Oral propranolol versus cryotherapy in the management of cutaneous hemangioma in infants and children

Almoutaz A. Eltayeb[a], Naglaa H. Ibrahim[b], Seham Moeen[c], Ragaa Herdan[c]

Departments of [a]Pediatric Surgery, [b]Pediatrics, [c]Anesthesiology, Assiut University, Assiut, Egypt

Correspondence to Almoutaz A. Eltayeb, MD, Department of Pediatric Surgery, Assiut University, Assiut, Egypt
Tel: 00201221657863;
e-mail: almoutazeltayeb@hotmail.com

Received 22 July 2015
Accepted 09 September 2015

The Egyptian Journal of Surgery
2016, 35:29–34

Objective
The aim of the study was to evaluate the efficacy, adverse effects, and success rate of oral propranolol versus liquid nitrogen oxide gas cryotherapy in the management of cutaneous hemangiomas in infants and children.

Patients and methods
A prospective study was conducted between March 2011 and May 2015 on 43 patients with cutaneous hemangioma treated either with oral propranolol (group A, 23 cases) or with liquid nitrogen (cryotherapy) (group B, 20 cases). The outcome of treatment was evaluated clinically and with serial photographs before starting treatment and monthly thereafter as regards the size and color of the lesion. Propranolol was given orally 2 mg/kg per day in two divided doses for 4–6 months. Cryotherapy settings were applied two to four times for a period of 2–6 months under inhalation anesthesia using sevoflurane.

Results
With propranolol, complete involution occurred in 78.2% of cases and good response in 17.3%. Regrowth of the lesion occurred after stopping propranolol in two cases; the parents of the children were instructed to continue the treatment for a further 3 months. With cryotherapy complete involution of the lesions occurred in 65% of cases. No recurrence was observed during the follow-up period. Hypopigmentation at the site of the treated area was evident in eight cases.

Conclusion
Oral propranolol could be considered a safe and effective treatment strategy for cutaneous hemangioma. Although inhalational anesthesia is needed for application of cryotherapy, it is a simple method for treatment of cutaneous hemangioma and has minimal side effects. However, a randomized controlled study on a large number of patients should be conducted.

Keywords:
cryotherapy, cutaneous hemangioma, liquid nitrogen oxide gas, propranolol

Egyptian J Surgery 35:29–34

1110-1121

Introduction

Infantile hemangiomas (IHs) are the most common benign tumors of infancy occurring in about 5–10% of newborns and infants, being more common in female children and in premature infants. Occasionally they present at birth and usually appear during the first weeks of life. They usually appear singly, except in 20% of cases, and are commonly located in the skin and subcutaneous tissues of the head and neck [1–3]. Although most of them grow rapidly during the first years of life with spontaneous involution, 10–20% require active intervention because of their aggressive growth, especially those involving the periorbital area, parotid region, airways, and anogenital area [4,5]. Hemangiomas may have great psychological impact on the parents of the affected children; they may feel panic, fear, sadness, guilt, personal shame, and a sense of loneliness [6].

Different treatment modalities have been adopted over the years. However, each of these modalities has its own side effects and sometimes potential serious complications [7–10].

Léauté-Labrèze *et al.* [8] were the first to report in 2008 that there is incidental regression of IH in children treated with propranolol for cardiopulmonary conditions. The relatively small number treated, the lack of long-term follow-up, the difference in behavior of IH, and the variable dose given in different studies make it difficult to assess the actual safety, efficacy, incidence, and cause of recurrence [11–14].

In the present work a comparative study for treatment of cutaneous hemangioma by oral propranolol or by liquid nitrogen (cryotherapy) was conducted to explore

the efficacy, adverse effects, regrowth rate, and feasibility of using either of these two lines for treatment.

Patients and methods

From March 2011 to May 2015 a prospective study was conducted at Assiut University Children's Hospital (a tertiary hospital that serves most of upper Egypt) on 50 cases having cutaneous hemangioma as defined by the international society for the study of vascular anomalies [15]. Children who received any previous form of treatment for their hemangioma or those with deep-seated hemangiomas, cardiac anomalies, heart failure, pulmonary hypertension, or bronchial asthma were excluded from the study. Four patients failed to attend during the follow-up period and three patients' parents refused to participate in this study. Forty-three patients, aged 3–36 months, were enrolled in this study with the following reasons for referral: cosmetic disfigurement in 31 cases, bleeding in seven cases, ulceration in three cases, and pain in two cases. These 43 cases were divided into two groups: group I (23 cases) was treated with propranolol (commercially available preparation inderal) (AstraZeneca plc, London, UK) given orally as a 10 mg tablet crushed and dissolved in 10 ml distilled water (1 mg/ml) starting with a dose of 1 mg/kg per day in two divided doses that was then increased after 1 week to 2 mg/kg per day in two divided doses; group II (20 cases) was treated with liquid nitrogen (cryotherapy) using a Brymill Cro-Ac (Ellington, CT 06029, USA) hand-held liquid nitrogen delivery system producing a temperature of −195.6°C (Fig. 1). Hemangiomas manifested in the 43 patients at 2–6 months of age, except in the case of eight children who were born with hemangiomas (five from group I and three from group II). Before start of either form of treatment a complete clinical and cardiac examination or preanesthetic fitness test was performed to detect any cardiac disease or unfit patients. Written informed consent was taken from the parents of the 43 patients about the line of treatment, and the study protocol was approved by the surgical ethical committee at Assiut University. Patients from both groups were admitted for 24 h after start of treatment and were monitored clinically for bradycardia, hypotension, and symptoms of hypoglycemia (i.e. lethargy, restlessness) or postcryotherapy complications. On discharge, parents of patients from group I were instructed to stop the drug if the child had a serious incidence of cough or dyspnea. Photographs of the hemangioma were taken before start of treatment and during the follow-up period. The clinical assessment during treatment included reduction in size, change in color, complications developed, and any relapse. The treatment period was either until complete involution had occurred or for 6 months at its maximum range for both groups, so as to have uniform results.

Figure 1

Brymill Cro-Ac hand held liquid nitrogen delivery system.

Cryotherapy technique

The procedure was performed in the operating theater without any premedication. Anesthesia was induced with 8% sevoflurane in 100% oxygen under standard monitoring, including ECG, noninvasive arterial pressure monitoring, and pulse oximetry, which were applied during induction and maintenance of anesthesia. After insertion of the intravenous line, children received 15 mg/kg paracetamol intravenously. End-tidal sevoflurane concentration was adjusted according to clinical signs (arterial pressure or heart rate within 20% of baseline). Spontaneous breathing was maintained throughout the procedure.

After disinfecting the target area and covering it with K-Y jelly to ensure better thermoconductivity, the target area was directly sprayed with liquid nitrogen for 20–30 s until an ice ball was formed over the lesion, followed by a thaw period of ~90 s. The freeze–thaw cycle could be repeated according to the size of the lesion. After completion of the procedure the child was sent to a postanesthetic care unit if there was no compromise in airway or hemodynamic instability perioperatively.

The final results of all patients in both groups were determined on the basis of four-point scale modified after Achauer *et al.* [16] based on improvement in volume, color, and texture after treatment. These parameters were rated using the following scales: poor (0 to 25% response rate), fair (26 to 50% response rate), good (51 to 75% response rate), and excellent (76 to 100% response rate).

Follow-up visits were scheduled every 2 weeks for the first month, and then monthly thereafter. During this period all comparative parameters were assessed, along with heart rate, blood pressure, and blood glucose level for patients from group I.

Statistical analysis

The data were analyzed using SPSS (version 16; SPSS Inc., Chicago, Illinois, USA). Descriptive statistics were calculated. Cross-tabulation using the χ^2-test for categorical data was presented in the form of frequency and percentage). The difference was considered significant if the *P* value was less than or equal to 0.05.

Results

The demographic and clinical data of all patients are summarized in Table 1. Nineteen cases from group I and 17 from group II had solitary lesions. There was no statistically significant difference between groups regarding the cause of referral, site, size, and type of the lesions (Table 1). The treatment period in group I ranged from 4 to 6 months. By the end of this period 18 cases had excellent response, four had good response, and one had fair response (Figs. 2–5). Nine cases developed bradycardia without any further clinical manifestations. Two cases (one from the good response group and one with fair response) developed regrowth of their lesion after stopping treatment and were instructed to continue the same dose for another 3 months. Thereafter, excellent response was obtained without further recurrence during the follow-up period.

No complications were observed from using sevoflurane as inhalational anesthesia. The number of cryotherapy applications ranged from two to four times at 4–6-week intervals depending on the size and response of hemangioma. Hyperemia, edema, and swelling occurred immediately after cryotherapy in five cases, which improved within 1–2 weeks. Cryonecrosis and formation of dark, dry eschar occurred in four cases. Separation of the eschar commenced and was completed by the end of the first month after cryotherapy, leaving a healthy smooth mobile scar. The main complication due to the use of liquid nitrogen was the hypopigmentation at the site of the lesion in eight cases.

The cryotherapy period ranged from 2 to 6 months by the end of this period 13 cases had excellent response,

Table 1 The demographic data, site, size, and type of the lesion in the 43 patients

Items	Propranolol (group I) (*N* = 23 cases) [*n* (%)]	Cryotherapy (group II) (*N* = 20 cases) [*n* (%)]
Number of preterm infants	5 (21.7)	3 (15.0)
Age at start of treatment (months)		
<6	9 (39.1)	7 (35.0)
6–12	11 (47.8)	12 (60.0)
13–36	3 (13.1)	1 (5.0)
Sex (female : male)	17 (73.9) : 6 (26.1)	15 (75.0) : 5 (25.0)
Site of lesions		
Head and neck	12 (52.2)	10 (50.0)
Trunk and back	7 (30.4)	6 (30.0)
Limbs	4 (17.4)	3 (15.0)
Genitalia	0 (0.0)	1 (5.0)
Size of lesions (cm)		
<2	4 (17.4)	2 (10.0)
2–5	14 (60.9)	16 (80.0)
>5	5 (21.7)	2 (10.0)
Type of lesion		
Solitary	19 (82.6)	17 (85.0)
Multiple	4 (17.3)	3 (15.0)

Figure 2

Patient before starting propranolol therapy.

Figure 3

Same patient at the end of treatment.

five had good response, and two cases had fair response (Figs. 6 and 7). No cases developed regrowth after cryotherapy. There was no statistically significant difference between the two groups regarding response to treatment or regrowth after treatment (Table 2). The start of response to propranolol therapy was noted from 3 to 4 weeks when the hemangioma started to decrease in size and become softer. This response was noted from the first session in cryotherapy.

All patients were followed up for 1 year, and the main persistent postcryotherapy complication (hypopigmentation) resolved over 3–4 months.

Table 2 Treatment response and regrowth of the lesion in the 43 patients

Item	Propranolol (group I) (*N* = 23 cases) [*n* (%)]	Cryotherapy (group II) (*N* = 20 cases) [*n* (%)]	*P* value
Response to treatment			
Excellent	18 (78.3)	13 (65.0)	0.531
Good	4 (17.4)	5 (25.0)	0.813
Fair	1 (4.3)	2 (10.0)	0.900
Poor	0 (0.0)	0 (0.0)	–
Regrowth of the lesion	2 (8.7)	0 (0.0)	0.532

Discussion

Propranolol is a nonselective beta-adrenergic antagonist that is well absorbed from the gastrointestinal tract and distributed throughout the body, with the highest level in the lungs, kidneys, brain, and heart. Oral propranolol, which markedly improved the medical treatment of Fallot tetralogy and hypertrophic obstructive cardiomyopathy in children, was also considered by many authors to be the first line of treatment for

Figure 4

Patient before starting propranolol therapy.

Figure 5

Same patient 2 months after starting treatment.

Figure 6

Male baby before starting cryotherapy.

Figure 7

Same patient at the end of cryotherapy.

IHs [5,17–19]. The mechanism of action of propranolol is not well understood. Potential explanations for the therapeutic effect of propranolol on hemangiomas include vasoconstriction, which is immediately visible as a change in color, associated with a palpable tissue softening. Other proposed mechanisms of action are a downregulation of angiogenetic factors such as vascular endothelial growth factor and basic fibroblast growth factor and an upregulation of apoptosis of capillary endothelial cells [5,8].

Hogeling *et al*. [20] reported that IH significantly dropped in volume, redness, and elevation with a 6-month course of propranolol. Bertrand *et al.* [21] reported good to excellent response to propranolol for the same duration. Hassan and Shreef [22] reported complete resolution after a treatment period of 6–14 months. In this study we had 78.2% excellent response after completing 6 months of treatment with propranolol.

Although a definite reduction or even disappearance of hemangioma is well documented with propranolol [5], some authors have observed that a relative number of these lesions recur after propranolol withdrawal without possible causes [23,24]. The reported recurrence rate after stopping propranolol therapy ranged from 6 to 19% in some studies [5,25]. Sans *et al.* [24] in their series reported 8% recurrence, all of which occurred before the age of 1 year. Hassan and Shreef [22] followed gradual withdrawal of propranolol therapy over 4 weeks and saw a 3.3% regrowth rate. In this study we did not follow the gradual tapering of the dose, and two out of 23 cases (8.6%) had regrowth of their lesion after cessation of propranolol treatment. Both cases were below 6 months of age at the start of treatment. This relatively high rate of regrowth could be related to sudden interruption of treatment and to continuation of the active proliferative phase of hemangioma in these cases. This finding is in agreement with the results obtained by other authors as well [5,26].

Although the safety and efficacy of propranolol as a treatment for hemangioma have been reported in a recent systematic literature review [27], other studies reported severe hypotension and hypoglycemia even when using propranolol in the recommended doses [28]. In this study we did not encounter any significant adverse effects from propranolol apart from bradycardia, which may be related to the adjusted dose given and the good monitoring especially at the beginning of treatment. This is in agreement with the results obtained by other authors [5].

Treatment by cold application has been in use since ancient Egyptian times (3500 BC), where they were using cold application in an attempt to treat various ailments [10]. Many researchers have described the use of cryosurgery in the treatment of lesions in the skin, anorectal region, and eyes, in autolaryngeal lesions, bone, and brain diseases [14,29]. Liquid nitrogen, the most popular and effective cryogen used today, became readily available only after 1945. Use of either closed probes or spraying proved to be the most effective because of its low temperature (–195.6˚C), easy availability from medical and commercial sources, low cost, and safety of use. Also it is not flammable and is inert chemically [30]. The results obtained in 1986 at Assiut University, Egypt [10], on the use of cryotherapy for treatment of cutaneous hemangioma stimulate us to compare its efficacy, adverse effects, advantages, and incidence of recurrence in comparison with oral propranolol.

The mechanism of cell death by cryo is through the formation of intracellular and extracellular ice crystals immediately after cryotherapy. The extracellular ice reduces extracellular water, increasing solute concentration and osmolality, which causes a fluid shift and disrupts the cell membranes. Further damage is produced during the thawing process when intracellular ice damages mitochondria and the endoplasmic reticulum decreases the cell survival. Large ice crystals are more damaging than small ones. Also slow thawing is associated with the recrystallization of ice and is more destructive than rapid thawing [31,32].

In this study 20 cases were treated by cryotherapy using liquid nitrogen. Excellent results with complete involution were obtained in 65%, good results in 25%, and fair results in 10%. These rates are comparable to those reported by other authors [31,33].

There was no regrowth of lesions in any case after cryotherapy during the follow-up period. All of the adverse effects were minor and comparable to those reported by others [31,33]. It was reported that melanocytes are more affected by cold than keratinocytes [10]. This may explain the hypopigmentation in the eight cases as a complication of cryotherapy, but all cases were self-limited and improved during the follow-up period.

Study limitation

The small sample size and lack of randomization of the treatment options are the main limitations of this study.

Conclusion

Oral propranolol is a safe and effective treatment modality for cutaneous hemangioma, provided the optimum dose at the start of treatment is established and proper monitoring of the patient is implemented. Although cryotherapy application needs general anesthesia, it has tolerable side effects, gives rapid response and could be considered a second effective line in the treatment of cutaneous hemangioma.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1 Huang SA, Tu HM, Harney JW, Venihaki M, Butte AJ, Kozakewich HP, *et al*. Severe hypothyroidism caused by type 3 iodothyronine deiodinase in infantile hemangiomas. N Engl J Med 2000; 343:185–189.

2 Muliken JB. Cutaneous vascular anomalies. Semin Vasc Surg 1993; 6:204–218.

3 Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in children. N Engl J Med 1999; 341:173–181.

4 Fisherman SJ, Muliken JB. Haemangioma and vascular malformation of infancy and childhood. Pediatr Clin North Am 1993; 40:1177–2000.

5 Xiao Q, Li Q, Zhang B, YU W. Propranolol therapy of infantile hemangiomias: efficacy, adverse effects and recurrence. Pediatr Surg Int 2013; 29:575–581.

6 Hasan M, Rahman M, Hoque S, Zahid Hossain AK, Khondker L. Propranolol for hemangiomas. Pediatr Surg Int 2013; 29:257–262.

7 Bruckner AL, Frieden IJ. Hemangiomas of infancy. J Am Acad Dermatol 2003; 48:477–493 quiz 494–496.

8 Léauté-Labrèze C, Taïeb A. Efficacy of beta-blockers in infantile capillary haemangiomas: the physiopathological significance and therapeutic consequences. Ann Dermatol Venereol 2008; 135:860–862.

9 Eltayeb AA, Khalil M, Hassan Y. Non invasive management of hemangioma using intralesional bleomycin injection. Assiut Med J 2012; 36:237–243.

10 Shaker M, Eltayeb A, Al-Ossely MA. Cryosurgical treatment of cutaneous hemangioma. Assiut Med J 1986; 10:508–532.

11 Betlloch-Mas I, Martínez-Miravete MT, Lucas-Costa A, Martin de Lara AI, Selva-Otalaurruchi J. Outpatient treatment of infantile hemangiomas with propranolol: a prospective study. Actas Dermosifiliogr 2012; 103: 806–815.

12 Mouhari-Toure A, Azoumah KD, Tchamdja K, Saka B, Kombaté K, Tchangaï-Walla K, Pitche P. Rapid regression of infantile haemangioma with 2% propranolol ointment. Ann Dermatol Venereol 2013; 140: 462–464.

13 Arneja JS, Pappas PN, Shwayder TA, Cullen ML, Becker CJ, Hamzavi FH, *et al.* Management of complicated facial hemangioma with beta-blocker (propranolol) therapy. Plast Reconstr Surg 2012; 126:889–895.

14 Truong MT, Chang KW, Berk DR, Heerema-McKenney A, Bruckner AL. Propranolol for the treatment of a life-threatening subglottic and mediastinal infantile hemangioma. J Pediatr 2010; 156:335–338.

15 Enjolras O, Wassef M, Chapot R. *Introduction: ISSVA classification. Color atlas of vascular tumours and vascular malformations*. New York: Cambridge University Press; 2007: 1–13.

16 Achauer BM, Chang CJ, Vander Kam VM. Management of haemangioma of infancy: receive of 245 patients. Plat Reconstr Surg 1997; 99: 1301–1308.

17 Riyush KT, Padam SB, Yogesh KS. Comparison of efficacy of intralesional belomycin and oral propranolol in management of hemangioma. Plast and Reconstr Surg 2012; 129:733–735.

18 Park YW, Yeom KB, Choi JW, Kim DY, Shin H, Kim KH. Effect of propranolol on the treatment of infantile hemangiomas: a single tertiary center 3-year experience. J Dermatolog Treat 2014; 25:391–395.

19 Xu DP, Cao RY, Xue L, Sun NN, Tong S, Wang XK. Treatment of severe infantile hemangiomas with propranolol: an evaluation of the efficacy and effects of cardiovascular parameters in 25 consecutive patients. J Oral Maxillofac Surg 2015; 73:430–436.

20 Hogeling M, Adams S, Wargon O. A randomized controlled trial of propranolol for infantile hemangiomas. Pediatrics 2011; 128:e259–e266.

21 Bertrand J, McCuaig C, Dubois J, Hatami A, Ondrejchak S, Powell J. Propranolol versus prednisone in the treatment of infantile hemangiomas: a retrospective comparative study. Pediatr Dermatol 2011; 28:649–654.

22 Hassan BA, Shreef KS. Propranolol in treatment of huge and complicated infantile hemangiomas in egyptian children. Dermatol Res Pract 2014; 2014:541810.

23 Buckmiller LM, Munson PD, Dyamenahalli U, Dai Y, Richter GT. Propranolol for infantile hemangiomas: early experience at a tertiary vascular anomalies center. Laryngoscope 2010; 120:676–681.

24 Sans V, de la Roque ED, Berge J, Grenier N, Boralevi F, Mazereeuw-Hautier J, *et al*. Propranolol for severe infantile hemangiomas: follow-up report. Pediatrics 2009; 124:423–431.

25 Bagazgoitia L, Hernandez-Martin A, Torrelo A. Recurrence of infantile hemangioma treated with propranolol. Pediatr Dermatol 2001; 28: 658–662.

26 Arneja JS, Pappas PN, Shwayder TA, Cullen ML, Becker CJ, Hamzavi FH, *et al*. Management of complicated facial hemangiomas with beta-blocker (propranolol) therapy. Plast Reconstr Surg 2010; 126:889–895.

27 Marqueling AL, Oza V, Frieden IJ, Puttgen KB. Propranolol and infantile hemangiomas four years later: a systematic review. Pediatr Dermatol 2013; 30:182–191.

28 Lawley LP, Siegfried E, Todd JL. Propranolol treatment for hemangioma of infancy: risks and recommendations. Pediatr Dermatol 2009; 26: 610–614.

29 Yu CH, Lin HP, Cheng SJ, *et al.* Cryotherapy for oral preconcers and cancer. J Formas Med Assoc 2014; 113:272–277.

30 Ameerally PJ, Colver GB. Cutaneous cryotherapy in maxillofacial surgery. J Oral Maxillofac Surg 2007; 65:1785–1792.

31 Chen WL, Zhang B, Li JS, Yang ZH, Wang YJ, Huang ZQ, Ye YS. Liquid nitrogen cryotherapy of lip mucosa hemangiomas under inhalation general anesthesia with sevoflurane in early infancy. Ann Plast Surg 2009; 62:154–157.

32 Gage AA, Guest K, Montes M, Caruana JA, Whalen DA Jr. Effect of varying freezing and thawing rates in experimental cryosurgery. Cryobiology. 1985; 22:175–182.

33 Zhang DM, Wang YY, Lin ZY, Yang ZH, Chen WL. Liquid nitrogen cryotherapy for lip mucous membrane venous malformation in infantile. Pediatr Surg Int 2015; 31:283–285.