

# Effectiveness of propranolol for treatment of infantile haemangioma

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## ABSTRACT

**INTRODUCTION:** Infantile haemangiomas (IH) are the most common benign tumours in children. They are characterised by rapid growth during the first year of life followed by spontaneous regression during childhood. Indications for treatment are functional impairment, bleeding/ulceration, rapid growth and severe aesthetic risk. Recently, systemic treatment with propranolol has become the first-line therapy. The objective of this study was to assess the efficacy of propranolol in the treatment of IH and to investigate whether treatment with a low dose of 1 mg/kg/day was sufficient.

**MATERIAL AND METHODS:** This study was retrospective and based on a review of children treated for IH with propranolol from the 2010-2012 period at Rigshospitalet.

**RESULTS:** Overall, propranolol was effective in all but one child (97%). The majority of the children (84%) were treated with an initial dose of 1 mg/kg/day, which was considered sufficient in most cases (71%). Children who started treatment before five months of age had a significantly better response than children who started treatment at a later age. No relation was found between location of IH and the effect of treatment. There were only few and mild side effects.

**CONCLUSION:** Propranolol is effective in the treatment of IH and it has only few and mild side effects. In most cases, a low dose of 1 mg/kg/day was sufficient. Early initiation of treatment is recommended as the response to treatment was better in younger children and because early initiation helps prevent large residual changes.

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cus is on the time of appearance and the growth pattern, as well as clinical examination supplemented by Doppler ultrasound and in some cases magnetic resonance imaging (MRI). Furthermore, ultrasound-guided biopsy or surgical biopsy can be useful in particular cases as the detection of glucose transporter protein 1 (GLUT1) is a highly selective marker of IH [3]. 70-80% of IH require no treatment owing to spontaneous involution [4]. Indications for treatment are functional impairment, bleeding/ulceration, rapid growth and severe aesthetic risk, for instance in case of facial IH [4]. Previously, the treatment for IH consisted primarily of systemic or intralesional steroids, laser or surgery [4].

Recently, systemic treatment with propranolol has become the first-line therapy. Leaute-Labreze et al were the first to describe the antiproliferative effect of propranolol on IH in 2008 [5]. The treatment has been used since 2010 at Rigshospitalet (RH). Hypotheses regarding the effect of propranolol on IH include vasoconstriction, decreased expression of vascular endothelial growth factors and induction of apoptosis [6]. Uncertainty remains about the optimal dosage and duration of treatment. Generally, a dose of 2-3 mg/kg/day given as 2-3 divided doses [7-13] is being used and found to be efficient and safe.

The objective of this study was to assess the efficacy of propranolol in the treatment of IH and to investigate whether sufficient effect could be achieved with treatment at a dose of 1 mg/kg/day, which is a lower dose than that used in other studies. Furthermore, we investigated whether the age at start of treatment and the location of IH influence the effect of treatment.

## MATERIAL AND METHODS

All children with complicated IH are referred to the Multidisciplinary Team of Vascular Lesions and the Department of Paediatrics and Adolescent Medicine at RH.

This study is retrospective and based on a review of children treated for IH with propranolol from 2010 to 2012. Children who had previously been treated with intralesional steroid injections or laser were excluded.

## Treatment protocol

Propranolol was administered as an initial dose of 1 mg/kg/day given as three divided doses [14]. In case of inad-

## ORIGINAL ARTICLE

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Infantile haemangiomas (IH) are the most common benign tumours in children (incidence 3-10%) and they occur more frequently in girls than in boys (sex ratio 3:1) [1]. IH are present as a faint red mark at birth or develop within the first weeks of life. They proliferate rapidly, particularly during the first 3-6 months after birth [1]. During the second year of life, spontaneous regression sets in and regression is typically complete before the age of ten years. Complete resolution is seen in 50% of children by the age of five years and in 70% by the age of seven years [2].

The diagnosis is based on clinical history where fo-

 **TABLE 1**

Location of infantile haemangioma (IH).

Location	IH, n (%)
Head and neck	19 (50)
Periocular	10
Cheek	4
Perinasal	2
Perioral	1
Periauricular	1
Forehead	1
Truncus/extremities	14 (37)
Extremities	4
Anogenital	4
Back	2
Chest	3
Abdomen	1
Visceral	5 (13)
Liver	5
Total	38 (100)

 **TABLE 2**

Age at start of treatment and response to treatment<sup>a</sup>.

Age at start of treatment	Excellent response, n (%)	Satisfactory response, n (%)	Total <sup>b</sup> , n
0-4 months	12 (71)	5 (29)	17
5-22 months	4 (25)	12 (75)	16

a)  $p = 0.015$ , Fisher's exact test.

b) 33 children with response to treatment.

equated response after two weeks of treatment, the dose was increased to 2 mg/kg/day. After a few weeks, the dose could be administered as two daily divided doses as may entail better compliance and because it allows the use of tablets instead of mixture. The daily dose was usually not adjusted to weight gain. Treatment was continued until at least one year of age or until the IH remained stable for 2-3 months. Half dose was given for two weeks before cessation of treatment.

All children were assessed clinically by a paediatrician before starting treatment. The assessment focussed on general and nutritional condition, cardiac or respiratory symptoms.

Children who were younger than one month of age and children with a low birth weight or failure to thrive were hospitalised for 1-2 days in order to monitor their blood pressure, pulse and blood glucose during initiation of treatment. Echocardiography was performed in children younger than three months of age in order to exclude cardiac anomalies. Response to treatment and side effects were evaluated after two weeks of treatment and then at 1-2-month intervals.

### Outcome measure

The outcome measure is based on the assessment of the response to therapy stated in the medical records. The following terms were considered as excellent response to treatment: decreased strongly/significantly, immediate/obvious regression. The following terms were considered a satisfactory response to treatment: decreased, improved, less tense/swollen. The following terms were considered an inadequate response to treatment: started to grow, no regression, unchanged.

*Trial registration:* not relevant.

### RESULTS

A total of 41 children with IH were treated with propranolol from 2010 to 2012 at the RH. Four children were excluded as they had previously been treated with intralesional steroid injections or laser. Therefore, 37 children were included in the study, 28 girls and nine boys (ratio = 3:1).

#### Number of infantile haemangioma cases

In total, 25 children (68%) had one IH. Twelve children (32%) had more than one IH, of whom two had more than five IH.

#### Location and indications for treatment

The majority of the children with multiple IH only had one IH that required treatment. One child had two IH requiring treatment (one periocular and one perioral). The locations of 38 IH requiring treatment are listed in **Table 1**. The indications for treatment of the 38 IH were as follows: functional risk 47% (periocular:  $n = 10$ , anogenital:  $n = 4$ , perinasal:  $n = 2$ , perioral:  $n = 1$ , periauricular:  $n = 1$ ), rapid growth 26% ( $n = 10$ ), bleeding/ulceration 13% ( $n = 5$ ) and intrahepatic location 13% ( $n = 5$ ).

#### Age at initiation of treatment

The median age at initiation of treatment was five months (0.1-22 months). In total, 27 children (73%) started treatment before the age of eight months. Six children (16%) were more than 12 months old when they started treatment.

#### Observation and duration of treatment

The median time of observation (time from first to last contact) was 7.5 months (1.5-27 months). The median duration of treatment was 6.75 months (1.5-12 months), and the median age at cessation of treatment was 10.75 months (3-30.5 months).

#### Initial dose of propranolol

In total, 31 children (84%) were treated with an initial dose of propranolol of 1 mg/kg/day in accordance with

the protocol. Five children (13%) were treated with an initial dose of 1.5-2 mg/kg/day. These children had intra-hepatic or periocular IH and/or started treatment relatively late (> 12 months). One child (3%) received an initial dose of 0.5 mg/kg/day for the first two weeks because of recent surgery for ventricular septal defect and ongoing treatment for heart failure.

### Effect of treatment

It was possible to assess the effect of treatment in a total of 34 out of 37 children, since one child could not be followed and two children discontinued treatment due to adverse events after a very short time. These three children were treated with a dose of 1 mg/kg/day. At the end of this study, 16 out of 34 children (47%) had completed treatment with propranolol, and 18 children (53%) were still under treatment.

An overall effect of treatment was seen in 33 out of the 34 children (97%) (**Figure 1**).

The response to treatment could be assessed in 28 of the 31 children treated with an initial dose of 1 mg/kg/day. It was necessary to increase the dose to 1.6-2.4 mg/kg/day in eight of these children (29%) due to inadequate response. The dose was increased within 1-4 weeks after initiation in three children and after 3-9 months in five children. After dose escalation, the children had a satisfactory response. Concerning the remaining 20 children (71%), 1 mg/kg/day was considered a sufficient dose (**Figure 2**).

### Effect of treatment in relation to age at start of treatment

Children who started treatment before five months of age had significantly better responses than those who started treatment later (**Table 2**).

### Duration of treatment for younger children compared with older children

Children who started treatment before five months of age were treated for a median of eight months (1.5-12 months), and children who started treatment at a later age were treated for a median of 4.25 months (1.5-8.5 months).

### Effect of treatment in relation to location of infantile haemangioma

An excellent response was observed in nine out of 18 children (50%) with IH in the head and neck area and in five out of 11 (45%) children with IH on the trunk/extremities.

### Side effects

Side effects were registered in a total of 12 children (32%). Some children had more than one side effect. The

side effects were as follows: sleep disorder (n = 9), agitation (n = 4), diarrhoea (n = 2), bronchospasm (n = 1) and cold hands (n = 1). The side effects were mild and disappeared completely after cessation of treatment. In all, two children discontinued treatment, one due to diarrhoea and one due to a bronchospasm incident.

### Rebound growth

In four children, propranolol was restarted due to rebound growth in the first few weeks after cessation of treatment at 13 months (n = 1), 12 months (n = 2) and seven months (n = 1), respectively.

### DISCUSSION

The majority of IH requiring treatment were located in the head and neck area, and like in other studies [9] functional risk was the most frequent indication for treatment.

FIGURE 1

The effect of treatment with propranolol.

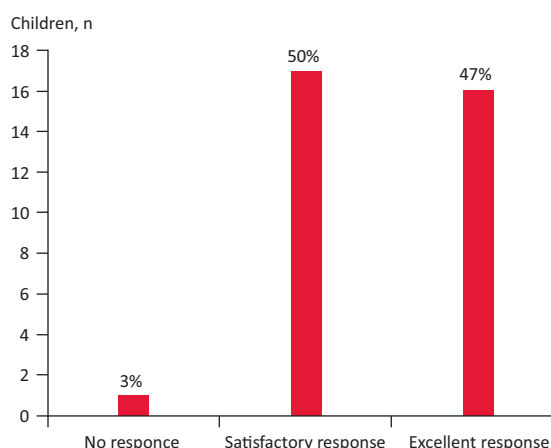
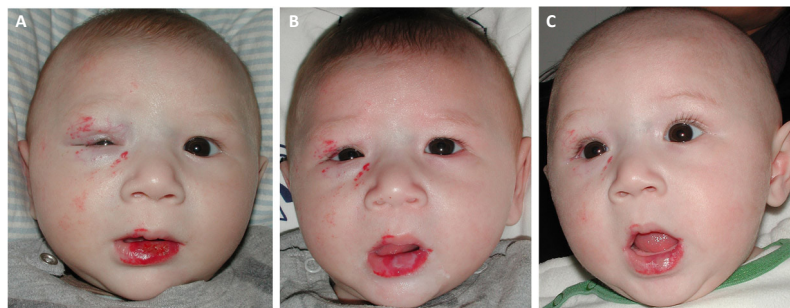


FIGURE 2

Clinical response to propranolol treatment in a child with a periocular and a perioral infantile haemangioma. A. Before treatment. B. After two weeks of treatment. C. After two months of treatment.



In accordance with recent literature [7-13, 15, 16], this study showed that propranolol is a successful treatment of IH, since 97% responded to the treatment. The response rates to treatment with propranolol range from 80 to 100% [7-13, 15, 16]. The one child who did not respond to treatment had an intrahepatic process compatible with IH, which was found incidentally at the age of 22 months. Following magnetic resonance angiography, this process has recently been resected. It was found to be negative for GLUT1 and consistent with a vascular tumour, which explains the lack of response to propranolol.

The majority of children were treated with an initial dose of 1 mg/kg/day according to protocol. This dose was considered sufficient in most cases (71%). Other studies have reported the use of 2-3 mg/kg/day [7-13] except for one study using 1.5-2 mg/kg/day [15]. Thus, treatment with 1 mg/kg/day is a lower dose than previously reported by others. In some studies [7-10, 12], the initial dose was 0.5-1 mg/kg/day, but regardless of the response, this was rapidly increased to a higher target dose. At an American consensus conference suggested an initial dose of 1 mg/kg/day followed by dose escalation to 2 mg/kg/day [17].

Children who started treatment before five months of age had a significantly better response than children who started treatment later. Similar results have been reported by Phillips et al [10]. IH proliferate rapidly in the first 3-6 months after birth [1] which may explain why the effect of treatment is most evident at this time. Furthermore, early initiation of treatment helps prevent large residual changes, which makes surgery less complicated or even unnecessary, leading to better cosmetic results.

Even children who started treatment relatively late (> 12 months) responded to therapy. Zvulunov et al have described response to treatment with propranolol in children up to the age of ten years [16]. Children who started treatment before five months of age required a longer treatment period than older children. Similar results were reported by Schupp et al [8]. This probably reflects that treatment is often continued until at least one year of age when spontaneous regression has set in.

Propranolol is a non-selective beta-blocker, which has been used in infants for cardiac problems for many years. A 40-year review of propranolol toxicity in children found no fatalities or serious cardiac events directly associated with the use of propranolol regardless of dosage [18].

As in other studies [9, 10], sleep disturbance was a frequent side effect. Other well-known side effects are bronchospasm in children with underlying reactive airways, which was registered in one child in this study, transient hypotension and hypoglycaemia. Neither

hypotension nor hypoglycaemia was registered in our study.

It is argued that the treatment should continue at least until the child is one year of age to avoid rebound growth [4, 11]. However, in accordance with other studies [7, 13] rebound was also observed in children older than one year of age at cessation. One possible explanation is the presence of remaining subcutaneous parts of IH at the time of discontinuation of therapy. Doppler ultrasound may be useful to determine when to stop treatment as it can detect the deep components of IH and the residual blood flow.

There has only been one prospective randomised study assigning a group to receive placebo [12]. Considering the current knowledge of the efficacy and safety of propranolol, it is no longer possible to conduct randomised trials with a group allocated to placebo. It is possible, though, to randomly assign groups to different target doses, and the recruitment of participants to such a multicentre study has just been completed [19].

The outcome measure in this study was subjective like in other studies. Some studies have been using blinded assessment of serial photographs [7, 16].

In a few studies, the response to treatment was measured using ultrasound [7, 9, 11]. Sans et al reported a mean regression in maximal thickness of IH of 40% after 60 days of treatment [11]. However, ultrasound examination may be difficult to perform due to location, extension and ulceration of IH and requires the child's active co-operation.

In future, the use of 3D photography [20] may be considered for calculation of volume and assessment of colour change, and it can be used for children who are not prone to co-operate.

## CONCLUSION

Propranolol is effective in the treatment of IH and it has only few and mild side effects. It is an advantage to start treatment as early as possible although younger children tend to require longer treatment periods. Children starting treatment before five months of age have a significantly better response than older children do. Furthermore, early initiation of treatment helps prevent large residual changes. No relation was found between location of IH and the effect of treatment.

This study shows that propranolol at 1 mg/kg/day was sufficient in most cases. However, an objective outcome measure, such as ultrasound or 3D photography, is desirable in future studies in order to determine when to increase dosage in case of inadequate response to treatment.

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