Journal of Paediatric Surgeons of Bangladesh (2014) Vol. 5 (1) : 12-19
Official organ of the Association of Paediatric Surgeons of Bangladesh

Journal of Paediatric Surgeons of Bangladesh

Original Article

COMPARATIVE STUDY BETWEEN INTRALESIONAL DEXAMETHASONE AND ORAL PREDNISOLONE IN THE TREATMENT OF INFANTILE HEMANGIOMA

T A CHOWDHURY[1], M A H BHUIYAN [2], M M HAKIM[3]

Abstract:

Background: Infantile Hemangioma (IH) is one of the most common childhood neoplasm. Current treatments for children with endangering Infantile Hemangioma are limited, and include primarily oral corticosteroid which has many systemic adverse effects. Furthermore, approximately one third of IH does not respond to oral steroids, prompting active investigations for new treatments.

Objective: To compare the efficacy, side effects, and influencing factors of oral Prednisolone and intralesional Dexamethasone (IL) in treatment of IH and thus to find out an effective, cheap and safe modality of treatment for this anomaly.

Materials and Methods: This study was carried out on 48 patients of IH with the age range from 1 day to 12 years. Group A (n_1=26) patients were treated by oral Prednisolone and group B (n_2=22) patients were treated by IL Dexamethasone .Periorbital Hemangioma and IH >54 cubic centimeter were excluded. Therapeutic response of Prednisolone and Dexamethasone was graded as excellent, good, poor and no response. We monitored volume of the lesion and its color change to evaluate the response to treatment.

Results: Overall therapeutic responses were 69.2% in Group A and 68.2% in group B. Side effects were noted in 65.4% patient of group A and 36.4% patient of group B. In group A, the commonest (38.5%) side effect was excessive weight gain with cushingoid facies and in group B, commonest (27.3%) side effect was ulceration at injection site. Side effects were more in children of group A. Range of treatment was 4-20 weeks in group A and in group B, it was 4-24 weeks.

Conclusion: IL Dexamethasone is effective as oral Prednisolone for treatment of IH .Unlike Prednisolone, IL Dexamethasone is devoid of systemic side effects.

Keywords: Infantile Hemangioma, Intralesional injection of Dexamethasone, Oral Prednisolone.

Introduction:

Hemangiomas are defined as benign neoplasm composed of proliferative and hyperplastic vascular endothelium. Although most of these tumors are small and innocuous, some may be life or function-threatening or have associated structural congenital anomalies[1].

IH is also, perhaps, the least understood. This is, in part, due to from a long history of confusing nomenclature for vascular anomalies that employed classification schemes based on superficial descriptions of the lesions. [2]

The 1st major step toward clarifying this nomenclatural confusion was made by Mulliken and Glowacki in 1982 which was adopted by the International Society for the Study of Vascular Anomalies (ISSVA) in 1996. The term “Infantile Hemangioma” or “Hemangioma of infancy” is the preferred and accepted term.[1]

1. Dr Tahmina Akhter Chowdhury, Registrar, Department of Pediatric Surgery, Chittagong Medical College & Hospital,Chittagong,
2. Dr Akbar Husain Bhuiyan, Associate Professor, Department of of Pediatric Surgery, Chittagong Medical College & Hospital, Chittagong
3. Dr Mohammed Monjurul Hakim, Lecturer, Department of Anatomy, Chittagong Medical College , Chittagong

Correspondence to: Dr. Tahmina Akhter Chowdhury, Registrar, Department of Pediatric Surgery, Chittagong Medical College &Hospital , Chittagong, e-mail: drpanna35cmc@gmail.com

Considerable controversy exists as to the management of IHs. The major goals of management of IH have recently been outlined in the Guidelines of Care for Haemangioma of Infancy by the American Academy of Derma-tology.[3]

Medical therapies have become the mainstay in the mana-gement and treatment of IHs. Since 1970, oral steroids have been the standard therapy worldwide for serious or life-threatening IH cases. Oral Prednisolone or prednisone was commonly used as systemic steroid. Prednisolone accelerates the involution of Infantile Hemangiomas through differentiation and inhibition of angiogenesis [4] .But only one third patient responds to systemic steroid. Moreover, these patients are at increased risk for infection, peptic ulceration, poor wound healing, stunted growth, and behavioural changes (crying, insomnia, irritability). Several authors have reported successful management of IH by systemic steroid, with potentially serious side effects. At present, oral steroid therapy has proven to be very effective in reducing the size of the lesion.[5]

Mazzola[6] first reported the use of intralesional steroid injection for the treatment of IHs in detail. Subsequently, other reports have appeared indicating good results with this technique. Many steroids were used as intralesional injection by many researchers. Most of the researchers used short actiong corticosteroid - injection Triamcinolone or diluted injection Triamcinolone .Some researchers used combination of short and long acting intralesional corticosteroids (Triamcenolone + Betamethasone) [6,7,8]

Data about the use of long acting corticosteroids - injection Dexamethasone for treatment of IH in vivo is lacking. But Hasan & co-worker's [3] study showed that both Prednisolone and Dexamethasone cause inhibition of neovessel growth in IH tissue in vitro.

In Bangladesh , randomized clinical trials and evidence based studies on the efficacy of newer modalities of treatment is still lacking . Keeping these facts in mind and getting idea from Hasan & co-worker's study, this comparative study was done to find out a cheap and effective modality of treatment with minimum side effects for treatment of IH . We compared the effectiveness and complications of intralesional injection of Dexamethasone with that of the oral Prednisolone in treatment of smaller sized IH.

Materials and Methods:

It was a prospective study conducted on patients of IH who were treated with intralesional Dexamethasone or oral Prednisolone and was carried out in the Department of Pediatric Surgery, Chittagong Medical College & Hospital, Chittagong, Bangladesh from January 2011 to December 2012.

Patient's age limit was 1 day to 12 years. The participating patients were divided into two groups: Group A- Patients were treated with Oral Prednisolone and Group B- Patients were treated with IL Dexamethasone. Each group was divided according to age into- Neonate (1-28 days),Infant (29 days to 1 year) and Children (2nd year to 12 years). During the study period only one neonate came, so it was excluded.

Sample size were 48 (n= 48). Among them twenty six patients were selected in group A ($n_{1=}$ 26) and twenty two patients were selected in group B ($n_{2=}$ 22). Inclusion Criteria were: Single IH with a volume of d" 54 cubic cm, patients who came for regular follow up up to 48 wks after starting treatment. Exclusion Criteria were: Multiple IH, patients who were treated before study period and Periorbital IH [4].

Diagnosis was confirmed by color Doppler ultrasound. Ultrasound also gave measurement of the volume of lesion. Indications for the treatment were rapidly growing lesions, lesions causing pressure effect to surrounding structure, bleeding, ulceration and cosmetic concern. Site, Color and Volume of the lesions were noted. Infected and bleeding cases were given admission. Infection was controlled by proper antibiotic. Bleeding was controlled by pressure bandage or diathermy cauterization. Pictorial documentation was carried out after taking informed written consent. After starting treatment, all patients were followed up; 1st follow up after 2 weeks and then at every 4 weeks interval up to 48 weeks. In each follow up; volume of the lesion, weight of the patient, blood pressure and any complications & side effects that arose after starting treatment were noted.

For group A; choice of oral steroid was Tab Prednisolone (5 mg).H2 receptor blocker was given to all patients to prevent gastric irritation. Live attenuated vaccine was restricted during the treatment period. Starting dose was 2-3 mg/kg/day at full stomach and at morning .If no response within 2 weeks, dose was increased to 4-5 mg/kg/day. If no response with increased dose within next two weeks-

treatment was stopped and these patients were considered as non responder. In case of responder, treatment continued till response of IH to oral Prednisolone persists .

In group B; IL Dexamethasone was given in a dose of 2 mg/kg body weight. The injection was given by a 26 ½ gauge needle and it was given directly into the IH in four directions (dividing the lesion in four quadrants by 2 imaginary lines perpendicular to each other) through the same needle puncture site. Direct pressure was applied with sterile gauze for 2 to 10 minutes until all bleeding had stopped. Injection was given at 4 weeks interval. If no response with 3 successive injection, treatment was stopped and patients were considered as non responder. In case of responders , IL Dexamethasone was continued at 4 weeks interval and continued till response of IH persists.

In both groups, when volume of the IH and it's color remain constant in 2 successive follow up, it was considered as lack of response to treatment and oral prednisolone was tapered over 7 days and IL Dexamethasone was discontinued respectively. Follow up was continued up to 48 weeks. Injections were given directly into the IH in four directions (dividing the lesion in four quadrants by 2 imaginary lines perpendicular to each other) through the same needle puncture site. Direct pressure was applied with sterile gauze for 2 to 10 minutes until all bleeding had stopped.

In both groups, the response to the treatment was analysed by grading scale of Table-1 which was used by Gangopadhyay et al [7] with modification . All patients were followed up at 4 weeks interval. In each visit, we monitored volume (length x breadth x depth) of the lesion and its color change to evaluate the response of IH to treatment . The color changes were monitored by color code of figure- 1[10] . Besides that, color Doppler study of the lesion and assessment were also made for any complication and side effect .At every follow up photograph of the lesion was taken and it was compared to previous photographs.

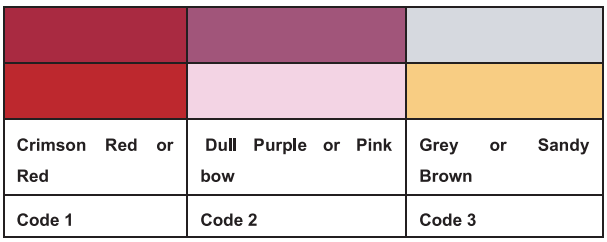

Fig.-1: *Three color codes used to monitor the response of IH to treatment*

Table-I

Parameters used for grading the responses of IH to treatment.

Excellent-Near total disappearance (more than 75% of pre-treatment size) and color change from pretreatment state to color of surrounding normal skin (or near to normal skin color) of the patient.
Good - 50% to 75% regression in size with color change from pretreatment state to code 3 (any one or in combination of grey and sandy brown) of figure 1.
Poor – 25% to 50% regression in size with color change from pretreatment state to color code 2 (any one or in combination of dull purple and pink bow) of figure 1.
No –No reduction in size or <25% regression in size with no color change .

All data were compiled and edited meticulously .For analysis of data SPSS version 18 software was used. Results were expressed as number and percent (%) of patients in contingency tables. The value of $P < 0.05$ was considered as statistically significant difference.

Results:

A total of 48 (forty eight) patients of IH were included in this study. Among them 26 patients were treated with oral Prednisolone and 22 patients were treated with intralesional injection of Dexamethasone. Out of 48 patients, there were 14 male and 34 female and male to female ratio was 1:2.43. In group A, there was 10 (38.5%) male and 16 (61.5%) female; and in group B there was 4 (18.2%) male and 18 (81.8%) female. Infants were the predominating age group in both groups.

In group A, 19 patients (69.2 %) and in group B, 15 patients (68.2%) responded to the treatment though there was no further proliferation of IH in the non responder group after starting treatment. Responses to treatment in both study groups were graded as excellent, good and poor according to Table 1. Chi square (÷2) test was done to see the association between study groups and responses to treatments among the different age groups and it is shown in Table 2. As P value is >0.05, the association was statistically not significant.

Therapeutic responses between 2 study groups according to anatomical site were shown in Table 3. In head and neck region, response was 66.7% in group A and in group B it was 63.6%.In upper limb, responses were 100% in group A and 66.7% in group B. Chi square (÷2) test was done to see the association between study groups and responses to treatments among the different anatomical site.

Table-II

*Therapeutic responses of both groups to treatment among the different age groups **(÷2 test**) (n=48)*

Age Groups	Study Groups	Responses				Total (%)	P Values
		No Response (%)	*Poor Response* (%)	*Good Response* (%)	*Excellent response* (%)		
Infant	Group A	4 (21.0)	2 (10.5)	1 (5.3)	12 (63.2)	19 (100.0)	**0.225 NS**
	Group B	2 (20.0)	4 (40.0)	1 (10.0)	3 (30.0)	10 (100.0)	
Children	Group A	4 (57.1)	0 (0.0)	0 (0.0)	3 (42.9)	7 (100.0)	**0.555 NS**
	Group B	5 (41.7)	1 (8.3)	2 (16.7)	4 (33.)	12 (100.0)	
Total	Group A	8(30.8)	2(7.7)	1(3.8)	15(57.7)	26(100.0)	**0.175NS**
	Group B	7 (31.8)	5 (22.7)	3 (13.7)	7 (31.8)	22 (100.0)	

Ï% NS = *Not Significant*

Table-III

Therapeutic responses of both groups according to different anatomical site (÷2 test) (n=48)

Anatomical Sites	Group A (n_1 = 26) Response			Group B (n_2 = 22) Response			Total(n = 48) (%)	P Values
	Yes	No	Total	Yes	No	Total		
	(%)	(%)	(%)	(%)				
Head & Neck region	12 (66.7)	6 (33.3)	18	7 (63.6)	4 (36.4)	11	29 (60.4)	P = 0.868 NS
Upper limb	2 (100.0)	0 (0.0)	2 (66.7)	2 (33.3)	1	3 (10.4)	5 NS	P = 0.361
Lower Limb	1(100.0)	0(0.0)	1	0(0.0)	1(100)	1	2(4.2)	P = 0.157NS
Trunk	2 (66.7)	1 (33.3)	3 (80.0)	4 (20.0)	1	5 (16.7)	8 NS	P = 0.673
Perineum	1 (50.0)	1 (50.0)	2	2 (100)	0 (0.0)	2	4 (8.3)	P = 0.248 NS
Total	18 (69.2)	8 (30.8)	26 (68.2)	15 (31.8)	7 (100.0)	22 NS	48	P = 0.938

Ï% NS = *Not Significant*

In group A, mean duration of treatment was 10.85± 5.48 weeks and in group B it was 12.91±4.26 weeks. Median duration of treatment in group A was 13 weeks and in group B it was 12 weeks. Table 4 is showing average length of treatment in both study groups . Here P value is statistically not significant. Table 5 is showing comparison between group A and group B regarding duration of treatment.

Table-IV

Duration of treatment in two study groups (Student's t tests significance)

Study Groups	Age Groups	N	Mean	SD	Median	Range	P Values
Group A	Infant	19	10.26	6.15	9.00	4 – 21	0.230NS
	Children	7	12.43	2.76	13.00	9 – 17	
	Total	26	10.85	5.48	13.00	4 – 21	
Group B	Infant	10	12.00	5.66	12.00	4 – 24	0.374NS
	Children	12	13.67	2.67	12.00	12 – 20	
	Total	22	12.91	4.26	12.00	4 – 24	

NS = Not significant.

Table-V

Comparison between two study groups regarding duration of treatment (Irrespective of age)

Study Groups	N	Mean	SD	Median	Range	P Values
Group A	26	10.85	5.48	13.00	4 – 21	P = 0.150
Group B	22	12.91	4.26	12.00	4 – 24	NS
Total	48	11.79	5.02	12.00	4 – 24	

During treatment period, side effects and some complications were noted in 16 patients (65.4%) of group A and in 8 patients (36.3%) of group B. In group A, some patients developed more than one side effect. Highest side effect was noted in children of group A (71.4%). Excessive weight gain with cushingoid facies was the commonest side effect in group. On the other hand, ulceration at the injection site was the commonest (27.3%) complication in group B.

However, none of the side effects was persistent. The side effects and complications of systemic and IL steroid therapy are shown in Table VI and VII respectively. Side effects and complications among different age groups of study population are shown in table - VIII.

Table-VI

Side effects noted during treatment of oral Prednisolone (n_1=26)

Age Group	No side effects No. (%)	Excess wt. gain No No. (%)	Increased appetite No. (%)	Behavioural changes (%) (%)	Increase in bowel frequency (%)	Apthous ulcer (%)
Infant	7	7	6	1	3	1
(n_i=19)	(36.84)	(36.84)	(31.58)	(5.26)	(15.8)	(5.26)
Children	2	3	2	1	3	-
(n_c=7)	(28.6)	(42.8)	(28.6)	(14.28)	(42.8)	
Total	9	10	8	2	6	1
(n_1=26)	(34.6)	(38.5)	(30.8)	(7.7)	(23.1)	(3.8)

Table-VII

Side effects noted during treatment with IL Dexamethasone (n_2=22)

Age Groups	No Effects	Ulceration at Side Injection Site	Hypo-pigmentation	Repeated Bleeding from Injection Site	Total
Infant	4 (18.2)	4 (18.2)	1 (4.5)	1 (4.5)	10 (45.5)
Children	10 (45.5)	2 (9.1)	0 (0.0)	0 (0.0)	12 (54.5)
Total	14 (63.6)	6 (27.3)	1(4.5)	1 (4.5)	22(100.0)

Table-VIII

Side effects and complications among different age groups of study population (÷2 test) (n=48).

Age Groups	Study Groups	Complications *Yes (%)*	*No (%)*	Total (%)	P Values
Infant	Group A	12 (63.2)	7 (36.8)	19 (100.0)	0.868 NS
	Group B	6 (60.0)	4 (40.0)	10 (100.0)	
Children	Group A	5 (71.4)	2 (28.6)	7 (100.0)	0.017 NS
	Group B	2 (16.7)	10 (83.3)	12 (100.0)	
Total	Group A	17 (65.4)	9 (34.6)	26 (100.0)	0.045 NS
	Group B	8 (36.4)	14 (63.6)	22 (100.0)	

NS= not significant , S = significant

Discussion:

Infantile Hemangioma is one of the most misdiagnosed and maltreated clinical problems in Bangladesh.

In this study, we found that female patient were greater in number and male to female ratio was 1:2.43 like many other centers[6,11]. In 48 patients of IH, we found that the most common age group was infant (64.8%).This data correlates with the study of Azizkhan [12].

In our study, 69.2 % patient of group A responded (excellent = 57.7%, good = 3.8% and poor =7.7 %) to oral prednisolone. These findings are near to other studies of the world [4,9] .On the other hand in group B, 68.2 % patient responded (excellent = 31.8%, good = 13.7% and poor = 22.7%) to Dexamethasone. Gangopadhyay et al [7] reported excellent result in 75% patient with intralesional Triamcinolone.

There was no statistical difference (P = 0.175) in grading of response of two study groups.

In this study, non responders were 30.6% (8 patient out of 26) in group A and 31.8 % (7 patient out of 22) in group B. It was seen that non responders were more in children (57.1% in group A and 41.7% in group B); but in case of infant , non responders were much lower (21% in group A and 20% in group B) i.e. response rate is more in infant by both oral Prednisolone and injection Dexamethasone. Klement and Fishman [4] reported that response is better in infant than children when treated with Prednisolone. The research results done by Gangopadhyay et al [7] on 105 patients found that infants yield more successful results with intralesional steroid, which is consistent with the present research work. So age of the patient is an important factor for successful treatment outcome in both oral Prenisolone and intralesional Dexamethasone.

We observed that, regression of IH was associated with lightening of color and decrease in volume. The lesion which was swollen above the surrounding skin surface before treatment, their swelling decrease when they respond to treatment. These findings were more marked in excellent responder. We found that color of the lesion at pre-treatment state became faded when they started to regress in size with treatment. Smithers and Fishman [1] also noted lightening of color when IH started to regress with corticosteroid therapy.

In our study, 61.2% of the IH was distributed in head and neck region. This is similar to Smithers and Fishman [1] finding . In this study, therapeutic response of IH in head and neck region was 66.7% in group A and 63.6% in group B. With oral Prednisolone responses in upper limb, lower limb, trunk and perineum were 100%,100% ,66.7% and 50% respectively and with injection Dexamethasone , responses were 66.7% in upper limb,80% in lower limb, and 100% in perineum.

Regarding duration of treatment, Klement and Fishman[4] recommended oral Prednisolone therapy

for 32-40 weeks; but according to Children's Hospital of Wisconsin, [13] the duration of treatment by oral Prednisolone ranges from a few weeks to many months. In our study, we found that mean duration of treatment by Prednisolone was 10.26±6.15 (range 4-21) weeks in infant and 12.43 ± 2.76 (range, 9-17) weeks in children. Student's t test shows no significant statistical difference among these age groups regarding duration of treatment (P= 0.230).

In group B, mean duration of treatment was 12.00 ± 5.66 (range, 4-24) weeks in infant and 13.67 ± 2.67 (range, 12-20) weeks in children. Student's t test was done to compare the duration of treatment between infant and children and it was statistically not significant (P=0.374).

Our study also showed that irrespective of age the mean duration of treatment in group A is 10.85 ± 5.48 weeks and in group B it is 12.91 ± 4.26 weeks which is statistically not significant (P=0.150).

We observed side effects in 65.4% (17 out of 26) of patient in group A. Nieuwenhuis et al [5] recorded side effects in 57% to 70% of their patient treated by systemic corticosteroid. This is consistent with our finding.

We found excessive weight gain with cushingoid facies as the commonest (38.5%) side effect of oral Prednisolone. For comparing the rate of weight gain we used WHO growth chart. Other side effects of oral Prednisolone were increased appetite (30.8%), behavioural changes i.e. irritability and crying (7.7 %) and increase in bowel frequency (23.1%).Only one infant (5.26%) developed apthous ulcer.

We measured blood pressure of all patients at every follow up but hypertension was not detected at any follow up. None of the side effects were persistent and all the side effects disappeared soon after treatment was stopped. Children's Hospital of Wisconsin [12] reported a number of side effects with systemic corticosteroids including irritability, gastrointestinal upset, hypertension and growth retardation and most of the side effects accompany prolonged use of systemic steroid. Nieuwenhuis et al [5] reported that hypertension developed more quickly in patients given a higher initial dose. We gave higher dose of Prednisolone in nine patients and none of them developed hypertension. For defining hypertension we followed the "Report of the Second Task Force on Blood Pressure Control in Children [14] .

Klement and Fishman[4] reported rebound growth when withdrawn of oral Prednisolone was too rapid. In each follow up we measured size of the lesion and in no patient (both group A and B) we found rebound growth after stoppage of treatment.

On the other hand, side effects and complications were noted in 36.3% patient of group B. The commonest complication with intralesional Dexamethasone was ulceration at injection site (27.3%). Only one infant out of twenty two (4.5%) developed hypo pigmentation of skin and another one infant (4.5%) developed repeated bleeding from injection site. Chantharatanapiboon [6] reported side effects in 9.1% to 16% patient who were treated with intralesional Triamcinolone and commonest side effect was ulceration and skin hypo pigmentation.

In this study we found that 71.4% children of group A developed side effects and in group B only 16.7% children developed side effects and complications which is statistically significant (p=0.017).

Conclusion:

Intralesional injection of Dexamethasone can be used like oral Preadnisolone for the treatment of smaller sized IHs. Side effect of oral Prednisolone is more in children than injection Dexamethasone. To get optimum response, both Prednisolone and Dexamethasone should be used in patients below one year of age. Unlike oral Prednisolone, injection Dexamethasone is free from systemic side effects.

Recommendation:

Intralesional Dexamethasone is preferable to oral Prednisolone in small IH in infants.

References:

1. Smithers C.J, Fishman S.J; Vascular Anomalies . In: Holcomb G.w. lll, Murphy J.P (eds). Ashcraft's Pediatric Surgery, 5th edn (2010) Saunders Elsevier, pp. 982-985.
2. Marchuk D.A, Pathogenesis of hemangioma. The journal of clinical Investigation 2001; 107(6).
3. Mabeta Peace and Pepper Michael S, Hemangiomas-current therapeutic strategies, The International Journal of Developmental Biology . 55: 431-437 doh: 10. 1387/ijdb.103221pm, published online: 27July 2011.
4. Klement G & Fishman S.J, Vascular Anomalies :Hemangioma and Malformations .In :Grosfeld

JL,O'Neil JA Jr.,Fonkalsrud E.W, Coran A.G(eds) Pediatric Surgery ,6th edn (2006).Mosby Elsevier,Philadelphia,pp. 2094-2106.

5. Nieuwenhuis Klaske, Laat PeterC.J, Janmohamed sherief R, Madern Gerard C , Oranje Arnold P. Infantile Hemangioma :Treatment with Short Course Systemic Corticosteroid Therapy as an Alternative for Propanolol. Journal of Pediatric Dermatology 2013;30(1): 64-70.
6. Chantharatanapiboon W. Intralesional Corticosteroid Therapy in Hemangiomas: Clinical Outcome in 160 cases. J Med Assoc Thai 2008; 9 (Suppl 3): S90-6; viewed 20 May 2011from medassocthai.org/journal
7. Gangopadhyay A.N, Sharma S.P, Gopal S. C, Gupta D.K,Panjawani K, Sinha J.K. Local steroid therapy in cutaneous hemangioma. Indian Pediatrics 1996; 33-January.
8. Saleh K.H, The steroid benefit in treating complicated Hemangioma. Indian Journal of Plastic Surgery 2009;42(2): 242-244 viewed 7 July 2011 from http://www.nebi.nlm.nih.gov/pmc/articles/pmc 2845373
9. Peralta R.J, Glavas I.P. Review of Capillary Hemangioma. EyeNet 2009; viewed 7 July 2011 from http://www.aao.org/publications/eyenet/200902/pearls.cfm.
10. HTML color codes and names viewed on 13 January 2013 from http://www.computerhope.com/htmcolor.htm
11. Cincinnati Children's Hospital Medical center, Hemangioma and Vascular Malformations Conditions and Diagnoses; viewed 20 May 2011 from http://www.cincinnatichildrens.org/health/info/vascular/diagnose/hema..
12. Azizkhan R. What is new in the Management of Hemangioma. Power point presentation in the 1st global congress for consensus in Pediatrics and child Health 17th-20th February 2011.
13. Children's Hospital of Wisconsin. Infantile Hemangioma and hemangioma treatment. viewed 7 July 2011 from http://www.chw.org/display/ppf/DocID/ 28482/router.asp;
14. Report of the Second Task Force on Blood Pressure Control in Children- 1987. Pediatrics. 1987;79:1. Gearhart J.P, Rink R.C,Mourriquand P.D.E. (ed.) p. e10