# Atenolol Versus Propranolol in The Treatment of Infantile Hemangioma: A Randomized Controlled Trial

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## Abstract

**Background:** Propranolol, a nonselective beta-blocker is recommended for the treatment of Infantile Hemangiomas (IHs). However, this treatment is not risk-free and it cannot be applied to many patients because of respiratory comorbidities. Atenolol is a cardioselective beta-blocker and recently, some studies have reported their experience in using oral Atenolol in IHs. The aim of this study was to compare the outcome of Atenolol versus Propranolol in the treatment of IHs.

**Materials and methods:** This randomized controlled trial was carried out in the Department of Pediatric Surgery of Chittagong Medical College Hospital from January 2020 to December 2020. 49 patients aged less than 7 years with a diagnosis of cutaneous IH were randomly assigned into two groups. Group A received oral Propranolol (2 mg/kg/day) and Group B received oral Atenolol (1 mg/kg/day). Follow-up was made at 1 month, 3 months and 6 months. Main outcome measures were changes in Hemangioma Activity Score (HAS) and adverse effects. 5 patients did not show up in any follow-up. Finally, a total of 44 patients (22 in Propranolol group and 22 in Atenolol group) were included in the analysis.

**Results:** There was no significant difference in age and sex between the groups. Mean age was 7.5 months in Group A and 11.5 months in Group B (p= 0.580). Pretreatment HAS was similar between groups (median 4.0 in Group A, 4.4 in Group B, p=0.208) and posttreatment HAS was also similar between two groups (median 1 in Group A, 0 in Group B, p=0.243). In Group A median hemangioma size reduced from 3.30 cm to 0.55 cm and from 3.28 cm to 0.76 cm in Group B, significantly size reduced in both groups (p=<0.001) after treatment. 9.1% of patients in Group A and 22.7% of patients in Group B had complete response but the difference was not significant (p=0.412). Although, patients in Group A had more adverse effects than Group B (18.2% vs 9.1%, p=0.945) and it was not statistically significant.

**Conclusion:** This study showed that Atenolol is as effective as Propranolol for treatment of IH with few adverse effects.

**Key words:** Atenolol; Hemangioma Activity Score; Infantile hemangioma; Propranolol.

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## Introduction

Infantile Hemangiomas (IHs) are the most common benign vascular neoplasms of infancy affecting as many as 5% to 10% of infants within the first year of life.[1,2] Although, IHs have a characteristic clinical course marked by early proliferation and followed by spontaneous involution, some IHs need treatment with medication. These include IHs that may cause permanent scarring and disfigurement (e.g. Facial IHs) hepatic or airway IHs and IHs with the potential for functional impairment (e.g. Periorbital IHs) ulceration (That may cause pain or scarring) and associated underlying abnormalities (e.g. intracranial and aortic arch vascular abnormalities accompanying a large facial IH).[2-4]

The Food and Drug Administration (FDA) of the USA approved beta (β) blockers as the first-line medications for the management of IH in 2014. Propranolol is a non-selective lipophilic β (β1, β2) blocker proven to be effective against IHs. [5] However, Propranolol treatment also has certain risks, including some AEs such as diarrhea, hyperkalaemia, hypoglycaemia and bronchial hyperreactivity. Propranolol also affects the Central Nervous System (CNS) as it crosses the blood-brain barrier due to its lipophilic nature and may cause AEs such as agitation and sleep disturbances.[2,6,7] In 2011, Raphael and colleagues first reported two IH patients who withdrew from Propranolol treatment due to bronchial hyper

reactivity and sleep disturbance and then switched to Atenolol with success.[8] Subsequently, some other studies have reported their experience in using oral Atenolol in IH, especially as an alternative to Propranolol and which have potential as preferable agents because of lower risk of bronchospasm, hypoglycemia, sleep disturbances and less frequent daily dosing.[9-17] Atenolol has a longer half-life and can be dosed once daily though twice daily dose can be given in young children.[18] Due to hydrophilic nature of Atenolol, it does not cross the blood-brain barrier and has limited AEs when compared to Propranolol.[19] In this background, this study was designed to compare the efficacy and safety of Propranolol and Atenolol in the treatment of cutaneous IHs in a prospective randomized design.

**Materials and methods**

This randomized control trial was carried out in Department of Pediatric Surgery of Chittagong Medical College Hospital (CMCH) from January 2020 to December 2020. Patients aging not more than 7 completed years who came for the management of IH in the Department of Pediatric Surgery of CMCH, during study period were the study population. The general objective was to compare clinical outcomes between patients treated with Atenolol and those treated with Propranolol in the treatment of IHs and specific objectives were to compare regression of IHs between patients treated with Propranolol and Atenolol, to compare HAS between two groups before and after treatment and to compare AEs of two drugs between two groups. Patients were screened consecutively by the following eligibility criteria to select the appropriate subjects for the trial and then the eligible subjects were randomly allocated in two treatment protocols (Figure 1).

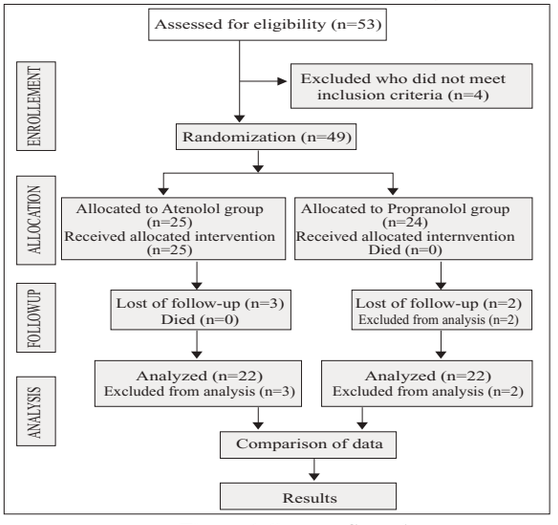


**Figure 1** Consort flow chart

Group A-Oral Propranolol 2 mg/kg/day as crushed tablets in two divided doses.

Group B- Oral Atenolol 1 mg/kg as crushed tablets as a single dose.

*Inclusion criteria*

Children with cutaneous infantile hemangiomas and age less than 7 years.

*Exclusion criteria*

History of previous treatment for IH, heart disease, cardiac arrhythmias, broncho -obstructive disease, known hypoglycemia, diabetes mellitus, hypertension/hypotension and those who refused to participate in the study.

Consecutive patients attending in the Department of Pediatric Surgery OPD of CMCH with a diagnosis of IH were assessed for eligibility. Informed written consent was obtained from the legal guardians of the patients after full explanation of the ultimate outcome, complications and purpose of the study.

Eligible individuals were recruited consecutively and randomly assigned to one of the two treatment groups with a computer-generated randomization list by block size of two in a ratio of 1:1.

Patients' demographic characteristics, such as age, sex, socio-economic status and characteristics of IHs were recorded in case record form. Determination of anatomical location and dimensions of hemangioma were done through direct measurements and photography (Figure 2). Measurement in centimeters of lesion along long axis and another one perpendicular to this axis by flexible measuring tape or slide calipers. Photograph was taken and obtained by the investigator himself using iPhone 8 plus camera and appropriate light source. Upon requirement, each lesion was evaluated clinically for color and consistency with the help of HAS was recorded. Heart rate, BP, respiratory rate, RBS and adverse effects were recorded. These observations were noted in the case record form.

The following were used to monitor IHs progression and response to treatment:

- Swelling: Reduction of swelling after activity at follow-up
- Color: Color change after activity at follow up
- Ulcer size (If present).

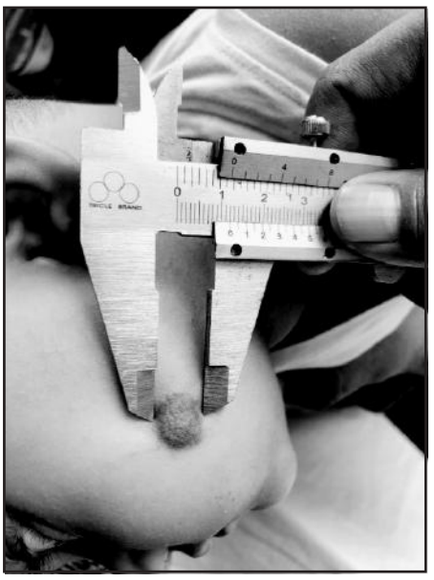

**Figure 2** Measure of size with slide calipers

Blood glucose level less than 60 mg/dl (3.3 mmol/L) at any time regardless of age or whether symptomatic or not is defined as hypoglycemia.[20]

Evaluation of improvement was done by assessing the size of hemangioma at every follow up. Serial photography was done at baseline and onward follow up. HAS was calculated at baseline and every follow up. All the subjects were reviewed at 1 month, 3 months and 6 months. A full clinical examination was performed during each visit, including cardiovascular status and any AEs such as sleep disturbances, hypoglycemia and hypotension were recorded in the case record form.

Regression of size, color and consistency of the lesion by HAS, heart rate, Blood Pressure (BP) respiratory rate, Random Blood Sugar level (RBS) and development of adverse effects. The outcomes were classified as excellent (Compete or nearly complete resolution of the IH, lesions' regression over 90% of their initial size) good (Partial resolution, defined as any size reduction) No response (Defined as no change between photographs and/or growth while in treatment) or deterioration at 6 months versus baseline according to the evaluation.

Data analysis were performed using the SPSS (Statistical Package for the Social Sciences) software, version 23.0. The quantitative data were expressed as median (Interquartile range) and range. Medians were compared between groups by Mann-Whitney U test. Paired comparison of pretreatment and posttreatment values of HAS and hemangioma size between groups were tested by Wilcoxon Signed Rank Test. Categorical variables were presented as number (Percentage). The Pearson Chi square or Fisher exact tests were used, as appropriate, for between group comparison of categorical data. p values less than 0.05 were considered to be statistically significant

The study was approved by Ethical review committee of Chittagong Medical College (CMC/PG/2020/639) and was performed according to Helsinki declaration.

**Results**

The median age at treatment initiation was 11.5 (IQR :5.0-19.8) months in the Atenolol group and 7.5 (IQR: 5.8-19.5) months in the Propranolol group, p=0.580. Overall, there was female predominance in both groups (Male 13, female 31) and majority (37) were from low socio-economic class.

The median age of appearance of hemangioma was 17 days and 8 days respectively in the Atenolol and Propranolol group. 63% of the patient in Atenolol group and 45.5% patients in Propranolol group reported to receive holistic treatment in the form of homeopathy (Table I).

**Table I** Time of appearance, growth of hemangioma, associated anomaly and complication in the patients stratified by study groups

| Characteristics | Atenolol (n=22) | Propranolol (n=22) | p value |
|---|---|---|---|
| Time of appearance (Days) | | | |
| Median (IQR) | 17.5 (3.8-32.5) | 8.0 (3.8-23.6) | 0.155* |
| Range | 0-90 | 0-45 | |
| Growth | | | |
| Slow | 19 (86.4) | 18 (81.8) | 1.0‡ |
| Rapid | 3 (13.6) | 4 (18.2) | |
| Congenital anomaly | 1 (4.5) | 2 (9.1) | 1.0‡ |
| Previous holistic treatment | 14 (63.6) | 10 (45.5) | 0.226† |
| IHs related problems: ulcer | 1 (4.5) | 1 (4.5) | 1.0‡ |

Data are expressed as frequency (Percentage) if not otherwise mentioned. p values were obtained from either *Mann Whitney U test or † Chi-square test or ‡Fisher's exact test.

Most common location of hemangioma in both groups were face (15) followed by scalp (7) leg (3) and chest (3). Both the groups were similar in terms of their baseline median hemangioma size, color and HAS (Table II).

**Table II** Baseline size, color of hemangioma and HAS of the patients stratified by study groups

| Characteristics | Atenolol (n=22) | Propranolol (n=22) | p value |
|---|---|---|---|
| Size ($cm^2$) | | | |
| Median (IQR) | 3.28 (1.62-10.23) | 3.30 (1.48-7.56) | 0.805* |
| Range | 0.47-36.92 | 0.56-38.35 | |
| Color | | | |
| Bright red | 12 (54.6) | 8 (36.4) | 0.723‡ |
| Matt red | 5 (22.7) | 8 (36.4) | |
| Others | 5 (22.7) | 6 (27.2) | |
| HAS | | | |
| Median (IQR) | 4.4 (3.7-5.0) | 4.0 (3.0-5.0) | 0.208* |
| Range | 3.0-5.0 | 3.0-5.5 | |

Data were expressed as frequency (Percentage) if not otherwise mentioned. p values were obtained from either *Mann Whitney U test or ‡ Chi-square test.

Hemangioma size, pre-treatment phase and 6 months after continuation of treatment phase were summarized in Table II by the study groups. There was no significant difference in pretreatment hemangioma size between the groups (p=0.805). After treatment, hemangioma size reduced significantly in both groups (p=<0.001). There was no significant difference in posttreatment hemangioma size between two groups (p=0.879).

**Table III** Pre- and Posttreatment Hemangioma size between two groups

| Time of assessment | Median (Range) size of hemangioma in $cm^2$ Atenolol (n=22) | Propranolol (n=22) | p value* |
|---|---|---|---|
| Pretreatment | 3.28 (0.47-36.92) | 3.30 (0.56-38.35) | 0.805 |
| Post treatment | 0.76 (0.03-33.50) | 0.55 (0.15-31.27) | 0.879 |
| p value# | <0.001 | <0.001 | |

p values were obtained from either *Mann Whitney U test or #Related-Samples Wilcoxon Signed Rank Test.

HAS in pretreatment phase and 6 months after continuation of treatment phase were summarized in Table IV by the study groups. There was no significant difference in pretreatment HAS between the groups (p=0.208). After treatment, HAS reduced significantly in both groups (p=<0.001). There was no significant difference in posttreatment HAS between two groups (p=0.243).

**Table IV** Pre- and Posttreatment HAS between two groups

| Time of assessment | Median (Range) HAS Atenolol (n=22) | Propranolol (n=22) | p value* |
|---|---|---|---|
| Pretreatment | 4.4 (3.0-5.0) | 4.0 (3.0-5.5) | 0.208 |
| Post treatment | 0 (0-1) | 1 (0-3) | 0.243 |
| p value# | <0.001 | <0.001 | |

p values were obtained from either *Mann Whitney U test or #Related-Samples Wilcoxon Signed Rank Test.

Majority of the patients in both groups had partial responses. In Atenolol group, 22.7% (5/22) patients had complete response of hemangioma and in the Propranolol group, 9.1% (2/22) patient had complete response (>90% reduction of hemangioma size). However, both the groups were similar in terms of treatment responses, as the difference was not statistically significant (p=0.412).

Most of the patients in both groups (90.9% in Atenolol group and 81.8% in Propranolol group) had uneventful follow-up period. However, AEs were more in Propranolol group than Atenolol group. But this difference did not reach up to a level of significance (p=0.945). Transient bloody diarrhea was reported in one patient and another patient developed restlessness in Atenolol group. Diarrhea was reported in two patients in Propranolol group. One patient (4.5%) in the Propranolol group developed bradycardia and another patient in the same group reported to had sleep disturbance (Table V). All AEs were treated accordingly.

**Table V** Comparison of adverse effect between two groups

| Adverse effect | Atenolol (n=22) | Propranolol (n=22) | p value‡ |
|---|---|---|---|
| No adverse effect | 20 (90.9) | 18 (81.8) | 0.945 |
| Bloody diarrhea | 1 (4.5) | 0 (0) | 1.0 |
| Diarrhea | 0 (0) | 2 (9.1) | 1.0 |
| Sleep disturbance | 0 (0) | 1 (4.5) | 1.0 |
| Bradycardia | 0 (0) | 1 (4.5) | 1.0 |
| Restlessness | 1 (4.5) | 0 (0) | 1.0 |

Data are expressed as frequency (Percentage)
‡p values were obtained from Fisher's exact test.

## Discussion

In the current study, overall age ranged from 3 months to 7 years and median age at treatment initiation was 11.5 months in the Atenolol group and 7.5 months in the Propranolol group. Dakoutrou et al reported that; mean age was 3.63 months and 5.95 months respectively for the Atenolol and the Propranolol group, respectively.[21] Overall mean age at the start of the study conducted by Ábarzúa-Araya et al was 5.2 ±3.5 months (Range 2-14 months). Cheryl et al. enrolled more younger patients in their study (Mean age was 2 months and 3 months respectively in Atenolol and Propranolol group) with an age range form 0-8 months.[9,11] The high enrollment age in the present study and wide age range could be explained by the socio-demographic characteristics of the patients as well as the type of study center. This study was conducted at a government tertiary care hospital of Bangladesh. Usually, patients from the low to middle socio-economic strata of the society attend this type of hospital. As majority of the studied patients in the present study was from low socio-economic strata, they usually sought formal medical management at last after trying traditional remedy. Also, more than half of the patients in the present study gave history of receiving homeopathic treatment.

There was female predominance in the present study. It was in agreement with other studies.[9,10,14] Female sex is a risk factor for IH.[22-24] In the current study the commonest location was face and scalp. It was similar with the findings of Dakoutrou et al. (61.5% Atenolol vs. 92.9% Propranolol), and the majority of the IHs were facial and/or neck (84.6% Atenolol vs. 60.7% Propranolol).[21]

Regarding treatment outcome, there was no significant difference between the two groups in the proportion of patients responding to treatment (Complete response: 22.7% Atenolol vs. 9.1% Propranolol). This non-significant higher response rate in the Atenolol group of the present study was in agreement with only one study. Other similar studies demonstrated a higher response rate in Propranolol group.[9,10,14,21] Moreover, the sample size of the present study might be responsible for these dissimilarities regarding response rate of Propranolol compared to those existing evidence. A recent meta-analysis reported that, the overall pooled odds ratio in the Propranolol arm was 1.36, indicating these infants had 1.36 times greater odds of having complete response (Reduction in lesion size) following the medication than those in the Atenolol group. However, the result was not statistically significant.[25]

Regarding AEs, the present study did not find any life-threatening AEs to beta blockers and suggests a good safety profile both for Propranolol and Atenolol. The proportion of patients with AEs was non-statistically higher in Propranolol group compared to Atenolol group (9.1% in Atenolol group vs. 18.2% in Propranolol group, $p > 0.05$). Of these AEs, transient bloody diarrhea was reported in one patient in Atenolol group when Atenolol was withheld for 7 days and restarted after that. Other AE like diarrhea, bradycardia and sleep disturbance did not require any intervention. Serious AEs including somnolence, hypotension, hypoglycemia and bronchospasm which have been reported in the literature but were not observed in the present study.[26] Dakoutrou et al reported that, the proportion of patients with AEs was similar between the two groups (15.4% Atenolol vs. 14.2% Propranolol).[21] Two patients in the Atenolol group experienced gastrointestinal symptoms and two had sleeping difficulties, while in the Propranolol group four patients experienced episodes of hypotension in their study. Liu et al reported that the patients receiving Propranolol had 2.17 times higher odds of developing AEs following the medication than those in the Atenolol group but the result was not statistically significant.[24] The favorable safety profile of Atenolol over Propranolol has been demonstrated through experience with both medications for indications other than IHs, although the present study was not appropriately powered to do so.[18] The present study observed a trend toward fewer AEs in Atenolol group, although this difference did not reach statistical significance.

## Limitation

One limitation of the study was that due to COVID-19 pandemic situation sample size was smaller than anticipated. Moreover, due to COVID-19 pandemic situation some patients failed to come for follow up on given dates. Those patients had taken their follow up over telephone, WhatsApp, IMO. Also, follow up period was short and sample was from single center.

## Conclusion

Atenolol was as effective as Propranolol in the treatment of IHs with respect to clinical outcome. However, Atenolol had fewer AEs (But statistically insignificant) than Propranolol.

## Recommendation

As Atenolol has the advantage of a single dose administration and a possible reduced number of 2 AEs, clinician could consider Atenolol instead of Propranolol in the treatment of IH. However, more RCTs with larger sample sizes and long term follow up are required to derive conclusive evidence towards efficacy, safety and dose-response association of Atenolol and Propranolol.

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## Contribution of authors

MAA-Concept, data collection, manuscript writing and final approval.
RK-Design, critical analysis, manuscript writing and final approval.
TAC-Interpretation of manuscript writing and final approval.
FT-Acquisition of data, critical analysis and final approval.
MAMR-Data analysis, critical analysis and final approval.
MZC-Data collection, manuscript writing and final approval
TKC-Protocol development, Data analysis, Manuscript writing and Final approval.

## Disclosure

All the authors declared no competing interest.

## References

**1.** Krowchuk, D. P., Frieden, I. J., Mancini, A. J. et al. Clinical Practice Guideline for the Management of Infantile Hemangiomas. Pediatrics. 2019;143(1):e20183475.

**2.** Léauté-Labrèze, C., Harper, J. I., & Hoeger, P. H. Infantile hemangioma. Lancet (London, England). 2017;390(10089):85–94.

**3.** Akcay, A., Karakas, Z., Saribeyoglu, E. T. et al. Infantile hemangiomas, complications and follow-up. Indian pediatrics. 2012;49(10):805–809.

**4.** Dickison, P., Christou, E., & Wargon, O. A prospective study of infantile hemangiomas with a focus on incidence and risk factors. Pediatric dermatology. 2011;28(6):663–669.

**5.** Léauté-Labrèze, C., Hoeger, P., Mazereeuw-Hautier, J. et al. A randomized, controlled trial of oral Propranolol in infantile hemangioma. The New England journal of medicine. 2015;372(8), 735–746.

**6.** Raphael, M. F., Breur, J. M., Vlasveld, F. A. et al. Treatment of infantile hemangiomas: therapeutic options in regard to side effects and adverse events : A review of the literature. Expert opinion on drug safety. 2016;15(2):199–214.

**7.** Chang, L., Gu, Y., Yu, Z. et al. When to stop propranolol for infantile hemangioma. Scientific reports. 2017;7:43292.

**8.** Raphaël, M. F., de Graaf, M., Breugem, C. C. et al. Atenolol: a promising alternative to Propranolol for the treatment of hemangiomas. Journal of the American Academy of Dermatology. 2011;65(2):420–421.

**9.** Ábarzúa-Araya, A., Navarrete-Dechent, C. P., Heusser, F. et al. Atenolol versus Propranolol for the treatment of infantile hemangiomas: A randomized controlled study. Journal of the American Academy of Dermatology. 2014;70(6):1045–1049.

**10.** de Graaf, M., Raphael, M. F., Breugem, C. C. et al. Treatment of infantile hemangiomas with Atenolol: Comparison with a historical Propranolol group. Journal of plastic, reconstructive & aesthetic surgery : JPRAS. 2013;66(12):1732–1740.

**11.** Cheryl, B. Bayart, Joan, E. Tamburro, Allison, T. Vidimos, et al. Atenolol Versus Propranolol for Treatment of Infantile Hemangiomas During the Proliferative Phase: A Retrospective Noninferiority Study. Pediatric dermatology. 2017;34(4):413–421.

**12.** Alexopoulos, A., Thanopoulou, I., Dakoutrou M et al. Atenolol treatment for severe Infantile Hemangiomas: A single-centre prospective study. J. Eur. Acad. Dermatol. Venereol. 2018; 32: e117–119.

**13.** Ji, Y., Chen, S., Xu, C. et al. The use of Propranolol in the treatment of infantile hemangiomas: An update on potential mechanisms of action. Br. J. Dermatol. 2015; 172: 24 –32.

**14.** Sharma, V. K., Fraulin, F. O., Dumestre, D. O. et al. Beta-blockers for the treatment of problematic hemangiomas. The Canadian journal of plastic surgery. 2013;21(1):23–28.

**15.** Sun, L., Sun, B., Ma, Y. et al. Comparison of the ef cacy and safety of Propranolol and Atenolol in the treatment of infant hemangioma. Progress Modern Biomed. 2018; 18: 108–112.

**16.** Ruitenberg, G., Young-Afat, D.A., de Graaf, M. et al. Ulcerated infantile hemangiomas: The effect of the selective betablocker Atenolol on wound healing. Br. J. Dermatol. 2016; 175: 1357–1360.

**17.** Tasani, M., Glover, M., Martinez, A.E. et al. Atenolol treatment for infantile hemangioma. Br. J. Dermatol. 2017;176: 1400– 1402.

**18.** Buck, M. L., Wiest, D., Gillette, P. C. et al. Pharmacokinetics and pharmacodynamics of Atenolol in children. Clinical pharmacology and therapeutics. 1989;46(6):629–633.

**19.** Wang, Q., Xiang, B., Chen, S. et al. Efficacy and safety of oral Atenolol for the treatment of infantile hemangioma: A systematic review. The Australasian journal of dermatology. 2019;60(3):181–185.

**20.** Molla, R. M. Concise Textbook of Pediatrics, Revised edition. Dhaka. Child friendly publications. 2009;333-339.

**21.** Dakoutrou M., Alexopoulos A., Miligkos M et al. Atenolol treatment for severe infantile hemangiomas: comparison with a Propranolol group of our centre. Journal of the European Academy of Dermatology and Venereology : JEADV. 2019;33(5):e199–e200.

**22.** Haggstrom, A. N., Drolet, B. A., Baselga, E. et al. Prospective study of infantile hemangiomas: Clinical characteristics predicting complications and treatment. Pediatrics. 2006;118(3):882–887.

**23.** Haggstrom, A.N., Chamlin, S.L. Infantile hemangiomas and other vascular tumors. In: Eichenfield LF, Frieden IJ, Mathes EF, Zaenglein AL, editors. Neonatal and Infant Dermatology. 3rd ed. Philadelphia, PA: Elsevier. 2015;336–351.
https://www.clinicalkey.com/#!/content/book/3-s2.0-B9781455726387000213.

**24.** Li, J., Chen, X., Zhao, S., Hu, X. et al. Safety of Oral Propranolol for the Treatment of Infantile Hemangioma: A Systematic Review Demographic and clinical characteristics and risk factors for infantile hemangioma: A Chinese case-control study. Archives of dermatology. 2011;147(9): 1049–1056.

**25.** Liu, Z., Wu, C., Song, D., Wang, L. et al. Atenolol vs. Propranolol for the treatment of infantile hemangiomas: A systematic review and meta-analysis. Experimental and therapeutic medicine. 2020;20(2):1644–1652.

**26.** Tiemann, L., & Hein, S. Infantile Hemangioma: A Review of Current Pharmacotherapy Treatment and Practice Pearls. The journal of pediatric pharmacology and therapeutics : JPPT : The official journal of PPAG. 2020;25(7):586–599.