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Original Article

Oral Propranolol and Prednisolone in the Treatment of Infantile Hemangioma: A Comparative Study

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Abstract

Purpose: Infantile Hemangioma is a common vascular tumor of infancy and children. Although the lesions involute, the results are unpredictable and the time taken is variable. Responses to commonly used drugs like corticosteroid are not satisfactory due to variable effectiveness. There are also hazards of surgical intervention. The aim of this study is to compare the oral propranolol & prednisolone for IH treatment. **Methods:** In this study 104 patients were included. They were divided into 2 groups by systematic sampling method. In Group-A 52 patients were treated with oral propranolol and in Group-B 52 patients with oral prednisololne as per the protocol at a dose of 2mg/kg/day in two divided doses. Measurements of the size (directly measured by soft flexible rubber tape and calipers) and color assessment (image based by Adobe Photoshop software) were recorded before starting of the treatment. Follow up was done on 15th day, after 1st, 2nd, 3rd and 4th month respectively. Evaluation of percentage of regression of size and color clearance, adverse effects and treatment cost was done at each follow up. Regression in the size and color clearance of IHs was clinically assessed. Data were analyzed with the help of SPSS. P value of < .05 was considered significant. **Results:** In group-A 42(80.76%) had an excellent response, compared to group-B only 5(9.61%). In group-A, 40(76.92%) had an excellent color clearance, compared to group-B where only 03(05.76%). Regarding adverse effects in group-A, only 08 children (15.38%) complained of mild adverse effects which were self- limiting compared tothat of group-B (47,90.38%). In group-A average treatment cost was 165tk/ patient and in group-B 580tk. During follow up in group-A one case relapse was seen, in group-B 8 patient. **Conclusion:** Propranolol was safe, more effective and economic than oral prednisolone.

Key words: Infantile hemangioma; propranolol; prednisolone; image based color evaluation.

INTRODUCTION

Hemangiomas are the most common tumors of infancy. Infantile hemangioma appears soon after birth characterized by an inconspicuous appearance at birth but undergo rapid and intermittent growth throughout the first year of life. Tumors that often require treatment include those involving the periorbital area, central face, airway, skin folds, and anogenital area, all these sites are at high risk for ulceration, dysfunction, or disfigurement. The most common complication is ulceration, which might result in bleeding, pain, infection, difficulty in feeding and residual scarring. IHs also causes airway obstruction and visual disturbance depending on their location. Large cutaneous plus visceral hemangiomas can be associated with high-output heart failure as a result of arteriovenous shunting within the hemangioma[1].

Treatment of IHs is indicated for approximately 20% of the cases. Two groups can be defined amongst indications for treatment: patients with absolute indication for treatment and patients with relative indication for treatment[2].

Although the lesions may involute, the results are unpredictable and incomplete, and the time taken is not definite. This may make parents more anxious; hence, treatment is needed.

Until now oral corticosteroids (prednisolone) are considered as first-line therapy for such troublesome and severe haemangiomas but the risks of long-term and high dose use include growth disturbances and immune system dysfunction as well as ulcerations up to severe tissue loss. Moreover, there are cases of fast growing infantile haemangiomas which show no response to steroid therapy. Other therapeutic options like interferon alpha, cyclophosphamide and vincristine are used less often because of alarming side effects and toxicity. Reported successful invasive treatments, include intralesional steroid injection, open excision, and laser therapy. The treatment plan depends on many factors, including the size and extent of the lesion, social situations, and surgeon's comfort or experience with any given treatment modality[3].

Systemic corticosteroid, even with high dosages response ranging from 30% to 60% and therapeutic effects appear usually after 1 or 2 weeks of treatment. Most common side effects are cushingoid face, insomnia, irritability, stunted growth, gastrointestinal symptoms, hypertension and hypertrophic obstructive cardiomyopathy[4].

Recently the use of propranolol in the treatment of haemangiomas was serendipitously discovered in the year of 2008.They showed rapid regression of IHs. After this notification several groups worldwide initiated propranolol therapy in children with haemangiomas and gained experiences with this treatment[5].

Propranolol has a well-documented safety and side effect profile. Its use in children has been limited to hypertention and cardiovascular diseases as a psycho-pharmaceutical agent. After more than 40 years of clinical use in infants with cardiac findings, there is no case of life-threatening complications as direct result of exposure to propranolol. Potential side effects of beta-blockers include bradycardia, hypotension, hypoglycemia, rash, gastrointestinal discomfort/reflux, fatigue and bronchospasm, all are rare and observed at higher doses (>2 mg/kg/day)[6].

Treatment protocol for propranolol use was developed by several groups to optimise drug safety and its comparability to other drugs. In the absence of cardiac conditions and airway diseases the patient is considered as a candidate for therapy[7].

The aim of this study was to assess the use of oral propranolol in the treatment of Infantile hemangioma, quantifying its effectiveness and safety under continuous monitoring and comparing it to the use of oral prednisolone.

MATERIALS & METHODS

This Interventional study (RCT) was carried out in the department of pediatric surgery, Dhaka shishu (children) DSH hospital during the period of May 01, 2011 to November 30, 2012.

Prior to commencement of this study the ethical review committee of Bangladesh Institute of Child Health (BICH) and Dhaka Shishu (Children) Hospital approved the protocol. The aims and objectives of the study, the nature of the disease, the investigations, treatment modalities and potential complications regarding propranolol and prednisolone medication and its advantages were explained to the patients' parents and informed consent was taken.

All the patients meeting selection criteria were enrolled consecutively. Sample size was determined using formula for Interventional study (clinical trial). A total of 104 patients of Infantile Hemangioma in different sites of body were treated by oral propanolol and prednisolone in two groups. In both Group A (Propranolol) and Group B (Prednisolone), 52 patients were included respectively.

Inclusion criteria wasAll patients (up to 5 years) of clinically diagnosed infantile hemangioma of either sex attending Surgery outpatient department of DSH with relative indication for treatment.

Exclusion criteria wereHemangioma with presenting life threatening condition ,Cardiovascular disorders contraindicating propranolol use andFamily history with regard to atopy, or recent/repeated outbreak of wheezing and low– birth weight newborns.

The outcome variables for studied were -Outcome measure. (Colour, size, consistency and others), Complications (adverse effect), and Cost of treatment.

Study Procedure

Epidemiological data concerning pregnancy, birth and family history were collected. Anatomical location (site), extent, phase of presentation and dimensions of hemangioma through direct measurements and photography were determined. Measurements were in centimeters of lesion along long axis and another one perpendicular to this axis. Photograph was taken with the same digital camera. Relevant investigations were done. Random sampling (systematic/alternate) was done and patients divided into two groups. Group – A treatment was with oral propranolol and Group – B treatment was with oral prednisolone.

Intervention

In group-A: before administration of propranolol electrocardiogram and echocardiography

(If ECG suggestive) to exclude cardiac disease were done. If the patient's vital functions were within the normal range, 2 mg kg per day of propranolol was administered in two divided doses. If no relevant adverse effects were detected after administrations and if this was well tolerated, treatment was continued. Blood glucose levels were obtained for risk of hypoglycemia of all patients. They were also advised to call over phone for any adverse effects. In group-B oral prednisolone was administered 2 mg kg per day in two divided doses along with H_2 blocker ranitidine. Parents were instructed to interrupt the administration of the drug if the child had a serious cough with dyspnea or gastroenteritis with vomiting or diarrhea. Follow up during treatment. Follow-up visits were initially scheduled after 2 and 4 weeks of therapy and then monthly for four months and at any time in case of complications. The dosage was adjusted to the weight of the patient. In each follow up pulse, blood pressure, percentage of regression (of size), color change, complications, compliance and laboratory assessment (blood glucose level) was recorded.

Outcome measures were done by reduction of tumor size/elevation, based on direct measurement (in centimeters in 2 axis) with flexible soft rubber tape and calipers, along with photographic evaluation (same digital camera)[8].

Color changes of IHs were digitally analyzed using Adobe Photoshop 6.0 ME Software (Adobe System Incorporation, USA). The following equation was used to evaluate the color clearance after treatment to minimize the possible artifacts during photo documentation:

Color Clearance(%)={(A B)÷(A)×100} {(C D)÷(C)×100}

A and B represent the numerical color values of identical areas of IHs at pretreatment and post treatment photographs respectively, whereas C and D represent the numerical color values of an identical area of normal skin at pretreatment and post treatment photographs respectively. The former fraction of the presented equation will serve to calculate the color clearance (percentages) of identical areas of IHs at pretreatment and post treatment photographs, whereas the later fraction of the presented equation will help to calculate the color clearance (percentages) of an identical area of normal skin at pretreatment and post treatment photographs. Accordingly, the color clearance (percentages) of identical area of normal skin at pretreatment and post treatment photographs will be added to or subtracted from the color clearance (percentages) of identical areas of IHs at pretreatment and post treatment photographs to bypass technical artifact[1]. Regression in the size and color clearance of IHs was clinically assessed. It was evaluated according to 0%-to-100% scale. An excellent response denotes 80% to 100% regression or color clearance. A good response denotes 50% to 80%. A fair response denotes 25% to 50% and finally a poor response denotes 25% or less. After evaluation both regression of size and color clearance separately, more than 80% regarded as cure and less than 80% as not cured[9].

Data collection and Data analysis

Data was collected from primary source in a predesigned data collection sheet.

Data were processed manually and analyzed with the help of SPSS (Statistical package for social sciences) 16.0 for windows. A probability value (p) of <0.05 was considered statistically significant. Figure-1 shows the flow chart of the study.

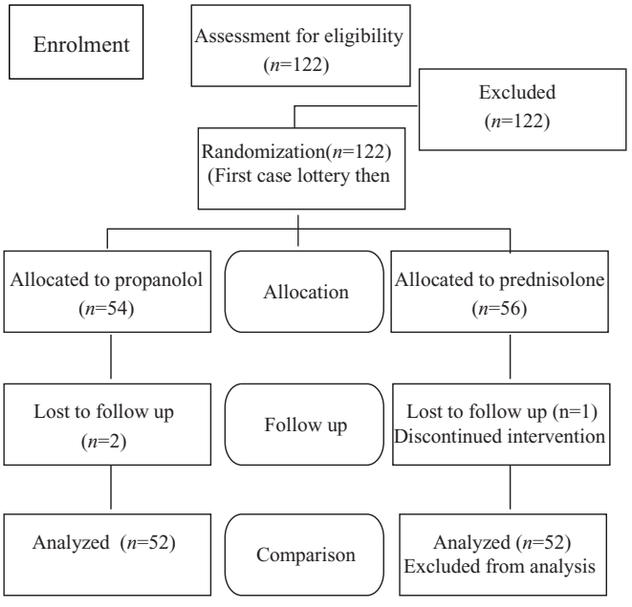

Figure 1 : Flow chart of the study

Limitations of the study

The study was carried out in a heterogeneous patient population and small numbers over a short duration. Short-term study is not enough to give the final outcome of the study. Infantile hemangiomas were of different sizes. Measurement error was a potential limitation of our percentage of regression (volume) measurements.

RESULTS

This study initially included a total of 122 patients with infantile hemangioma in different parts of their body. 12 patients were excluded and 6 not attending to follow up visit in time. So, finally 104 patients were studied for analysis. The age of the patients in the study group ranged from 1 month to 42 months. Mean ± SD was 6.05 ± 5.08 months and median was 4.8 months. Mean age at initiation of treatment was similar in both groups and statically insignificant [Table-1]. Male and female ratios between two groups were more or less similar and not statistically significant. The ratio in whole study group was M: F = 1:3.52. Five patients in group A and two patients in group B had consanguineous parents and in group A seven patients, in group B five had positive family history of haemangioma.

Most of the patients (82.7%) lesions were in the head and neck region (Group A: 45 and Group B: 41), other sites were trunk and limbs: 9 patients, anogenital: 3 patients. Multiple lesions found 14 patients in group A and 11 patients in group B.

Table 1: Distribution of the age of the patients between two study groups

Age (In month)	Group-A (propranolol)	Group-B (prednisolone)	P-value
<6 month	32	28	
>6 month	20	24	
Median	4.9	4.5	
Mean± SD	6.3 ± 5.03	5.6 ± 5.3	p>0.05

Status of the patients of infantile hemangioma (IH) by pulse rate at pre and post treatment follow-up in group-A (propranolol) were measured and Table-1 shows change in pulse rate. Mean pulse rate per minute change from pre treatment is between value '-11.00 to -12.31' (11.57%-13.67%) during the period of immediate and subsequent follow-up. Maximum fall of pulse rate were seen within six hours of treatment and no major changes during this period.

Mean blood glucose levels of the patients treated with oral propranolol during follow-up are shown in Table- 2. None of the patients suffered from hypoglycemia. In this series minimum level was 3.4 and maximum was 7.8mmol/l.

Table 2: Change of pulse rate in propranolol group (N=52)

Follow up Time	Pulse/min (Mean ±SD)	Mean change	Percentage change
Pre treatment	100.89 ±7.56	--	--
After 6 hours	98.05±7.23	-11.12	-12.10
14 days	97.19±5.59	-11.00	-11.87
1 month	95.67±5.59	-12.10	-11.57
2 month	94.05±7.23	-12.31	-12.89
3 month	93.59±4.65	-12.00	-13.67
4 month	92.33±4.68	-11.59	-11.36

Table 3: Mean blood glucose level in propranolol group. (N=52)

Follow-up	Mean blood glucose level (mmol/l)
After 6 hours	5.44 ± 2.4
14 days	5.54 ± 1.6
1 month	4.89 ± 2.5
2 month	5.23 ± 2.3
3 month	5.56 ± 3.1
4 month	5.00 ± 3.4

The first noticeable effects of the treatment were the changes in color and softening of IHs, followed by regression of their sizes. Color changes of IHs were digitally analyzed using Adobe Photoshop 6.0 ME Software (Adobe System Incorporation, USA).

Color clearance was evaluated according to 0%-to-100% scale. An excellent response denotes 80 - 100% clearance, good: 50 - 80% clearance, fair: 25 - 50% clearance and poor: <25% clearance.

After 4 months of treatment, overall color clearance was seen in all patients, in group-A (Propranolol) 40(76.92%) had an excellent response, and in group -B, only3 (05.76%) had an excellent response.

Table 4: Comparison of color clearance after 4 months treatment between two groups.

Outcome of color clearance	Group-A n=52 (propranolol).	Group-B n=52 (prednisolonel).	P-value
Excellent	40(76.92%)	03(05.76%)	p<0.001
Good	10(19.23%)	18(34.61%)	c^2=10.82
Fair	02(3.84%)	21(40.38%)	
Poor	00	10(19.23%)	

Chi-square= 10.82, (p <0.001) result is significant.

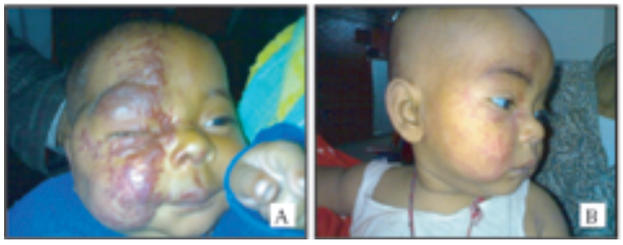

Figure 2: A- Before treatment with propranolol.
B-Three months after treatment with propranolol.

Reduction (Regression) of IH size/elevation, based on direct measurement (in centimeters, 2 axis) measured with flexible soft rubber tape and calipers in two groups (Table-4). After 4 months of treatment, overall regression was seen in all patients. In group-A (Propranolol) 42(80.76%) had an excellent response, but, in group-B (Prednisolone) only 5(9.61%) had an excellent response. An excellent response denotes 80 - 100% regression, good: 50 - 80% regression, fair: 25 - 50% regression and poor :<25% regression(figure-3A,3B).

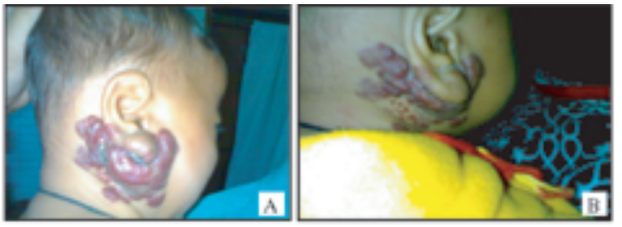

Figure 3: A-Before treatment with prednisolone.
B- Four months after treatment with prednisolone.

No severe adverse effects of oral propranolol group were noted in this study. One patient (1.92%) had gastroenteritis in the form of vomiting and diarrhoea, another had a nonspecific skin allergy. Propranolol therapy was discontinued in these 2 patients and then restarted at a later date, without recurrence. Therefore, their adverse effects were determined unlikely to be related to propranolol therapy. Six patients had sleep disturbances (11.53%).

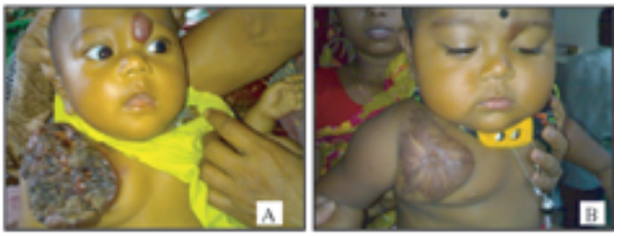

Figure 4: A-Before treatment with propranolol.
B-Two months after treatment with propranolol.

Table 5: Outcome comparison of regression of size after 4 months treatment between two groups.

Outcome of regression of size	Group-A n=52 (propranolol).	Group-B n=52 (prednisolonel).	P-value
Excellent	42(80.76%)	05(9.61%)	p<0.01
Good	07(13.46%)	15(28.84%)	χ^2=11.533
Fair	03(5.76%)	20(38.46%)	
Poor	00	12(23.03%)	

Chi-square c^2= 11.533 , (p <0.01) result is significant.

In oral prednisolone group most of the patients 47(90.38%) exhibited with known adverse effects of prednisolone. Out of them irritability 02(4.34%); gastroenteritis 10(19.23%); fungal infection 12(23.07%) (Oral thrush:2), neck and groin:10]; insomnia 07(13.46%); hypertension 04(07.69%); cushingoidfacies 05(09.61%); local ulceration 04(07.52%); bleeding from lesion 03(05.76%).Chi-square χ^2= 11.41, (p <0.001). Result is significant.

Mean total cost of the oral drugs (propranolol and prednisolone + ranitidine) were calculated. Investigation charges or adverse effect management or further referral charges were not included in the calculation. Mean cost of drugs, in group-A, 2.07 USD per patient and in group-B, was 7.25 USD per patient.

DISCUSSION

In our prospective study, initially a total of 122 patients with infantile hemangioma in different parts of their body were recruited, of them 12 patients were excluded and 6 not attending to follow up visit in time. So, finally 104 patients were studied for analysis. In Group-A 52 patients were treated with oral propranolol and in Group-B 52 patients with oral prednisololne. Among this two groups (32+28) 60 patients (57.69%) were less than 6 months of age. 44 patients (42.30%) were more than 6 months. In Marcia Hogeling et al. 2011 study less than 6 month age group was 52.45%. According to Bennet et al. 2008 study most infantile hemangiomas (IHs) complete their proliferative growth phase before 9 months of age and they identified 29.6% patients of IHs show prolonged growth after 9 months of age. In this study 31.33% Hemangiomas had prolonged growth pattern. Natural history of IH is rapid growth during 1st 6 months of life which is similar to this study.

Regarding distribution of Infantile hemangioma in different parts of the body 67.34% were in head- neck and face (face, orbital/periorbital, scalp, lip) region in our study which were cosmetically very much important site. In Anand Pandeyet al.2009 study most of cases lesions were in head and face region (64.9%)[10]. According to Sans et al.2009, Smithers and Fishman.2010 most of the lesion were in the same area 60% and 63% respectively[11]. So sites of the infantile hemangiomas are similar in all these studies. Small lesions in trunk and limbs usually failed to draw attention, in our study they mostly presented due to their extensive nature or complications.

As bradycardia is potentially common after ingestion of propranolol, in this study every patient was monitored for this effect. Mean change of pulse rate during first six hours of ingestion was -11.12 and no remarkable decrease was seen in next hours. In subsequent monthly follow-ups (during routine scheduled follow up) the change was 2-5 beats per minute (age wise). In none of the patients pulse rate dropped below 80 beats per minute. No major bradycardia was also seen in Sans et al.2009 study. Mahmudul 2010 at BSMMU found likely result in his thesis study.[12] No fall of blood pressure was seen in any of our 52 patients. Observations are similar in both study and indicate propranolol can be used safely in children as outpatient basis.

Most of the studies showed color change within 10-30 minutes of starting treatment. Mahmudul, 2010 in his study little change of color during 1st hour of treatment, at 2nd hour 13.55% patients illustrated initial response of stabilization (purple color of the lesion ,diminished shininess and softening of the surface)[12]. All of these studies use visual analog score which is totally subjective evaluation. In our study we used totally objective digital evaluation of color change[9]. By this method photographic computer based evaluation was compared between two groups.

In group-A (Propranolol) out of 52 patients overall color clearance was seen in all patients that is 100 %(n=52) during different follow up of treatment. Among them 40(76.92%) had an excellent response, 10(19.23%) had a good and 2(3.84%) had a fair response. In group-B (Prednisolone) out of 52 patients overall color clearance was seen during different follow up of treatment. Among them 03(05.76%) had an excellent response, 18(34.61%) had a good, 21(40.38%) had a fair response and 10(19.23%) had poor response. Janie Bertrand, M.D,2011 showed excellent 80% response in propranolol and 5.6% in prednisolone recipient[10]. Regarding regression of tumor (IHs) it is very important to measure the percentage of regression. Many studies used VAS scoring to assess the tumor regression which is subjective evaluation. But some centre used direct measurement by soft flexible measuring tape and calipers[10,13]. Though it was a bit difficult, we used this technique for better objective comparison between two groups. In group-A (Propranolol) out of 52 patients overall regression was seen in all patients that is 100 %(n=52) during different follow up of treatment. Among them 42(80.76%) had an excellent response, 7(13.46%) had a good and 3(5.76%) had a fair response. Among them 61.53% was within two month and after four month only 19.23% showed variable regression. In contrast in group-B (Prednisolone) out of 52 patients overall regression was seen during different follow up of treatment. Among them 5(9.61%) had an excellent response, 15(28.84%) had a good, 20(38.46%) had a fair response and 12(23.03%) had poor response. A multicentre retrospective comparative study by Cynthia J. Price et al showed duration of treatment 2-7 month and 85.3% of the patients receiving propranolol got regression >75%. On the other hand prednisolone recipient only 20% got >75% regression[14]. A Randomized Controlled Trial of Propranolol for Infantile Hemangiomas by Janie Bertrand, M.D. et al 2011 showed similar result.[10] All these results significantly proved that tumor regression by propranolol is early and better than prednisolone.

Three patients of IHs came with bleeding and five presented with ulceration and infection during initiation of treatment. Among them 5 received propranolol and 3 got prednisolone. Bleeding episode did not occur in any case after starting treatment with propranolol and all 3 cases with ulcer were healed within one month. But in prednisolone group bleeding was controlled by surgical dressing and pressure bandage.

Patient presented with periorbital/eyelid IHs were able to open their eyes after 14 days (1st follow-up) of treatment with propranolol but with prednisolone after 2 months. Ulcerated Hemangiomas were healed completely within 2 months and spontaneous ocular opening was possible within 7 days in patients of hemangioma in eyelid treated with propranolol in Sans et al.2009 study[12].

Propranolol was generally well tolerated in this trial. Children remained hemodynamically stable with 01 child experiencing gastroenteritis, 01 skin allergy and 06 sleep disturbances. But these were not severe to discontinue drugs. In the study by Janie Bertrand, M.D. et al 2011, only 1 of 68 patients had hypoglycemia, 2 of the 68 patients experienced nonspecific skin eruptions, neither of the eruptions had a clear correlation to propranolol therapy, and neither recurred on retreatment.[10] On the other hand known adverse effects of corticosteroid (prednisolone) are well established. In our study we found irritability 02(4.34%); gastroenteritis 10(19.23%); fungal infection 12(23.07%) [Oral thrush (n = 2), neck and groin (n=10]; insomnia 07(13.46%); hypertension 04(07.69%); cushingoidfacies 05(09.61%); local ulceration 04(07.52%); bleeding 03(05.76%).

But all were reversible and mild because probably for moderately low dose. In our study we considered 4 months treatment for both groups. In group-A (Propranolol) average treatment cost was 165tk per patient. In group-B (Prednisolone) average treatment cost was 580tk per patient.

During our limited short follow up in propranolol group no re-coloration was found but in one case relapse (rebound) was seen, in which propranolol was administered again. In prednisolone group 8 patients presented with re-growth and then they were treated with propranolol.

CONCLUSION

Propranolol is clinically more effective with minimum adverse effects and cost-effective than oral prednisolone in the treatment of infentile hemangioma. The percentage of regression of size and color clearance was sufficient to justify the use of propranolol as the first-line option for treatment of IHs. Large multicenter trials may confirm these results and provide more detailed information regarding the use in different age groups and anatomic sites, and the safety of propranolol.

DISCLOSURE

All the authors declared no competing interest.

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