

REVIEW ARTICLE

Propranolol is an effective treatment for airway haemangiomas: a critical analysis and meta-analysis of published interventional studies

Il propranololo è efficace per il trattamento degli emangiomi delle vie aeree: analisi critica e meta-analisi degli studi interventistici pubblicati

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SUMMARY

Haemangiomas represent the most common benign tumours in infancy, affecting 1-2% of newborns. The present meta-analysis aimed to critically review the current evidence on the efficacy of propranolol in the management of airway haemangiomas, and explore potential adverse events and treatment failures. A literature review was performed in Medline and other available database sources, along with critical analysis of pooled data. Seventeen studies were included in the analysis. No study represented Level I evidence. The total number of treated patients was 61; 14 patients received propranolol as single-treatment. The comparative effectiveness of propranolol vs. systemic steroids was documented in 35 children, and showed superior outcome in the vast majority (94%, $p < 0.001$). The mean obstruction before propranolol administration was 72%, and after intervention was 20% ($p < 0.001$). The mean referral-age for children with airway haemangiomas was 2.4 months, the mean starting-age of propranolol treatment was 5.1 months and the mean follow-up period was 8.4 months. Four children failed to respond (6.5%), and in seven the haemangioma relapsed after discontinuation of treatment (11.5%). The results of the present study suggest that propranolol can be recommended for the treatment of airway haemangiomas, as it was found to be effective and outperformed the previously-considered gold standard treatment methods, with fewer side-effects. Immediate treatment with propranolol should be initiated once a diagnosis of symptomatic airway haemangioma is confirmed, and cardiovascular assessment has been performed. Children should remain on propranolol until the haemangioma enters the phase of involution. Active parental monitoring is essential to ensure treatment safety.

KEY WORDS: Haemangioma • Airway • Propranolol • Steroids

RIASSUNTO

Gli emangiomi rappresentano i tumori benigni più comuni durante l'infanzia, interessando l'1-2% dei neonati. L'obiettivo della nostra meta-analisi è stato una revisione critica delle attuali evidenze sull'efficacia del propranololo nel trattamento degli emangiomi delle prime vie aeree, sottolineando in particolare i potenziali eventi avversi e i fallimenti terapeutici. Un'analisi critica è stata fatta su dati raccolti dopo un'accurata revisione della letteratura effettuata mediante Medline e gli altri database disponibili. Diciassette studi sono stati inclusi nell'analisi. Nessuno studio ha riportato prove di I livello. In totale sono stati trattati 61 pazienti di cui 14 avevano ricevuto propranololo come singolo trattamento. In 35 bambini è stato possibile confrontare l'efficacia del propranololo con quella degli steroidi per via sistemica dimostrando la superiorità del primo nella maggioranza dei casi (94% - $p < 0,001$). L'ostruzione media prima della somministrazione di propranololo era del 72%, dopo la terapia invece del 20% ($p < 0,001$). L'età media alla diagnosi dei bambini affetti da emangioma delle prime vie aeree era di 2,4 anni, l'età media di inizio del trattamento con propranololo era invece di 5,1, e il periodo medio di follow-up di 8,4 mesi. Quattro bambini non hanno risposto (6,5%), e in sette casi l'emangioma ha recidivato dopo interruzione del trattamento (11,5%). In conclusione, i risultati della presente metanalisi dimostrano che il propranololo può essere raccomandato per il trattamento degli emangiomi delle prime vie aeree, in quanto di efficacia superiore e con minori effetti collaterali rispetto ai metodi precedentemente considerati come il gold standard terapeutico per questo tipo di patologia. Il trattamento con propranololo dovrebbe essere iniziato non appena confermata la diagnosi di emangioma sintomatico delle prime vie aeree ed effettuata una valutazione cardiovascolare. I bambini devono essere trattati con propranololo fino a quando l'emangioma entra nella fase di involuzione. Il monitoraggio attivo dei genitori è essenziale per garantire la sicurezza del trattamento.

PAROLE CHIAVE: Emangioma • Prime vie aeree • Propranololo • Steroidi

Introduction

Haemangiomas represent the most common benign tumours in infancy, affecting 1-2% of newborns ¹. Although they are often confused with other vascular malformations, they demonstrate a unique course characterized by proliferation during the first year of life, and involution thereafter. Fortunately, many haemangiomas are superficial involving only skin and subcutaneous tissue, and can be allowed to follow their self-limiting natural course, and resolve with minimal sequelae. However, approximately 10% of haemangiomas can affect the child's quality of life due to aesthetic reasons or cause functional impairment, which can even be life-threatening ².

Airway haemangiomas in particular may lead to feeding difficulties, barking cough, stridor, respiratory distress and even acute airway obstruction. Hence, such haemangiomas usually require early and aggressive treatment; however, the treatment modalities employed so far have been associated with their own co-morbidities and potential long-term adverse effects for the developing child. In other words, the traditional management (medical or surgical) of severe or life threatening airway haemangiomas may have a serious impact on the child's quality of life, or be associated with severe complications.

Recently, Leaute-Lambreze et al. reported the accidental regression of an infantile haemangioma following the administration of propranolol for steroid-induced hypertrophic cardiomyopathy ³. This had led other otolaryngology centres to try the same method of management in order to achieve a good clinical result with minimal complications. The first related studies, usually case reports or case series, were very encouraging claiming that a new revolutionary method of management had been discovered ⁴⁻⁷.

The aim of the present meta-analysis is to critically review the current evidence on the efficacy of propranolol in the management of airway haemangiomas. Adverse events and treatment failures are also explored.

Materials and Methods

An extensive search of the literature was performed in

Medline and other available database sources, establishing two main categories of outcomes:

a) assessment of the clinical effectiveness of systematically administered propranolol in halting the progress of growing airway haemangiomas, and b) comparison of the clinical outcome of propranolol versus the systemic, or intralesional steroid administration as a first-line approach for the treatment of proliferating airway haemangiomas.

Using this framework of results, the retrieved studies were critically appraised according to evidence-based guidelines for the categorization of medical studies (Tab. I). In addition, three secondary end-points were also analysed: a) clinical effectiveness of propranolol in eradication of proliferating airway haemangiomas, b) clinical effectiveness of propranolol compared to previously utilized second-line treatments for infantile haemangiomas, and c) protocol for the safe administration of propranolol, and appropriate patient follow-up until complete resolution of the disease.

During the search, the keywords "haemangioma", "infantile", "airway", "proliferation", "propranolol", "steroids", and "treatment" were utilized. The keywords "haemangioma", "airway", and "propranolol" were considered primary, and were either combined to each of the other keywords individually, or used in groups of three. In addition, reference lists from the retrieved articles were manually searched. Language restrictions limited the search to English-language articles only.

The clinical effectiveness of propranolol was assessed using chi-square analysis. Chi-square was also used to determine the comparative effectiveness of propranolol vs. steroid administration. The degree of airway obstruction before and after treatment with propranolol was compared using a paired t-test. The correlation coefficient between treatment with propranolol and the change in the percentage of airway obstruction post-treatment was calculated using linear regression. Statistical importance was accepted at the level of $P < 0.05$.

Results

Eighteen studies met the defined criteria and were initially included in study selection. Among these studies,

Table I. Levels of evidence regarding in studies that investigate the results of treatment.

Category of evidence	Study design
Level I	<ul style="list-style-type: none"> • High quality randomized trial with statistically significant difference, or no statistically significant difference, but narrow confidence intervals • Systematic review of Level I randomized control trials (and study results were homogenous)
Level II	<ul style="list-style-type: none"> • Lesser quality randomized control trial (e.g. < 80% follow up, no blinding, or improper randomization) • Prospective comparative study • Systematic review of Level II studies or Level I studies with inconsistent results
Level III	<ul style="list-style-type: none"> • Case control study • Retrospective comparative study • Systematic review of Level III studies
Level IV	<ul style="list-style-type: none"> • Case series
Level V	<ul style="list-style-type: none"> • Expert opinion

one included patients with overlapping haemangiomas, frequently involving more than one anatomic site in the same patient, without, however, clear identification of the number of patients with airway haemangiomas. This study was therefore excluded from the analysis of pooled data.

Overall, one multi-centre retrospective cohort study, two prospective cohort and two retrospective studies, six case-series, and six case reports were systematically analyzed. Two studies represented Level II, three studies Level III and 12 studies Level IV evidence (Tab. I).

The total number of treated patients was 61; among these 35 had exclusive airway lesions. Co-existing segmental distribution of haemangiomas was present in 11 children, cutaneous lesions in nine, deep neck/mediastinal compo-

nents in four and finally PHACES syndrome (posterior fossa malformations, haemangiomas, arterial anomalies, coarctation of the aorta/cardiac defects, eye abnormalities and sternal defects) in two of the treated children. The vast majority of patients (n = 43) received 2 mg of oral propranolol per day divided in 2 or 3 doses; a dose of 3 mg per day was given in 10 children, whereas the administered dose was not reported in 4 cases.

Fourteen patients received propranolol as single treatment. Four patients were treated with another selective β -blocker (acebutalol), but showed similar responses, and were hence included in further analysis of treatment outcomes. The comparative effectiveness of propranolol vs. systemic steroids was documented in 35 children (Tab. II). Propranolol

Table II. Comparative effectiveness of propranolol vs. systemic steroids in the management of airway haemangiomas (raw data).

Case	Systemic prednisolone	Steroid effectiveness	Propranolol	β -blocker efficiency	Additional treatment
1	High doses (details missing)	No	3 mg/kg/day	Success	No
2	High doses (details missing)	No	2 mg/kg/day	Success	No
3	2 mg/kg/day	No	2 mg/kg/day ^a	Success	No
4	3 mg/kg/day	No	3 mg/kg/day	Success	No
5	2 mg/kg/day	No	3 mg/kg/day	Success	No
6	2 mg/kg/day	No	2 mg/kg/day	Success	No
7	2 mg/kg/day	No	2 mg/kg/day	Success	No
8	2 mg/kg/day	No	2 mg/kg/day	Success	No
9	2 mg/kg/day	No	3 mg/kg/day	Success	No
10	1 mg/kg/day	No	8 mg/kg/day [†]	Success	No
11	1 mg/kg/day	No	8 mg/kg/day [†]	Success	No
12	1.5 mg/kg/day	No	3 mg/kg/day	Success	No
13	3 mg/kg/day	No	2 mg/kg/day	Success	No
14	3 mg/kg/day	No	2 mg/kg/day	Success	No
15	3 mg/kg/day	No	2 mg/kg/day	Success	No
16	3 mg/kg/day	No	2 mg/kg/day	Success	No
17	3 mg/kg/day	No	2 mg/kg/day	Success	No
18	3 mg/kg/day	No	2 mg/kg/day	Success	No
19	High doses (details missing)	No	2 mg/kg/day	Success	No
20	High doses (details missing)	No	2 mg/kg/day	Success	No
21	High doses (details missing)	No	2 mg/kg/day	Success	No
22	High doses (details missing)	No	2 mg/kg/day	Success	No
23	High doses (details missing)	No	2 mg/kg/day	Success	No
24	3 mg/kg/day	No	2 mg/kg/day	Success	No
25	3 mg/kg/day	No	2 mg/kg/day	Success	No
26	3 mg/kg/day	No	2 mg/kg/day	Success	No
27	0.1 mg/kg/day [‡]	No	2 mg/kg/day	Success	No
28	High doses (details missing)	No	2 mg/kg/day	Success	No
29	3 mg/kg/day	No	2 mg/kg/day	Success	No
30	3 mg/kg/day	No	2 mg/kg/day	Success	No
31	3 mg/kg/day	Yes	2 mg/kg/day	Failure	No
32	High doses (details missing)	No	2 mg/kg/day	Success	No
33	100 μ g/kg/day [§]	No	2 mg/kg/day	Success	No
34	High doses (details missing)	No	Details missing	Success	No
35	High doses (details missing)	Yes	Details missing	Failure	No

^a the patient was initially treated with propranolol, but later received acebutalol, due to asthmatic attack

[†] the patient received acebutalol

[‡] the patient received betamethasone

[§] the patient received dexamethasone

treatment outperformed steroids in the vast majority of patients (33 cases, 94%), whereas steroids showed superior outcome only in two cases (6%). The result was statistically significant ($p < 0.001$). Propranolol was also used as salvage therapy in 10 children previously treated with laser, and in three children who had previously received vincristine; better results demonstrating a clear advantage for propranolol were reported in all of these patients.

Drawing on the degree of improvement of airway obstruction, this was clearly documented as a respective percentage in 21 patients. The mean obstruction before the administration of propranolol was 72%, and after intervention was 20%. The result proved statistically significant ($p < 0.001$).

The mean referral age for children with airway haemangiomas was 2.4 months (range 0.7-8 months), and the mean starting age of propranolol treatment 5.1 months (range 0.75-22 months). Treated children were followed up for a mean of 8.4 months. Four children from our study population failed to respond to propranolol treatment (6.5%), and in seven the haemangioma relapsed after discontinuation of treatment (11.5%).

Discussion

Epidemiology-Pathophysiology

Infantile haemangiomas seem to affect 4-10% of Caucasian infants, with a female to male ratio of 2.5-4:1⁸⁻¹⁰. They have also been associated with prematurity, low birth weight and multiple pregnancies¹¹⁻¹³. Sixty per cent of haemangiomas represent single lesions, and 80% are found in the head and neck area^{8,14}. Airway haemangiomas can involve any site from the nares to the tracheo-bronchial tree. However, they are most commonly seen in the subglottis, and account for approximately 1.5% of congenital laryngeal anomalies¹⁵. The natural history of haemangiomas in the subglottis may be accompanied by an alarming mortality rate of around 50% if left untreated^{16,17}. Indeed, approximately two-thirds of these haemangiomas present with 70% or worse airway narrowing^{18,19}. Histologically, infantile haemangiomas are composed of a complex mixture of clonal epithelial cells associated with pericytes, fibroblasts, dendritic and mast cells^{6,8-10,20,21}. Although theories regarding their origin involve potential somatic endothelial mutations, intrinsic defects, extrinsic factors (i.e. tocolytics) and placental derivation^{8,22,23}, no current hypothesis can explain all their characteristics. It has been proposed recently that the tumour may be a developmental disorder of primitive mesodermal proliferation and differentiation governed by the renin-angiotensin system^{24,25}.

Haemangioma growth is controlled by pro-angiogenic factors during the proliferative phase, predominantly basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). Conversely, the involutional phase is associated with cell apoptosis resulting in tumour regres-

sion⁶ and replacement with fibro-fatty tissue²⁶. Immunohistochemistry shows persistent reactivity to the erythrocyte-type glucose transporter protein isoform 1 (GLUT-1)^{8,27}.

Treatment modalities-Mechanism of propranolol action

A variety of treatment modalities have been used in the management of airway haemangiomas. Although the treatment plan depends on many factors (i.e. size and extend of the lesion, social situations, clinical experience etc.), a widely accepted aim is to maintain airway patency, promote lesion regression, avoid tracheostomy and minimize therapeutic side effects until the lesions enter the natural phase of involution^{4,15}. Unfortunately, a watchful-waiting policy can only be applied in the minority of patients who do not demonstrate respiratory or feeding difficulties¹⁹.

The gold standard for the treatment of symptomatic airway haemangiomas until recently has been the administration of steroids. Systemic steroids can be effective in controlling haemangioma growth in over 50% of patients^{10,28-30}, even though subglottic lesions tend to show poorer response²⁹. However, their side-effects are also well known; cushingoid face, insomnia, irritability, growth retardation, gastro-intestinal lesions, delayed wound healing, hirsutism, and even adrenal suppression, hypertension, or hypertrophic cardiomyopathy.

Interferon- α , on the other hand, has been widely used for the treatment of refractory haemangiomas, but is associated with significant neurotoxic effects, such as spastic diplegia and developmental delay⁹, especially in young infants¹⁸, while it may also be responsible for a variety of other side-effects (flu-type malaise, neutropenia, elevation of liver enzymes, hypothyroidism). Vincristine therapy has also been employed in life-threatening conditions, but may cause peripheral neuropathy resulting in constipation, abdominal pain and paraesthesia, in addition to inappropriate secretion of antidiuretic hormone. In these latter cases, cyclophosphamide has also been reported to have promising results³¹. However, the serious side-effects related to cyclophosphamide (i.e. avascular necrosis, cardiomyopathy, pulmonary fibrosis, gonadal damage, and later malignancies³²) have to be carefully considered prior to the initiation of treatment. In addition, it should not be forgotten that vincristine and cyclophosphamide are mainly anti-cancer drugs with potentially very serious side effects in the long-term, especially when given to very young children.

A number of surgical interventions have also been attempted, especially in cases that do not respond to medical therapy. Tracheostomy³³ can no longer be considered as first-line treatment, not only because of the relatively low risk of mortality (approximately 1%), but also for the associated morbidity (including the serious impact on the child's and family's quality of life), and the need for close postoperative tracheostomy care^{19,34}. However, in emergency cases tracheostomy may be the only immediate solution to save the child's life.

Intra-lesional steroids may reduce the related systematic morbidity, although their results have been variable³⁵, and they often involve prolonged intubation and stay in a paediatric ICU; the associated risks are also not considered acceptable by many authors¹⁵.

Laser ablation is considered a reasonable option for localized haemangiomas not causing extreme airway narrowing. As with other modalities of treatment, the respective efficacy varies, whereas the associated risk includes high recurrence rates that may lead to multiple treatments^{36,37}. Extensive circumferential narrowing is not suitable for laser debulking, due to the risk of postoperative scarring, and the ensuing subglottic stenosis. Hence, open resection and laryngo-tracheal augmentation may be ultimately required. However, these are relatively major surgical procedures with potentially serious complications. Moreover, they demand inpatient management, intensive care units and vast related experience on behalf of the operating surgeon.

The incidental discovery that propranolol induced early regression of infantile haemangiomas during their proliferative phase by Leaute-Labreze et al, along with its low side-effect profile, attracted significant attention, and propranolol-based regimens have emerged as a new method of treatment in a growing volume of literature. However, the use of propranolol for proliferative infantile haemangiomas in the first year of life is still officially considered "off label".

The exact mechanism of propranolol action in infantile haemangiomas is equally unclear to their origin. Propranolol is a non-selective β -blocker inhibitor, with pure antagonistic effects. Proposed mechanisms of action include control of hypoxic stress, vasoconstriction, inhibition of angiogenesis and induction of endothelial cell apoptosis. Vasoconstriction can be visible as a change in colour, associated with palpable tissue softening, which can be observed as early as 1-3 days from treatment onset^{8,15,38}. The anti-angiogenic effect of propranolol can be exercised through its anti-VEGF activity^{3,11}, as well as through reduced activity of the renin-angiotensin system and reduced expression of matrix metalloproteinases (MMPs)⁸. The resulting growth arrest is followed by regression of the lesions through an increase in the rate of apoptosis. The latter, however, is not complete in young infants, as partial re-growth of haemangiomas has been observed after the discontinuation of propranolol administration. In addition, variability in response can be suggestive of variability in tumour composition³⁹.

Meta-analysis

The results of the present meta-analysis suggest that propranolol is indeed effective in the treatment of airway haemangiomas ($p < 0.001$). The vast majority of children that received propranolol for airway hemangiomas showed improvement or resolution of symptoms, and normal thriving. Non-responsiveness to propranolol was

only reported in four children (6.5%), whereas seven additional children relapsed following the discontinuation of treatment (11.5%). An interesting observation is that the administration of propranolol as monotherapy for airway haemangiomas in 14 infants resulted in 2 treatment failures (14.3%), but only one relapse after cessation of therapy (7.1%). Considering the respective percentages of the entire study population, this observation suggests that enhanced alert is required, when it is decided to treat infants exclusively with propranolol for airway haemangiomas, as the risk of non-responsiveness is increased. Indeed, in an area where compromise can be lethal, these patients should be monitored closely as they may require adjuvant therapy. In addition, despite the great efficiency of propranolol, recurrences of airway haemangiomas are possible after early or even late discontinuation of treatment. The cause of these relapses is equally unknown to the mechanism of propranolol action; the present meta-analysis identified a specific cause of haemangioma recurrence in only one of the 7 relapsing infants (administration of a sympathomimetic drug during cardiac surgery). It should be noted, however, that the mean follow up period of treated children identified in the present meta-analysis (8.4 months) is somewhat restrictive in assessing the above-mentioned important issues.

Unfortunately, sizing of the obstructed airway in order to quantify the exact value of improvement following the administration of propranolol, especially in cases of subglottic haemangiomas, was not reported in all studies. However, the present meta-analysis identified a subpopulation of treated children ($n = 21$), where such measurements had been performed during microlaryngoscopy and bronchoscopy under general anaesthesia (MLB), before and after intervention. As seen in Figure 1, the percentage of obstruction had dramatically decreased following propranolol administration in most cases. The related difference was statistically significant ($p < 0.001$). In addition, the correlation co-efficient between treatment with propranolol and the change in the percentage of obstruction post-treatment was found to be moderately positive ($r = 0.39$), and again statistically significant ($p < 0.05$) (Fig. 2).

The administration of propranolol as single-therapy is also a case-in-point, especially if we consider the relatively increased risk of non-responsiveness mentioned above. In particular, among the aforementioned 21 cases, five children had received propranolol as monotherapy. The mean obstruction before the administration of propranolol was 66%, and after intervention was 24%. Despite the small number of cases, the result was statistically significant ($p = 0.01$).

It should be noted that not all children show complete eradication of the haemangioma after being treated with propranolol. Indeed, only four children were reported as having no obstruction, and two additional children as having 5% of the subglottic airway obstructed. However, ster-

oids and other medical methods of treatment do not eradicate the disease either. Therefore, symptom improvement/resolution and the ability of the infant to thrive, although subjective, can be considered the most important criteria of success. Nevertheless, if we put an arbitrary cut-off criterion of success – 10% of the airway to be obstructed after the intervention – then over 50% of responders can be expected to reach this significant target. The latter observation can be used for parent counselling before obtaining consent for the initiation of treatment.

In addition, propranolol was found more effective than steroids in treating airway haemangiomas ($p < 0.001$). Indeed, the respective odds ratio for successful outcome for propranolol vs. steroid treatment was positive and statistically significant ($p < 0.05$). In comparison to the previously considered second-line treatments for proliferating infantile haemangiomas, propranolol tended to outperform both laser treatment and vincristine, although the small number of patients treated with these modalities did not allow significant comparisons to be made. Nevertheless, when propranolol was used as salvage therapy in 10 children previously treated with laser, and in three children who had previously received vincristine, it achieved better symptom control in all.

Admittedly, the present meta-analysis did not identify any Level I studies regarding the administration of propranolol for the treatment of proliferating airway haemangiomas. The vast majority of studies were small case series, and the number of treated children was also relatively small. However, the reported results seem encouraging. In addition, the uniform nature of these results, along with the quality of the studies performed, allow us to adopt a grade C strength of recommendation regarding the effectiveness of propranolol in airway haemangiomas (Tab. III). However, the rather small number of patients with airway haemangiomas, who were treated solely with propranolol (Tab. IV), precludes us from drawing definite conclusions regarding the strength of recommendation for the effectiveness of propranolol as single-therapy for airway haemangiomas. We hope that the results of the present study will encourage further high quality studies with long term follow-up in order to clarify this important issue.

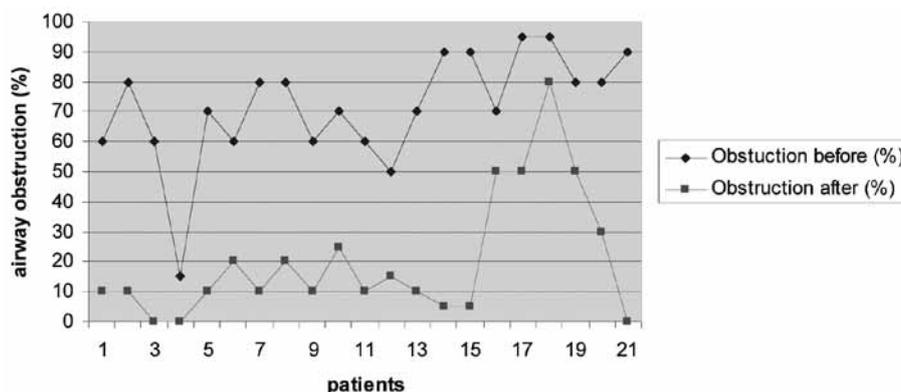


Fig. 1. Percentage of airway obstruction before and after propranolol treatment.

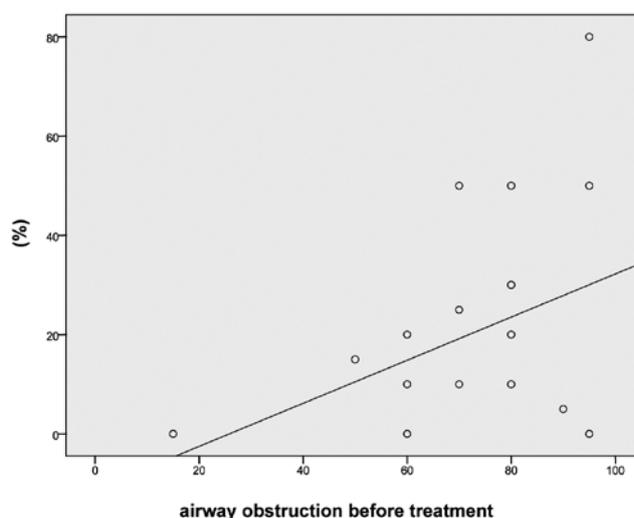


Fig. 2. Scatter plot illustrating the relationship of propranolol to the result of treatment. The line of best fit shows a moderately positive correlation ($r = 0.39$).

Treatment regimen-Follow up algorithm

Propranolol, a non-selective β -blocker, was considered one of the most important contributions to clinical medicine and pharmacology of the 20th century⁸. It is almost completely absorbed from the gastro-intestinal tract, highly protein-bound (80-95%), and there is a significant first pass metabolism and hepatic tissue binding, with up to 90% of an oral dose being eliminated. Like many drugs adapted for use in infants, there are no pharmacokinetic data in this specific population, and no prospective, controlled studies have described optimal dosing or monitored the respective side-effects in this age group⁵¹.

Table III. Strength of recommendation by category of evidence for guideline development⁴⁰.

Strength of recommendation	Category of evidence
A	Directly based on category I evidence
B	Directly based on category II evidence or extrapolated recommendation from category I evidence
C	Directly based on category III evidence or extrapolated recommendation from category I or II evidence
D	Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence

Table IV. Propranolol administration for airway haemangiomas (patient series).

Authors	Study type	Evidence level	Number of subjects with airway haemangioma	Treatment failure/relapse	Adverse effects
Holmes et al., 2011	Prospective study	II	1	0	None
Guye et al., 2011 ⁴¹	Case report	IV	1	0	None
Leboulanger et al., 2010 ⁴²	Multicentre retrospective cohort	III	14	2	Asthma (n = 1)
Blanchet et al., 2010 ⁴³	Case series	IV	4	1	None
Truong et al., 2010 ⁴⁴	Case series	IV	6	0	None
Santos et al., 2010	Case series	IV	6	1	Pallor (n = 1) Asthma (n = 1)
Rosbe et al., 2010 ⁴⁵	Case series	IV	3	1	Soft palate ulcer (N = 1)
Canadas et al., 2010 ⁴⁶	Case report	IV	1	1	None
*Manunza et al, 2010 ⁴⁷	Case-series	IV	9		
Jepshon et al, 2009	Case report	IV	1	0	None
Maturo and Hartnick, 2010 ⁴⁸	Case series	IV	2	0	None
Larrier, 2010 ⁴⁹	Retrospective study	III	3	2	None
Anderson de Moreno et al, 2009 ⁵⁰	Retrospective study	III	4	0	None
Sans et al, 2009	Prospective cohort	II	4	0	Not specified for patients With airway haemangiomas
Buckmiller et al, 2009	Case report	IV	1	0	None
Theletsane et al, 2009	Case report	IV	1	0	None
Mistry and Tzifa, 2009	Case report	IV	1	0	None

* authors belong to the same investigating team

The potential risks associated with the use of propranolol include cardio-pulmonary complications, such as bradycardia, and hypotension, especially in syndromic children (i.e. PHACES, PELVIS etc.) and neonates in the first week of life⁴⁸, bronchospasm in patients with atopic predisposition or underlying spastic respiratory illness⁵², hypoglycaemia, especially in low birth weight newborns⁹ and children with low caloric intake⁵³ or diabetes, electrolytic abnormalities (i.e. hyperkalaemia⁵²), gastro-oesophageal reflux, somnolence/fatigue, agitated sleep, rash and resistance to the drug's re-introduction after early discontinuation of therapy⁴². These effects, however, appear minor, compared to the serious side effects of more conventional agents, such as the ones mentioned earlier. In addition, after over 40 years of extensive clinical experience with propranolol, no serious cardiovascular event has been recorded in a child on chronic β -blocker therapy⁵⁴. Nevertheless, the adoption of this treatment modality by non-familiar specialties, such ENT, certainly warrants careful monitoring, close liaison with the affiliated paediatric Cardiology Department, and a treatment algorithm to minimize the potential adverse effects^{15 28 39 51 55}. The present meta-analysis identified only four adverse effects in children receiving propranolol for the treatment of airway haemangiomas; two asthmatic attacks, which had necessitated cessation of treatment, one episode of pallor without loss of consciousness, which was attributed to a

possible vagal reaction, but did not require discontinuation of treatment or dose adjustment and a soft palate ulcer, which responded to steroid treatment.

The pharmacologically optimal dosing interval for propranolol is 6 hours, although better compliance is achieved when the medication is given 2 or 3 times daily. Before starting the treatment, baseline vital signs are obtained⁵¹, along with blood glucose, especially if the child has not established a routine feeding pattern⁴⁸. Electrocardiogram and echocardiogram are also necessary, and if either is abnormal a cardiology review is required⁵¹. Infants with large haemangiomas and especially segmental distribution are at increased risk of high output cardiac failure, and propranolol can conceal the related tachypnoea and hyperidrosis⁵¹. Syndromic children are also evaluated with trans-cranial Doppler and/or MRI/MRA of the head and neck⁴⁸. Otherwise, a CT scan of the neck with intravenous contrast gives optimal resolution of the haemangioma⁵⁶, without the need to intubate the infant.

Hospitalized infants receive a starting dose of 0.17 mg/kg three times daily. Vital signs and blood glucose are checked 1 hour after each dose, as this corresponds to the peak absorption time. If the first 2 doses are tolerated, the dose is doubled to 0.33 mg/kg, and after 2 more doses to 0.67 mg/kg. For infants less than 3 months of age, slower dose escalation to avoid hypoglycaemia may be required. Frequent feeds are strongly encouraged. Parents need to be informed

about the clinical signs of hypotension, bradycardia and hypoglycaemia, as for the need of dose adjustment according to the child's weight⁴⁸. The optimal duration of treatment is not known, but it is currently believed that the child should remain on propranolol until the haemangioma enters the phase of involution, which usually happens after the first year of life. Earlier discontinuation of treatment may result in unresponsiveness to propranolol re-introduction, should the latter be required. Moreover, the lack of long-term follow up in the published studies does not allow any definite conclusions with regard to relapses, even after the beginning of the involutorial phase.

If a child is unresponsive to propranolol, biopsy (taking all the necessary precautions to control a potentially persistent and life threatening bleeding) and immunohistochemical staining for GLUT-1 may be considered to confirm diagnosis^{28,44}. Finally, propranolol is gradually tapered over 2-3 weeks, and not stopped immediately, due to issues involving cardiac hypersensitivity.

Conclusions

Airway haemangiomas may require early and aggressive treatment in life-threatening cases. However, the treatment modalities employed so far have been associated with their own comorbidities and potential long-term adverse effects for the developing child. Propranolol has the potential to alter the management of proliferating haemangiomas in infancy radically. Although high-quality evidence is still not available, the results of the present study suggest that propranolol can be recommended for the treatment of airway haemangiomas, as it was found to be effective and outperformed the previously-considered gold standard methods of treatment ($p < 0.001$) with fewer side-effects. Immediate treatment with propranolol should commence once a diagnosis of symptomatic airway haemangioma is confirmed and a cardiovascular assessment has taken place. Active parental monitoring is also essential to ensure treatment safety.

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