Received: 5 March 2024 | Accepted: 27 April 2024

DOI: 10.1111/pde.15652

Pediatric Dermatology WILEY

RESEARCH IN BRIEF

The burden of treatment of propranolol for infantile hemangiomas: A mixed methods study

Cathal O'Connor MD [1,2,3] | Michelle Murphy MD [1,2]

[1]Dermatology, South Infirmary Victoria University Hospital, Cork, Ireland

[2]University College Cork, Cork, Ireland

[3]INFANT Research Centre, University College Cork, Cork, Ireland

Correspondence
Cathal O'Connor, Department of Dermatology, SIVUH, Cork, Ireland.
Email: cathal.oconnor@ucc.ie

Funding information
The City of Dublin Skin and Cancer Hospital Charity; Wellcome Trust; Health Research Board, Grant/Award Number: 223047/Z/21/Z; Health Service Executive National Doctors Training and Planning; Health and Social Care, Research and Development Division, Northern Ireland

Abstract

The burden of treatment (BOT) related to propranolol treatment for infantile hemangiomas (IH) has never previously been explored. A modified validated questionnaire, the Treatment Burden Questionnaire, and one-on-one semi-structured interviews were used to assess the BOT for propranolol for IH. Out of 80 caregivers, the overall burden score was very low at 1.2 out of 10; thematic analysis of interviews grouped themes into administration, monitoring, financial, and associated anomalies. The BOT of propranolol for IH is very low but could be reduced further by offering age-based risk stratification related to feeding frequency and risk of hypoglycemia, pragmatic advice around timing of doses before sleep, and reducing frequency of vital sign monitoring.

KEYWORDS
burden of treatment, caregiver burnout, infantile hemangioma, patient burnout, pediatric dermatology, propranolol, vascular anomalies, vascular tumors

1 | INTRODUCTION

Burden of treatment (BOT) is the workload of healthcare experienced by patients with chronic conditions and consequences on well-being.[1] BOT is proportional to the complexity and intensity of treatments prescribed by healthcare professionals. High BOT results in reduced adherence to treatment plans and poorer outcomes for patients.[1] Infantile hemangiomas (IH), the most common tumor in infancy, are frequently treated with propranolol, a safe and highly effective medicine.[2] However, the BOT of propranolol for IH has never previously been studied. While few studies have assessed burden of disease in infants treated with propranolol for IH,[3] the aim of this study was to assess the BOT of oral propranolol for IH.

2 | METHODS

Ethical approval was granted by our Clinical Research Ethics Committee [ECM 4 (l) 19/10/2021]. Mixed methods research design was used to assess the BOT of propranolol for IH on caregivers. The quantitative component applied a modified validated questionnaire, the Treatment Burden Questionnaire,[4] ranking various burdens on a Likert scale from 0 (indicating no burden) to 10 (indicating maximal burden), with subcategories of medication burden, healthcare burden, and financial burden. The qualitative component involved one-on-one semi-structured telephone interviews with parents of infants treated with propranolol for IH (Appendix S1).

3 | RESULTS

The questionnaire was completed by parents of 80 consecutive infants treated with propranolol for IH for at least 3 months; 80% (64/80) were female; age range was 4–26 months. Most (75%, 60/80) IH were located on the head and neck, most (85%, 68/80) were single, and most (90%, 72/80) had not ulcerated. Two infants had PHACE syndrome. The overall burden score was very low at 1.2/10 (range 0–5/10), with very low subcategory scores (Figure 1). The

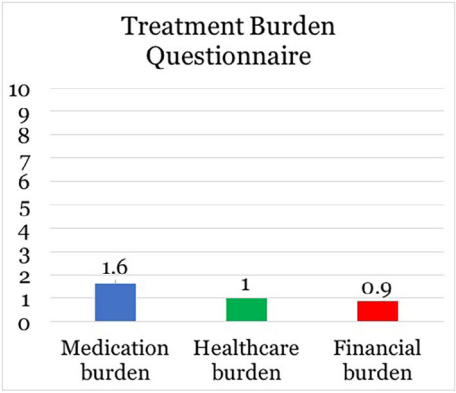

FIGURE 1 Mean treatment burden scores for propranolol for infantile hemangiomas from the Treatment Burden Questionnaire, ranked on a Likert scale from 0 (indicating no burden) to 10 (indicating maximal burden).

average burden score was 1/10 in infants without a history of ulceration, and 2.4/10 in infants with a history of ulceration ($p = .11$). Regarding medication burden, the most burdensome aspect was "precautions taken when giving propranolol" at 2.4/10. The effort to remember to give propranolol was rated 2.1/10, need to continue therapy long term 1.6/10, frequency of therapy 1.4/10, and administration 0.8/10. In terms of healthcare burden, physical checks (blood pressure, heart rate, etc.) were rated 1.5/10, clinic visits 1.4/10, scheduling 1.1/10, self-monitoring 0.7/10, and interaction with healthcare professionals 0.1/10. In terms of other burdens, administrative burden was ranked 0.4/10, financial burden 0.8/10, and childcare burden 1.1/10.

Semi-structured interviews were conducted by telephone with parents of 10 infants on propranolol for IH, including two infants with PHACE syndrome. Thematic analysis grouped experiences into administration, monitoring, financial, and associated anomalies (Table 1).

Parents found administration of propranolol easy, but some found timing of doses around feeding and sleeping challenging. Parents found monitoring of vital signs onerous, particularly blood pressure. Parents described the expense of purchasing the propranolol suspension. Parents of infants with PHACE or multiple IH described the burden related to management of associated anomalies.

TABLE 1 Illustrative statements from the qualitative statements from parents related to burden of treatment of propranolol for infantile hemangiomas and associated anomalies ($n = 10$), divided according to themes of administration, monitoring, financial, and associated anomalies.

Administration
"When she was very small it wasn't so hard feeding her every four hours, but as the feeds spaced out I got more nervous about sugar levels, especially overnight."
"We always dreaded the clinic visits because her dose went up with her weight and her sleep would be thrown off for another week."
Vital sign monitoring
"The bigger he got the more the blood pressure cuff annoyed him, the nurses had to hold him down towards the end."
Financial burden
"The price was the same whatever the strength, and the bigger she got the less time we got out of the bottle."
Associated anomalies
"She improved so much after getting the (ventriculoperitoneal) shunt, although it was traumatising at the time."

4 | DISCUSSION

This study shows that the BOT of propranolol for complex IH is very low, especially compared to other common pediatric dermatologic disease, such as severe atopic dermatitis or severe acne.[5,6] Higher BOT may be seen with propranolol for ulcerated IH and PHACE syndrome (especially related to neurovascular involvement), although numbers in this study were too low to draw any significant conclusions.

The interviews identified some areas of treatment where burden could be reduced further. Advice regarding increased feeding frequency should be risk-stratified due to the rare occurrence of hypoglycemia (except if fasting), even in the neonatal period.[7] However, premature and low-birthweight infants may require more frequent feeding, due to lower glycogen stores.[7] Administering propranolol several hours before nocturnal sleep is safe and may reduce sleep disturbance as the half-life of propranolol is only 3–6 h,[8] leading to negligible plasma levels overnight. Alternatively, a hydrophilic beta-blocker such as atenolol (which may have less propensity to cause sleep disturbance)[9] could be considered. Monitoring of vital signs should be reduced to the safest minimum required, due to infrequency of clinically significant aberrations.[10] Finally, prescribing concentrated propranolol syrup can facilitate the delivery of smaller volumes and reduced costs, or alternatively considering propranolol tablets for older children, due to the expense of syrup formulations.

This study highlights the low impact of treatment with propranolol for IH on caregivers. Given the impressive efficacy and reassuring safety of propranolol for treating IH, the low BOT associated with its use increases the benefit–risk ratio even further. This study should encourage pediatric dermatologists to consider a lower threshold for prescribing oral beta-blockade for infants with complex IH.

AUTHOR CONTRIBUTIONS

COC designed the study, distributed the questionnaires, performed the interviews, collected the data, analyzed the data, wrote the manuscript, and revised the manuscript. MM co-designed the study, analyzed the data and reviewed the manuscript.

ACKNOWLEDGMENTS

We thank the patients and caregivers who completed the questionnaires and participated in the research interviews. Open access funding provided by IReL.

FUNDING INFORMATION

Funding for this study was received from The City of Dublin Skin and Cancer Hospital Charity. The study was performed within the Irish Clinical Academic Training (ICAT) programme, supported by the Wellcome Trust and the Health Research Board (grant number 223047/Z/21/Z); the Health Service Executive National Doctors Training and Planning; and the Health and Social Care, Research and Development Division, Northern Ireland. The funders had no role in the design of this study, nor any role in the collection, analysis, or interpretation of data.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ORCID

Cathal O'Connor https://orcid.org/0000-0001-7084-5293
Michelle Murphy https://orcid.org/0000-0003-2431-076X

REFERENCES

1. Dobler CC, Harb N, Maguire CA, et al. Treatment burden should be included in clinical practice guidelines. *BMJ*. 2018;363:k4065. doi:10.1136/bmj.k4065
2. Léauté-Labrèze C, Hoeger P, Mazereeuw-Hautier J, et al. A randomized, controlled trial of oral propranolol in infantile hemangioma. *N Engl J Med*. 2015;372(8):735-746. doi:10.1056/NEJMoa1404710
3. Cazeau C, Blei F, Gonzáles Hermosa MDRF, et al. Burden of infantile hemangioma on family: an international observational cross-sectional study. *Pediatr Dermatol*. 2017;34(3):295-302. doi:10.1111/pde.13133
4. Tran VT, Harrington M, Montori VM, Barnes C, Wicks P, Ravaud P. Adaptation and validation of the Treatment Burden Questionnaire (TBQ) in English using an internet platform. *BMC Med*. 2014;12:109. doi:10.1186/1741-7015-12-109
5. O'Connor C, Dhonncha EN, Murphy M. "His first word was 'cream'." The burden of treatment in pediatric atopic dermatitis—a mixed methods study. *Dermatol Ther*. 2022;35(3):e15273. doi:10.1111/dth.15273
6. Kiely L, O'Connor C, Moosa AA, Dight E, Murphy M. Burden of treatment in severe acne vulgaris. *JEADV Clin Pract*. 2023;3(1):239-241. doi:10.1002/jvc2.266
7. Ji Y, Chen S, Xiang B, Yang Y, Qiu L. Safety and tolerance of propranolol in neonates with severe infantile hemangiomas: a prospective study. *Sci Rep*. 2017;7(1):1503. doi:10.1038/s41598-017-01321-2
8. Del Frari L, Léauté-Labrèze C, Guibaud L, et al. Propranolol pharmacokinetics in infants treated for infantile hemangiomas requiring systemic therapy: modeling and dosing regimen recommendations. *Pharmacol Res Perspect*. 2018;6(3):e00399. doi:10.1002/prp2.399
9. Zhao ZL, Liu C, Wang QZ, Wu HW, Zheng JW. Oral atenolol treatment for infantile hemangiomas: clinical analysis of 133 consecutive patients. *Ann Transl Med*. 2021;9(2):116. doi:10.21037/atm-20-5359
10. Püttgen KB, Hansen LM, Lauren C, et al. Limited utility of repeated vital sign monitoring during initiation of oral propranolol for complicated infantile hemangioma. *J Am Acad Dermatol*. 2021;85(2):345-352. doi:10.1016/j.jaad.2020.04.013

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

How to cite this article: O'Connor C, Murphy M. The burden of treatment of propranolol for infantile hemangiomas: A mixed methods study. *Pediatr Dermatol*. 2024;1-3. doi:10.1111/pde.15652