

# Oral B-blockers versus intralesional corticosteroids in treatment of infantile cutaneous hemangiomas

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## Aim

Infantile hemangioma (IH) is one of the most common benign tumors of childhood, with an incidence of between 4 and 10%. Multiple modalities for treatment for IH were proposed, most commonly B-blockers and corticosteroids. Our study objective was to compare between oral B-blockers and intralesional corticosteroids injections in treatment of IHs.

## Patients and methods

This was a prospective study that included 52 patients diagnosed with IH in two pediatric surgery tertiary centers in Egypt. Patients were divided into two groups: group A patients underwent intralesional injection of betamethasone at a dose of 10–40 mg/ml in three to six separate sessions at an interval of 1 month, whereas group B patients were given oral propranolol at a low dose of 0.5–1 mg/kg/day for 3–6 months. Changes in size and color of the hemangioma each month and the occurrence of any complications were recorded for 6 months. Regression of size was classified into excellent (75–100% decrease in size), good (50–75% decrease), poor (25–50% decrease), and no response.

## Results

'Good' response to intralesional corticosteroids was achieved in nine patients, whereas most patients had either 'poor' or 'no response' ( $n=14$ ). On the contrary, most patients in the propranolol group exhibited 'excellent' or 'good' response ( $n=21$ ) with only four patients not responding to treatment. Ulceration occurred in two patients who underwent intralesional steroid injection, whereas hypotension occurred in one patient with B-blockers.

## Conclusion

Our study confirms the superiority of oral B-blockers in treatment of superficial IH when compared with intralesional injection of steroids.

## Keywords:

infantile hemangioma, intralesional corticosteroids, oral B-blockers

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## Introduction

Infantile hemangiomas (IH) are the most common benign vascular tumors of infancy, occurring in 1–4% of the white infants and are less common in the African and Asian races [1,2].

IH natural course consists of a rapid proliferative phase in infancy which is followed by a gradual involutinal phase over the next several years of life. Most cases of IH are treated by active nonintervention and observation. In cases of any function-threatening hemangiomas or airway lesions, active intervention is required. Psychological affection of the child or parents and the number of lesions are also associated factors to be considered [3,4].

After being first reported by Léauté-Labrèze *et al.* [5], multiple studies have confirmed the therapeutic effect of propranolol on IH [6,7]. Before propranolol, systemic corticosteroids have been the mainstay of

treatment for several decades. However, owing to the systemic adverse effects of the drug, topical corticosteroids were used as an alternative. This was either by topical application or intralesional injections.

Our study aimed to compare between oral B-blockers and intralesional corticosteroids in treatment of infantile cutaneous hemangioma.

## Patients and methods

Two pediatric surgery tertiary centers participated in this study: Menoufia University and Benha Children Hospital. The study included 52 patients diagnosed with infantile cutaneous hemangioma. The study was

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registered and approved by the review board of the University of Menoufia. After obtaining consent, patients were randomized into two groups: group A patients underwent intralesional injection of corticosteroids (betamethasone) at a dose of 10–40 mg/ml in three to six separate sessions at an interval of 1 month, and group B patients were given oral B-blockers (propranolol) at a low dose of 0.5–1 mg/kg/day for 3–6 months.

All patients were subjected to the following: detailed history taking; thorough clinical examination to assess any associated congenital anomalies; cardiovascular workup, which was done with the help of pediatric cardiologists and involved baseline clinical observations (pulse, blood pressure, respiratory rate, weight and height); and echocardiogram. Routine laboratory investigations, including complete blood picture, liver and kidney function tests, blood glucose level, were also done. Determination of the location and dimensions of hemangioma was based on direct measurement and photographic analysis. Radiological assessment was done using Doppler ultrasound to obtain baseline data with regards to site, size, depth, vascularity and flow.

In group A patients, local injection of betamethasone was done under local anesthesia using a 22-G needle until blanching of the hemangioma is observed. According to the initial size of the hemangioma and the response to treatment, the number of sessions was calculated.

In group B patients, parents were educated about the potential complications such as vomiting, hypoglycemia, and hypotension. Moreover, they were advised to keep a record of their child's blood pressure and blood sugar at a regular interval of 2 weeks.

Patients were followed up monthly for changes in size and color of the hemangioma and the occurrence of any complications for 6 months. Regression size was classified into excellent (75–100% decrease in size), good (50–75% decrease in size), poor (25–50% decrease in size), and no response.

## Results

A total of 26 patients were included in each group, where most patients were females (15 in group A and 14 in group B), with a median age of 2 years in both groups. Patients' demographics in each group are illustrated in Table 1. Most common sites were the face followed by abdomen and back.

**Table 1 Demographics of patients included in the study**

	Group A (intralesional steroids)	Group B (oral B-blockers)
Sex	Male=11 Female=15	Male=12 Female=14
Median age (years)	1.9 (1–7–2.5)	2.4 (1.9–2.6)

In the intralesional corticosteroids group (group A), 'good' response to treatment was observed in nine patients, and 14 patients had either poor or no response. Only three patients exhibited more than 75% decrease in size after 6 months. On the contrary, most patients in the B-blockers group had either excellent or good response ( $n=21$ ), and four patients did not respond to treatment, one of which had stopped treatment owing to development of hypotension and another was noncompliant. One patient had poor response to treatment. Apart from two patients, all patients in group B displayed an improvement or fading of the color of the lesion. This was better than patients in group A, where only 19 reported improvement of appearance. Ulceration occurred in two patients after steroids injection, whereas treatment with B-blockers had to be stopped in one patient after developing hypotension.

## Discussion

Multiple treatments for treating hemangiomas have been investigated including corticosteroids (systemic or intralesional), B-blockers, interferon alpha, laser, immunomodulators, embolization, and surgery [8].

Propranolol is a nonselective  $\beta$ -adrenergic receptor blocker that was found to have three different pharmacological effects on IH: early, intermediate and long-term effects. After initiation of therapy, the B2 inhibitory effect decreases the release of vasodilator transmitters such as nitric oxide causing vasoconstriction of feeding capillaries eventually leading to a visible change of color and softening of the lesion. The intermediate effects are owing to downregulation of pro-angiogenic factors such as vascular endothelial growth factors and basic fibroblast growth factors. Finally, propranolol causes apoptosis in the post-proliferative phase, resulting in regression of the hemangioma [9].

There is no consensus on the initiation age of propranolol in treatment of hemangiomas. A recent meta-analysis showed that oral propranolol was initiated at a mean age of 6.6 months (range, 3 days to 10 years) [10] In a single-center prospective study of 174 children, propranolol was administered at a mean

age of 4.8 months (0.9–29 months) [11]. In another recent review of 28 studies on IH, propranolol was initiated during infancy at a mean age of 4.5 months (range, 27 days to 12 months). In 11 cases, propranolol was started after 12 months of age [12].

In the recent consensus conference report on hemangioma, a target dose of 1–3 mg/kg has been recommended [4]. Few authors have also used a maximum dose of 4 mg/kg/day [13].

The duration of therapy depends on the morphological type of hemangioma, extent of involvement, and the treatment indications. In a recent randomized controlled trial by Hogeling *et al.* [14], treatment was for 6 months and can be increased up to 1 year in cases of deep and mixed IH. Marqueling *et al.* [10] in their meta-analysis of 1264 children in 41 studies found that the propranolol was administered for an average duration of 6.4 months (range, 1 weeks to 15 months).

Multiple studies agreed on the therapeutic efficacy of propranolol. Again, Marqueling's *et al.* [10] meta-analysis shows that the overall response of IH to propranolol rate is 98% (range, 82–100%). The treatment response in most of the published studies is based on the visual changes in the color and volume and assessment of serial photographs. Only few studies categorized the response in terms of percentage reduction. In a study by Price and colleagues, response was categorized in terms of percentage reduction. They report more than 75% clearance in 81% of the cases over a mean period of 7.9 months. Similarly, Talaat *et al.* [7] reported 75% clearance in 75% and more than 50% clearance in 94% of their 80 cases with IH in 5–8 months (mean±SD, 6.53±0.75).

Moreover, propranolol was found to have the same therapeutic effect on life-threatening and complicated hemangiomas. Hermans *et al.* [11] reported improvement of respiratory symptoms in airway hemangioma within hours of treatment initiation with propranolol. In a recent study of 20 children with ulcerated IH, oral propranolol significantly decreased the duration of ulceration compared with the control group (8.7 vs. 22.4 weeks) [15]. Our study confirmed the therapeutic effect of B-blockers, as 80% of our patients who underwent this treatment showed more than 50% regression in size of the hemangioma.

Further studies established additive value in the treatment of superficial periocular hemangioma from combining topical beta-blockers (timolol maleate) with systemic administration [16].

Documented adverse effects of propranolol include hypoglycemia, hypotension, pulmonary symptoms, sleep disturbances, somnolence, cold extremities, and gastrointestinal complaints. These adverse reactions are found to be reversible and dose dependent [4]. In 174 patients treated for IH from a single center, 62.1% had one or more adverse reactions. The two most common problems were cold extremities and nocturnal restlessness. Lower blood pressure was observed in six (3.4%) cases. Sixteen (3.2%) patients had pulmonary symptoms, of whom nine needed treatment. In 12 (6.9%) children, gastrointestinal complaints were recorded [12]. The other adverse effects reported in the literature include irritability, profuse sweating, and temporary hypotonia [10].

Systemic corticosteroids (prednisolone) have been the mainstay of treatment for IH for several decades. The mechanism of action of steroids is not entirely clear, though it is postulated to have an inhibitory effect on the production of vascular endothelial growth factor A by stem cells in hemangiomas [17,18]. Steroids are most effective in the early proliferative phase. The usual recommended dose is 2–4 mg/kg/day, which should be continued until cessation of growth or shrinkage of hemangioma followed by gradual tapering [19].

However, long-term steroid use is associated with many adverse effects. Boon *et al.* [21] studied the complications of systemic steroids in treatment of hemangiomas, and they identified Cushingoid facies in 44 of 62 children, which began 1–2 months after starting a dose of 2–3 mg/kg/day. This was more common in patients who received therapy for more than 6 months [20]. Other adverse effects included faltering growth, weight gain, and personality changes such as mood changes, irritability, insomnia, and restlessness. Other adverse effects include gastric irritation, oral and/or perineal candidiasis, and steroid myopathy. Mazzola [22] first reported the use of intralesional corticosteroid injection for the treatment of hemangiomas in an attempt to overcome the steroidal systemic effects.

A systematic review by Prasetyono and Djoenaedi [23] found excellent results in 71% and good results in 23.4% in cases of head and neck hemangiomas treated by intralesional steroids, most commonly triamcinolone acetonide. Few cases exhibited systemic complications, with 42% of cases reporting no complications, either systemic or local. The most common local complication reported was ulceration

(10 cases) followed by atrophy of skin (six cases). In a smaller study including six patients, all patients were reported to experience adrenal suppression [24]. In our study, 53% of our patients exhibited poor or no response to treatment, and ulceration occurred in two patients.

## Conclusion

Our study confirms the superiority of oral B-blockers in the treatment of superficial IH when compared with intralesional injection of steroids. B-blockers display more effective lesion clearance whether in size or color and are associated with fewer complications. Combining that with the easier administration orally when compared with intralesional injections, we believe oral B-blockers should be considered as the first-line agent in treatment of IH.

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## Conflicts of interest

There are no conflicts of interest.

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