Journal Homepage: -www.journalijar.com

INTERNATIONAL JOURNAL OF ADVANCED RESEARCH (IJAR)

Article DOI:10.21474/IJAR01/11302
DOI URL: http://dx.doi.org/10.21474/IJAR01/11302

RESEARCH ARTICLE

TO DETERMINE THE EFFICACY OF TOPICAL TREATMENT WITH 1% PROPRANOLOL FOR INFANTILE HEMANGIOMA

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Manuscript Info

Manuscript History
Received: 10 May 2020
Final Accepted: 15 June 2020
Published: July 2020

Key words:-
Infantile Hemangioma (IH), Topical Propranolol, Birthmark, Topical Treatment

Abstract

Objective: To determine the efficacy of topical treatment with 1% propranolol in the infants with hemangioma.

Methodology: This was a prospective study conducted from August 2018 till December 2019 through non-probability convenient sampling technique. Study comprised of 27 infants from the Dermatology Department of Dow University Hospital, Karachi. Infants having hemangioma in any part of body except near orifical opening were included in the study. 1% topical propranolol was applied twice daily to the lesion and any change is size, colour , discharge before and after treatment was noted at each follow up till 3 months.Resolution was recorded at each follow up. Data was analysed in SPSS version 20.0. P-value ≤0.05 was taken as significant.

Results: From the total of 27 infants enrolled in the study, 09 (33.3%) were male and 18 were female (66.7%). After treatment, 26 (96.3%) hemangiomas had shrunken. 14 (51.9%) of patients parents termed it as a very good response to treatment and 07 (25.9%) felt complete satisfaction to treatment. On first follow up, only 01 (3.7%) had complete resolution, 04 (14.8%) on second follow up and 06 (22.2%) on third follow up.

Conclusion: The present study concluded that 1% topical propranolol was effective as well as safe and convenient to apply for treating infantile hemangiomas.

Introduction:-

The most common tumour in infant age group is Infantile hemangioma (IH), appearing in 4-10% of infants (Frieden et al., 2005)[1] . The primary clinical sign of IH is a characteristic surface of pallor that is visible after several days of birth. The phase of proliferation of hemangioma is characterised by disproportionately excessive angiogenesis that takes place over three to six months, however the phase of involution takes years to occur. Despite several years taken by complete involution to occur, there are case that persist and stay unresolved. The lesions change texture in 40% of cases and some undergo fibro-fatty scarring (Cheng et al., 2010)[2] . Such a vascular lesion that changes

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texture and follows the aforementioned pattern is considered to be IH until clinically proven to defer. Doppler ultrasound, angiography or magnetic resonance imaging (MRI) is used to establish the diagnosis if the appearance of lesion tends to vary from pattern described (Darrow et al., 2015)[3]. There is a cosmetic concern regarding cutaneous IH and can be disfiguring. The cutaneous IH ulcerate in about 5-13% of cases, which causes pain and may lead to bleeding and scarring (Barreau and Dompmartin, 2017)[4]. There is clonal expansion vascular endothelial cells in IH. There have been documented that mutations in angiogenesis- related protein expression may be involved. There has been noted that alkaline phosphatase, factor VIII antigen, and cluster of differentiation are characteristically elevated in IH (Phung and Hochman, 2012)[5]. Increased cellular expression of pro-angiogenic factors, such as vascular /basal fibroblast growth factor and proliferating cell nuclear antigen may stimulate endothelial growth and lead to uncontrolled angiogenesis. The over expression of glucose transporter 1 (GLUT-1) is unique to IH and is not found in other vascular tumours (Greenberger and Bischoff, 2013)[6].

Treatment of IH is required in patients to cure or recover functional impairment or pain, prevent or decrease scarring or disfigurement, and avoid lethal complications. The most common treatment options include use of corticosteroids either intralesional or systemically, chemotherapy (vincristine and interferon alpha), cryotherapy with liquid nitrogen, ablation using laser and surgical excision (Raphael et al., 2016)[7]. The most preferred treatment for most types of IH is currently corticosteroid therapy. The use of propranolol in treatment of IH was followed by a report by Leìauteì et alin 2008, following their subsidiary finding. The randomized control trial [RCT] was performed on twenty patients for further investigation purposes (Leaute-Labreze et al., 2008)[8]. Multiple mechanisms have been suggested for propranolol action. Reduced vascular density have been suggested as by combined grayscale and colour Doppler ultrasound imaging after use of propranolol. The cytotoxic effect of propranolol has a been noted on cultured vascular endothelial cells via the hypoxia-inducible factor pathway, leading to decreased secretion of VEGF (Bingman et al., 2012)[9]. In vitro propranolol decreases plasmalemmal expression of GLUT-1, none the less this hypothesis has not been evaluated by any study till date in reference to IH. Other possible mechanisms of action include inhibition of matrix metalloproteinases, down-regulation of interleukin-6 and modulation of stem-cell differentiation (Storch and Hoeger, 2010)[10].

This rapid propagation and prompt acceptance of this treatment regimen undoubtedly requires careful monitoring and a reliable treatment system or recommendation to reduce adverse events (Laeley et al., 2009)[11]. Thus, this publication aims to study the effect of topical propranolol in infants with hemaniomas, as systemic therapy would require pre assessment, monitoring and management of adverse affects.

Methodology:-

Study Design:
This study was a prospective experimental study

Setting:
Conducted at Dermatology OPD of Dow university hospital, Dow International Medical College.
Duration of Study: August 2018 till December 2019.

Sampling technique:
The sample was collected using convenient, non-probability sampling technique.

After explaining and obtaining consent from the parents, a detailed history was taken, followed by detailed cutaneous examination. Diagnosis was made clinically. Size of lesion was recorded on first day followed by monthly examination and third recording was taken as final reading. Topical propranolol 1% was advised to apply twice daily on lesion and changes noted periodically on every visit, however if there was a sudden change in size, colour or bleeding parents were asked to bring infant immediately. Parents response to the improvement in the treatment was classified subjectively as poor, moderate, very good and complete satisfaction.

Initially 35 infants who were diagnosed with hemangioma on clinical basis were included in the study, from which 27 continued with regular follow-ups. The rest were lost to follow-up after one or two visits. Any association with any internal organ involvement were excluded (only cutaneous lesions included).
Infants having hemangioma near orificial opening (like eye or mouth) any other abnormality such as limb defects, bleeding disorders, known syndrome like Downs etc were all excluded from the study.

Data Analysis:
Data was gathered and analysed using SPSS version 20.0. Data was presented as mean, median, interquartile range and standard deviation. Wilcoxon rank was used to assess the difference. Bar graphs were used to present the qualitative data. P-value of ≤ 0.05 was considered as significant.

Results:-

At the time of Presentation:
From the total of 27 infants enrolled in the study, 09(33.3%) were male and 18(66.7%) were female. The mean age of infants was 5.75±2.43 months. 13(48.1%) infants had hemangioma in the head and neck area, 08(29.6%) infants had hemangioma at the trunk and pelvis region and 06(22.2%) infants had hemangioma at the limbs. With regards to color, 06(22.2%) infants violacious color, 20(74.1%) infants had bright red color and 01(3.7%) had light erythematous color. 21(77.8%) of the total hemangiomas had a swelling. Only 03(11.1%) of infants were observed to have discharge. 21(77.8%) infants were reported to have an increase in the size of the hemangioma of which all 21(77.8%) had a gradual increase in size. 13(48.1%) of hemangioma had a change of color while 14(51.9%) did not have any color change. None of the hemangioma was reported to be associated with congenital anomaly. [Table 1]

After Treatment:
Effective rating from parents after treatment was done by 20(74.1%) of parents. According to parents assessment, 02(7.4%) of hemangioma were declared as poor, 04(14.8%) as moderate, 14(51.9%) as very good and 07(25.9%) of the hemangioma were regarded as complete resolution. With regards to color, 02 (7.4%) infants had violacious color, 11 (40.7%) infants had bright red color and 14 (51.9%) had light erythematous color. 17 (63%) of the hemangioma were smooth and round in texture, 02 (7.4%) were reddish and smooth, 06 (22.2%) were smooth and flat while 02 (7.4%) of the hemangioma were boggy and raised. 26 (96.3%) of the hemangioma experienced a decrease in swelling, while only 01 (3.7%) suffered no change in swelling. Only 01 (3.7%) of the hemangioma had a discharge. [Table 2]

Size Comparison after follow-ups:
Mean size of hemangioma at baseline was 3.88 ± 1.52 cm with median and IQR of 3.50(2.50-5.0). Mean size of hemangioma after first follow up was 2.67 ± 1.40 cm with a significant difference (p-value≤0.001). Mean size of hemangioma after second follow up was 1.79 ± 1.15 cm with a substantial difference (p-value≤0.001). Mean size of hemangioma after third follow up was 0.92 ± 1.05 having a significant difference (p-value≤0.001). [Table 3]

Resolution after Treatment:
On the first follow up, only 01 (3.7%) of the hemangioma were observed to be completely resolved. 04 (14.8%) of the hemangioma were completely resolved at the second follow up. 06 (22.2%) of the hemangioma resolved after third follow up. [Figure 1]

Discussion:-

In many cases hemangiomas have a tendency to resolve on their own and do not require any treatment whatsoever in infants. Although few hemangiomas tend to progress exponentially. As the scar formed at the end of some hemangiomas is large and disfiguring, leading to indication of treatment in selected cases.

In our study we observed that after applying topical propranolol, complete resolution was not seen in majority of the patients even after their third follow-up, however 26 (96.3%) of the hemangioma had shrunken in size without any discharge and 20 (74.1%) of parents regarded topical propranolol as an effective treatment without any adverse effects.

In a study by Xu et al., who applied 1% propranolol ointment three times a day on 28 lesions in children up to 10 months old; good or partial response was observed in 90% of IHs without side effects (Xy et al., 2012)[12]. A similar response rate was observed in our study in which moderate to good and complete response rate of above 90% overall was reported. Kunzi-Rapp et al., treated 45 children (from preterm infants to 33 months of age) with 65 IH with 1% propranolol ointment twice daily. The best outcome was observed when topical propranolol was administered in the first 6 months of life, with regression in 59% and growth cessation in 26% of the hemangiomas. Good therapeutic response was also observed in patients 7 to 33 months of age with improvement in all cases. No side effects were noticed regardless of age and lesion size (Kunzi et al., 2012)[13].However in our study 26(96%) of

hemangioma had a regression in growth. Wang et al. applied 3% propranolol gel three times a day in 28 patients 28 days to 12 months old with superficial IHs. Reduction in size from 50% to more than 75% was observed in 20 patients (Wang et al., 2012)[14]. Niu et al., treated 49 children with age of 1 to 10 months with 58 superficial IHs with 1% propranolol ointment; 53.1% showed good response and 34.7% partial response (Niu et al., 2013)[15]. The findings of the above study is consistent with our study in which we observed good response in 14(51.9%) cases.

In another study (Mouhari-Toure et al., 2013)[16] successful treatment of two superficial IHs in an 11-week-old infant with 2% propranolol ointment was reported and rapid regression was observed on the 45th day of treatment with 75% reduction of the lesions . Our study observed a greater response rate of 96.3% with regards to reduction of size of the lesion.

The idea for topical treatment of superficial hemangiomas is based on the need to deliver greater concentrations of medicine directly to focused skin area and avoid undesirable systemic effects. Guoet al., first applied 0.5% topical timolol solution as a treatment for superficial capillary hemangioma of the eyelid in a 4-month-old infantwith very successful results (Guo et al., 2010)[17].Topical propranolol therapy for superficial IHs in concentrations of 1% to 3% has recently been suggested(12).

On contrary to hypoglycemia, bradycardia or hypotension caused by systemic use of propranolol, such effects are unlikely to appear with topical use of propranolol.The drug concentration achieved after topical treatment are not similar to ones achieved after systemic administration. The local treatment takes twelve weeks which is much less as compared to duration of systemic treatment (Schiestl et al., 2011)[18]. The results after systemic treatment arecertainlyremarkable in a short period. However, two treatments are nearlyalike in a long period. There is a significance difference in indication for systemic or topical use of propranolol. The recognition of hemangiomas that are amenable to topical treatment or systemic treatments is very important (Chantasart et al., 2013)[19]. Thus, theevaluationbetween two treatments is of partialsignificance. In this study, the effect of treatment with topical propranolol application was seen in many infants.

The topical propranolol provides a bridge between cryotherapy and systemic treatment with propranolol in an ideal way, and therefore acquires utmost importance as adjunct therapy for the treatment of hemangiomas. Potential adverse effects have not been observed till now. If it is specified, propranolol cream has an encouraging result in most patients treatment with propranolol (Greensberger,2018)[20].

The qualitative approach of our study has assured that we have assessed the characteristics of hemangioma before and after treatment with topical propranolol. However, our study might not be immune from observer and practice bias. Considering the finding of our study and to what extent it is consistent with other studies would be enlightening to establish the exact concentration of propranolol in the formulation, optimal duration of treatment, and possible inclusion of other β-adrenergic receptor antagonists in the treatment of superficial IHs.

Conclusion:-

Our preliminary study suggested that 1% topical propranolol appeared to be safe and effective for treatment of superficial Infantile hemangiomas with majority of them shrinking and having cessation of its growth, having substantial difference between baseline and subsequent follow-ups. Parents were content and satisfied, therefore can be prescribed during early stages rather than just wait for natural resolution after long period of time.

However studies with larger sample size and long term follow-ups are required.

Conflicts of Interest:
Authors disclose no conflict of interest.

Table 1:- Characteristics of hemangioma at the time of presentation.

Variable		**Frequency**	**Percentage**
Gender	**Male**	9	33.3
	Female	18	66.7
Site of Hemangioma	**Head Neck**	13	48.1
	Truck and Pelvis	8	29.6

	Limbs	6	22.2
Color of Hemangioma	**Violacious**	6	22.2
	Bright Red	20	74.1
	Light Erythema	1	3.7
Swelling	**Yes**	21	77.8
	No	6	22.2
Discharge	**Yes**	3	11.1
	No	24	88.9
Increase in Size	**Yes**	21	77.8
	No	6	22.2
If Yes	**Suddenly**	0	0.0
	Gradually	27	100.0
Change of Colour	**Yes**	13	48.1
	No	14	51.9
Congenital Anomaly	**Yes**	0	0.0
	No	27	100.0

Table 2:- Characteristics of hemangioma after treatment (n=27).

Variable		**Frequency**	**Percentage**
Effective Rating by Parents	**Yes**	20	74.1
	No	7	25.9
Parents Assessment	**Poor**	2	7.4
	Moderate	4	14.8
	Very Good	14	51.9
	Complete	7	25.9
Color After Treatment	**Violacious**	2	7.4
	Bright Red	11	40.7
	Light Erythema	14	51.9
Texture After Treatment	**Smooth**	17	63.0
	Reddish and Smooth	2	7.4
	Smooth Flat	6	22.2
	Boggy and Raised	2	7.4
Swelling Decreases	**Yes**	26	96.3
	No	1	3.7

Table 3:- Comparison of size of hemangioma at Baseline, 1st, 2nd and 3rd month after treatment (n=27).

Size of lesion (cm)	**Mean**	**SD**	**Median**	**IQR**	**p-value**
Baseline	3.88	1.52	3.50	2.50 – 5.0	<0.001
First Follow up	2.67	1.40	2.50	2.0 – 3.50	
Baseline	3.88	1.52	3.50	2.50 – 5.0	<0.001
Second Follow up	1.79	1.15	1.50	1.0 – 2.20	
Baseline	3.88	1.52	3.50	2.50 – 5.0	<0.001
Third Follow up	0.92	1.05	0.50	0.1 – 1.50	
First Follow up	2.67	1.40	2.50	2.0 – 3.50	<0.001
Second Follow up	1.79	1.15	1.50	1.0 – 2.20	
First Follow up	2.67	1.40	2.50	2.0 – 3.50	<0.001
Third Follow up	0.92	1.05	0.50	0.1 – 1.50	
Second Follow up	1.79	1.15	1.50	1.0 – 2.20	<0.001
Third Follow up	0.92	1.05	0.50	0.1 – 1.50	

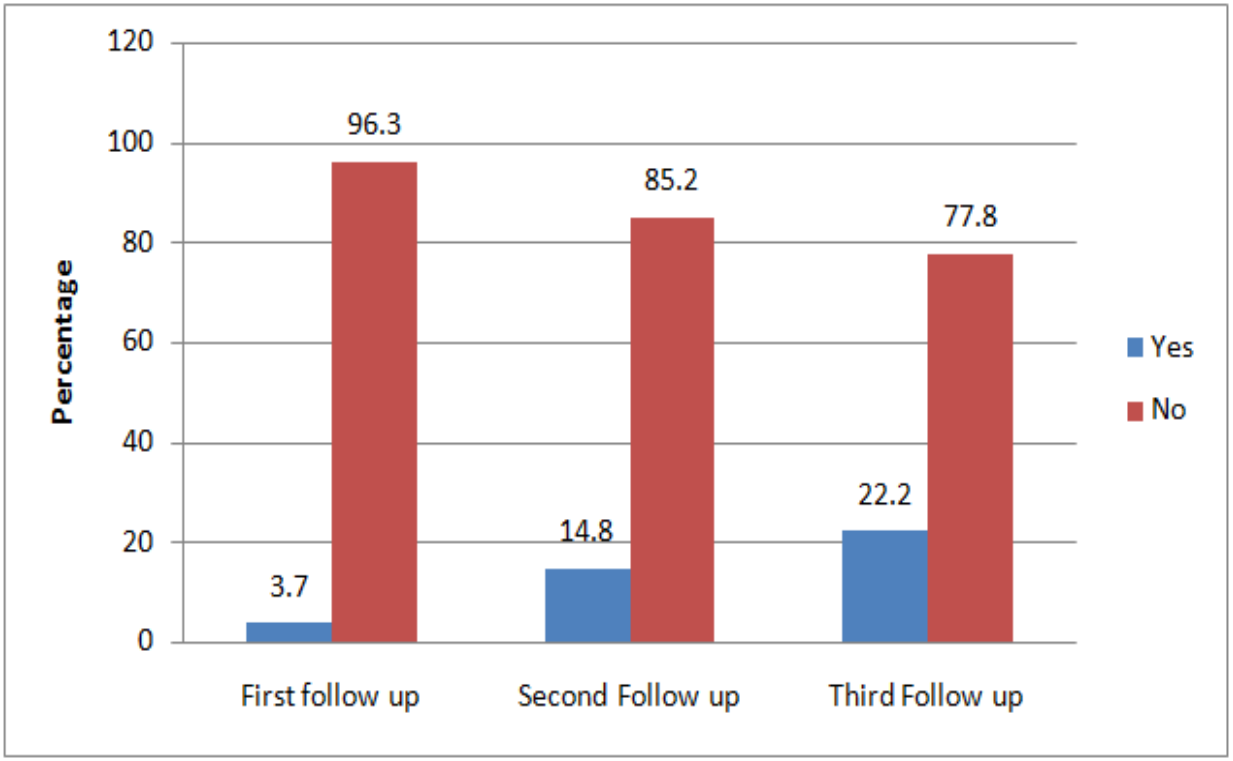

Figure 1:- Percentage of complete resolution of hemangioma at different follow ups (n=27).

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