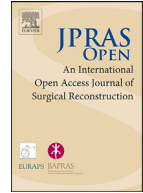




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## Original Article

# Cost-effectiveness of atenolol compared to propranolol as first-line treatment of infantile haemangioma: A pilot study <sup>☆</sup>

Sasha Wilson\*, Deniz Hassan, Molly Jakeman, Eleonore Breuning

Department of Plastic Surgery, Alder Hey Children's Hospital, Liverpool, L14 5AB

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## ABSTRACT

Propranolol is the first-line agent for the treatment of infantile haemangioma (IH). Due to its non-selective beta blockade respiratory adverse events are commonplace. Atenolol is a selective beta-1 antagonist and is a second line for patients with a significant respiratory history or those intolerant of propranolol. Previous studies suggest that the two treatments are equally efficacious; however; the narrow side effect profile and once-daily administration of atenolol makes it an attractive alternative. The aim of this study was to compare the cost-effectiveness of atenolol and propranolol in the treatment of IH.

Over a two-year period, five patients with nine IH received the first-line treatment with atenolol. Nine individual lesions from six propranolol patients were matched to these lesions, according to patient demographics and IH characteristics. Treatment response was determined by two independent clinician using both the Visual Analogue Score (VAS) and Haemangioma Activity Score (HAS). A cost-analysis of those treated with atenolol was undertaken and compared to the equivalent costing for standard and maximum dose propranolol. Treatment efficacy of atenolol was comparable to propranolol with mean change in VAS and HAS scores of -7.0

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\* Editorial correspondence: Dr Sasha Wilson, Flat 4 Clayton's Yard L8 7PL.

E-mail address: [sasha\\_eve\\_wilson@hotmail.co.uk](mailto:sasha_eve_wilson@hotmail.co.uk) (S. Wilson).

(vs -7.2) and 6.1 (vs 5.7), respectively. The cost analysis revealed atenolol was over 20 times less expensive than standard dose propranolol. In conclusion, the findings of this study suggest that atenolol is significantly less expensive and at least as effective as propranolol. These findings highlight the need for a multicentre randomised controlled trial to further investigate the cost-effectiveness of these two agents in the treatment of IH.

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## Introduction

Infantile haemangioma (IH) is the most common vascular tumour of childhood affecting 5–10% of children and following a well-documented pathogenesis of proliferation, plateau and involution.<sup>1–3</sup> During the proliferation phase, IH can be associated with ulceration, infection and can lead to functional sequelae such as visual impairment and distortion of surrounding anatomical structures.<sup>4</sup> Following involution, IH can result in significant residual cosmetic deformity as a result of skin excess and altered pigmentation.<sup>4</sup> Approximately, 12% of all IH will exhibit complications and in such cases beta-blocker treatment is initiated to arrest the proliferation phase.<sup>4</sup> In the case of IH, the exact mechanism of action of beta blockers is relatively unknown, however, theories include the inhibition of vascular endothelial growth factor (VEGF) and vasoconstriction of the vascular bed.<sup>5</sup>

Over the past decade, oral propranolol has become widely accepted as the gold standard treatment of IH; however, due to its non-selective beta antagonism, it is linked with a wide range of adverse events including cold peripheries, wheeze and bronchospasm.<sup>4–5</sup> Furthermore, its ability to cross the blood-brain barrier may contribute to central side effects, such as sleep disturbance.<sup>5–6</sup> Consequently, atenolol is used in patients with a personal or family history of respiratory problems because its cardio-selectivity is thought to reduce the risk of respiratory side effects.<sup>6–7</sup> In addition, its hydrophilic nature prevents it from crossing the blood-brain barrier, and therefore thought to lower the risk of central side effects.<sup>6–7</sup>

A number of systematic reviews have concluded that atenolol is at least as efficacious as propranolol in treating IH and has a lower rate of adverse events when compared to propranolol.<sup>6–10</sup> Therefore, the primary aim of this study is to assess the cost-effectiveness of atenolol compared to propranolol because there is no available literature assessing the potential economic advantage of atenolol as first-line treatment for this commonly cited pathology.

## Methods

A retrospective observational study was undertaken at the Alder Hey Children's Hospital over a 24-month study period (November 2017 – November 2019). A prospective institutional database of all IH patients treated by both dermatology and plastic surgery was used to identify 16 patients treated with atenolol over the study period. Further data analyses revealed only five patients were given atenolol as a first-line treatment.

As Alder Hey is a tertiary centre for IH, the institutional database highlighted vast numbers of patients receiving first line propranolol over the study period. To manage this large data set and create a manageable workload for the required data collection and subsequent matching, a random sample of 37 propranolol patients was taken. Detailed data collection was then carried out for the five atenolol patients and 37 propranolol patients. Finally, the five atenolol patients were matched with suitable propranolol patients based upon patient demographics and IH characteristics.

Of the five atenolol patients identified, two had single IH and three had multiple IH that resulted in a total of nine individual lesions treated with atenolol. The atenolol patients with multiple IH

**Table 1.**

	Atenolol	Propranolol
Sex of Patients	6 female lesions 3 male lesions	6 female lesions 3 male lesions
Location of IH Lesions	4 Head and Neck 2 Trunk 3 Limb	4 Head and Neck 2 Trunk 3 Limb
Mean Age at Initiation (days)	127 (80-170)	101 (69-168)
Mean Treatment Length (days)	155 (85-226)	187 (112-229)

were matched to propranolol patients with multiple IH and from here individual lesions were then matched. One of the many IH patients treated with atenolol had three individual lesions for matching, and there was no single propranolol patient with this number of lesions; and therefore, this patient's IH lesions were matched with IH from two different propranolol patients. This approach of matching individual lesions was chosen to optimise the clinical data available for analysis from a very limited number of first line atenolol patients.

Once matching was complete, a retrospective analysis of clinical photographs of individual IH before, during and after treatment was undertaken by two independent clinician utilising both the visual acuity score (VAS) and haemangioma activity score (HAS).<sup>6,11</sup> The numerical difference in both VAS and HAS between stages of treatment was calculated for each patient and a mean change in VAS and HAS was taken for both the atenolol and propranolol groups. Ultimately, this data was used to compare the efficacy of atenolol and propranolol in the treatment of IH which was the secondary aim of this study. Furthermore, the details of adverse events during the treatment were also recorded for both groups.

To fulfil the primary objective of the study, a bottom-up cost analysis was carried out by calculating the total cost of standard dose (1 mg/kg/day) atenolol treatment for the five atenolol patients and compare this to the equivalent cost if these patients had received propranolol at both standard dose (2 mg/kg/day) and maximum dose (3 mg/kg/day) for the duration of their treatment. Costing information was taken directly from Alder Hey's Hospital Pharmacy that quoted the cost of atenolol 300 mL (25 mg/5 mL strength) as £3.11 and for propranolol 150 mL (50 mg/5 mL strength) as £36.54.

As previously stated, beta-blocker treatment for IH follows weight-based dosing, and patients are regularly weighed to ensure accurate dosing. Therefore to calculate overall treatment cost for each atenolol patient, the number of days of treatment at every weight interval was recorded. Using this data, the patient's weight (kg) was multiplied by the cost of standard dose atenolol (1 mg/kg/day) and multiplied by the number of days the patient received this weight-based dose. The cost of each weight-based treatment interval was combined to give the total cost of that patient's treatment course with atenolol. This process was then repeated, substituting the cost of standard dose atenolol for both standard dose propranolol (2 mg/kg/day) and maximum dose propranolol (3 mg/kg/day).

## Results

Within the 24-month study period, five patients with a total of nine individual IH were commenced on atenolol first line. Detailed data collection was carried for these five patients and 37 propranolol patients which allowed for subsequent matching based upon patient's gender, IH location and characteristics. Details of the matched groups can be seen in [Table 1](#).

As previously stated, cost analysis was carried out on the five atenolol patients based upon patient weight and treatment duration that resulted in a total cost of £22.92 for the cohort. Equivalent treatment cost for standard (2 mg/kg/day) and maximum (3 mg/kg/day) dose propranolol was found to be £539.24 and £811.33, respectively ([Table 2](#)).

To fulfil the secondary objective of the study, the treatment efficacy of the two drugs was assessed using VAS and HAS and the mean change before and after the treatment for individual IH was calculated ([Appendix 1](#)). The mean change in VAS was -7.0 for atenolol and -7.2 for propranolol, and the

**Table 2.**

	Cost (£) of Atenolol treatment course (1mg/kg/day)	Equivalent cost (£) of Propranolol standard dose (2mg/kg/day)	Equivalent cost (£) of Propranolol maximum dose (3mg/kg/day)
Atenolol pt 1	1.79	42.11	62.15
Atenolol pt 2	2.24	52.70	79.10
Atenolol pt 3	8.66	203.75	305.82
Atenolol pt 4	4.93	115.99	174.10
Atenolol pt 5	5.30	124.69	187.16
Total cost for Cohort (£)	22.92	539.24	811.33

mean change in HAS was 6.1 and 5.7 for atenolol and propranolol, respectively. The small sample size did not allow for statistical analysis.

In addition, adverse events were recorded for each cohort. Adverse events in the atenolol cohort included cold extremities (20%), wheeze (40%) and sleep disturbance (20%).

Within the propranolol, cohort adverse events included cold extremities (33%) and GI disturbance (16%).

## Discussion

In response to the primary objective of this study, it has been demonstrated that when given in standard dosing regimen atenolol is more than 20 times less expensive than standard dose propranolol. This presents a significant saving to the NHS as whole considering that IH is present in 5–10% of the UK's infant population.<sup>1–3</sup> Further benefits of atenolol are its once daily dosing which may improve parent satisfaction and treatment compliance when compared to three times daily dosing of propranolol.<sup>12</sup> Notwithstanding, it must be noted that if the patient vomits, the entire daily dose is lost that could lead to significant under treatment if this was a recurring issue.

The findings of this study echoes the current body of evidence that atenolol is at least as effective as the current gold standard therapy in the treatment of IH.<sup>6–10</sup> In addition, there was an absence of serious adverse events within the two groups, which again echoes the current body of evidence that these agents are as safe as one another.<sup>6–10</sup> It must be noted that the atenolol group did exhibit a significant increase in the rate of wheeze when compared to the propranolol group; however, this is likely due to an unavoidable selection bias as the atenolol patients are known to have pre-existing personal or a family history of respiratory conditions.

As this is a pilot study, it does have a number of limitations such as the small numbers of patients, along with a lack of standardised treatment protocol, blinding or randomisation.

One such limitation was in the scoring process of IH lesions using VAS and HAS which are subjective, and therefore vary from professional to professional causing variable reproducibility and a possibility of bias as this study was not blinded. To minimise the impact of such bias, two professionals calculated these scores independently, and a mean was taken for pre- and post-treatment photographs.

A further limitation of this study was that some patients had multiple haemangiomas, each of which were scored within the study; however, they may not have been treated if they were found in isolation. Ultimately, this area of study would greatly benefit from a blinded randomised control trial with treatment protocol to further explore the interesting findings of this Alder Hey Pilot Study.

## Conclusion

The key finding of this small pilot study was that first-line treatment with standard dose atenolol is more than 20 times less expensive than equivalent propranolol therapy given at standard dosing. Furthermore, the results from this limited data set demonstrated that atenolol is at least as effective and safe as propranolol which echoes the findings of recent meta-analysis which includes results from a total of 608 patients.<sup>7</sup> Ultimately, the findings of the pilot study suggest that the need for further

exploration into the suitability of atenolol to be considered as a first-line agent for IH, ahead of the current gold standard therapy propranolol.

### Declaration of Competing Interest

No conflicts of interest have been identified.

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### Ethical Approval

This study was registered with the research department at Alder Hey Children's Hospital, and was found to conform to the World Medical Association Declaration of Helsinki (June 1964) and subsequent amendments.

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### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi: 10.1016/j.jpra.2022.05.010](https://doi.org/10.1016/j.jpra.2022.05.010).

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