Journal of Pakistan Association of Dermatologists. 2023;**33(3)**:1023-1030.

Original Article

Safe effective triple therapy of infantile hemangioma using oral Propranolol and oral prednisolone plus topical timolol drops in series of 182 infants

Khalifa E. Sharquie, Raed I. Jabbar*

Department of Dermatology, College of Medicine, University of Baghdad. Medical City Teaching Hospital, Baghdad, Iraq.
* Department of Dermatology, Fallujah Teaching Hospital, Al-Anbar Health Directorate, Anbar, Iraq.

Abstract

Objective To record personal experience in treating infantile hemangioma using triple therapy on home basis.

Methods This is a case series cross sectional clinical study and therapeutic trial of infantile hemangioma (IH) was carried out during the period from 2014-2022 where all cases with infantile hemangioma were evaluated. All types of hemangioma were included single or multiple superficial and deep. Oral propranolol was given at home in a dose of 1-2 mg/kg body weight a day in two divided doses. Oral prednisolone was started as 5mg syrup once a day for one month and then tapered gradually. Also timolol drop 0.5% was applied to hemangioma twice a day till the end of therapy. The duration of treatment ranged from 3-6 months with a median of 4 months. Objective scoring was used to assess the response to therapy. All side effects were carefully recorded by the mothers and dermatologist.

Results A total of 182 infants, 129 (70.87%) females and 53 (29.12%) males with IHs were included and analyzed. The age of the patients ranged from 1-6 months with a mean of 4 months. The sites of lesions were mostly on heads including face and neck in 106 (58.24%) cases while in other parts of body in 76 (41.75%) cases, with size ranged from 2 cm^2 to 23 cm^2. The response to triple therapy was noticed week after starting treatment protocol but was obvious at 2 weeks. There was gradual reduction in color and size of lesions. In most of patients, there was about 25% reduction in the first two weeks that reached to 75-100% after 3-6 months. No adverse or side effects were seen in all infants even with normal growth development.

Conclusion This triple therapy is the first study using oral propranolol and oral prednisolone plus topical timolol drops together on a home basis. It is safe effective therapy for infantile hemangioma and is more effective than single drug use. No need for hospital admission or cardiac assessment during treatment course and no laser therapy is recommended.

Key words
Infantile hemangioma; Triple therapy; Propranolol; Prednisolone; Timolol; Laser therapy.

Introduction

Infantile hemangiomas (IHs) are the most common vascular tumor arising in the neonatal period,[1] with an incidence rate ranging from 0.2-10.0%.[2] The face and neck are the most commonly involved sites and the lesions are usually noted within the first few weeks of life. They grow rapidly during the first several months of life, followed by slow spontaneous involution at the age of 3-7 years.[3]

Till now several theories have been suggested to elucidate the pathogenesis of IHs, but no single theory accounts for all their features. During the proliferative phase, there is an imbalance of

angiogenic factors and an increase in the levels of basic growth factor of fibroblasts (bFGF), vascular endothelial growth factor (VEGF), and matrix metalloproteinases (MMPs) 2 and 9.[4-6] In the regression phase, the levels of antiangiogenic factors, including tissue inhibitors of metalloproteinases (TIMP) increase, whereas these of angiogenesis factors (bFGF,VEGF and MMPs), decrease.[7,8]

Nevertheless, during the course of its growth, 15% of children will experience complications, which can be life-threatening, such as visual and auditory impairment, local tissue ulcers, permanent deformities, infection, bleeding, and airway damage.[9-11]

In the last years, many therapeutic methods including drugs, surgical excision and laser have emerged.[12,13] Drugs mainly include steroids,[14] propranolol[15] bleomycin[16] vincristine[17] and interferon.[18] In the past, systemic corticosteroids were considered as a first-line drug used for IHs treatment.[19] Steroids inhibit VEGF synthesis by hemangioma-derived stem cells and prevent vasculogenesis in a murine hemangioma model.[20]

Propranolol is a non-selective β-adrenergic receptor blocker.[21] It has multifaceted action against IHs. Vasoconstriction reduces the blood supply to the IH. Moreover, propranolol blocks angiogenesis by reducing the expression of VEGF, MMP-2, MMP-9 and bFGF and induction of endothelial cells apoptosis in IH.[22-25]

Address for correspondence
Professor Khalifa E Sharquie
Department of Dermatology ,College of Medicine, University of Baghdad, Iraqi and Arab Board of Dermatology and venereology, Center of Dermatology and venereology, Baghdad Teaching Hospital, Medical City, Medical Collection Office, P.O. BOX 61080 , Postal code 12114, Baghdad, Iraq.
Email: ksharquie@ymail.com

In addition to IH treatment, propranolol has been used for the treatment of many dermatological diseases such as Kaposi's sarcoma,[26,27] burn hemangioma,[28,29] pyogenic granuloma[30] and others.[31,32] Also, oral propranolol has been used with TCA peeling in the treatment of acne scarring to reduce post-inflammatory erythema and decrease the probability of hemangioma formation.[33]

Recently, timolol maleate, a nonselective β-blocker medication, has emerged as a novel treatment of superficial IHs. A new meta-analysis[34] concluded that topical timolol is an effective and safe drug for management of superficial IHs.

Combined treatment using oral propranolol and topical timolol has been found to be more effective for treating IHs over either drug alone.[35,36] While Aly *et al*. reported the therapeutic superiority with limited side effects of combined propranolol with short course of steroid compared to propranolol monotherapy.[37]

So, the aim of the present study is to evaluate the efficacy and safety of oral propranolol and oral prednisolone plus topical timolol drops in treating infantile hemangioma on home basis.

Patients and Methods

This is a case series cross sectional clinical study and therapeutic trial of infantile hemangioma during the period from 2014-2022 where all cases with IH were evaluated. Mothers mentioned that all hemangiomas were started immediately after birth. Clinical assessment was carried out including, sites, type and size. All types of hemangioma were included single or multiple, superficial and deep.

Informed consent was taken from the infants' parents. All cases had been receiving a thorough

history, physical examination and pretreatment assessments.

Before treatment, blood glucose, complete blood picture, and renal and liver functions. An electrocardiography (ECG) and echocardiography were carried out in only few selected cases. Also, pictures of IH were taken before treatment and at each visit. The following cases were excluded from the study like infants with history of asthma, history of cardiac disease, cardiac arrhythmia, diabetes mellitus, hypotension, hypertension and hypersensitivity to any of the medications used in this study.

Oral propranolol was given at home in a dose of 1-2 mg/kg body weight a day in two divided doses every 12 hrs:1mg/kg in first two weeks and then increased into 2mg/ kg. The tablet was dissolved in sugary water and the mothers were advised to give it with food to decrease the risk of hypoglycemia. The duration of therapy ranged from 3-6 months with a median of 4 months or until infants lost follow up. Oral prednisolone was started as 5mg syrup once a day for one month and then tapered gradually. Also timolol drop 0.5% was applied to hemangioma twice a day till the end of therapy. Subjective measures and objective scoring were considered in assessing the response to treatment according to the following score: Poor response, if regression was 0-25%; mild response, if regression from >25%-50%; moderate response, if regression >50%-75% and marked to complete clearance, if regression was >75%-100%.

Mother's satisfaction to response to the treatment was assessed as follows:

Full satisfaction: the patient's mother is completely satisfied with the result and needs no more interference.

Partial satisfaction: The patient's mother although satisfied with the result but wants more interference.

No satisfaction: The patient's mother is not satisfied with the result because there is no change in the hemangioma.

The follow-up was done every 2 weeks in the first month, then monthly during the next 3-6 months. The general health of infants was watched before and after initiation of therapy and all side effects were carefully recorded by the mothers and dermatologists.

Results

A total of 182 infants, 129 (70.87%) females and 53 (29.12%) males with IH were included and analyzed. The ages of the patients ranged from 1-6 months with a mean of 4 months. The sites of lesions were mostly on head including face and neck in 106 (58.24%) cases while other parts of body in 76 (41.75%) cases, with size ranged from 2 cm^2 to 23 cm^2. Both subjective and objective measures showed marked response to therapy both in color and size. There was gradual reduction in color and size of lesions. The response to triple therapy was started after week as the mother mentioned but was obvious at 2 weeks and complete after 3-6 months as follow:

Two weeks after starting treatment: 169 (92.85%) cases revealed mild regression while 13 (7.14%) cases revealed no regression.

Four weeks after starting treatment: 11 (6.04%) cases showed marked, 47 (25.82%) cases with moderate regression and 135(68.13%) cases with mild regression.

Two months after starting treatment: 120 (65.93%) cases revealed moderate regression

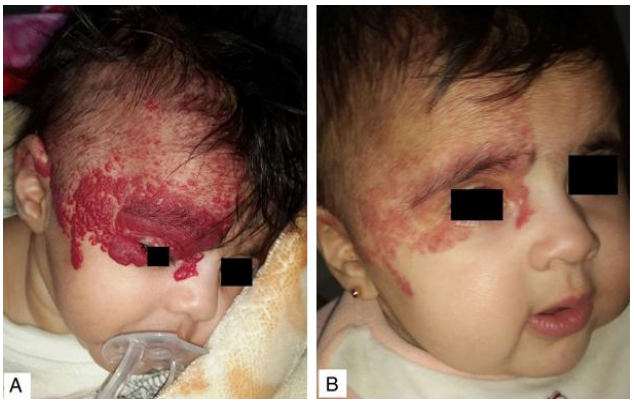

Figure 1 Two months old female patient with large hemangioma involving the right side of the face and part of the scalp. Before treatment (A) and 3 months after treatment with the triple therapy(B).

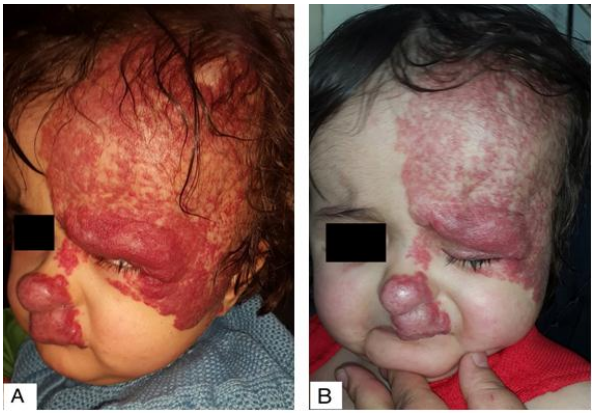

Figure 2 Five months infants(A) showing marked response after 4 weeks after triple therapy(B)

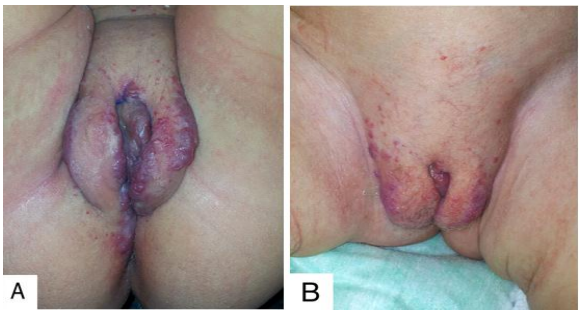

Figure 3 Six months old female with hemangioma involving vulva and perianal area.Before treatment (A) and 2 months after treatment with the triple therapy (B).

and 62 (34.06%) with mild regression.

Three months after starting treatment: 141 (77.47%) cases showed marked regression to complete clearance and 41 (22.52%) with moderate regression.

These 41 (22.52%) cases with moderate regression needed another 1-3 months of course therapy to get marked or complete regression. So at the end of the therapy course, all cases showed 100% marked to complete clearance **(Figures 1-4)** and all mothers' infants showed full satisfaction to the results. Many infants were seen accidentally for other reasons years after completion their therapy **(Figure 4C)**.

No adverse events or side effects were seen in all infants even with normal growth development. Most of the infants lost follow after 3-6 months of therapy without obvious reasons but most probably related to marked response or complete clearance with no recurrence of the lesion.

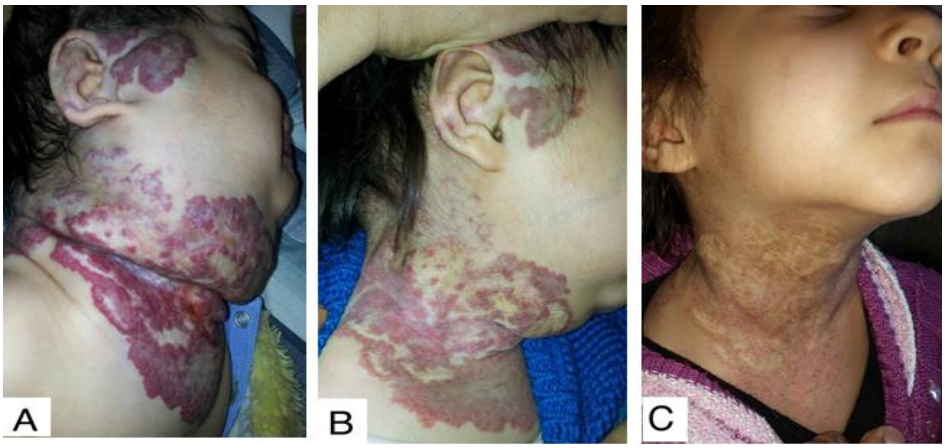

Figure 4 Four months female infant with giant hemangioma (A) treated with triple therapy for three weeks (B) and showed marked response after 2months of therapy. This child was seen accidentally for other reason after 4 years (C).

These results also discovered many observations as there was an individual variation to therapy response. Also, the larger the lesions, the more the rapid response to drugs. The hemangioma on the face and vulva were more responsive to treatment than other sites like limbs. In addition, in many patients, although there was marked and complete response but there were some post-therapy residual changes like telangiectasia.

Discussion

To our knowledge, this is the first clinical study and therapeutic trial evaluating the efficacy and safety of oral propranolol and oral steroid plus topical timolol drops in the management of IH.

In vitro study, steroids suppressed VEGF synthesis by hemangioma-derived stem and prevent angiogenesis.[38] While propranolol exerts its effect on IH through vasoconstriction, inhibition of angiogenesis by down-regulation of angiogenic factors, VEGF and bFGF; and induction of endothelial cells apoptosis.[39] So oral propranolol has become the standard therapy for high-risk and deep IH, whereas topical timolol is commonly used for superficial lesions to minimize systemic adverse effects.

In the present study, we introduced a combined therapy consisting of oral propranolol, oral steroid plus topical timolol aiming to target both superficial and deep components of IHs.

As there is no standard optimal therapy for IHs, we supposed that combining oral propranolol with short course of oral steroids plus timolol drops could give a faster and better response compared to either drug alone assuming that these medications have various mechanisms of action while avoiding the side effects of prolonged corticosteroids use. Accordingly, the present work had shown that the combination of these drugs with their synergistic actions against IH associated with rapid response, minimal side effects, better tolerability, shorter duration and no rebound cases after stopping the treatment in comparison to other studies that used either of these medications as a monotherapy in the treatment of IH.[40-42] The head and neck (58.24%) were the most commonly affected sites as observed in our study. This result was comparable to previous studies.[37,43]

In this study, the triple therapy was started at the mean age of 4 months, hence the early treatment of IH, especially during the proliferative phase, is associated with best results as shown in our results. Therefore, the early onset of treatment is the better effective response and can also reduce the frequency of complications.[44]

In the present work, 77.47% of patients showed marked to complete clearance at the end of the third month of therapy while 22.52% of patients needed another 1-3 months with oral propranolol and topical timolol to get complete clearance. So, all treated infants showed complete clearance at the end of 6 months therapy in comparison to other studies that used oral propranolol, oral steroids or topical timolol as monotherapy and gave excellent response in 81%, 78.05% and 56.4% respectively.[40-42] Similarly all patients' mothers were fully satisfied to the results achieved at the end of therapy. Accordingly, this complete clearance with full satisfaction could minimize the physical and psychological trauma for children and their parents.

For unknown reason, the lesions affecting the face and vulva showed higher response rate in comparison with other affected sites despite the fact these sites are exposed to continuous friction which might increase ulceration and subsequent infection resulting in delayed healing. This observation, to the best our knowledge was not recorded before.

The most commonly reported side effects of oral

propranolol in the treatment of IH were hypoglycemia[45] bronchospasm and gastrointestinal upset.[46] While the most documented side effects of oral steroids recorded by other studies were Cushingoid facies, weight gain, hypertension, gastric irritation and fungal infection.[47-49] Fortunately, these side effects were not recorded in our study. The cause of this discrepancy is not well known but the counteracted side effects of oral steroid and oral propranolol might give satisfactory explanation. Also, this triple therapy used in this study provides advantages of shorter duration and relatively lower dosage than either agent alone and this might also give additional explanation for this absence of side and adverse effects.

In addition, these adverse effects of systemic propranolol are generally recorded with a dosage at ≥2 mg/kg/day[50] while all cases in the current work received propranolol at a dose of 1-2 mg/kg/day. Also, the propranolol was given in 2 divided doses at 1- 2 mg/kg/day and the parents were advised to give it with sugary water and with food. This maneuver provides easier administration of the drug and possibly decreased risk of nocturnal hypoglycemia.

Although laser, especially pulsed dye laser(PDL) is effective in the treatment of IH but the costly multiple treatment sessions, earlier initiation of treatment during the proliferating phase, residual changes while treating deeper component, and possible complication of treatment including scars, ulcers and permanent pigmentation are the main drawback of this treatment modality.[51-53]

So the medical treatment regimen used in this study is particularly important due to it is safe, non-invasive, economical and convenient for all types of IHs whether superficial, deep or combined, single or multiple and at any site with excellent response and no recurrence.

Conclusion

This triple therapy is the first study using oral propranolol and oral prednisolone plus topical timolol drops together on a home basis. It is safe effective therapy for infantile hemangioma and is probably more effective than single drug with full parent satisfaction and convenient for all types of hemangiomas. Also, this study showed no significant side effects and no recurrence of hemangioma during or after completion of therapy. So this study recommends no need for hospital admission or cardiac assessment during the treatment course and no need for laser therapy.

References

1. Aizman L, Van Den Anker J, Tender J, *et al*. Special management considerations for propranolol use in breastfed infants of mothers taking antihypertensives. *Pediatr Dermatol*. 2020;**37**:537–40.
2. Munden A, Butschek R, Tom WL, *et al*. Prospective study of infantile haemangiomas: Incidence, clinical characteristics and association with placental anomalies. *Br J Dermatol*. 2014;**170**:907–913.
3. Maguiness SM. Vascular tumors and malformations in children, Introduction. *Semin Cutan Med Surg*. 2016;**35(3)**:107.
4. Greenberger S, Bischoff J. Pathogenesis of infantile haeman- gioma. *Br J Dermatol*. 2013;**169(1)**:12–9.
5. Itinteang T, Withers AH, Davis PF, Tan ST. Biology of infantile hemangioma. *Front Surg*. 2014;**1**:38.
6. Boscolo E, Bischoff J. Vasculogenesis in infantile hemangioma. *Angiogenesis*. 2009; **12(2)**:197–207.
7. Marler JJ, Fishman SJ, Kilroy SM *et al*. Increased expression of urinary matrix metalloproteinases parallels the extent and activity of vascular anomalies. *Pediatrics*. 2005;**116(1)**:38–45.

8. Kleinman ME, Greives MR, Churgin SS *et al*. Hypoxia-induced mediators of stem/progenitor cell trafficking are increased in children with hemangioma. *Arterioscler Thromb Vasc Biol*. 2007;**27(12)**: 2664–70.
9. Howard MA, Olitsky SE, Rychwalski P, Mungan N: Management of periocular infantile hemangioma. *J Pediatr Ophthalmol Strabismus*. 2019;**56**:344–6.
10. Léauté-Labrèze C, Harper JI, Hoeger PH: Infantile haemangioma. *Lancet*. 2017; **390**:85–94.
11. Yuzuriha S, Nagai F, Noguchi M. How to manage disfiguring scars in involuted infantile hemangioma. *Adv Wound Care (New Rochelle)*.2019;**8**:221–9.
12. Chen ZY, Wang QN, Zhu YH, *et al*. Progress in the treatment of infantile hemangioma. *Ann Transl Med*. 2019;**7(22)**:692.
13. Chinnadurai S, Sathe NA, Surawicz T. Laser treatment of infantile hemangioma: A systematic review. *Lasers Surg Med*. 2016; **48**:221–33.
14. Chai Y, Zhou Z, Song J, *et al*. Safety of intralesional injection of lauromacrogol combined with triamcinolone for infantile hemangiomas. *J Dermatol*. 2019;**46**:770–6.
15. Sinha S, Lloyd MS: Propranolol for surgeons in the treatment of infantile hemangiomas. *J Craniofac Surg*. 2020; **31**:134–7.
16. Qiu Y, Lin X, Ma G, *et al*. Eighteen cases of soft tissue atrophy after intralesional bleomycin a5 injections for the treatment of infantile hemangiomas: A long-term follow-up. *Pediatr Dermatol*. 2015;**32**:188–91.
17. Techasatian L, Phukam N. Treatment modalities and outcomes of infantile hemangiomas at srinagarind hospital. *J Med Assoc Thai*. 2016;**99 (Suppl 5)**: S74–S80.
18. White CW, Sondheimer HM, Crouch EC, *et al*. Treatment of pulmonary hemangiomatosis with recombinant interferon alfa-2a. *N Engl J Med*.1989; **320**:1197–1200.
19. Soliman YS, Khachemoune A. Infantile hemangiomas: Our current understanding and treatment options. *Dermatol Online J*. 2018;24(13030/qt5jt8q9km).
20. Greenberger S, Boscolo E, Adini I,*et al*. Corticosteroid suppression of VEGF-A in infantile hemangioma-derived stem cells. *N Engl J Med*. 2010;**362(11)**:1005-13.
21. Town WG. The Merck index 13.2 CD-ROM edition from Cambridge Soft. *J Chem Inf Comput Sci*. 2004;**44(5)**:1883–5.
22. Moisan F, Oucherif S, Kaulanjan-Checkmodine P, *et al*. Critical role of Aquaporin-1 and telocytes in infantile hemangioma response to propranolol beta blockade. *Proc Natl Acad Sci USA*. 2021; **118**:7.
23. Chim H, Armijo BS, Miller E, *et al*. Propranolol induces regression of hemangioma cells through HIF-1alpha-mediated inhibition of VEGF-A. *Ann Surg*. 2012;**256(1)**:146–56.
24. Tani S, Kunimoto K, Inaba Y, *et al*. Change of serum cytokine profiles by propranolol treatment in patients with infantile hemangioma. *Drug Discov Ther*. 2020;**14(2)**:89–92.
25. Pandey A, Singh A, Ali W, *et al*. Evaluation of effect of propranolol on serum vascular endothelial growth factor and tissue inhibitor of metalloproteinase-2 levels in infantile hemangioma. *J Indian Assoc Pediatr Surg*. 2020;**25(2)**:96–102.
26. Sharquie K E, Noaimi A A. Treatment of Kaposi's Sarcoma by combination of zinc sulfateand propranolol. *J Cosmet Dermatol Sci Appl*. 2018;**8**:249-55.
27. Sharquie KE, Jabbar RI. Triple therapy of Kaposi's sarcoma using oral propranolol,oral zinc sulfate and oral acyclovir as new initiative study. *J Pak Assoc Dermatol*. 2023;**33(1)**:72-7.
28. Sharquie KE, Noaimi AA, Radhi SK. Burn hemangioma (scalded pyogenic granuloma) versus infantile hemangioma: Report of six cases of burn hemangioma and its effective therapy with oral propranolol. *J Cosm Dermatol Scien Applicat*. 2017;**7**:229-44.
29. Sharquie KE, Al-Dhalimi MA, Kawen AA, Dhaher SA. Burn Hemangioma: A New Variant of Hemangioma. *Dermatology*. 2022;**238(4)**:793-8.
30. Wine Lee L, Goff KL, Lam JM, *et al*. Treatment of pediatric pyogenic granulomas using ß-adrenergic receptor antagonists. *Pediatr Dermatol*. 2014;**31**:203-7.
31. Craige H, Cohen JB. Symptomatic treatment of idiopathic and rosacea-associated cutaneous flushing with propranolol. *J Am Acad Dermatol*. 2005;**53**:881-4.
32. McCourt C, Coleman HG, Murray LJ, *et al*. Beta-blocker usage after malignant melanoma diagnosis and survival: A

population-based nested case-control study. *Br J Dermatol*. 2014;**170**:930-8.
33. Sharquie KE, Jabbar RI. Heat dermabrasion with needle diathermy combined with 35% TCA peeling as an innovative therapy for acne scarring in patients with a dark complexion. *Our Dermatol Online*. 2021;**12(3)**:230-7.
34. Khan M, Boyce A, Prieto-Merino D, *et al*. The role of topical timolol in the treatment of infantile hemangiomas: a systematic review and meta-analysis. *Acta Derm Venereol*. 2017;**97(10)**:1167-71.
35. Ge J, Zheng J, Zhang L, *et al*. Oral propranolol combined with topical timolol for compound infantile hemangiomas: a retrospective study. *Sci Rep*. 2016;**28(6)**:19765.
36. Tong S, Xu DP, Liu ZM, *et al*. Evaluation of the efficacy and safety of topical timolol maleate combined with oral propranolol treatment for parotid mixed infantile hemangiomas. *Oncol Lett*. 2016; **12(3)**:1806-10.
37. Aly MM, Hamza AF, Abdel Kader HM, *et al*. Therapeutic superiority of combined propranolol with short steroids course over propranolol monotherapy in infantile hemangioma. *Eur J Pediatr*. 2015;**174(11)**:1503-9.
38. Heredea R E, Melnic E, Cirligeriu LE, *et al*. VEGF pathway gene expression profile of proliferating versus involuting infantile hemangiomas: Preliminary evidence and review of the literature. *Children*. 2022;**9**:908.
39. England RW, Hardy KL, Kitajewski AM, *et al*. Propranolol promotes accelerated and dysregulated adipogenesis in hemangioma stem cells. *Ann Plast Surg*. 2014;**73**:S119–24.
40. Price CJ, Lattouf C, Baum B, *et al*. Propranolol vs. corticosteroids for infantile hemangiomas: A multicenter retrospective analysis. *Arch Dermatol*. 2011;**147**:1371-6.
41. Jalil S, Akhtar J, Ahmed S. Corticosteroids therapy in the management of infantile cutaneous hemangiomas. *J Coll Physicians Surg Pakistan JCPSP*. 2006;**16(10)**:662–5.
42. Yu L, Li S, Su B, *et al*. Treatment of superficial infantile hemangiomas with timolol: evaluation of short-term efficacy and safety in infants. *Exp Ther Med*. 2013; **6**:388–90.
43. Wu HW, Wang X, Zhang L, *et al*. Topical timolol vs. oral propranolol for the treatment of superficial infantile hemangiomas. *Front Oncol*. 2018;**8**:605.
44. Zhang L, Wu HW, Yuan W, Zheng JW. Propranolol therapy for infantile hemangioma: Our experience. *Drug Des Devel Ther*. 2017;**11**:1401–8.
45. Holland KE, Frieden IJ, Frommelt PC, *et al*. Hypoglycaemia in children taking propranolol for the treatment of infantile haemangioma. *Arch Dermatol*. 2010; **146(7)**:775-8.
46. Zimmermann AP, Wiegand S, Werner JA, Eivazi, B. Propranolol therapy for infantile haemangiomas: Review of the literature. *Int J Ped Otorhinolaryngol*. 2010;**74(4)**:338-42.
47. Boon LM, MacDonald DM, Mulliken JB. Complications of systemic corticosteroid therapy for problematic hemangioma. *Plast Reconstr Surg*. 1999;**104**:1616-23.
48. Rössler J, Wehl G, Niemeyer CM. Evaluating systemic prednisone therapy for proliferating haemangioma in infancy. *Eur J Pediatr*. 2008;**167**:813-5.
49. Malik MA, Menon P, Rao KL, Samujh R. Effect of propranolol vs prednisolone vs propranolol with prednisolone in the management of infantile hemangioma: a randomized controlled study. *J Pediatr Surg*. 2013;**48(12)**:2453-9.
50. Lou Y, Peng WJ, Cao Y, *et al*. The effectiveness of propranolol in treating infantile haemangiomas: A meta-analysis including 35 studies. *Br J Clin Pharmacol*. 2014;**78**:44–57.
51. Witman PM, Wagner AM, Scherer K, *et al*. Complications following pulsed dye laser treatment of superficial hemangiomas. *Lasers Surg Med*. 2006;**38(2)**:116–23.
52. Batta K, Goodyear HM, Moss C, *et al*. Randomised controlled study of early pulsed dye laser treatment of uncomplicated childhood haemangiomas: results of a 1-year analysis. *Lancet*. 2002;**360(9332)**:521–7.
53. Kessels JP, Hamers ET, Ostertag JU. Superficial hemangioma: pulsed dye laser versus wait-and-see. *Dermatol Surg*. 2013;**39(3 Pt 1)**:414–21.