Combined Therapy of Mixed Hemangiomas with Systemic Beta-Blockers and Pulsed Dye Laser

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ABSTRACT

Background*: Due to deep and superficial parts of mixed hemangioma have different characteristics the clearance may be slow or incomplete in response to pulsed dye laser (PDL) alone or propranolol alone.* ***Methods****: sixty patients presented with mixed hemangiomas treated by oral propranolol at a dose of 2 mg/kg body weight per day combined with pulsed dye laser 5-7Jcm^2 over a 6-9 months period. The Treatment outcomes were clinically evaluated.* ***Results:*** *The combined therapy shows changes in color and softening of the hemangioma, followed by regression of their sizes. The clinically elicited color changes have been objectively proven by statistically significant color clearance ($p \leq .001$). Moreover, the softening of lesions followed by the clinically elicited regression of sizes has been objectively proven by statistically significant changes at lesions' thickness ($P \leq .01$) (>50% regression).* ***Conclusions:*** *Collectively, high efficacy and tolerance of combined treatment have been elicited.*

INTRODUCTION

Hemangioma is the most common benign tumor of infancy. It affects 5% to 10% of all infants and up to 30% of premature infants with a clear female predominance [(1)]. The natural history of this benign tumor is unique. Most hemangiomata usually appear during the first few weeks of life, despite of approximately 30% of lesions do present since birth [(2)]. The natural history of hemangioma shows a proliferation during the first year of life and then involutes during childhood period. This two phase history is mandatory to clinically distinguish hemangioma from vascular malformations that neither proliferate nor involute [(3)].

By the end of the first year of life, an overlap from proliferation to involution is gradually elicited, when hemangioma is gradually changing from the predominantly cellular into the predominantly vascular nature.[(4)] This change continues with progressive deposition of perivascular fibrofatty tissue, abundant mast cells, and less active endothelial cell. Several hypotheses, including the possible somatic mutation in vascular endothelial growth regulatory pathways, have been put forth concerning the process of hemangiogenesis [(5)].

Blood vessels are formed by two processes, (vasculogenesis and angiogenesis). The regulating mechanisms for both are not fully understood yet; however, several regulators have been postulated including the role of the vascular endothelial growth factors (VEGFs) and basic fibroblast growth factor (bFGF). Also mesenchymal stem cells were recognized as a novel cellular constituent in hemangioma that may contribute to the process of adipogenesis during involution of hemangioma [(6)].

The clinical aspect of hemangiomas varies according to its depth hence hemangiomas are divided into superficial, deep and mixed types. The superficial hemangiomas involve the superficial layer of the dermis and they are clinically seen as elevated, well-limited and bright red lesions surrounded by normal skin and poorly compressible upon palpation. The deep hemangiomas affect the deep dermal layers and the subcutaneous tissue, thus sparing the papillary dermis. They present as skin color or bluish, compressible nodules, and they can present telangiectasias in their surface and drainage vessels in the peripheral areas [(7)].

Given the wide spectrum of disease and the natural tendency for involution, the greatest challenge in caring for infants with hemangiomas is predicting which infants need treatment or are at highest risk for complications [(8)]. Non-intervention continues to be the mainstay of therapy for most uncomplicated hemangiomas, as spontaneous involution is the rule. When a hemangioma poses primarily cosmetic concerns,

therapeutic intervention must be tailored on an individual basis. Although the final outcome of most hemangiomas cannot be predicted, lesions in certain locations are at greater need for early interventions such as the head and neck area [(9)]. Standard treatment options for hemangioma include the use of drugs that can be used systemic or as intralesional injections e.g. corticosteroid, interferon, and vincristine. Each of these treatment options has its restrictions and/or side effects [(10)].

Since the serendipitous accidental and innovative observation by Léauté-Labrèze et al, the use of propranolol for treatment of hemangioma has become a subject of extensive investigations [(11)]. Propranolol is a pure selective β-adrenergic antagonist, which competitively inhibits β1- and β2-adrenoceptors with the same affinity. On account of its lipophilic properties, propranolol also exhibits certain membrane-stabilizing characteristics. Herein, current hypotheses of how propranolol interferes with endothelial cells, vascular tone, anangiogenesis, and apoptosis to induce early, intermediate, and long-term effects of propranolol on hemangioma have been postulated [(12)].

Laser treatment of hemangioma with the pulsed dye laser (PDL) is effective and may be the treatment of choice for superficial cutaneous hemangiomas. In contrary hemangiomas with a deep component do not benefit from PDL treatment because the efficacy of the PDL is limited by its penetration depth through the tissues. Furthermore, early therapeutic intervention with the PDL may not prevent proliferative growth of the deeper or subcutaneous component of the hemangioma despite early intervention [(13)]. The combination of PDL and systemic drugs seem to be a safe and effective therapy, and results in a better clinical responses in the treatment of mixed hemangiomas than PDL therapy alone [(14)].

Although during the past five years many authors around the world publish their studies about the use of propranol as a sole treatment of hemangiomas. Combination studies between beta-blockers and PDL are lacking. This randomized clinical trial was carried out to assess the possible better therapeutic responses to propranolol combined with PDL treatment of mixed hemangiomas lesions.

PATIENTS AND METHODS

This study was conducted in the surgery outpatient clinic at laser institute, Cairo University, Between December 2012 and February 2015.

Sixty patients with haemangiomas at different body regions were included in the present study; mixed hemangiomas were only included the other types excluded. Every patient was subjected to a thorough history talking and physical examination. Parents were thoroughly given a complete discussion about how hemangiomas grow in stages, possible treatment modalities and side effects. After written informed consent had been obtained from the parents, oral propranolol combined with pulsed dye laser treatment were started. Infants with cardiovascular disorders contraindicating propranolol use, family history with regard to atopy, or recent/repeated outbreak of wheezing, low-birth weight newborns especially with decreased energy intake were excluded from the present study.

Propranolol was given at a dose of 2 mg/kg body weight per day in three divided doses. Treatment was given at home and child was reevaluated after a week, two weeks, and then every month. Clinical evaluation including photo-documentation was carried out before starting treatment, as well as at each monthly follow-up visits. Monitoring of treatment compliance and tolerance, as well as measuring of body weight for dosage adjustment were done at each monthly evaluation.

Flashlamp-pumped pulsed dye laser FPDL (Cynergy^{TM} vascular workstation, Cynosure,MA, USA) was used, it is a Class IV laser. The used fluence ranged from 5-7 J/cm^2. The pulse duration was 450 – 1500 μsec, with spot sizes of 5 and 7 mm. It was used for the treatment of superficial component of proliferating, mixed lesions. The applied fluence on the second and the following treatment sessions depended on the result of the first testing treatment session. Treatment was done with pulses overlapping up to 10%. Surface cooling was carefully maintained all through the treatment sessions. Immediately after treatment, the treated area turned bluish, with surrounding erythematous flare; this took 7 to 14 days to resolve. After treatment, the treated areas were covered with antibiotic ointment. In case of blistering or crusting, patients' parents were

instructed to cleanse the area with povidone-iodine solution. Furthermore, we instructed parents to keep their children's fingernails short or to have the children wear gloves to avoid trauma to the treated areas.

The objective of combined treatment was to inhibit further growth of the lesions or even to induce regression in their size. Treatment was continued until the objective goals were obtained or no further improvement could be achieved.

Clinical Evaluation

Regression in the size of mixed hemangiomas were clinically assessed by an independent physician. It was evaluated according to 0 – 100% scale. An excellent response denotes 76 – 100% regression. A good response denotes 51 – 75% regression. A fair response denotes 26 – 50% regression. Finally, a poor response denotes ≤25% regression. Continued growth, post-treatment complications and/or relapse of growth were also reported. Finally, all infants were followed up for up to 6 months after cessation of the combined laser and propranolol treatment.

Colour changes of superficial component of mixed hemangiomas were digitally analyzed using Adobe Photoshop 6.0 ME Software (Adobe System Incorporation, USA). The following equation was used to objectively evaluate the colour clearance after treatment to minimize the possible artifacts during photodocumentation.

Colour Clearance (%) =

(A – B ÷ A × 100) – (C – D ÷ C × 100)

A and B represent the numerical colour values of identical areas of hemangiomas at pre- and post-treatment photographs, respectively; whereas, C and D represent the numerical colour values of an identical area of normal skin at pre- and post-treatment photographs, respectively.

Statistical analysis:

Results are presented in numbers, percentages, mean values ± standard deviation (SD), and ranges. Data were statistically analyzed using Student's t-test and statistical significance was set at $p \leq 0.05$.

RESULTS

This study was conducted for sixty infants and children with hemangiomas. The gender of patients showed female predominance as 42 (70%) patients were females whereas 18 (30%) were males with ratio 3:1. Consanguinity was positive in 5 patients (8.3%) and positive family history was seen in 7 patients (11.6%). There were 32 (53.4%) hemangiomas that appears shortly after birth while the other 28 (46.6%) hemangiomas were congenital because the parents confirms it starts small red area since birth then gradually grows. Lesion multiplicity was seen in 14 (23.4%) patients.

The mean±SD age at the start of treatment 6.5 ± 4.93 months (range, 1.5 – 22 months) while mean±SD age at end of treatment was 13.03 ± 5.69 months (range, 7 – 30 months). The mean±SD duration of Treatment was 6.53 ± 0.75 months (range, 5 – 8 months).

Nine infants (15%) had previously received corticosteroid treatments with no response. Corticosteroid treatments were already discontinued before the infants were enrolled in the present study. None of the enrolled infants has been a candidate for interferone or vincristine treatment.

The data presented in this study is for the sixty patients continued and completed all treatment courses. The types of their hemangiomas were deep in 13 (21.6%) hemangiomas and mixed with both deep and superficial part in 47 (78.6%) hemangiomas. The sites of hemangioms on the different body locations was distributed as follows: Scalp 8 (13.3%), Face 31(51.6%), Trunk 5 (8.3%), Upper limbs 7 (21.6%), Lower limb 5 (8.3%), and anogenital 4 (6.6%). Most of the parents seek treatments due to cosmetic disfigurement of the hemangiomas only few complained about ulceration or obstruction

FPDL was used at a mean of 5.15±0.8 sessions (range, 4-7 sessions) and a mean fluence of 6.55±0.37J/cm^2 (range, 5-7J/cm^2).

Mixed hemangiomas have elicited dramatic colour changes primarily from intense red to purple colour, followed by a progressive lightening of the lesions' colour (Fig. 1). This clinically-based colour changes on treatment could be objectively proved by the statistically significant colour clearance ($p \leq 0.001$). According to the red colour clearance equation used in this study the mean±SD numbers of the red colour abstracted from adobe before treatment was 153.2 ± 21.7 (171.5 – 103.7) that was decreased significantly (p-Value≤0.001) after treatment to mean±SD of 41.6 ± 13.2 (57.3 – 18.9) the percent of red color reduction is 72.6%.

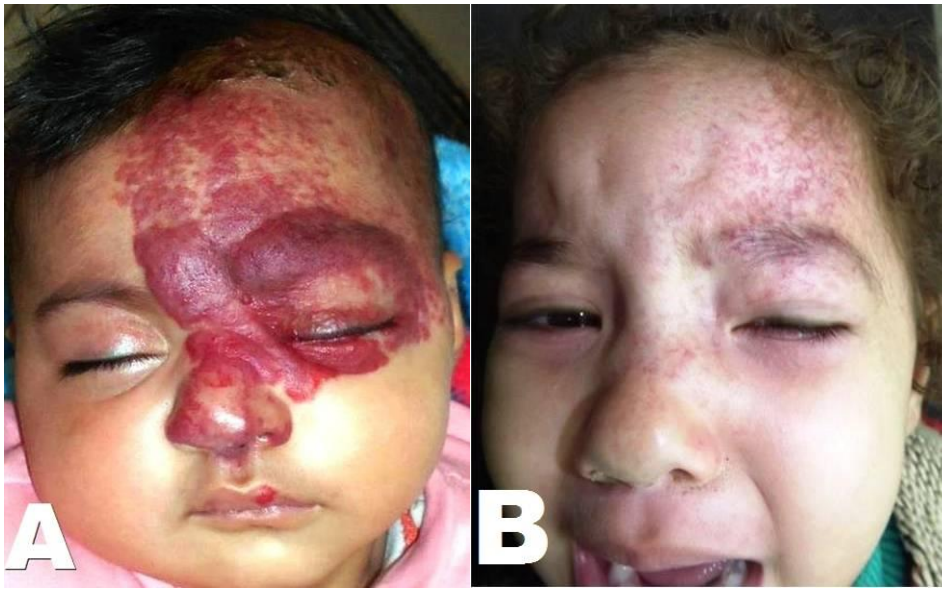

Fig. (1): Frontal view for a patient with mixed hemangioma at the forehead, glabella, and nose. (A) before treatment and (B) after treatment and 11 months period of follow up.

Softening of the lesions on palpation, followed by noticeable regression of their sizes could be elicited after propranolol treatment of mixed hemangiomas (Fig. 2). These clinically-based changes in the lesions' sizes under treatment could be objectively proved by the statistically significant changes at lesions' thickness ($p \leq 0.01$) (~ 50% regression). Regression of The Size was excellent in 40 (66.6%) patients, good in 15 (25%) patients and Fair 5 (8.3%) there was no single case showed poor or no Response (Fig. 3).

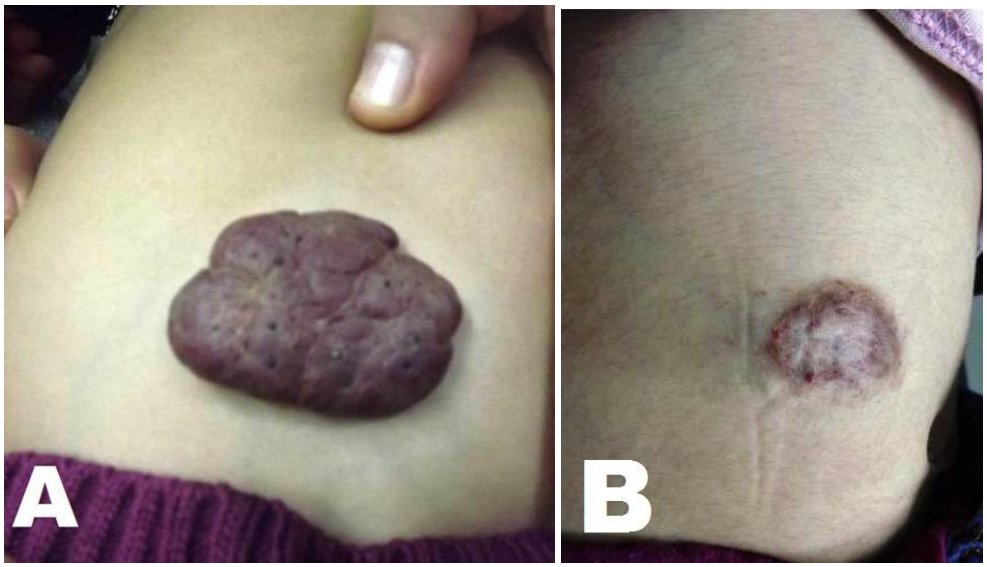

Fig. (2): Frontal view for a patient with mixed nemangioma at the abdomen. (A) before treatment and (B) after treatment and 6 months period of follow up.

Collectively, the clinically-elicited colour changes and sizes' regression proved by the statistically significant changes at the lesions' thickness ($p \leq 0.01$), as well as by the statistically significant change on clinical examination could be noticeable in the superficial components and deep components of mixed hemangiomas. Such appropriate results could be indeed noticed accompanied by satisfactory cosmetic and functional outcomes with early spontaneous ocular opening and healed painful ulcerations. On cessation of propranolol treatment and follow-up period, the hemangiomas had become nearly flat. However, few expected self-limited adverse effects were noted after propranolol treatment. These included persistence of residual skin telangiectasias in 6 lesions (7.50%), mild residual and/or recolouration in 5 lesions (6.25%), epidermal atrophy in 2 lesions (2.50%), self-limited ulceration in 1 lesion (1.25%), and residual fibrofatty tissue in 10 lesions (12.50%). Finally, mild and slow regrowth was elicited in 2 lesions (2.50%), where propranolol treatment was found to be needed to be administered again at 8 and 10 months of age.

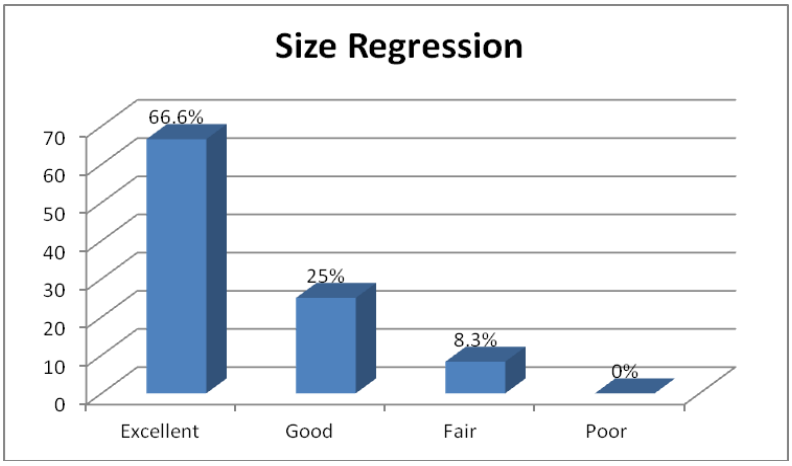

Fig. (3): Shows the percent of regression of hemangiomas

DISCUSSION

Although the hemangiomas involute in most cases the results are unpredictable and incomplete, and the time taken is not definite. This may make parents more anxious; hence, treatment is needed. Till now there is no way to predict the size that proliferative hemangiomas can reach as well as to expect rate of involution and complication [(15)]. Current practice dictates that most hemangiomas should be left untreated conversely, the unpredictable outcome after proliferation and the associated psychologic trauma is why intervention is frequently indicated[(16)]. Intervention should be tailored for each hemangioma individually because it depends upon its stage (proliferating or involuting), and its type (superficial, deep, or mixed) [(17)].

The most common form of Medical therapy used was corticosteroids in different forms: Systemic, topical or Intralesional. Interferon, vincristine or cyclophosphamide have been used in rare cases in which the hemangioma fails to respond to treatment with corticosteroids. Early surgical intervention is used in cases in which the condition has the potential to affect patients' self-esteem. Cryosurgery is more effective when performed in older children and in small lesions. Sclerotherapy is indicated for some deep hemangiomas. Different types of laser may be used in the management of hemangiomas, including argon, CO_2, Nd:YAG and, dye laser. Each of aforementioned therapies has its risk of serious side effects [(18)].

Undoubtedly, the most exciting development in the treatment for hemangiomas over the last few years has been the serendipitous discovery of

propranolol's inhibitory effects during the proliferative phase of the hemangioma[19].

Nearly all published reports of propranolol as single-agent treatment describe favorable outcomes, albeit with variable definitions and degrees of success. Pulsed dye laser treatment, used for many years as a safe and effective option concurrently administered combination treatments for IH have occasionally been used so it was the motive to evaluate the efficacy and tolerance of this combination treatment of a relatively larger series of hemangiomas in the present study.

The possible mechanisms of action of propranolol include vasoconstriction, inhibition of angiogenesis, and induction of apoptosis, propranolol as β-adrenoceptor antagonist inhibits vasodilation mediated by adrenaline leading to vasoconstriction induces a reduction of blood flow within the lesions [20]. This vasoconstriction increases the efficacy of pulsed dye laser on the vessles and alone leading to early and long-standing clinically evidenced color changes and softening of superficial components of mixed hemangiomas on comination treatment in the present study.

Regarding angiogenesis, hemangiomas results from an imbalance between proangiogenic and antiangiogenic factors during proliferation, endothelial cells exhibit an increased expression of proliferating cell nuclear antigen, type IV collagenase, and proangiogenic factors, in particular, VEGF more than bFGF. Conversely, expression of VEGF and bFGF is significantly reduced during involution phase as well as in completely involuted hemangiomas[21]. Physiologically, hypoxemia leads to increased expression of VEGF. This effect was found to be mediated by the transcription factor hypoxia-inducible factor 1a. As a result, VEGF is secreted from the cell, diffuses into the surrounding tissue, and induces proliferation of adjacent endothelial cells, which, in turn, leads to secretion of proteases necessary for reorganization of matrix metalloproteinases, and the coordinated differentiation of vascular cells (endothelial cells, smooth muscle cells, pericytes) into functional vessels (angiogenesis)[22].

Conversely, propranolol as β-receptor blocker leads to a reduced expression of VEGF and, thus, to an inhibition of angiogenesis. Collectively, this antiangiogenic effect of propranolol could explain once more the early and long-standing clinically evidenced color changes of superficial components of mixed hemangiomas on propranolol treatment in the present study.

Regarding apoptosis, it was reported that during proliferation, hemangiomas express a low rate of apoptosis, whereas during involution of hemangiomas, apoptosis increases [23]. It was hypothesized that β-adrenergic antagonists are capable of disengaging the inhibition of apoptosis caused by β-adrenergic agonists, resulting into an increased apoptosis rate[20]. Accordingly, induction of apoptosis represents another possible mechanism of action of propranolol in the treatment of hemangiomas in the present study. This could explain softening of lesions, followed by the noticeable regression of sizes of deep hemangiomas and deep components of mixed hemangiomas that could be objectively proven by the changes of the thickness of lesions in the present study. Collectively, high efficacy and tolerance of propranolol treatment of hemangiomas have been elicited in the present study. The first noticeable effects on propranolol treatment were the changes in color with continuing brightening of the lesions as well as softening of the lesions, followed by regression of their sizes.

The clinically based color and size reduction after combined therapy has been objectively proven by the statistically significant color clearance ($P \leq .001$) within hemangiomas. Moreover, the clinically based changes in lesions sizes on combined treatment of deep hemangiomas and deep components of mixed hemangiomas have been objectively proven by the statistically significant changes at lesions thickness ($p \leq .01$) (~50% regression.

That is why the objective of treatment in the present study was to to induce regression in their size. In cases of early combined treatments in the present study, a considerable shortening of treatment course could be achieved especially for those lesions at proliferative phase than the reported course of treatment either for propranolol alone or dye laser alone [24].

However, stopping combined treatment before the age of 9 months results in relapses in the present study. This suggests that the optimal combined treatment must be continued until the age of 12 months to cover the entire proliferative phase. On the other hand, for late combined

treatments started after the end of one year, treatment should be continued until the no improvement has been achieved. The problem with oral propranolol treatment was has to be prepared from tablets dissolved to suitable smaller dosages, which may complicate dose adaptation and drug administration.

Deep or large hemangiomas are not suitable for pulsed dye laser treatment because of its limited penetration depth in tissues so the potential for growth to cause permanent complications still a defect in laser therapy [(25)]. On the other hand although propranolol treatment has improved outcomes but clearance frequently remains gradual, prolonged, or incomplete, and there are potentially serious risks of treatment[(26)]. For these reasons, Combination treatments may have potential benefits, including possibilities of greater efficacy, synergistic effects, and lower toxicity. Given that propranolol is a systemic drug with risks of hypoglycemia or cardiovascular effects, it combination with dye laser will lower propranolol dose and decreases the duration of therapy could lead to an improvement in the risk–benefit profile. Further and larger studies are warranted to investigate these important clinical questions

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