Infantile hemangiomas (IH) are the most common childhood tumors [1]. They typically occur in infants after a few weeks of life and are more frequent in girls [2]. Despite their usually benign, self-limited course, IH can impair vital or sensory functions, or cause disfigurement that is difficult to correct later in life [3]. Hemangiomas can also be complicated by painful ulcerations that are very slow to heal [4]. There has been no effective treatment for IH until now, so a conservative management approach has generally been adopted [5]. However, approximately 10% suffer from problematic IH and require medical intervention [1]. The gold standard treatment has been the use of corticosteroids [6]. Other treatment options include interferon alpha [7], vincristine [8] and pulsed dye laser therapy [9]. These therapeutic modalities have recently been over-shadowed by the use of oral propranolol, a non-selective beta-blocker that can inhibit the vascular proliferation of IH [10].

In 2008, Labreze first reported the serendipitous effect of propranolol on a child with facial hemangioma [3]. Since then, other case reports and cohort studies have documented the effectiveness of propranolol in causing accelerated involution of IH, with a relatively high safety margin [11]. This prompted us to conduct a prospective study on thirty infants with problematic IH. The aim of this study was to assess the efficacy and safety profile of oral propranolol at a fixed dose of 2 mg kg\(^{-1}\) in the treatment of IH in Egyptian patients.

Patients and methods

This prospective, clinical study was approved by the Dermatology Research Ethics Committee, Faculty of Medicine, Cairo University and informed consents were obtained from the parents of all infants before conducting the study. Thirty consecutive patients with problematic IH were recruited from Cairo University Hospital and Abo El-Reesh Pediatric Hospital. Problematic IH was defined as any rapidly progressive, and/or ulcerating and/or recurrently bleeding IH. Also, any IH compromising any vital structure (vision, airways ...), or normal physiological function (feeding, micturition, defecation ... ) were considered problematic. In addition, any IH that most likely would lead to a cosmetic deformity in the future or was causing psychological distress to the parents was included.

Any child with a cardiovascular disorder or bronchial asthma or insulin dependent diabetes mellitus (IDDM) was excluded from the present work. This was revealed in the pre-treatment evaluation (figure 1). Any alternative treatment prescribed for IH was discontinued for six months prior to inclusion.

Initial cardiac evaluation

Prior to inclusion in the present study, all patients were subjected to a detailed cardiac evaluation through:
Propranolol was given at a dose of 2 mg kg\(^{-1}\), in 3 equally divided doses. This fractionization was advised by our pediatric cardiologist as the safety of propranolol on cardiac rhythm and rate has always been a concern. In the arrhythmology service unit, Faculty of Medicine, Cairo University, it was noticed that 3 divided doses is accompanied by relatively fewer side effects and equal efficacy to 2 divided doses, when given to infants below one year. For standardization purpose we used 3 divided doses for all included children. Patients were kept under observation for the first 24 hours, where blood pressure and heart rate were measured every 30 minutes for 4 hours after each dose. Blood glucose was measured if clinically indicated, based on symptoms of clamminess, distress or irritability.

If observations were stable, patients were discharged to be followed up on a weekly basis for the first month, then every 2 weeks in the second month, and finally at a 4 week interval till a period of 4 months after the treatment was stopped (follow up period).

Follow-up work up

All patients in their follow-up visits were subjected to full clinical evaluation and photographic documentation. Doses were adjusted according to any changes in the body weight. Echocardiographic examination, ECG and laboratory investigations were repeated at two month intervals, unless indicated otherwise by the pediatrician, based on clinical symptomatology. Any side effects associated with propranolol treatment were recorded, as well as any relapse episodes after stopping the treatment. Treatment was stopped if complete resolution occurred, or if a sustained plateau in the size of the hemangioma was reached with a period of 2 months of treatment, or if any intolerable side effects from propranolol developed.

A subjective grading system was designed to evaluate the effectiveness of oral propranolol in the treatment of IH. The response to propranolol therapy was evaluated by 2 fixed investigators by comparing the improvement seen in the photographic documentation before and after therapy. Together they gave a final grade of excellent (Complete resolution achieved), good (Sustained plateau, with \( \geq 50\% \) reduction in size of IH), fair (Sustained plateau, with \(< 50\% \) reduction in size of IH) or poor (No response, worsening of IH, intolerable side effects necessitating stopping therapy).

Statistical analysis

Data were presented as means±standard deviations, median and number percentage for frequency distributions. Analytical tests used included unpaired student \( t \) test (two sided) for comparing two groups. A p value less than 0.05 was considered statistically significant. The statistical analysis was done using the Statistical Package for Social Sciences (SPSS software v. 15, SPSS Inc. Chicago, IL, USA).

Results

A total of 30 patients (21 females (70%), 9 males (30%)), aged 3-20 months (mean 6 months±23 days) with problematic hemangioma were included in our prospective clinical study. The patients received oral propranolol therapy at a fixed dose of 2 mg kg\(^{-1}\), in 3 equally divided doses. The location of the IH varied as follows: 50% in head and neck area (n=15), 10% on the chest (n=3), 20% on the genitalia (n=6), 10% on upper limbs (n=3) and 10% on lower limbs (n=3).

In our study, recurrent attacks of bleeding was the major indication for starting treatment (n=15, 50%). This was followed by ulcerating infantile hemangioma (n=9, 30%). Other indications included impairment of normal functions such as breast feeding (n=2, 6.66%), micturition (n=1, 3.33%) and defecation (n=2, 6.66%). Only one patient...
Propranolol treatment outcome

The initial response seen in all patients was the change in the hemangioma color from intense red to a lighter purple-blue, associated with palpable softening of the lesion. This initial response was evident in 10% of the patients (n=3) within the first 24 hours. At the first week follow-up another 33.3% (n=10) showed a similar response. By the end of the third week the blanching and softening was evident in 90% of the patients (n=27). After this initial response, hemangiomas continued to improve as regards regression of their size, flattening of the lesion and more evident blanching of the color. The extent of regression was documented in each visit.

As regarding the ulcerating hemangiomas, 5 out of the 9 cases (55.5%) showed successful epithelialization and complete resolution of the pain by the 4th-6th week. Other cases showed a gradual improvement of pain but complete healing of the ulcer did not occur until between the 8th-12th week. Only one case was resistant and stopped treatment by the 8th week.

The propranolol treatment was continued for a duration of 2-14 months (mean duration 7 months ± 6 days) (table 1). It is worth noting that the 2 month duration is that of the failed patient where treatment was discontinued after sustained failure to respond according to the protocol. 60% of the patients (n=18) showed a final excellent response with complete resolution of the lesion (P<0.001). 20% of the patients (n=6) showed a good response with a more than 50% reduction in the size of the IH. 16.6% showed a fair response (n=5) with less than 50% reduction in the size of the IH (figure 2). Only one patient (3.3%), previously mentioned, was resistant to treatment i.e. showed a final poor response.

Rebound growth

Of the 29 patients who showed various degrees of response to the propranolol therapy, 17.24% (n=5) showed evidence of rebound growth after cessation of therapy. This rebound growth occurred in the form of sudden increase in size and/or worsening of color in 4 patients, while the 5th patient showed re-emergence of ulceration (table 2). These patients received oral propranolol at a dose of 2 mg/kg-1 and were reassessed in the same way as for the initial therapeutic regimen. All patients responded to the treatment after a shorter duration than the first time.

Cardiovascular follow up

All patients had baseline resting heart rates normal for their age with a range of 98-117 BPM. All patients had systolic and diastolic blood pressures between the 5th and 70th percentiles for age. Echocardiographic assessment revealed normal examinations in all the study group. All measurements were within normal ranges for age, with an average left ventricular end diastolic diameter (LVEDd) of 25.1±2.5 mm, a fractional shortening averaging 32.7±2.1% and an ejection fraction of 67.2±5.1%.

Upon regular follow up at two monthly intervals; none of the assessed parameters (heart rate, blood pressure or echocardiographic measurements) showed any statistically significant differences as compared to baseline parameters (p>0.05).

Side effects

No major side effects were noted in any of our 30 patients either throughout the treatment period nor during the follow-up period. Propranolol therapy was not stopped in any patient because of side effects.

Discussion

In this prospective clinical study, conducted on 30 consecutive patients with problematic infantile hemangioma, the efficacy of propranolol at a fixed dose of 2 mg/kg-1 was confirmed. 80% of our patients showed a final “excellent-good” response (60% excellent with complete resolution of the lesion, 20% good with >50% reduction in the size of the hemangioma) irrespective of size or location of IH. Also (8/9) cases of ulcerating hemangiomas showed successful healing and resolution of pain within 4-12 weeks. This response rate is in agreement with the results attained by other several studies that have shown successful response of IH to oral propranolol with doses ranging from 1-2 mg/kg-1/day using different modes of administration [14]. Qin et al. (2009) [15] conducted one of the largest studies to date using propranolol on 58 infants with IH at a dose 1-1.5 mg/kg-1/day. They reported a response rate “good to excellent” in 67% of patients. We achieved better clinical results and speculated that this could be due to using a larger dose. Recent in vitro studies suggested that the efficacy of propranolol in reducing proliferation of tumor stem cells [16] and placental endothelial cells [17] is dose-dependent. On the other hand we achieved a higher response rate than Holmes et al. (2010) [1], who used a higher dose (3 mg/kg-1/day) than the one used in the present study. 13% of their cases showed no evidence of regression during the treatment course in comparison with 3.3% in our clinical study. This may be related to the age of beginning of the oral propranolol therapy. We, however, achieved a slower rate of response than in that study, which reported an initial response of halting hemangioma proliferation and marked change in color from intense red to dark blue/purple in 74% of patients within 48 h and 97% of patients within 2 weeks. Healing of ulcerating hemangiomas was reported to be as early as 3 weeks. In the present study, this initial response was observed in only 10% within 24 h and 90% by the end of the third week. Also, our ulcerating hemangiomas took a longer time to show complete healing [8/9 cases within 4-12 weeks]. It could be hypothesized that the higher propranolol dose may be related to the rapidity of the response.
Table 1. Summary of the age of initiation (months), duration of treatment (months) and response achieved of all included patients.

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of IH to oral propranolol. This assumption was further supported by the fact that the healing rate in the present study was faster than that achieved when using propranolol at lower doses 1 mg/kg⁻¹ (8-18 weeks) [18]. Again this speculation was contradicted by the results achieved by Manuza et al. (2010) [10] who reported a rapid initial response, within 1 week in (26/30) infants included in their study using only 1 mg/kg⁻¹/day and when they increased the dose to 2 mg/kg⁻¹/day the other 4 patients responded within 1 month.

According to those previously mentioned contradictions, it was speculated that other factors than the propranolol dose may be influential on the response achieved from using oral propranolol in treating IH. One of those factors may be that suggested by Tan et al. (2010) [5], which is the crucial role for the renin-angiotensin system (RAS) in IH. This is supported by the clinical observation of a higher incidence of the tumor in Caucasians, females and premature infants in whom renin is naturally higher [19]. It has been shown that RAS is responsible for controlling the endothelial

Figure 2. A 4-month old girl presented with a large hemangioma on the right side of forehead, upper eye lid (A), nasolabial fold and lip (C). B, D) Same patient after 4 months of oral propranolol showing complete involution of the lesions. E) A 5-month old boy with hemangioma on the right thigh and scrotum and same patient after 5 months of therapy with complete resolution of lesion on thigh and scrotum (F). G) An 18 month old patient with hemangioma on the right cheek, upper part of the neck and behind the ear, and a fair response after 6 months of therapy (H).
progenitor cells within the proliferating hemangiomas [20]. There is evidence of genetic polymorphisms [21] and possible racial variations [22] in the RAS system which might influence the response of the IH to oral propranolol; as we notice a difference in the pattern of response observed in our Egyptian patients from other Caucasian IH patients [1-5].

The whole hemangioma/propranolol picture is not fully clear. The regulators of hemangioma growth and involution are poorly understood. During the growth phase, two major pro-angiogenic factors are involved: basic fibroblast growth factor (bFGF), and vascular endothelial growth factor (VEGF) [6]. During the involution phase, apoptosis has been shown [7]. Potential explanations for the therapeutic effect of propranolol on IH include vasoconstriction [23], and which is supported by the initial response of color change from deep red to blue/purple and continuous blanching of the lesion, as well as the palpable softening of the IH. Propranolol then leads to decreased expression of VEGF and bFGF through the down-regulation of the RAF-mitogen-activated protein kinase pathway [24], and apoptosis of capillary endothelial cells [25]; this explains the progressive improvement of hemangioma. Storch and Hoeger (2010) speculate it may be a combination of all this [26].

Despite the great efficacy of propranolol, relapses may occur. In this study 17.24% (n=5) patients showed evidence of rebound growth after cessation of therapy. Looking closer at our patients, 4/5 patients were less than a year old when the treatment was stopped, highly suggesting that the age at treatment cessation may be the most important factor related to relapse events. This is supported by many other studies [1, 2, 5], in which the rebound growth was significantly higher when propranolol was stopped at younger ages. This can be explained by the fact that in the first year the IH is in its active proliferative phase, and then this phase gradually comes to an end and the balance between pro-angiogenic and pro-apoptotic factors is shifting [27]. These data plead for the prolongation of the propranolol therapy without interruption, at least until the age of spontaneous regression of IH, beyond 12-18 months of age.

In the present study the high safety profile of propranolol was confirmed as we did not face any side effects related to the oral propranolol. Propranolol has been used extensively in the pediatric population for a wide range of medical conditions in doses as high as 7 mg/kg -1/day [28]. The known side effects of propranolol include bronchospasm, hypoglycemia, mood disturbances, bradycardia and hypotension. However, a recent 40-year review of propranolol toxicity in children found no fatalities and side effects that either resolved once propranolol was stopped, or resolved spontaneously [29]. This high safety profile gives the propranolol therapy an edge over other modes of IH treatment.

Despite this documented high safety profile, still Holmes et al. [1] and Leboulanger et al. [2] recommended a full cardiovascular work-up to be performed prior to the initiation of propranolol therapy, to identify patients in whom the commencement of propranolol therapy could be dangerous. There is as yet no generally accepted consensus on the ideal treatment regime with propranolol [1]. In the present study, it was shown that propranolol therapy, at 2 mg kg-1 in three equally divided doses, given without the need for gradually increasing the dose or gradual weaning, is a very safe and effective regimen in the treatment of IH. As we reported, there were no side effects and significant regression up to complete resolution of the lesions in 80% of our patients was achieved. Only one patient was resistant to the treatment.

Still, larger clinical studies are needed to establish the best regime for oral propranolol as regarding the dose and duration of treatment. Also, further understanding of the exact mode of action of propranolol, and the factors influencing the response rate will be very beneficial. We believe that more studies should be done to clarify the impact of racial and genetic differences on the response rate of infantile hemangioma to oral propranolol.


**References**


