Results of Minimal Dosage Propranolol in the Management of Infantile Haemangioma

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ABSTRACT:

BACKGROUND:

Infantile haemangioma one of the most common tumour of new borns , a safe and effective treatment options are under ongoing research .

OBJECTIVE:

The authors show the effectiveness and safety of low dose propranolol as a method for infantile haemangioma treatment .

METHOD:

In this study twenty- four patients with infantile haemangioma in different anatomical locations were treated with oral propranolol and the result were assessed in a retrospective analysis of the results patients were kept on 0.25 mg/kg/day for one month , then on 0.5mg/kg/day in 2 divided doses for another one month , in the third month the dose will be increased to 1 mg/kg/day in 2 divided doses , then the propranolol were given in a maintenance dose ranging between 1-1.5 mg/kg/day in 2 divided doses according to the clinical response .The duration of treatment ranging from 6-18 months as a small dose increasing over a long time .

RESULTS:

We had achieved excellent result in most of our patients, with reduction of size and fade of color of hemangioma within 1 month from the initiation of treatment, when we stop the treatment no relapses were noticed during our follow up period after finishing the course.

CONCLUSION:

Propranolol is one of the safest and most effective treatment options for the infantile haemangioma even in low dose, with lower relapse rates and minimal consecutive side effects and drawbacks.

KEYWORDS: propranolol, infantile, haemangioma

INTRODUCTION:

Infantile heamangioma is a benign tumor of the endothelium , it is regarded as the most common benign tumor of infancy and early childhood with an incidence of 5-10% .

Typically ,infantile heamangioma appears at birth or within the first 2 weeks of life , it is most common occurring in girls , high maternal age and premature infants . Both head and neck are regarded as the most common site of its occurrence (60%) ,followed by trunk (25%) and the least common site is the extremities (15%) [1,2,3,4].

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Infantile hemangioma (IH) has three phases, during the proliferative phase (first 9 months) it grows rapidly. After the proliferative phase, it enters in a stable period, where it tend to shrink and reduce in its size and activity. lastly infantile hemangioma enters in the involuted phase (5-10 years) , Although complete regression could occur in 50% of children during the involuted phase, permanent deformity such as fibrofatty changes , redundant , scarring … etc, still can be presented [5,6,1].

Although , infantile hemangioma is considered to be a self-limited condition , nearly 10% of cases need medical or surgical intervention especially that involved the critical area that may caused permanent damages such as periorbital hemangioma or area that can lead to ulceration such as anogenital area . Also intervention is appreciated to reduce the

residualtelangiectasias or skin redundancy that followed involuted phase [7,8,9].

Leaute-Labreze et al. In 2008 reported for the first time on management of sever type of infantile hemangioma that was associated with cardiac complications by using propranolol (non-selective ß-blocker) [10]. Since then , many cases reported and cohort studies have presented the usefulness of using of propranolol in acceleration of infantile hemangioma involution with less side effects and morbidity in comparison with other methods which had being used for the treatment such as corticosteroid therapy [11].

Although , propranolol was approved by the FDA for the treatments of infantile hemangioma up to 3mg/kg/day there is no fixed regimen and guidance for the optimum dosage and duration of its used in infantile hemangioma [7] .

The aim of this study is to evaluate the use of oral propranolol at a low dose of 1-1.5 mg/kg/day in two divided doses and asses its efficacy and safety at this dose in the treatment of infantile heamangioma.

PATIENTS AND METHODS:

This is a prospective study which was done at the medical city teaching complex hospital, in the plastic and reconstructive surgery department between May 2015 - September 2016 , In this

study 24 patients with problematic infantile hemangioma (periorbital hemangioma , ulceration and bleeding , rapidly progressive facial hemangioma , and functional impairment including lesion on genital or extremities) .

Our results were evaluated both clinically and photographically by the same surgeon team , adverse side effects of propranolol was taken in consideration when we assessed our result , parents opinion regarding improvement during treatment was also taken in consideration .

Clinical evaluation was based on reduction of the size of hemangioma . relapsing rate of infantile hemangioma after stopping of treatments was part of our clinical evaluation where our results were categorized into excellent result where the size of hemangioma was noticeably reduced with fade of its colour , disappearance of ulceration and bleeding(depending on the wound healing potentials) , and no relapse of infantile heamangioma after stopping the treatment , clinical response was graded as good when the size and the color of hemangioma is reduced , but relapse when the treatment is discontinued . lastly absent response when no change in the size of hemangioma or its color was noticed in infantile hemangioma .Patients ages were ranging between (1month – 12 months) patients data are shown in table -1- below;

All infants who were included in this study were full term and their weights were ranging between (4.5 kg.-6kg.) those patients who had previously treated by other methods of treatment (e.g. corticosteroids) were excluded from our study , also we exclude those patients who are syndromic (e.g. PHACES syndrome) , patients with visceral involvements , and those who had history of cardiac respiratory problems and those who had contraindication for propranolol treatment.

Before the initiation of oral propranolol treatment patients were sent for blood biochemistry investigations namely blood glucose and renal function test. Patients were checked by pediatric cardiologist where ECG and in selected cases echo-cardio-study were performed to exclude any cardiac abnormalities . Abdominal Doppler ultrasound was performed to exclude those with visceral hemangioma .

The treatment regimen and its potential side effects were clearly explained to the patient’s parents before initiation of the treatments as a part of the informed consent, all patients included in this study had pretreatment photography

Table 1: Patient's age by months ,gender, lesion location ,lesion's dimension and number of lesion in each patient.

Pat.	Age(mo.)	Gender	Lesion's site	Lesion's dimension(cm)	No. of lesions
1	1 mo	♂	Perioral	5*7	Single
2	1mo	♂	Perioral	3*1	Single
3	2mo	♀	Periorbital	5*5	Single
4	2.5 mo	♂	Periorbital	3*4	Single
5	5 mo	♀	Rt. Check	1.5*2.5	Multiple
6	4mo	♀	Genital	3.5* 4	Multiple
7	3mo	♀	Rt. Forearm	2.5*2	Single
8	6 mo	♀	Lt.leg	5*7	Single
9	12 mo	♀	Rt. Check	3.5*2	Single
10	3 mo	♂	Nose	3*2	Single
11	4 mo	♂	Perioral	3*2	Multiple
12	4.5 mo	♀	Periorbital	2.5*3	Single
13	1.5 mo	♀	Genital	3*3	Single
14	6 mo	♀	Nose	1.5*2	Multiple
15	3 mo	♀	Lt. check	2*3	Multiple
16	2mo	♂	Rt. Forearm	4*2	Single
17	11mo	♀	Perioral	1.5*2	Multiple
18	11 mo	♀	Periorbital	2*2.5	Single
19	3 mo	♀	Lt. check	3*3	Multiple
20	5 mo	♂	Nose	1.5*2	Single
21	3mo	♀	Nose	3*2	Multiple
22	12mo	♀	Eyelid	3*3	Single
23	9mo	♀	Forehead, eyelid&chin	3*4	Multiple
24	7mo	♀	Eyelid	3.5*4	Single

Treatment protocols :

We used 10 mg propranolol tablets which either were dissolved in 10 cc of water with sugar or crushed into small pieces and swallowed with sips of water , initial dose of propranolol was 0.25mg/kg/day in 2 divided doses.

In order to reduce the risk of hypoglycemia , the patients were instructed to feed their children immediately after treatment and every 3-4 hours , patients were kept on 0.25 mg/kg/day for one month , then on 0.5mg/kg/day in 2 divided doses for another one month , in the third month the dose will be increased to 1 mg/kg/day in 2 divided doses , then the propranolol were given in a maintenance dose ranging between 1-1.5 mg/kg/day in 2 divided doses according to the clinical response .The duration of treatment ranging from 6-18 months .

The treatment was stopped when infantile hemangioma started to shrink its size and its color is faded with appearance of white spots ,at that time the dose gradually taper over 4 weeks , if rebound growth noticed , the treatment restarted for longer period i.e. till the child reaches 18 months old.

RESULTS:

According to the mentioned criteria in method , we had achieved excellent result in 21 patients ,with reduction of size and fade of color of hemangioma within 1month from the initiation of treatment , when we stop the treatment no relapses were noticed during our follow up period . two out of 24 patients developed relapses after discontinuation of their treatments for those patients the treatment regimen were re established again till the children are 18 months and no relapsing had being noticed after that

age when the treatment is discontinued .Only one of our patients had no response on this maintained dose of propranolol i.e. 1- 1.5 mg/kg/day and this patient was subjected to oral steroids as an alternative modality of treatments and still under observation.

Regarding the side effects , none of our patients showed sever side effect at the beginning of the treatment or at the course of regimen . only 3 patients developed transient reduction in blood pressure measured at the child welfare hospital in the out patients department during initiation of the treatment which didn't affect the use of the drug later on , and one of our patients had low heart rate also during first dose first which did not require to discontinue of her treatment , no reported case of hypoglycemia was noticed in all of our patients .

Figure 1: Female patient with auricular IH before starting the treatment (right), two weeks after the initiation of propranolol treatment (middle) and three months after treatment (left)

Figure 2: female infant with periorbital haemangioma ,at presentation (right), two weeks after initiation of propranolol (middle) and two years follow up result (left).

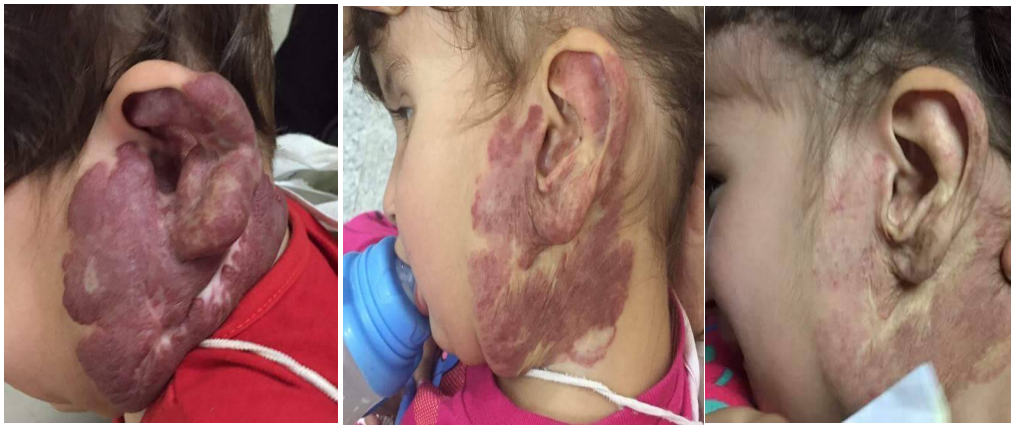

Figure 3: female infant with periauricular haemangioma ,at presentation (right), four weeks after initiation of propranolol (middle) and one year follow up result (left).

Figure 4: female with haemangioma of the lower lip , at presentation (right), three months after initiation of propranolol (middle) and (left) .

DISCUSSION:

Generally speaking most cases of infantile haemangioma are non-problematic and has no harm to the patients apart from family stress and most of them are completely disappeared at age of 5 years , others may leave residual scar and telangectasia .

However , few of infantile heamangioma causing problem that need intervention

Systemic corticosteroids, particularly oral predinoselon was the main drug used for management of the infantile heamangioma, steroids can also be given intralesional particularly for small localized heamangioma . whatever systemically given or intralesionally given , steroids had many systemic and local side effects like Cushing's syndrome, hypertension , diabetic , gastric upset and growth retardation , while local steroids injection may lead to blindness due to central retinal artery occlusion , response to steroids is depending on the presence of certain receptors in heamangioma[12,13].

Both interferon alpha and vincristine had been used for the management of heamangioma , both are associated with adverse side effects like neurotoxicity (spastic diplegia ,hematological and hepatic toxicity in case of interferon and peripheral neuropathy and syndrome of inappropriate secretion of antidiuretic hormone in case of vincristine [14].

Topical Timolol is another option which had been used for the managements of IH , it can be safely given for complicated and uncomplicated heamangioma during proliferative phase . However

,it is still associated with side effects like asthma exacerbation and Chynestoke breathing when used for treating very large lesions [15]

Since the first use of propranolol for the treatment of infantile hemangioma in 2008 by Leaue-Labraeze et.al neumerous research had been written about the efficacy and the safety of its use in children that associated with few side effects, it is important to remember that propranolol had been used since 50 years ago both for adult and children and it was proven to be safe [16,17].

In the treatment of infantile hemangioma , there is no single regimen or appropriate dose had been established for its use , although FDA recently approved propranolol to be used for treatment of infantile heamangioma in a dosage of up to 3mg/kg/day , still no obvious standard regimen used in the treatment of infantile heamangioma [7].

In this study 24 patients presented to us their ages ranging between (1-12 months) , with history of problematic heamangioma i.e. heamangioma that interfere with the function periorbital heamangioma ,rapidly enlarging , and heamangioma with ulceration and bleeding .

In this study most of our patients had shown initial response to small dose of propranolol (0.25mg/kg/day) within one month , this response was noticed by gradual fading of the colour of IH together with shrinking of its size . within 4-6 months of gradual increment of propranolol dose till it reached to 1.5mg/kg/day , we noticed nearly complete shrinkage of infantile heamangioma with changing of its colour to be nearly the same colour of the surrounding skin .

Although ,complete disappearance of IH was not noticed , the results was quite satisfactory to the patient's parents . This response to propranolol at this low dose (1.5mg/kg/day) was significant in term of no serious side effects was noticed in all of our patients , apart from mild transient hypoglycemia (3 patients) measured three time a day only in symptomatic patients and bradycardia (1 patient) which was seen when we initiated the treatment. The most common and serious side effects of propranolol is hypoglycemia , this was not encountered in any of our patients.

Most commonly reported dose of propranolol for the treatment of infantile heamangioma in the literature is 2mg/kg/day , In other studies there randomized control trials that compared the dose of 3mg/kg/day and placebo , these studies found that higher doses of propranolol are superior than lower dose . However , in this study the propranolol was used just for 24 weeks and exclude those with problematic heamangioma [18].

Tan et.al. criticized the need for higher dose of propranolol and they conclude that 1.5 mg/kg/day is sufficient dose that can be used to treat infantile heamangioma [5] , Din et.al. in 2009 conducted study on 58 infants presented with infantile heamangioma , and they treated by using of 1-1.5 mg/kg/day , their result showed good to excellent response in 67% of patients [19].

Another study which was conducted by Manuza et.al. in 2010 ,they showed rapid response in 26 out of 30 infants when they treated with 1mg/kg/day propranolol , However there are contradictions between studies that suggested to use propranolol in high dose . it was assumed that other factors may play role in response to propranolol other than its dose . one of these factors which was suggested by Tan et.al. is the role of rennin-angiotensine system in formation of infantile heamangioma [11] .

In a study which was conducted by Oumama El Ezzi et.al. , daily dose of 2mg/kg./day of propranolol was given to all of their patients .Two of their patients because of hypotension they were given 1mg/kg/day propranolol and even with such a low dose , the effectiveness of treatment with propranolol was obvious after second day of initiation of the treatment they conclude that we underestimate the effectiveness of using propranolol in 1mg/kg/day in treatment of infantile heamangioma and they suggested to create two groups of children in two different dose to determine the response according to dose of the propranolol [8].

Anderson et.al. had used 1mg/kg/day propranolol with 97% response [16]. Tan et.al. had reported the effectiveness of using of propranolol in a dose of 1.5mg/kg/day in 13 patients and had achieved good results [17]. In Tan et.al. study , none of his patients had orbital lesion , while in our study we did include patients with periorbital heamangioma (17 cases) and we achieved good results on using propranolol in a dose of 1-1.5 mg/kg/day.

Although we did not encounter any case of hypoglycemia in our study , most of other reports suggested that the hypoglycemia that may be associated with propranolol it is not a dose dependant as it has been showed to occur in patients with low dose of propranolol of 1-2 mg/kg/day .we instructed

our patients to frequently feed their children every 4-6 hours to avoid long periods of fasting , although as it reported in the literature that frequent feeding of infant did not provide infant with safeguard against hypoglycemia , we did not encounter any hypoglycemic complication in our patients [16,20].

The ideal duration of propranolol use in the treatment of infantile heamangioma has not being established yet, in one study concluded that the treatment should be continued till the heamangioma is fully involutes or the child at 12 months [10] . in one study it showed that patient treated for 3-8 months had relapse rate of 90% where as patents who were treated for more than 8 months had much lower relapses rate (5%) [21] . it is seem that the longer duration of treatment through the proliferation phase is associated with reduced relapse rate . suggested that the therapy should be continued beyond 12-18 months of age in order to reduce the relapse rate[22].

However ,in our study the treatment was ranging between 6-18 months and we didn't encounter relapse when we discontinue the treatment till 18 months of age[22] .

CONCLUSION:

It seems that low dose propranolol (1-1.5mg/kg/day) is as effective in the managements of infantile heamangioma as recommended high dose (3mg/kg/day) and eliminate the need for surgical intervention especially for periorbital cases with minimum side effects and low rates of relapses after discontinuation of the treatment.

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