hémangiomes infantiles à l'aide de bêtabloquants par voie orale est très efficace et bien toléré. En effet, plus de 94 % des patients répondent au traitement et 90 % présentent une résolution de l'indication thérapeutique fonctionnelle primaire.

Vascular anomalies are common pediatric conditions and are subdivided into vascular tumours and vascular malformations (1). Hemangiomas are the most common vascular tumours, occurring in 8% to 12% of all infants and in 22% of premature infants (2). They usually occur sporadically with an unknown etiology. The natural history is rapid growth over the six to nine months following birth (proliferative phase), followed by a prolonged period of involution over a variable period of five to 10 years (3-5). Most hemangiomas are treated expectantly because of their eventual spontaneous involution (6). Some hemangiomas, however, cause significant morbidity including ulceration, visual impairment, airway compromise and significant disfigurement. In such cases, intervention may become necessary. For many years, first-line medical management of these lesions has involved systemic corticosteroids. Other interventions have included the use of vincristine, interferon-alpha, pulsed-dye laser and surgical debulking (7).

In 2008, Leauté-Labrèze et al (8) reported a series of 11 cases in which oral propranolol dramatically improved the colour and texture of severe or disfiguring hemangiomas. Since then, others have reported similar observations. The exact mechanism of action of propranolol is unclear but may involve microvascular vasoconstriction as well as modulation of angiotensin II (9). Alterations in the cell signalling of angiogenic factors such as vascular endothelial growth factor, basic fibroblast growth factor and metalloproteinases, as well as early apoptosis of endothelial cells, may also be involved (7,10-12). Propranolol appears to have relatively few major side effects and a good safety profile and, consequently, is replacing systemic corticosteroids as first-line therapy for problematic hemangiomas (7). Because this therapy is

Department of Surgery: [1]Section of Plastic Surgery; [2]Section of Pediatric Surgery; [3]University of Calgary Medical School; [4]Department of Pediatrics, University of Calgary, Alberta Children's Hospital, Calgary, Alberta

Correspondence: Dr Frankie OG Fraulin, Pediatric Plastic Surgery, Alberta Children's Hospital, 2888 Shaganappi Trail Northwest, Calgary, Alberta T3B 6A8. Telephone 403-955-2840, fax 403-955-7634, e-mail frankie.fraulin@albertahealthservices.ca

TABLE 1
Treatment algorithm for patients put on beta-blockers

Starting propranolol dose based on age	
If premature and CGA <42 weeks; or term <2 weeks of age	0.5 mg/kg/day divided QID, Follow up weekly until effective dose reached.
2–12 weeks of age	0.5 mg/kg/day divided TID; increased to 1 mg/kg/day TID after 4 days. Follow-up every 2 weeks until effective dose reached.
>12 weeks of age	0.7 mg/kg/day divided TID; increased to 1 mg/kg/day after 4 days then up to 1.2 mg/kg/day after another 4 days if tolerated. Follow-up every 2–3 weeks until effective dose reached.
Admission considerations	
PHACES; CGA <42 weeks; high risk for complications; planning for rapid dose increase due to severity of hemangioma	
Monitoring and investigations	
HR, BP at each visit; thyroid studies for PHACES, liver or large lesions. Consider chemstrip in CGA <42 weeks or if symptomatic.	
If patient diagnosed with PHACES:	ECG and ECHO, MRA and MRV, cardiology, neurology and ophthalmology consults; baseline bloodwork
Dosing range	
Determine effective dose based on response to treatment and tolerance to medication.	0.5–2.0 mg/kg/day (2.5–3.0 mg/kg/day in some cases with PHACES, visceral or periocular hemangiomas)
If not tolerating propranolol	Change to atenolol 2 mg/mL BID
Illness management	
If patient ill and decreased feeding (ie, URTI with wheezing; gastroenteritis,etc)	Hold propranolol until patient resumes normal feeding and illness resolved (due to risk of hypoglycemia, bronchospasm)
Discontinuation of treatment	
Between 12–15 months of age for most patients (some may require longer duration)	
Dose cut by 50% with follow-up in 1 month; if no significant rebound then discontinued	

BID Twice per day; BP Blood pressure; CGA Corrected gestational age; ECG Electrocardiogram; ECHO Echcardiography; HR Heart rate; MRA Magnetic resonance angiography; MRV Magnetic resonance venography; PHACES Posterior fossa abnormalities and other structural brain abnormalities/ Hemangioma(s) of the cervical facial region/Arterial cerebrovascular anomalies/Cardiac defects, aortic coarctation and other aortic abnormalities/Eye anomalies/Sternal defects and/or Supraumbilical raphe; QID Four times per day; URTI Upper respiratory tract infection; TID Three times daily

relatively new in the management of hemangiomas, most reports to date consist of small case series. More information is required to clarify indications, dosing and potential side effects.

Propranolol has been in use at the Alberta Children's Hospital Vascular Birthmark (ACH VBM) Clinic (Calgary, Alberta) since January 2009. The purpose of the present study was to examine treatment indications, efficacy and side effects of oral beta-blockers for the treatment of problematic hemangiomas at the ACH VBM Clinic from 2009 to 2011.

METHODS

All patients presenting to the ACH VBM Clinic are entered into the clinic database, which has been previously described (13,14). The children are initially assessed by both a plastic surgeon and pediatrician. The recommendation for treatment with oral beta-blockers is a consensus recommendation to the parents by the clinic team. The standard approach to beta-blocker initiation, dosing and monitoring is outlined in Table 1.

TABLE 2
Beta-blocker medications used for treatment and reasons for modifications

Beta-blocker medication	Patients, n	Reason for medication change
Started on propranolol	98	
No changes	83	
Switched to atenolol	15	Emesis (n=9)
		Minimal response to propranolol (n=2)
		Desire for less frequent dosing (n=2)
		Emesis with little response (n=1)
		No response (n=1)
(Switched back to propranolol)	(2)	Minimal response with atenolol (n=2)
Started on atenolol	7	
No changes	5	
Switched to propranolol	2	Hypotension
		Rebound growth after attempting discontinuation with atenolol

Patients treated with oral beta-blockers between January 2009 and December 2011 were identified using the clinic database. The records of these children were reviewed retrospectively. Data pertaining to patient demographics, location and behaviour of their hemangiomas, details of beta-blocker treatment and treatment outcomes were collected. All patient records included photographs of the individuals before, during and after treatment, and were reviewed in detail.

RESULTS

Between January 2009 and December 2011, 311 new patients with hemangiomas were seen and treated at the ACH VBM Clinic. Of these patients, 105 (33.8%) were treated medically with beta-blockers, while the remainder were either serially observed clinically or underwent another form of treatment that did not include beta-blockers.

Among the 105 patients, 74 were female (70.5%) and 31 were male (29.5%). Fifteen children (14.3%) were born prematurely (eight female, seven male). Forty-five patients (42.8%) completed beta-blocker therapy in the three-year observational period; the remaining 60 patients (57.1%) were still receiving treatment as of January 1, 2012. Propranolol alone was given to 83 patients and atenolol alone was used in five patients. The remaining 17 patients were given both medications at different points during therapy (Table 2). The majority of the hemangiomas treated with beta-blockers were located in the head and neck region (74 patients [70.5%]).

The indications for treatment with beta-blockers fell into one of two broad categories: functional concerns and disfigurement. Seventy-two patients (68.6%) were treated for functional reasons, while the remaining 33 patients (31.4%) received beta-blockers because the hemangiomas were judged by the team and patients' families to be significantly disfiguring. Functional concerns were further subdivided into six categories including the following: ulceration within the lesion; periocular location with the risk of vision interference; airway interference; presence in the setting of PHACES syndrome; obstruction of the external auditory canal; and visceral hemangioma with congestive heart failure.

The details of beta-blocker treatment are shown in Table 3. The median patient age at presentation to the ACH VBM Clinic was three months (range 0.5 to 11.5 months). Presentation to the clinic occurred earlier in children with PHACES (1.6 months) and in those with hemangiomas causing airway interference (2.3 months), compared with children in the other categories. The median age at beta-blocker initiation was 3.3 months (range 0.8 to 18.5 months). In the 45 children who

TABLE 3
Outcome data for patients treated with beta-blockers

	Age, months		Maximum dose, mg/kg/day		Treatment duration, months*
	At presentation	At start of treatment	Propranolol*	Atenolol*	
Mean	3.3	4.1	1.4	1.7	11.3
Median	3.0	3.3	1.5	1.6	10.6
Range	0.5–11.5	0.8–18.5	0.6–1.8	1.3–2.5	3.3–28.3

**Only for those who completed treatment*

TABLE 4
Side effects of beta-blocker treatment

Side effect	n (%)
Minor (76%)	
Cool extremities	28 (26.7)
Irritability	18 (17.1)
Lower gastrointestinal upset	15 (14.3)
Poor feeding	8 (7.6)
Lethargy	5 (4.8)
Rash	1 (0.8)
Major (24%)	
Emesis	12 (11.4)
Hypotension	11 (10.5)
Bronchospasm	1 (0.8)

completed treatment by the end of 2011, the median duration of therapy was 10.6 months (range 3.3 to 28.3 months). The median maximal dose for patients who finished the medication course was 1.5 mg/kg/day (range 0.6 mg/kg/day to 1.8 mg/kg/day) for propranolol and 1.6 mg/kg/day (range 1.3 mg/kg/day to 2.5mg/kg/day) for atenolol (Table 3).

The incidences of major and minor side effects from beta-blocker therapy is shown in Table 4. There were 57 patients (54.3%) who experienced one or more side effects while on treatment. The majority (76%) of side effects were minor and included cool extremities, irritability, lower gastrointestinal upset, poor feeding, lethargy and the development of rash. Major side effects (24%) included emesis, hypotension and bronchospasm. In no cases did these side effects prompt the complete termination of beta-blocker therapy. In some cases, however, patients were switched from one beta-blocker medication to another because of side effects (Table 2). Patients with emesis were switched to a different formulation. Patients with hypotension were managed by dose reduction and slowing the rate of dose increase to target dose; none required cessation of treatment and none experienced adverse outcomes as a result of hypotension. One patient on propranolol developed an upper respiratory tract infection and associated wheezing (bronchospasm); in this case, propranolol was temporarily discontinued. It was not clear whether respiratory wheezing was due to the viral bronchiolitis – which is not uncommon in this age group – or related to the propranolol. The wheezing resolved after the respiratory illness resolved and the propranolol was restarted without incident.

Twelve patients (11.4%) received other treatment modalities in addition to beta-blockers including one or more of the following: steroids (n=11), surgical debulking (n=3), embolization (n=1) and laser treatment (n=1). A detailed review of these patients showed that systemic prednisone had been given to four children before the initiation of beta-blockers for hemangioma treatment. Prednisone and propranolol were administered concomitantly to an additional four individuals early in the study period because of severely disfiguring hemangiomas. Two other patients received prednisone after starting propranolol because of poor response to beta-blockers. One child underwent pulsed-dye laser treatment for an ulcerated hemangioma on a lip. Surgical debulking was used as an adjuvant in two patients (one with

TABLE 5
Description of patients not responding to beta-blocker treatment

Nonresponder	Indication	Details
Patient 1 (female)	Disfigurement	No decrease in size seen with propranolol or atenolol after 2 years, no further growth, continues to be on treatment; maximum dose 2.3 mg/kg/day atenolol
Patient 2 (female)	Disfigurement	No decrease in size seen with propranolol after 5 months, no further growth, continues to be on treatment; max dose 1.5 mg/kg/day
Patient 3 (female)	Ulceration	Uncertain whether the diagnosis is a NICH or infantile hemangioma; max dose atenolol 2.5 mg/kg/day
Patient 4 (female)	Periocular	Slight increase in size despite being on propranolol continuously for 2 months; dose increased and continues to be on treatment (early)
Patient 5 (male)	Periocular	Deep hemangioma treated for 14.5 months with no decrease in size, stopped treatment; max dose 1.8 mg/kg/day propranolol

NICH Noninvoluting congenital hemangioma

PHACES syndrome) with periocular lesions causing vision impairment not responding rapidly enough to propranolol alone. Finally, one patient underwent presurgical embolization before debulking in addition to the use of prednisone for a complex lesion.

Treatment response to beta-blockers was deemed to have occurred when any of the following changes were observed: reduction in size; lightened colour; softened texture; or healing of an ulcer. No response was recorded if none of these features were apparent or if the hemangioma remained the same size while on treatment. Overall, 99 patients (94.3%) demonstrated a response to beta-blocker treatment, while five patients (4.8%) did not respond to therapy. Detailed review of these five patients, however, revealed no progressive growth of the hemangiomas in all but one patient (Table 5). One additional patient with an ulcerated hemangioma was lost to follow-up when the family moved out of the province.

Depending on the primary indication for administration of beta-blockers, resolution was deemed to have occurred when one of the following was observed: visual interference resolved; ulcer healed; growth subsidence in PHACES patients; airway interference resolved; external auditory canal patency achieved; resolution of complications related to visceral hemangiomas; and improved cosmesis following previously disfiguring hemangiomas. As shown in Table 6, resolution of the original indication for treatment occurred in 87 patients (82.9%) and required a median time of three months to achieve (range 0.5 to 17.5 months). Thirteen patients demonstrated some response to beta-blockers; however, they were still being treated at the end of the study because the original treatment indication had not yet resolved. The four patients with PHACES syndrome all showed marked reduction in hemangioma size. All five patients for whom airway interference was a concern demonstrated resolution of this problem. One patient with a hemangioma in the liver with congestive heart failure showed symptomatic improvement; however, complete resolution has not yet occurred and the patient remains on treatment. As mentioned above, five patients exhibited no response to treatment and one patient was lost to follow-up.

The presence or absence of rebound growth of the hemangiomas is described for 52 patients (Table 7). Among 45 patients who have completed therapy, 29 did not demonstrate signs of rebound growth. Conversely, 23 patients did show evidence of rebound growth, which in turn necessitated resumption of treatment. Of these individuals, 16 progressed to ultimately complete beta-blocker therapy, while the

TABLE 6
Treatment response and resolution of the primary indication in patients who were treated with beta-blockers

Indication	Pts, n (%)	Treatment response, pts/total (%)	Resolution of indication, pts/total (%)	Median time to resolution, months
Functional	72 (68.6)	68/72 (94.4)	65/72 (90.3)	
Ulceration within lesion	31 (29.5)	29/31 (93.5)	29/31 (93.5)	1.50
Risk of vision interference (periocular location)	30 (28.6)	28/30 (93.3)	27/30 (90.0)	3.00
Airway interference	5 (4.8)	5/5 (100)	5/5 (100)	4.50
Presence in setting of PHACES syndrome	4 (3.8)	4/4 (100)	4/4 (100)	6.75
Obstruction of external auditory canal	1 (0.95)	1/1 (100)	0/1 (0)	–
Visceral hemangioma with complication (CHF)	1 (0.95)	1/1 (100)	0/1 (0)	–
Disfigurement	33 (31.4)	31/33 (93.9)	22/33 (66.7)	8.00
Total	105 (100)	99/105 (94.3)	87/105 (82.9)	

CHF Congestive heart failure; PHACES Posterior fossa abnormalities and other structural brain abnormalities/Hemangioma(s) of the cervical facial region/Arterial cerebrovascular anomalies/Cardiac defects, aortic coarctation and other aortic abnormalities/Eye anomalies/Sternal defects and/or Supraumbilical raphe; Pts Patients

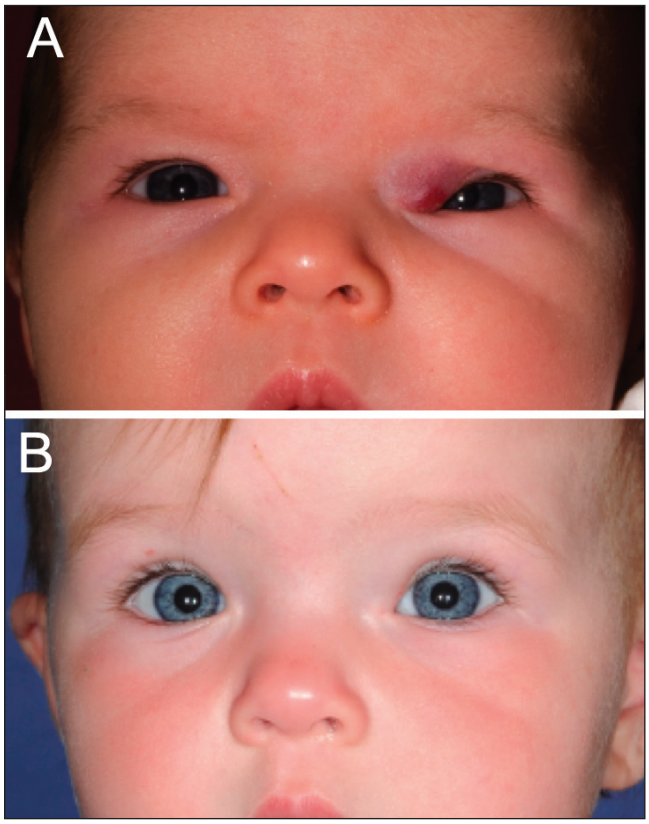

Figure 1) A *1.5-month-old girl with left upper eyelid hemangioma causing ocular obstruction and astigmatism before starting propranolol.* **B** *Twelve months of age. Total propranolol treatment 8.5 months. Maximum dose 1.5mg/kg/day. She had some irritability and cold extremities while on treatment, neither of which necessitated discontinuing treatment*

TABLE 7
Data regarding the presence or absence of known rebound growth

	Patients, n	Mean age at discontinuation of therapy, months	Mean duration of treatment before discontinuation, months	Mean maximal treatment dose of beta-blocker (propranolol/atenolol), mg/kg/day
Rebound	23	12.2	7.5	1.4/1.4
No rebound	29	14.8	9.8	1.4/1.7

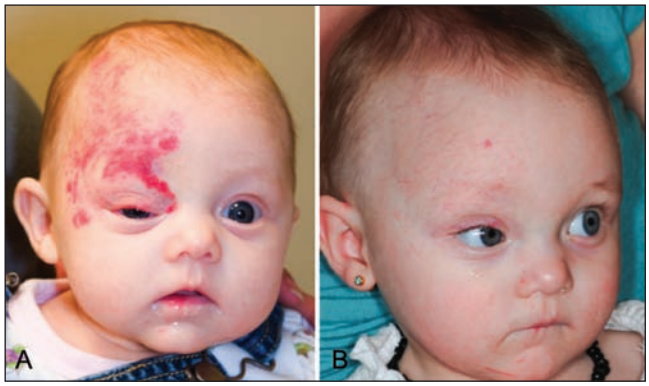

Figure 2) A *1.75-month-old girl diagnosed with PHACES syndrome. Large segmental hemangioma causing ocular obstruction before starting propranolol.* **B** *Ten month of age reaching a maximum dose of propranolol 2.8 mg/kg/day at eight months of treatement. She has had some trouble with emesis and slowed growth while on propranolol, neither of which necessitated discontinuing treatment. She continues to receive treatment*

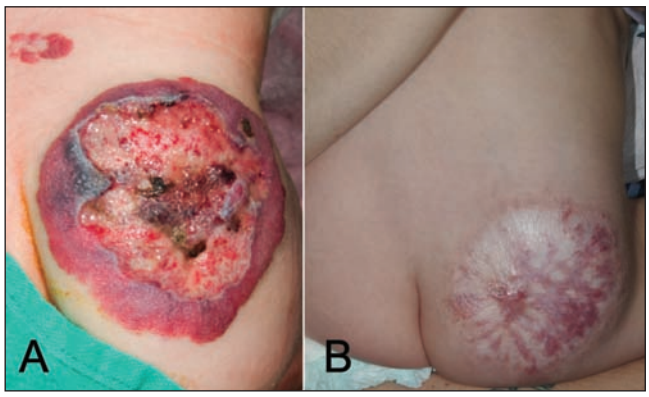

Figure 3) A *Three-month-old girl with large hemangioma with ulceration on buttock before starting propranolol.* **B** *Same patient at 16 months of age. Ulcer healed after 2.5 months of propranolol and maximum dose of 3 mg/kg/day. She continued on propranolol until 15 months of age. Her only side effect was slight slowing of weight gain*

remaining seven individuals continue to receive treatment. The mean duration of treatment was found to be significantly shorter in patients exhibiting rebound growth compared with those not exhibiting rebound growth (7.5 months versus 9.8 months; P=0.04). The mean maximal dose of both propranolol and atenolol in the rebound group was 1.4 mg/kg/day. In patients who did not demonstrate rebound growth, the mean maximal dose was 1.4 mg/kg/day for propranolol and 1.7 mg/kg/day for atenolol. These differences were not statistically significant.

Figures 1 to 4 depict examples of treatment responses in four representative patients with hemangiomas who were administered oral beta-blockers for different indications including periocular location, presence in the setting of PHACES syndrome, ulceration and disfigurement.

DISCUSSION

Between 2009 and 2011, 311 new patients with hemangiomas presented to the ACH VBM Clinic, of whom 105 were treated with oral beta-blocker therapy. Indications for treatment included functional problems (most commonly vision-threatening periocular hemangiomas and ulcerated lesions) or significant disfigurement. Hemangiomas that are ulcerated, at risk for compromising airway, vision or hearing, found in the liver, occupying extensive segments of the face or disfiguring, have all been proposed as indications for therapy in other studies (6,15). The vast majority (94%) of hemangiomas in the present study responded favourably with reduction in size, colour change, softened texture and/or ulcer healing. Complete resolution of the primary indication for treatment occurred in 83% of cases. Children for whom the indication for treatment was disfigurement tended to be treated for a longer period of time than those for whom treatment indication was a functional concern. The present study represents one of the largest series to date of patients with hemangiomas treated with beta-blockers, and shows treatment response rates similar to previous reports. Other smaller case series have reported response rates for propranolol between 75% to 100% (16-24).

Serious side effects including somnolence, bradycardia, hypotension, hypoglycemia and bronchospasm (25,26) have been reported in the literature. Of these side effects, we report an incidence of 10.5% for hypotension, which did not require intervention. Of course, monitoring blood pressure in infants is difficult at the best of times due to a variety of reasons, most commonly patient cooperation and equipment reliability. If a low blood pressure due to propranolol was accurate, we would expect bradycardia to also be present. Our rate of 10.5% is probably overly conservative because we were trialling a new treatment and did not want to cause harm. Although not generally considered to be a serious side effect, emesis (11.4%) was found to be the most frequent reason to change beta-blocker formulations. Atenolol is a hydrophilic selective beta-1 blocker that can be administered less frequently and may have fewer side effects than propranolol while still remaining effective; however, there is less experience with use of this medication (27). The present study did not find any life-threatening side effects to beta-blockers, and suggests a good safety profile for propranolol and atenolol.

The maximum median dosage in the present study was 1.5mg/kg/day for propranolol and 1.6 mg/kg/day for atenolol. While this represents (for propranolol) a slightly lower dosing than the 2 mg/kg/day to 3 mg/kg/day recommended by others (28-30), we nonetheless still observed good response rates and possibly fewer side effects. Patients in our study were started on therapy at a median age of 3.3 months and treated for a median duration of 10.6 months. Other studies have shown good response with propranolol initiation at 3.6 to 4.5 months of age and median treatment durations between three to 10.5 months (16,20,31-34). The patients reviewed in our study were generally treated at an earlier age and for a longer period of time with a lower beta-blocker dosage. It is possible that the need for a longer duration of treatment than other studies may relate to our relatively lower dosing. Despite showing early response and resolution of the primary indication, many children were kept on treatment for prolonged periods of time, and there is evidence to suggest that continued therapy past the proliferative phase is beneficial (35). Future studies are needed to study the optimal balance among dosage, duration, response to treatment and the incidence of side effects.

In our experience, many patients encountered rebound growth when discontinuation of therapy was initially attempted, prompting resumption of treatment. The mean duration of therapy was significantly shorter (7.5 months) for patients who rebounded compared with those who did not show evidence of further growth (9.8 months). This may suggest that prolonged treatment may be necessary to avoid rebound growth. Recurrence rates of between 20% and 40% have been reported but are usually mild and respond to additional beta-blocker treatment (31). Analysis of the 45 (64.4%) patients who completed treatment (29) did not reveal evidence of recurrent growth.

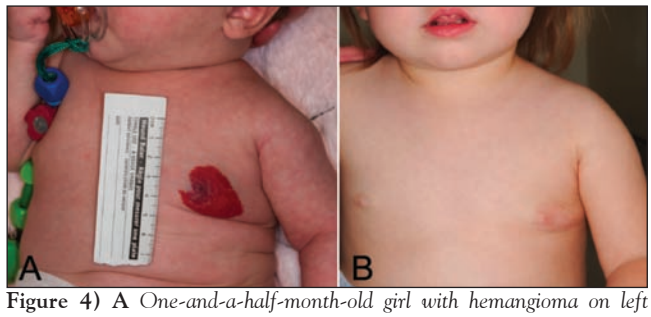

Figure 4) A *One-and-a-half-month-old girl with hemangioma on left chest wall causing disfigurement before starting propranolol.* **B** *Same patient at 16 months age. Hemangioma mostly cleared. She was treated for eight months with a maximum dose of atenolol 1.4 mg/kg/day. She experienced trouble with emesis while on propranolol*

Previously, medical management of problematic hemangiomas involved the administration of systemic corticosteroids, the side-effects of which included changes in behaviour, insomnia, gastrointestinal symptoms, hypertension, hypothalamic-pituitary-adrenal axis suppression, growth delay and immunosuppression, and required careful observation (36,37). Beta-blockers are rapidly replacing systemic corticosteroids as the preferred medical treatment for problematic hemangiomas. Studies of propranolol versus oral corticosteroids have shown that propranolol is more clinically effective and is better tolerated, with fewer and less severe side effects (38,39).

Limitations of the present study include its retrospective nature without formal comparison with other types of medical management. Because systemic steroids, the previous mainstay of medical management, are associated with a spectrum of serious side effects, we believe that a prospective comparative study would be unethical at this stage. Other limitations include observation bias in establishing the degree to which hemangiomas respond to treatment and lack of long-term follow-up data.

CONCLUSIONS

The treatment of infantile hemangiomas with oral beta-blocker therapy is highly effective, with more than 94% of patients demonstrating a response to treatment and 90% showing resolution of the primary functional indication for treatment within the study period. Beta-blockers used for these indications are well tolerated with few serious side effects. While still considered an off-label use, beta-blockers are rapidly becoming a mainstay in the treatment of difficult hemangiomas.

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