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Original Article

COMPARISON BETWEEN THE EFFECTS OF PROPRANOLOL VS PREDNISOLONE VS PREDNISOLONE WITH PROPRANOLOL IN THE MANAGEMENT OF INFANTILE HEMANGIOMA

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Abstract

Background: Infantile hemangiomas are the most common soft tissue tumors in infancy, Systemic pharmacologic intervention is necessary for endangering, ulcerating, problematic, or life-threatening IHs . These include oral corticosteroid therapy as first-line treatment and interferon -alfa or vincristine as second- or third-line therapeutic agents. Since 2008, use of propranolol has come to the forefront because of its efficacy & minimal side effects.

Aims and Objectives: The purpose of this study was to compare the efficacy of orally administered propranolol versus prednisolone versus both in the treatment of potentially disfiguring or functionally threatening infantile hemangiomas.

Material and Methods: A prospective study of 24 patients aged 1 week to 12 years child with infantile hemangiomas was randomized into three equal groups. These were as follows: A, Propranolol (1–2 mg/kg/d); B, Prednisolone (1–2 mg/kg/d); and C, receiving both for a minimum duration of 3 months. Dimensions, color, consistency, ultrasonography, photographic documentation based on Visual Analogue Scale (VAS) were recorded before and periodically after starting treatment. A minimum 75% improvement was considered as success with no regrowth up to 1 month of stopping treatment.

Results: Mean initial response time (days) in A (4.0 ± 3.3 SD) and C (4.5 ± 3.4SD) was significantly lower than B (8.79 ± 7.8SD) Significant change in consistency was noted very early in A (24 hours) compared to B (8days) and C (6 days). VAS results are as follows: (a) color fading—significant reduction in A within 48 hours compared to B and C (b) flattening—more significant and earlier in A and C than B ,and (c) mean reduction in size: significant in A and C at 3 months), 6 months whereas in B, it was seen only at 6 months.

Conclusions: Though it's a ongoing study, only result of 24 patient had been analysed. Propranolol had a consistent, rapid therapeutic effect compared to prednisolone. A combination of the two had a comparable but not higher efficacy than propranolol alone. Prednisolone was associated with a higher number of complications, thereby decreasing patient compliance.

Key words: Infantile hemangioma; Propranolol; Prednisolone.

Introduction

Infantile hemangiomas (IHs) are benign tumors of the endothelium. Infantile hemangiomas (IHs) are the most common soft tissue tumors in infancy, occurring 4% to 10% of children under 1 year of age.[1]The incidence is lower in dark-skinned babies. There is a female-to-male preponderance of 3:1 to 5:1.[2] Extremely-low-birth-weight infants (<1000 g) have the highest incidence of IHs, approaching23%.[3] Additional risk factors include advanced maternal age, multiple gestations, and placental abnormalities.[4] Infantile hemangiomas have a unique and characteristic life cycle of rapid growth in the first year of life (proliferative phase) followed by spontaneous slow regression from ages 1 to 7 years (Involuting phase). During the proliferating phase, there is rapid growth of the tumor which typically lasts until 10 to 12 months of age. By 5 years of age, 50% of tumors have completed involution, which increases to 70% at 7 years of age. There is often continued gradual regression of the color and bulk of the tumor until 10 to 12 years of age.[5] Median age of onset is 1 to 2 weeks. Superficial hemangiomas are red; deeper lesions may be noted later as a blue mass visualized through the skin. Around 12 months of age, growth of the IH plateaus,

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marking the beginning of the involuting phase. Over the next 6 to 7 years, the crimson color fades, the center becomes pale, and the lesion appears to deflate.[6] Once involuted, they never recur. IHs most often occur as a cutaneous lesion (80%)with a predilection for the head and neck (60%), trunk(25%), and extremities (20%).[7].Multiple tumors are present in up to 20% of patients and, when present may signal involvement of extracutaneous organs such as the liver or gastrointestinal (GI) tract.[8] The occurrence of multiple IHs is called hemangiomatosis. The proliferating phase of hemangioma is characterized by angiogenesis in the tumor. The tumor is composed of plump, rapidly dividing endothelial cells, forming a mass of sinusoidal vascular channels. Enlarged feeding arteries and draining veins vascularize the tumor.[9-11]

The exact etiology and pathogenesis of IH remains to be elucidated. There is emerging evidence for an endothelial stem/progenitor cell as the cellular origin of hemangioma.[12-14] Some studies suggest a population of resident angioblasts, arrested in an early stage of vascular development, as a source. Hemangioma endothelial cells may be of placental origin. Disruption of the maternal-fetal barrier may allow an embolic nidus of placental endothelial cells to reach fetal tissues through the permissive right to left shunt of fetal circulation.[15] The majority of infantile hemangiomas do not require any specific treatment other than observation and reassurance of the parents. Systemic pharmacologic intervention may be necessary for endangering, ulcerating, problematic, or life-threatening IHs.

These include oral corticosteroid therapy as first-line treatment and interferon - alfa or vincristine as second- or third-line therapeutic agents**.** Corticosteroids inhibit the vasculogenic potential of hemangioma-derived stem cells, as well as the expression of vascular endothelial growth factor.[16] Since 2008, use of propranolol has come to the forefront because of its efficacy & minimal side effects. The mechanism of action for propranolol is unknown; theories include vasoconstriction of the tumor vasculature or downregulation of angiogenic proteins.[17-19] Other treatment options are embolic therapy, laser therapy & surgical therapy.

Materials and Methods

We are conducting a prospective comparative study with the intention to include 90 purposively selected patients of 1 week to 12 years of children with infantile hemangioma in the Department of Pediatric surgery, Dhaka Medical College Hospital (DMCH), Dhaka, over a period of 18 months from March, 2014 to September, 2015. The patients are going to divided into 3 groups by random sampling- Group A received Propranolol alone, Group B received Prednisolone alone and Group C received a combination of both. Ten patients were included in each group. Random sequence was generated using a computer program in a 1:1:1 ratio. The following were excluded: uncomplicated lesions of trunk, extremities; presence of heart disease, cardiac. arrhythmia; bronchoobstructive disease; history of hypoglycemia; diabetes mellitus; hypertension; hypotension; liver failure;; visceral lesions and prematurity. Informed written consent from parents or legal guardian is taken after describing the study objectives. Ethical clearance has been sought from the Ethical Committee of Dhaka Medical College.

The drug protocols used in the three groupswere as follows:

- Group A: Tab Propranolol (10mg & 40 mg tab.)- Given at a starting dose of 1 mg/kg per day, in two divided doses and increased to 2 mg/kg/d on the second day. Blood pressure, heart rate and blood glucose will be monitored 1 hour after the first dose and 4 hourly thereafter during the first 24 hours of treatment and then at 48 hours
- Group B: Commercially available Prednisolone will be started at 2 mg/kg/d in the morning doses after feed.
- Group C: This group will receive a combination of both the drugs as per above protocol.

Treatment was initiated during a short hospitalization of48 hours. At inclusion, each lesion was evaluated clinically for size, color, and consistency. Lesions were categorized into superficial, mixed and deep according to the depth measured on ultrasonography (USG). The maximum diameter in two axes perpendicular to each other was measured. The lesion was photographed with and without flash with a standard 5- megapixel digital camera at 30-cm distance and approximately 2-Mb resolution. Electrocardiographic (ECG) evaluation was done to rule out treatment contraindications. Clinical assessment with measurements and photographs was repeated at 24 and 48 hours of starting treatment. Measure of assessment for color and size was based on Visual Analogue Scale (VAS) ranging from “10 to

+10 by comparing follow-up images to the baseline photograph pretreatment. Here, 0 represented the baseline photograph, a decrease resulting in a minus number and an increase in + number. Measurements were available at time points 0, 1 day, 2 days, 1 week, 1 months, 3 months. The images were evaluated by two independent blinded examiners who scored the improvement as: 0–24%, 25%–49%, 50%–74% and 75%–100%. Treatment was considered complete when (a) normal skin color was achieved, (b) VAS reduction was N75% with residuum and (c) there was no regrowth until 1 month of stopping treatment.

Primary outcome measures are as follows

(a) Clinical evaluation: assessment of healing, change in consistency and geometric measurements

(b) Change in VAS based on clinical photographs

(c) Parental satisfaction

Results

Total 24 patients are studied till now. No detailed statistical analysis is done yet. The overall male/female ratio was 2:3 (A 1:1, B 2:3 and C 1:2). Mean initial response time (days) in A (4.0 ± 3.3 SD**)** and C (4.5 ± 3.4SD) was significantly lower than B (8.79 ± 7.8SD) Significant change in consistency was noted very early in A (24 hours) compared to B(8 days) and C (6 days). VAS results are as follows: (a) color fading—significant reduction in A within 48 hours compared to B and C (b) flattening—more significant and earlier in A and C than B ,and (c) mean reduction in size: significant in A and C at 3 months), 6 months whereas in B, it was seen only at 6 months.

Table-I

Comparison of mean initial response time between the study subjects

	A (Propra-nolol)	B-olone) (Prednis	C (Combin-ation of A & B)
Mean initial response time	4.0 ± 3.3 SD	8.79 ± 7.8SD	4.5 ± 3.4SD

Table-II

Change in consistency

	A (Propra-nolol)	B-olone) (Prednis	C (Combin-ation of A & B)
Change in consistency	1 day	8 days	6 days

Discussion

The overall objective of this study is to evaluate the effectiveness of a single drug(Propranolol vs Pednisolone)vs combined drugs Propranolol with Prednisolone in the management of infantile hemangioma. We have planned to conduct a prospective comparative study with the intention to include 90 purposively selected patients of IHs in the Department of Pediatric surgery, DMCH, over a period of 18 months from March, 2014 to September, 2015.. Our hypothesis is combination of two drugs (Prednisolone and Propranolol) is more effective than a single drug(Prednisolone or Propranolol) in management of infantile hemangioma. To date from the data we have realized it is very hard to comment on this topic due to very small sample size. Data regarding comparative efficacy of steroid and propranolol and effect of single versus combination of two drugs are inadequate in spite of the high incidence of IHs. Effectiveness and side effect profile appear more favorable with propranolol compared to prednisolone alone or in combination. Prednisolone is associated with a higher number of complications like Cushingoid features, GI upset, regrowth and infection, thereby decreasing patient compliance**.**

Conclusion

This is an on-going study. Definite conclusion could not be drawn at this preliminary stage. Data regarding comparative efficacy of steroid and propranolol and effect of single versus combination of two drugs are inadequate in spite of the high incidence of IHs. Although we are doing a prospective randomized study, we acknowledge the limitations of our study. The relatively small sample size of our groups due to shorter study period may limit the inferences. So the final comment can only be made after proper analysis and interpretation of all the data obtained at the conclusion of the study. To confirm and elevate the reliability of the present results, more extensive clinical studies may be required**.**

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