Oral atenolol compared to oral propranolol for infantile hemangioma

Victor Meza Viteri[a], Ligia Aranibar[b,c]

[a] Departamento de Dermatología, Facultad de Medicina, Universidad de los Andes, Santiago, Chile
[b] Departamento de Dermatología, Universidad de Chile, Santiago, Chile
[c] Clínica Universidad de los Andes, Departamento de Dermatología, Universidad de los Andes, Santiago, Chile

*Corresponding author
victormezaviteri@gmail.com

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Correspondence to
Monseñor Álvaro del Portillo 12455, Santiago, Chile

Abstract

Introducción

Infantile hemangioma is the most frequent benign vascular tumor in childhood, with an incidence of 3 to 10%. When patients require treatment, oral propranolol, a non-selective lipophilic beta-blocker, is usually considered the therapy of choice. However, its use has been associated with several adverse events related to its β-2 action and its ability to cross the blood-brain barrier. Because of this, oral atenolol, a hydrophilic β-1 receptor-selective beta-blocker, may represent a valid treatment alternative. Nonetheless, there is still controversy regarding the efficacy and safety of atenolol when compared with propranolol as monotherapy for this condition.

Methods

Se realizó una búsqueda en Epistemonikos, la mayor base de datos de revisiones sistemáticas en salud, la cual es mantenida mediante el tamizaje de múltiples fuentes de información, incluyendo MEDLINE/PubMed, EMBASE, Cochrane, entre otras. Se extrajeron los datos desde las revisiones identificadas, se analizaron los datos de los estudios primarios, se realizó un metanálisis y se preparó una tabla de resumen de los resultados utilizando el método *Grading of Recommendations Assessment, Development and Evaluation*, GRADE.

Results

Nine systematic reviews were identified, including 10 primary studies and three randomized trials. The three randomized trials were included in the analysis of this investigation.

Conclusion

The use of oral atenolol compared with oral propranolol as monotherapies may result in little or no difference in terms of likelihood of complete remission, decrease in Hemangioma Activity Score, likelihood of post-treatment relapse, and risk of adverse events and severe adverse events, in infantile hemangioma (low certainty of evidence).

Main messages

- There is still controversy regarding the efficacy and safety of treating infantile hemangioma with atenolol compared to propranolol as monotherapy.
- Through the FRISBEE (Friendly Summaries of Body of Evidence using Epistemonikos) and GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) methodologies, a summary and analysis comparing atenolol versus atenolol in monotherapy is presented, which allows evaluating its efficacy and safety.
- This work also presents a series of considerations that seek to guide decision-making in infantile hemangioma cases requiring treatment.
- The limitations of this work are those inherent to the applied methodologies.

Problem

Infantile hemangioma is the most common benign vascular tumor in childhood, with an estimated incidence of 3 to 10% [1–3].

Its clinical course is characterized by rapid growth during the first 3 to 12 months of life, to later involute spontaneously between 3 to 7 years of life [4]. Because of this, it is estimated that only 10 to 15% of patients with infantile hemangioma require some type of treatment during the proliferative phase of the disease. This treatment is usually indicated when there is ulceration, bleeding, infection, ocular or airway impairment, and/or for cosmetic reasons, such as extensive involvement of the facial region [5–7]. In addition to these possible complications, studies have shown that infantile hemangioma can affect the mental health of both children and their families [8,9].

Among the available treatment options, propranolol, a non-selective beta-blocker, is usually considered the first-line therapy [2,9,10]. However, its use may be associated with various adverse events, mainly related to its β-2 action and its ability to cross the blood-brain barrier due to its lipophilic nature [6,11,12]. Among these adverse events, bronchial obstruction, hypotension, hypoglycemia, seizures, sleep disturbances, and gastrointestinal symptoms, among others, have been described [5,6,11,12].

On the other hand, atenolol, a β-1 receptor selective beta-blocker, could represent a valid treatment alternative, potentially avoiding the adverse events described with the use of propranolol due to its lack of β-2 activity and its hydrophilic nature, which prevents it from crossing the blood-brain barrier [11].

Other therapeutic alternatives that have been studied are the topical use of timolol and/or imiquimod; intralesional or oral corticosteroid therapy; chemotherapeutic drugs such as vincristine and interferon; use of different laser modalities; and surgery [5,10].

This review aims to evaluate the efficacy and safety of using oral atenolol in patients with infantile hemangioma, compared to oral propranolol as monotherapy.

Methods

We searched Epistemonikos, the largest database of systematic reviews in health sciences, which is maintained by searching multiple sources of information, including MEDLINE/PubMed, EMBASE, and Cochrane, among others. Data were extracted from the identified reviews, and data from the primary studies were analyzed. With this information, a structured summary called FRISBEE (Friendly Summaries of Body of Evidence using Epistemonikos) was generated, following a pre-established format, including key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the studies when possible, a summary table of results with the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) method, and a section of further considerations for decision-making.

Regarding the body of evidence for this question

What evidence is available? See the evidence matrix in Epistemonikos below.	We found nine systematic reviews [2–4,9,10,13–16], including 10 primary studies [5,11,17–24], three of which are randomized trials [5,11,17].
What type of patients did the studies include?*	All trials [5,11,17] included patients diagnosed with infantile hemangioma needing treatment. This was defined by two trials [5,17] as the presence of functional impairment, cosmetic disfigurement, ulceration, or localization in fold areas, while the other trial [11] defined it as hemangiomas greater than or equal to 1.5 centimeters on the face, 3.0 centimeters outside the face, or 1.5 centimeters if ulceration was present. The average age of the patients included in the trials was 2.8 months. Regarding exclusion criteria, all three trials [5,11,17] excluded patients with contraindications to beta-blocker use, including previous history of allergy or hypersensitivity, heart disease, arrhythmias, asthma, or bronchial obstruction. One trial [17] excluded patients with type-2 diabetes mellitus, a history of hypoglycemia, hypertension or arterial hypotension, hepatic failure, carriers of visceral hemangiomas, PHACES syndrome, and preterm infants with correctional age less than 40 weeks. In addition, two studies [5,11] excluded patients previously treated with any therapy for infantile hemangioma.
What type of interventions were included in the studies? *	All trials [5,11,17] compared the use of atenolol versus propranolol as monotherapy.Atenolol doses were at 1 mg/kg/day in a daily dose for six months for one trial [5], 0.5 mg/kg/day for 24 hours, and then 1 mg/kg/day in a daily dose for nine months for another trial [17]; and 0.5 mg/kg/day for one week and then 1 mg/kg/day in a daily dose for six months for another study [11].As for propranolol doses, they were 2 mg/kg/day divided into three daily doses for six months for one trial [5]; 1 mg/kg/day, and then 2 mg/kg/day divided into two daily doses for nine months for another trial [17]; and 1 mg/kg/day for one week and then 2 mg/kg/day divided into three daily doses for six months for another study [11].
What type of outcomes were measured?	Trials reported multiple outcomes, which were grouped by the systematic reviews as follows: • Complete remission • Decrease in Hemangioma Activity Score • Post-treatment relapse • Adverse events • Severe adverse events The average follow-up of the trials was 12 months, ranging from six to 24 months.

mg/kg/day, milligrams per kilogram per day; PHACES, posterior fossa malformations, hemangioma of the cervicofacial region, arterial anomalies, cardiac anomalies, eye anomalies, and sternal or abdominal clefting or ectopia cordis.

Notes: [1]Information on primary studies is extracted from the identified systematic reviews, not directly from the studies unless otherwise specified.

Source: tThis table and the summary are based on the three randomized trials [5,11,17], as information from observational studies does not increase the certainty of the evidence, nor does it add additional relevant information.

Summary of results.

Information on the effects of oral atenolol compared with oral propranolol is based on three trials [5,11,17] involving 440 patients. All trials measured complete remission following the completion of treatment. Two trials [11,17] evaluated the decrease in Hemangioma Activity Score, and two trials [5,11] measured post-treatment relapse. All trials [5,11,17] analyzed the presence of adverse events and severe adverse events in both groups.

The summary of the results is as follows:

1. The use of atenolol compared with the use of propranolol as monotherapy may result in little or no difference in the likelihood of complete remission of infantile hemangioma (low certainty of evidence).
2. The use of atenolol compared with the use of propranolol as monotherapy could have little or no difference in terms of decreasing the Hemangioma Activity Score in infantile hemangioma (low certainty of evidence).
3. The use of atenolol compared with the use of propranolol as monotherapy could result in little or no difference in the likelihood of post-treatment relapse in infantile hemangioma (low certainty of evidence).
4. The use of atenolol compared with the use of propranolol as monotherapy could result in little or no difference in the risk of adverse events and severe adverse events (low certainty of evidence).

Atenolol compared to propranolol for infantile hemangioma

Patients Patients with infantile hemangioma
Intervention Oral atenolol monotherapy
Control Oral propranolol monotherapy

Outcomes	Absolute effect*		Relative effect (IC 95%)	Certainty of evidence (GRADE)
	Propranolol	**Atenolol**		
	Difference: patients per 1000			
Complete remission	826 per 100	793 per 1000	RR 0,96 (0,87 a 1,05)	⊕⊕◯◯[I] Low
	Difference: 33 less(Margin of error: from 107 minus to 41 plus)			
Decrease in Hemangioma Activity Score **	The decrease in Hemangioma Activity Score was, on average, 0.08 standard deviations lower in the intervention group compared to the control.		--	⊕⊕◯◯[I] Low
	SMD: 0.08 less(Margin of error: from 0.29 less to 0.13 more)			
Post-treatment relapse	128 per 1000	77 per 1000	RR 0,60 (0,32 a 1,13)	⊕⊕◯◯[I] Low
	Difference: 51 less(Margin of error: 87 less to 17 more)			
Adverse events †	662 per 1000	550 per 1000	RR 0,83 (0,46 a 1,51)	⊕⊕◯◯[I] Low
	Difference: 112 less(Margin of error: 358 minus to 338 plus)			
Severe adverse events ††	23 per 1000.	14 per 1000	RR 0,61 (0,15 a 2,51)	⊕⊕◯◯[I] Low
	Difference: 9 less(Margin of error: from 19 less to 34 more)			

Margen de error: intervalo de confianza del 95% (IC 95%).
RR: riesgo relativo.
DM: diferencia de medias.
DME: diferencia de medias estandarizada.
GRADE: grados de evidencia del GRADE *Working Group* (ver más adelante).

**Los riesgos/promedio con Propranolol están basados en los riesgos/promedio del grupo control en los estudios. El riesgo/promedio con Atenolol (y su margen de error) está calculado a partir del efecto relativo/diferencia de medias (y su margen de error).
** El Hemangioma Activity Score corresponde a un instrumento validado, que se calcula como un puntaje en base a tres subítems: grado de hinchazón profundo, color y ulceración del hemangioma. El puntaje calculado puede variar de cero a ocho puntos, y se considera que un cambio en un punto es clínicamente relevante [25].
† El desenlace "efectos adversos" incluyó la presencia de síntomas gastrointestinales (diarrea, náuseas), alteraciones del sueño, agitación y/o extremidades frías.
†† El desenlace "efectos adversos severos" incluyó la presencia de hiperreactividad bronquial, hipotensión, bradicardia asintomática, hipoglicemia y/o hiperkalemia.
[I] Se disminuyeron dos niveles de certeza de evidencia per riesgo de sesgo e imprecisión. En los desenlaces, los límites del intervalo de confianza son amplios, favoreciendo una terapia u otra en cada límite del intervalo de confianza.

About the levels of evidence (GRADE)*

⊕⊕⊕⊕
High: the research provides a very good indication of the likely effect. The probability that the effect is substantially different† is low.

⊕⊕⊕◯
Moderate: the research provides a good indication of the likely effect. The probability that the effect is substantially different† is moderate.

⊕⊕◯◯
Low: research provides some indication of the likely effect. However, the probability that the effect will be substantially different† is high.

⊕◯◯◯
Very low: research does not provide a reliable estimate of the likely effect. The probability that the effect is substantially different† is very high.

*This is also called 'quality of evidence' or 'confidence in the effect estimate'.

†Substantially different = a difference large enough to affect a decision.

Further considerations for decision-making

To whom does this evidence apply?

The evidence applies to pediatric patients diagnosed with infantile hemangioma who have not received treatment for this pathology.

It does not apply to patients with contraindications to beta-blockers, including a history of allergy or hypersensitivity, heart disease, arrhythmias, asthma, and/or bronchial obstruction.

Regarding the included outcomes in this summary

Outcomes of complete remission, post-treatment relapse, adverse effects, and severe adverse effects were included, as these are the most important outcomes for patients and their caregivers, according to the authors of this review.

Despite being a secondary outcome, we evaluated the outcome decrease in the Hemangioma Activity Score since it is associated with a better response to treatment.

The outcomes included in the summary are those considered relevant for decision-making by the authors, which coincide with those reported by the included systematic reviews.

Risk/benefit assessment and certainty of the evidence

When comparing the benefits and risks between both therapies, the use of atenolol compared to the use of propranolol could result in little or no difference in terms of the probability of complete remission of infantile hemangioma, the decrease in the Hemangioma Activity Score, the probability of relapse after treatment, and the risk of presenting adverse and/or severe adverse events (low certainty of evidence).

However, it is impossible to perform a correct risk/benefit assessment, given the uncertainty in the evidence, so further aspects should be considered for decision-making.

Resources considerations

The included systematic reviews did not perform a cost-effectiveness analysis between the two treatments.

Atenolol and propranolol, however, are low-cost and widely available drugs, so a formal economic analysis does not seem necessary for clinical decision-making.

What do caretakers and treating physicians think?

Based on the evidence provided by this summary, it is unclear whether patients' caregivers and treating physicians should favor or oppose the use of atenolol, considering the uncertainty of its superiority compared to propranolol monotherapy.

The ideal dose and duration of atenolol treatment for infantile hemangioma have not yet been studied or defined. However, the once-daily dosing of atenolol may represent an advantage over the use of propranolol.

Differences between this summary and other sources

The conclusions of this summary are in tune with the nine included systematic reviews [2–4,9,10,13–16] because, given the existing uncertainty in the evidence, it is not yet possible to establish the superiority of a treatment.

When comparing with international clinical guidelines, it is observed that both the Clinical Practice Guideline for the Management of Infantile Hemangioma of the American Academy of Pediatrics [26] and the Spanish Consensus on Infantile Hemangioma of the Spanish Association of Pediatrics [27] still establish propranolol as the first line of treatment for infantile hemangioma. However, in both guidelines, atenolol is mentioned as a potential valid therapeutic alternative, according to the emergence of new evidence.

Consequently, new randomized comparative studies are still needed, which can be extrapolated to the results of this review.

May this information change in the future?

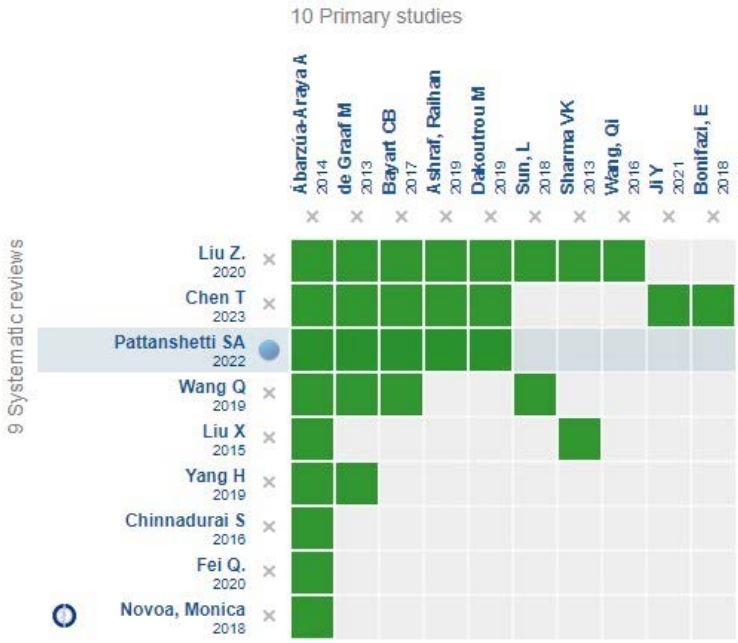
The likelihood that future evidence will change the conclusions of this summary is high due to the existing uncertainty.

A systematic review was identified in the PROSPERO (International Prospective Register of Systematic Reviews) platform that compares the use of atenolol monotherapy against other therapeutic alternatives for infantile hemangioma, including propranolol monotherapy [28]. This systematic review could shed new light on the subject.

No new trials were found in recruitment on the ClinicalTrials.gov platform of the National Institutes of Health (NIH), comparing the use of atenolol versus propranolol as monotherapy for infantile hemangioma.

How we conducted this summary

Using automated and collaborative methods, we compiled all the evidence relevant to the question of interest and presented it in an evidence matrix



An evidence matrix is a table that compares systematic reviews that answer the same question.

The rows represent the systematic reviews, and the columns show the primary studies.

The green boxes correspond to studies included in the respective reviews.

The system automatically detects new systematic reviews, including any primary studies in the matrix, which will be added if they answer the same question.

Follow the link to access the interactive version: Atenolol versus propranolol para hemangioma infantil

Notes

If new systematic reviews on this topic are published after this abstract is published, a "new evidence" notice will be displayed at the top of the matrix. While the project envisages regular updating of these abstracts, users are invited to comment on the Medwave website or contact the authors by e-mail if they believe there is evidence that warrants an earlier update.

After creating an Epistemonikos account, by saving the matrices, you will receive automatic notifications whenever there is new evidence that potentially answers this question.

This article is part of the Epistemonikos evidence synthesis project. It is elaborated with a pre-established methodology, following rigorous methodological standards and an internal peer-review process. Each of these articles corresponds to a summary called FRISBEE (Friendly Summary of Body of Evidence using Epistemonikos), whose main objective is to synthesize the body of evidence for a specific question in a friendly format for clinicians. Its main resources are based on the Epistemonikos evidence matrix and analysis of results using GRADE methodology. Further details of the methods to elaborate this FRISBEE are described here (http://dx.doi.org/10.5867/medwave.2014.06.5997).

The Epistemonikos Foundation is an organization that seeks to bring information closer to health decision-makers through the use of technologies. Its main development is the Epistemonikos database (www.epistemonikos.org).

Authorship contributions
VMV: methodology, validation, formal analysis, research, resources, data curation, draft writing, fund acquisition. LA: review and editing, visualization, fund acquisition.

Competing interests
The authors declare no conflicts of interest regarding the subject matter of this article.

Declaración sobre aspectos éticos
The present study did not require evaluation by an ethics committee, as it is a structured summary of evidence using secondary data sources.

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Referencias

1. Drolet BA, Esterly NB, Frieden IJ. Hemangiomas in children. N Engl J Med. 1999;341: 173–81. | CrossRef
2. Wang Q, Xiang B, Chen S, Ji Y. Efficacy and safety of oral atenolol for the treatment of infantile haemangioma: A systematic review. Australas J Dermatol. 2019;60: 181–185. | CrossRef
3. Novoa M, Baselga E, Beltran S, Giraldo L, Shahbaz A, Pardo-Hernandez H, et al. Interventions for infantile haemangiomas of the skin. Cochrane Database Syst Rev. 2018;4. | CrossRef
4. Pattanshetti SA, Mahalmani VM, Sarma P, Kaur H, Ali MM, Malik MA, et al. Oral Atenolol versus Propranolol in the Treatment of Infantile Hemangioma: A Systematic Review and Meta-Analysis. J Indian Assoc Pediatr Surg. 2022;27: 279–286. | CrossRef
5. Ábarzúa-Araya A, Navarrete-Dechent CP, Heusser F, Retamal J, Zegpi-Trueba MS. Atenolol versus propranolol for the treatment of infantile hemangiomas: a randomized controlled study. J Am Acad Dermatol. 2014;70: 1045–9. | CrossRef
6. Léaute-Labrèze C, Boccara O, Degrugillier-Chopinet C, Mazereeuw-Hautier J, Prey S, Lebbé G, et al. Safety of Oral Propranolol for the Treatment of Infantile Hemangioma: A Systematic Review. Pediatrics. 2016;138. | CrossRef
7. Shayan YR, Prendiville JS, Goldman RD. Use of propranolol in treating hemangiomas. Can Fam Physician. 2011;57: 302–3. | Link
8. Csoma ZR, Dalmády S, Ábrahám R, Rózsa T, Rácz K, Kemény L. Infantile haemangioma: clinical and demographic characteristics, experiences in the treatment. Orv Hetil. 2017;158: 1535–1544. | CrossRef
9. Liu Z, Wu C, Song D, Wang L, Li J, Wang C, et al. Atenolol vs. propranolol for the treatment of infantile haemangiomas: A systematic review and meta-analysis. Exp Ther Med. 2020;20: 1644–1652. | CrossRef
10. Chen T, Gudipudi R, Nguyen SA, Carroll W, Clemmens C. Should Propranolol Remain the Gold Standard for Treatment of Infantile Hemangioma? A Systematic Review and Meta-Analysis of Propranolol Versus Atenolol. Ann Otol Rhinol Laryngol. 2023;132: 332–340. | CrossRef
11. Ji Y, Chen S, Yang K, Zhang X, Zhou J, Li L, et al. Efficacy and Safety of Propranolol vs Atenolol in Infants With Problematic Infantile Hemangiomas: A Randomized Clinical Trial. JAMA Otolaryngol Head Neck Surg. 2021;147: 599–607. | CrossRef
12. de Graaf M, Breur JMPJ, Raphaël MF, Vos M, Breugem CC, Pasmans SGMA. Adverse effects of propranolol when used in the treatment of hemangiomas: a case series of 28 infants. J Am Acad Dermatol. 2011;65: 320–327. | CrossRef
13. Liu X, Qu X, Zheng J, Zhang L. Effectiveness and Safety of Oral Propranolol versus Other Treatments for Infantile Hemangiomas: A Meta-Analysis. PLoS One. 2015;10. | CrossRef
14. Yang H, Hu DL, Shu Q, Guo XD. Efficacy and adverse effects of oral propranolol in infantile hemangioma: a meta-analysis of comparative studies. World J Pediatr. 2019;15: 546–558. | CrossRef
15. Fei Q, Lin Y, Chen X. Treatments for infantile Hemangioma: A systematic review and network meta-analysis. EClinicalMedicine. 2020;26. | CrossRef
16. Chinnadurai S, Fonnesbeck C, Snyder KM, Sathe NA, Morad A, Likis FE, et al. Pharmacologic Interventions for Infantile Hemangioma: A Meta-analysis. Pediatrics. 2016;137. | CrossRef
17. Ashraf R, Mahajan R, Abas M, Handa S, Sinha A, De D, et al. Comparing the Clinical, Radiologic and Biochemical Effectiveness of Atenolol and Propranolol in the Treatment of Infantile Hemangioma - A Randomized Controlled Trial. SSRN Journal. | CrossRef
18. Wang Q, Xiang B, Yi JI, Fuyu LI, Zhicheng XU, Zhong L. Propranolol versus atenolol in the treatment of infantile hemangioma: a comparative study. Chinese Journal of Dermatology. 2016;683–7. | Link
19. Sun L, Sun B, Ma Y. Comparison of the efficacy and safety of propranolol and atenolol in the treatment of infant hemangioma. Progress Modern Biomed. 2018;18: 108–12.
20. de Graaf M, Raphael MF, Breugem CC, Knol MJ, Bruijnzeel-Koomen CAFM, Kon M, et al. Treatment of infantile haemangiomas with atenolol: comparison with a historical propranolol group. J Plast Reconstr Aesthet Surg. 2013;66: 1732–40. | CrossRef
21. Bayart CB, Tamburro JE, Vidimos AT, Wang L, Golden AB. Atenolol Versus Propranolol for Treatment of Infantile Hemangiomas During the Proliferative Phase: A Retrospective Noninferiority Study. Pediatr Dermatol. 2017;34: 413–421. | CrossRef
22. Dakoutrou M, Alexopoulos A, Miligkos M, Georgiadou E, Kanaka-Gantenbein C, Kakourou T. Atenolol treatment for severe infantile hemangiomas: comparison with a propranolol group of our centre. J Eur Acad Dermatol Venereol. 2019;33: e199–e200. | CrossRef
23. Sharma VK, Fraulin FO, Dumestre DO, Walker L, Harrop AR. Beta-blockers for the treatment of problematic hemangiomas. Can J Plast Surg. 2013;21: 23–8. | CrossRef
24. Bonifazi E, Milano A. Atenolol in the atopic child with infantile hemangioma. European Journal of Pediatric Dermatology. 2018;28: 165–71. | CrossRef
25. Janmohamed SR, de Waard-van der Spek FB, Madern GC, de Laat PCJ, Hop WCJ, Oranje AP. Scoring the proliferative activity of haemangioma of infancy: the Haemangioma Activity Score (HAS). Clin Exp Dermatol. 2011;36: 715–23. | CrossRef
26. Krowchuk DP, Frieden IJ, Mancini AJ, Darrow DH, Blei F, Greene AK, et al. Clinical Practice Guideline for the Management of Infantile Hemangiomas. Pediatrics. 2019;143. | CrossRef
27. Baselga Torres E, Bernabéu Wittel J, van Esso Arbolave DL, Febrer Bosch MI, Carrasco Sanz Á, de Lucas Laguna R, et al. Spanish consensus on infantile haemangioma. An Pediatr (Barc). 2016;85: 256–265. | CrossRef
28. Zhisheng Z, Xianying Z, Xingong L, Chaoyang W, Shize Z. In: Efficacy and safety of oral atenolol in infantile hemangioma: a meta analysis of comparative studies [Internet]. | Link
1.