

## Research Article

# Surgical Treatment of Infantile Hemangiomas in the Era of Propranolol

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**Abstract**

**Background:** Despite the proven efficacy and safety of beta-blockers in the management of infantile hemangiomas (IH), there are still many patients requiring surgical treatment. The aim of our study is to analyze the current indications for surgical treatment of IH in the era of propranolol.

**Methods:** This is a retrospective study from 2009 until 2014, including 45 children (38 females and 7 males) referred from other centers to our institution for surgical treatment of an IH. Epidemiological, clinical and treatment data were collected and variables analyzed.

**Results:** Of the 45 patients included in the study, 22 patients were not offered any treatment as it was not considered necessary, 16 were treated with a systemic b-blocker, 3 patients, despite being considered candidates for propranolol therapy, refused it for fear of potential adverse side effects and the remaining 4 received an alternative treatment. The average age of patients at their first visit to surgery consultation was 32.41 months (SD 36.71), the average age of initiation of treatment with propranolol was 10.58 months (SD 7.99) and the average age at time of surgery was 29.11 months (SD 16.10).

**Conclusion:** No indication for propranolol treatment or the delays in its administration are the main current causes of surgical treatment of IH. Therefore it is important to improve protocols to establish more effective and preventative guidelines that would reduce the need for subsequent surgery.

**ABBREVIATIONS**

**IH:** Infantile Hemangiomas ; **SD:** Standard Deviation.

**INTRODUCTION**

The infantile hemangioma (IH) is the most common benign tumor in children with an incidence of 4-10% in children with a predominance in the female sex [1-2]. It is usually not present at birth and has a natural characteristic history with a rapid proliferative phase during the first months of life followed by a slow proliferative phase and an involutonal period which can last until the 5th-7th year of life [2]. Around 40-50% of hemangiomas lead to sequelae as telangiectatic residual lesions, skin atrophy or pigmentary changes. 10-15% may develop complications such as ulceration, bleeding or infection [2].

Due to their usual spontaneous involution, only 10% of IH require treatment, mainly those whose location may compromise

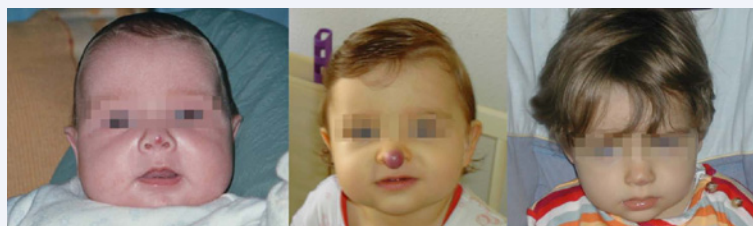
a function (periorbital, perioral, nasal or airway), large segmental hemangiomas and complicated hemangiomas [2-5].

Indications for surgical treatment of IH have been significantly reduced due to recent improvements in their pharmacological treatment. After the discovery in 2008 by Léauté-Labrèze et al. of the effectiveness of propranolol treatment, the systemic beta-blockers have emerged as a first-line treatment, with a 98% success rate in both cutaneous and visceral hemangiomas [1, 6-9].

However, despite propranolol's proven effectiveness, too many patients still require surgical treatment. The aim of our study is to evaluate why patients with infantile hemangiomas are still being treated surgically and if surgery could be avoided.

**MATERIALS AND METHODS**

We present a retrospective study reviewing 45 children



**Figure 1** Patient considered not candidate for propranolol therapy due to minimal size of a nasal tip IH. Aggressive proliferation in the following weeks needed later surgical correction.



**Figure 2** Very low birth weight patient result of a IVF with nasal IH. Parents refused propranolol administration due to the potential side effects. Final result after resection of the IH and rhinoplasty.

referred from other hospitals to our Vascular Anomalies Clinic for surgical removal of an IH in the last six years. Excluded from the study were those patients who required surgery to correct post involutonal IH sequales, since many of them were not given the option to be treated with propranolol before 2009.

The natural history of all of them was typical for IH. Resected specimens uniformly stained positively for GLUT-1.

Of the 45 patients (38 female and 7 male) 6 were the result of an in vitro fecundation, 4 were twins and 8 had a birth weight less than 2000g. Of the 45 hemangiomas treated, 36 were mixed and 9 were superficial. Hemangiomas were located as follows : 9 periorbital, 10 nasal, 3 on the cheek, 7 on the lip, 4 on the ear, 3 on the scalp, 2 on the upper extremities, 1 on the lower extremities, 1 on the back, 3 on the thorax and 2 on the abdomen.

Collected information included sex of the patient, location and size of the hemangiomas, age of the first evaluation by a surgeon , age at surgery, previous treatments, and in patients receiving propranolol, information about the specialist who prescribed the treatment, age at the initiation of treatment and duration.

Continuous quantitative variables were defined with descriptive statistics, mean and standard deviation (SD). By having parameters showing a normal distribution, the different data were studied using parametric tests: the Chi-square test for comparing proportions and the Student t test to compare the means of two groups. A confidence level of 95% ( $p = 0.05$ ) for comparison was established.

## RESULTS AND DISCUSSION

All IH included in our study fulfil the criteria accepted by consensus documents for pharmacological treatment: functional compromise, ulceration and size [2-5]. However, only 16 were treated with propranolol.

The average age of patients at the time of the first visit to our

unit was 32.41 (SD 36.71) months, 14 patients had been referred by a pediatrician while 31 patients had been previously evaluated by a dermatologist.

Among the 29 patients who did not take propranolol, 22 patients were not treated, as the specialist in charge predicted a complete involution without sequelaes. Parents of 3 of the patients, despite being prescribed propranolol, declined its administration because of potential side effects and the remaining 4 patients were offered an alternative treatment: topical b-blocker (which was ineffective) in 2 cases , and prednisolone which was partially effective in one patient and ineffective in the other (Table 1).

Of the 16 patients treated with propranolol, 11 patients were treated at a dose of 2 mg/kg/day and 5 at a dose of 3 mg/kg/day. In 6 patients, propranolol had a poor effect with minimal reduction in size and color, in 9 patients the effect was moderate (significant but incomplete reduction in both size and coloration). One patient showed a rebound after treatment withdrawal. The mean age at the initiation of treatment was 10.58 (SD 7.99) months and if we divide the patients according to their response to treatment we can highlight that the age of initiation of treatment in the group of patients in which treatment with propranolol had a mild effect was 16 months (SD 9.03), the average age of initiation of treatment in cases in which it had a moderate effect was 9.03 months (SD 5.77), with a statistically significant difference ( $p = 0.036$ ) in the age of initiation of treatment between the two groups.

Two patients treated with propranolol had been wrongly diagnosed as venous malformation and this error being the reason for delay in the initiation of treatment.

The average duration of treatment in the group of patients where the drug had a mild effect was 6.83 months (SD 4.30) and among patients who partially responded to treatment was 15.87 months (SD 6.97). These two groups showed a statistically significant difference ( $p=0.012$ ). The distribution by sex in the

**Table 1:** List of patients who did not receive treatment with oral propranolol.

	Sex	Location of IH	Referred to our Specialist Unit	Reason for absence of treatment with propranolol	Age in months at surgery
1	Male	Periorbital	Pediatrician	Not offered	9
2	Female	Scalp	Pediatrician	Not offered	33
3	Female	Nose Tip	Pediatrician	Not offered	32
4	Female	Periorbital	Pediatrician	Not offered	12
5	Male	Chest Wall	Dermatologist	Not offered	25
6	Female	Periorbital	Dermatologist	Not offered	27
7	Female	Nose Tip	Dermatologist	Fear of side effects	26
8	Female	Cheek	Dermatologist	Fear of side effects	6
9	Male	Nose Tip	Dermatologist	Not offered	17
10	Female	Ear	Pediatrician	Not offered	26
11	Female	Chest wall	Pediatrician	Not offered	30
12	Female	Scalp	Dermatologist	Not offered	35
13	Male	Cheek	Dermatologist	Not offered	35
14	Female	Ear	Pediatrician	Not offered	39
15	Female	Lip	Dermatologist	Not offered	21
16	Female	Lip	Dermatologist	Not offered	45
17	Female	Upper extremity	Dermatologist	Fear of side effects	21
18	Female	Lip	Dermatologist	Not offered	46
19	Male	Ear	Dermatologist	Not offered	18
20	Female	Nose Tip	Pediatrician	Not offered	20
21	Female	Upper Extremity	Dermatologist	Not offered	39
22	Female	Back	Pediatrician	Not offered	7
23	Female	Periorbital	Dermatologist	Not offered	16
24	Female	Lower Extremity	Pediatrician	Not offered	34
25	Female	Nose Tip	Dermatologist	Not offered	19
26	Female	Ear	Pediatrician	Not offered	14
27	Female	Cheek	Pediatrician	Not offered	5
28	Female	Scalp	Dermatologist	Not offered	57
29	Female	Chest Wall	Dermatologist	Not offered	37

**Abbreviations:** IH : infantile hemangiomas

group of patients with mild effect (1 man and 5 women) compared to the group with partial effect (1 man and 9 women) showed no statistically significant difference ( $p = 0.696$ ). The treatment was prescribed in 1 case by a pediatrician, in 6 cases by a surgeon and in 9 cases by a dermatologist. One patient of 13 months with a facial hemangioma showing partial response during the 4 months of treatment presented a rebound at the end of treatment (Table 2). The average age at the time of surgery was 29.11 (SD 16.10) months. Despite two patients needing a scar revision all patients were satisfied with the final cosmetic outcome.

The institutional protocol for IH propranolol therapy at The Vascular Anomalies Center in La Paz Children's Hospital consider as candidates patients with potentially deforming facial hemangiomas in addition to those that may compromise function or develop complications. This group of patients is reviewed weekly rather than monthly as changes may be irreversible if

the proliferation is aggressive. Propranolol administration is initiated between the 4th or 6<sup>th</sup> week of life for those IH. In this study, patients were referred from other centers and received different treatment protocols.

Particularly striking was that despite the proven superiority of systemic propranolol over other treatment options, 26 patients were not offered this treatment, 2 patients were given topical propranolol and the other 2 a corticosteroid [1]. Most patients who were prescribed a pharmacological treatment for IH would probably have evolved more favorably if the treatment had been introduced earlier as evidenced by the low incidence of surgical treatment in children treated with propranolol early. In fact, in our experience of the last five years, only one child treated before 6 weeks of life required surgical correction for non-response, which corresponded to an inappropriate administration of the medication.

**Table 2:** List of patients treated with propranolol orally.

	Sex	Location of IH	Referred to our Specialist Unit	Age at start of treatment with propranolol (months)	Effect of propranolol	Age at surgery (months)
1	Female	Periorbital	Pediatrician	12	Mild	21
2	Female	Periorbital	Dermatologist	12	Mild	11
3	Female	Periorbital	Pediatrician	0.3	Moderate	3
4	Female	Nose tip	Dermatologist	12	Moderate	22
5	Female	Nose tip	Dermatologist	6	Moderate	20
6	Female	Chest Wall	Dermatologist	3	Moderate	31
7	Male	Periorbital	Dermatologist	30	Mild	47
8	Female	Nose tip	Dermatologist	9	Rebound effect	56
9	Female	Periorbital	Dermatologist	24	Mild	46
10	Female	Lip	Dermatologist	12	Moderate	24
11	Female	Chest Wall	Dermatologist	12	Mild	23
12	Female	Lip	Dermatologist	18	Moderate	50
13	Female	Lip	Dermatologist	4	Moderate	64
14	Female	Lip	Dermatologist	7	Moderate	61
15	Female	Nose tip	Dermatologist	6	Mild	19
16	Female	Nose tip	Dermatologist	2	Moderate	61

**Abbreviations:** IH : infantile hemangiomas

Of the 16 patients who were treated with propranolol it was only moderately effective for 9 patients. We believe that this is related to a delay in the start of treatment since the average age of initiation of treatment with propranolol in our study is 10.58 (SD 7.99) months which is near the end of the proliferative phase and when the hemangioma has already reached its full size. When comparing the average age in the group of patients in which propranolol had a moderate effect, 9.03 (SD 5.77) months, compared to the average age of patients in the group that had a mild effect, 16 (SD 9.03) months, we obtained a statistically significant difference supporting the theory that propranolol is more effective the sooner the treatment starts even in locations where treatment seems difficult [13]. We found a statistically significant difference between the mean duration of treatment in the group of patients where treatment had a mild effect [6.83 (SD 4.30)] and among patients who responded moderately to the treatment [15.87 (SD 6.97)].

Research is still needed in order to elucidate which IH need short or long propranolol courses.

No blood markers are available to predict different behaviour between two IH. In addition, two IH in the same individual can present a different behaviour. Unlike other studies we have not found a different response to treatment with beta-blockers according to the sex of the patient. Male and female in the groups of patients with a mild response and a partial response did not show statistically significant differences [4].

When reviewing the age of the first evaluation by a surgeon we can detect a delay in the average age of the first assessment being 32.41 (SD 36.7) months. In addition, of the 45 patients in the study, 14 patients were directly referred by a pediatrician while 31 patients had been previously evaluated by a dermatologist.

However, the treatment was prescribed by 9 dermatologists, 1 by a pediatrician and 6 by a surgeon. Not one single patient was previously evaluated by a multidisciplinary team. Therefore, these data confirm that the best option for an optimal IH management is the evaluation in the first month of life by a specialized referral vascular anomalies team.

## CONCLUSION

This study shows evidence that inappropriate management with absence or delay in the administration of propranolol are the main causes of surgical indication for treatment of infantile hemangiomas. All patients with facial infantile hemangiomas should be reviewed weekly for 4-6 weeks by a multidisciplinary team setting guidelines for early treatment to reduce the need for surgical treatment.

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