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Case Report

Treatment of ulcerated hemangiomas with propranolol: an evidence-based case report

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Hemangiomas are the most frequent vascular tumors observed in early childhood. The presentation is unique, with an initial phase of proliferation, followed by a phase of slow, spontaneous regression after the age of 1 year.[1,2] Most hemangiomas are uncomplicated and do not require intervention. However, therapy may be needed if the hemangioma is located at certain body sites, such as the face, or if it results in a functional handicap, such as limitation of eye opening. In addition, ulcerated, rapidly growing hemangiomas may require treatment.[3]

Ulceration occurs in about 16% of patients with hemangiomas. Additional complications due to ulceration are bleeding in 41% of patients or infections in 16% of patients.[4] Wound therapy with different dressings, compresses or topical antibiotics have been used as treatments, but ulcerated hemangiomas have also been reported to respond to flashlamp-pulsed dye laser (FPDL) as well as drug therapy with steroids, chemotherapeutic agents, interferon and propranolol.[5]

Patients with complicated proliferating hemangiomas who underwent propranolol treatment have shown excellent response. Hence, propranolol has rapidly entered the field of hemangioma therapy.[6] Propranolol appears to be safe, with high efficiency and acceptable toxicity. However, a scientifically-driven clinical study of propranolol for hemangioma treatment was lacking, and the mechanism of propranolol action is still speculative.

Oral corticosteroids have been used to treat problematic infantile hemangiomas for decades and have been shown to help shrink them. However, steroids have many side effects,[7] so physicians have sought other treatments. More recently, the use of propranolol, a heart medication, was serendipitously found to reduce the size of hemangiomas. Propranolol appears to have fewer side effects than steroids, but its effectiveness compared to steroids is not yet known. We aimed to determine if propranolol could be used as a treatment of choice, in terms of efficacy and safety, to manage ulcerated hemangiomas, in place of corticosteroids.

Here, we present two pediatric cases of ulcerated hemangioma from the Hemato-Oncology Center in Manado, who were treated with propranolol.

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Case Report

The first case was an 8-month-old boy with an ulcerated hemangioma on the right cubital fossa (**Figure 1**). The hemangioma was first observed when the patient was 3 month old, after which it proliferated in size. No other hemangiomas were found in this patient.

The second case was a 6-month-old girl with a hemangioma at the left thoracic region, measuring 7 cm in diameter with a 2 cm infected ulceration. The hemangioma was noticed immediately 3 days after birth and it proliferated thereafter. No other hemangiomas were found in this patient.

No treatment was initiated for the hemangiomas in either patient until the ulcerations occurred. Propranolol was given to both patients in increasing dosages starting from 1 mg/kg/day on day 1, 2 mg/kg/day on day 2, and 3 mg/kg/day on day 3, three times daily in divided doses. Prior to therapy, vital sign measurements, serum electrolytes, and blood glucose tests were performed. All results were normal in both patients.

Two to three weeks after treatment, the hemangiomas in both patients were lighter in color, smaller in size, and less ulcerated. No side effects from propranolol treatment were experienced by either patient. Durations of propranolol treatment until the last follow-up visit were 5 months for the first case and 3 months for the second case. The characteristics of case subjects are shown in **Table 1**.

Methods

A literature search using search engines from Pubmed, the Cochrane Library, Google™ Scholarship, Medscape and Yahoo was performed to identify studies relevant to the our cases. Keywords used were *infantile hemangioma, propranolol,* and *corticosteroid*. The search was limited to human studies in children aged 0-2 years, English publications, keywords in titles or abstracts, as well as published case reports, randomized clinical trials, meta-analyses, and systematic studies.

Through this filtering method, 32 articles were initially found that fulfilled the criteria. Further investigation was manually carried out in the relevant bibliography resulting in 18 articles relevant to the

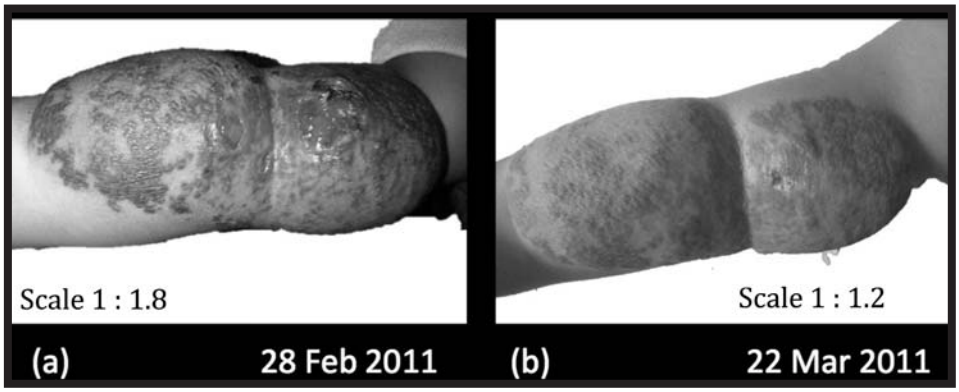

Figure 1. Case 1. (a) Upon presentation at the hospital. (b) On the 22nd day of follow-up

Table 1. Characteristics of two infants with ulcerated hemangioma

Case	Sex/Age	Localization	Hemangioma size, cm	Ulceration size, cm	Therapy other than propranolol	Propranolol therapy
1.	M / 8 mo	Right cubital fossa	4 x 10	2 x 3	Wound care with 1% ferriculum and oral antibiotics	1 mg/kg/day on day 1 2 mg/kg/day on day 2 3 mg/kg, day on day 3
2.	F / 6 mo	Left thoracic region	7 x 7	2 x 2	Wound care with 1% ferriculum and oral antibiotics	1 mg/kg/day on day 1 2 mg/kg/day on day 2 3 mg/kg/day on day 3

problem. These articles consist of one meta-analysis, five cohort studies, eight review articles, and four case reports. The level of evidence was determined based on classifications in the *Oxford Centre for Evidence-based Medicine Levels of Evidence*.[8]

This study was approved by the Ethics Committee of the Prof. DR. R. D. Kandou Hospital, Manado. Subjects' parents provided written informed consent.

Results

Stamatios *et al* did a meta-analysis on the effectiveness of propranolol versus different therapies for treating infantile airway hemangiomas.[9] Random-effect, meta-analytical techniques were conducted for the outcome measures. Thirteen studies, comprising 36 patients, were included in their analysis. Propranolol was found to be an effective intervention for the resolution of infantile airway hemangiomas ($P < 0.00001$). Meta-analysis of the effectiveness of propranolol versus steroids, CO_2 laser treatment, or vincristine, showed propranolol to be the most effective treatment (**Table 2**).

Four case reports[10-13] concluded that propranolol was a highly effective and safe, new treatment modality for ulcerated hemangioma in infants. However, a clinical trial on the preferred dosage and duration of therapy, as well as side effects and mechanism of action, is urgently needed. De Graff *et al*[11] concluded that propranolol appeared to be an effective treatment option for infantile hemangioma, even in the non-proliferative phase and after the first year of life. Potentially harmful adverse effects included hypoglycemia, bronchospasms, and hypotension. Of 28 patients, 2 patients had symptomatic hypoglycemia, 16 patients had hypotension, but only 1 had symptomatic hypotension, and 3 patients had bronchial hyperactivity.

A follow-up report on 32 children showed that propranolol administered orally at 2-3 mg/kg per day had a consistent, rapid, therapeutic effect. Propanolol use led to considerable shortening of the natural course of infantile hemangiomas, and patients showed good clinical tolerance. At 60 days, ultrasound examinations showed regression in maximal thickness (mean regression 40%) associated with increased mean resistivity index (from 0.495 before treatment to 0.63 at day 60; +27%; by paired Student's *t* test, $P < 0.0002$ for thickness and $P < 0.0003$ for resistivity index).[14] Chik *et al*[15] concluded from their retrospective study that propranolol was useful as a first-line or single-agent treatment of facial infantile hemangioma in children. It showed minimal side effects compared to steroid treatment. Only 2 of 12 patients (17%) had transient asymptomatic hypotension while taking propranolol, one of whom tolerated the drug well when it was reintroduced at a later time.

Discussion

A thorough discussion of the management of infantile hemangiomas demand a working knowledge of their natural history, as well as what they are their associated with and potential complications. In general, hemangiomas are not present at birth, but appear shortly afterward. In some cases, a precursor lesion, such as vascular patch or area of pallor/

Table 2. Sensitivity analysis of outcomes of interest[9]

Outcome of interest	No. of studies	No. of patients	OR	95% CI	P value	HG P value
Studies reporting ≥ 3 patients						
Propranolol effectiveness	4	24	0.01	0.00 to 0.07	P<0.00001	P=0.96
Propranolol vs. steroids	2	9	0.01	0.00 to 0.20	P=0.002	P=0.68
Propranolol vs. CO_2 laser	2	9	0.01	0.00 to 0.20	P=0.002	P=0.68
High-quality studies (≥ 8 stars)						
Propranolol effectiveness	6	21	0.03	0.01 to 0.14	P<0.0001	P=0.92
Propranolol vs. steroids	3	6	0.04	0.00 to 0.52	P=0.01	P=0.86
Propranolol vs. CO_2 laser	3	6	0.04	0.00 to 0.52	P=0.01	P=0.86
Propranolol vs. vincristine	3	6	0.04	0.00 to 0.52	P=0.01	P=0.86

OR = odds ratio; CI = confidence interval; HG = heterogeneity

vasoconstriction, may precede hemangioma growth and may be present at birth. Hemangiomas tend to "mark out their territory" early in development. They then proliferate within their predetermined borders and tend to grow in volume rather than diameter. During the first 3 to 5 months, superficial infantile hemangiomas proliferate rapidly, and in most cases (80%) growth is completed by 5 months of age.[4] Deep infantile hemangiomas often lag in growth by about 1 month compared to superficial infantile hemangiomas, but they proliferate for 1 month longer on average.[4] Despite these well-defined parameters, infantile hemangiomas are heterogeneous and during the early proliferative phase, growth characteristics of infantile hemangiomas can be difficult to predict. Some hemangiomas barely proliferate at all beyond their nascent phase. These hemangiomas have a minimal or absent growth phase.[5] At the other end of the growth continuum, some hemangiomas, particularly large ones with a deep component, have been observed to grow for longer than expected, occasionally up to 1 to 2 years.[6] This heterogeneity makes treatment decisions difficult and mandates both close observation in the first few months of life and reevaluation of advice given to parents if any unexpected growth occurs. In general, most infantile hemangioma requiring treatment are best treated early in the proliferative phase when there is still time to prevent possible adverse sequelae.[16]

Ulceration may also be the cause of permanent, unsightly scars. Therefore, ulcerated hemangiomas require treatment independent of their location or presence of any functional discomfort. In addition to therapy aiming to stop proliferation and further ulceration, supportive therapy such as local wound care, or administration of pain medications and antibiotics may be necessary.[10] In eight review articles,[15-21] propranolol, a nonselective β-blocker, was recently introduced as novel modality for the treatment of proliferating hemangiomas.

Propranolol is a nonselective β-blocker that blocks the action of adrenaline on both β1- and β2-adrenergic receptors. Leaute-Labreze *et al*[6] first reported the effectiveness of propranolol for the treatment of infantile hemangiomas. They presented 11 cases of children with severe infantile hemangiomas, which improved after the first day of treatment. After this report, many physicians have used propranolol for infantile hemangiomas.[6] Some studies confirmed that propranolol at 2-3 mg/kg per day was a useful treatment for severe or complicated infantile hemangiomas, achieving rapid and significant reduction in their sizes. This reduction was mainly achieved during the first 3-5 weeks of treatment, with further treatment inducing a less dramatic therapeutic effect. In our cases, improvement was seen after 2-3 weeks of treatment.

Our two ulcerated hemangioma patients underwent treatment with propranolol as first-line therapy, in addition to antibiotics. Hemangiomas in both patients responded well. Our patients' clinical courses demonstrated that propranolol may be an option in the treatment of ulcerated hemangiomas. Our cases showed success of therapy with propranolol for ulcerated hemangiomas, similar to that of Sans *et al*[13] who gave detailed information about the course of disease under this new treatment option.

We found no side effects with propranolol in either case. The pre-treatment assessment and the safety of β-blockers in infants are controversial.[9-11] Nevertheless, no serious complications with the therapy have been reported,[6,9] and β-blockers may have a better safety profile than previously used therapy for the treatment of proliferating hemangiomas.

The striking effect of propranolol on growing infantile hemangiomas can be attributed to three molecular mechanisms: vasoconstriction, down-regulation of angiogenic factors, such as VEGF and basic fibroblast growth factor (bFGF), and up-regulation of apoptosis of capillary endothelial cells. They correspond to early (brightening of hemangioma surface), intermediate (growth arrest), and long-term (regression) clinical observations. Apoptosis is not complete, as partial regrowth of hemangiomas after discontinuation of propranolol has been observed.[17] During 40 years of extensive clinical experience no serious cardiovascular event has been recorded for children on chronic β-blocker therapy.[22] Complications from propranolol treatment of infantile hemangiomas reported so far (hypotension, sinus bradycardia, and hypoglycemia)[23] were not life-threatening, but certainly warrant careful monitoring of all infants with infantile hemangiomas before and during propranolol therapy.

Superficial ulceration was present in our two patients, but this low sample number does not allow

us to draw firm conclusions about the efficacy of propranolol for ulcerated infantile hemangiomas. Nevertheless, both patients' ulcers healed within one month of therapy. It was our impression that propranolol was helpful for treatment of ulcerated infantile hemangiomas, but we had no control group for comparison. Based on our experience, propranolol's therapeutic effects were at least as fast-acting as corticosteroids. The duration of propranolol therapy is not well established, and possible regrowth of infantile hemangioma after propranolol withdrawal needs to be assessed in long-term studies. The optimal dosage of propranolol for infantile hemangioma is also not yet known. Sans *et al*[14] gradually increased the dosage of propranolol from 2 mg/kg/day to 3 mg/kg/day, given in 2 or 3 divided doses to minimize side effects. Chik *et al*[15] also gradually increased the dosage from 0.5 mg/kg to 2 mg/kg per day for the same purpose. In our series, a gradual increase of propranolol dosage from 1 mg/kg per day to 3 mg/kg per day was administered daily.

The potential side effects of β-blockers are well known and include bradycardia, hypotension, and hypoglycemia.[15] Propranolol is contraindicated in patients with asthma,[16] and it is not recommended during episodes of bronchiolitis. A propranolol dosage of over 4 mg/kg per day seems to put the pediatric patient at risk for development of hypoglycemic events.[11] None of our patients had symptoms of hypoglycemia, although glucose levels were monitored only over a short period of time. Since we had only 2 patients, warning of future subjects to the possibility of hypoglycemia may be necessary. Neither of our patients had hypotension that might have led us to reduce the dose.

The appropriate monitoring protocol for evaluation of infants with infantile hemangiomas before and during propranolol treatment has been established. We performed a completed cardiac study including physical examination, ECG, complete blood count, blood glucose, and serum electrolyte levels.

In children with conflicting results or those at high risk, an echocardiogram may also be advisable. Monitoring blood pressure and heart rate during the first days of treatment are also recommended. Clinical signs of low glucose levels should be sought, and parents must be advised to help their child avoid long periods of fasting. Sustained or repetitive hypoglycemia may have untoward effects on a developing brain.[6] As there may be unknown side effects of propranolol, regularly scheduled follow-up visits should be established.

Propranolol could be the treatment of choice in the management of ulcerated hemangiomas. Oral propranolol at 3 mg/kg per day was well-tolerated, effective, and safe in the treatment of infantile hemangiomas. Further studies are needed to establish the optimal dose of propranolol and the appropriate duration of treatment, as well as the comparative efficacy between propranolol and corticosteroids.

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