Efficacy of propranolol in infantile hemangioma

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Abstract

Hemangiomas, are the most common benign tumors of infancy. Despite their selflimited course, infantile capillary hemangiomas can cause local complications e.g. pain, ulceration, bleeding etc. The usual treatments include oral/intralesional steroids, alpha interferon, cytotoxins, pulsed dye laser and cosmetic surgery resection. These treatments are not free of multiple complications and toxic side effects. We report our experience with the use of propranolol in 2 children with haemangiomas along with review of relevant literature. Both the hemangioma cases promptly responded to low-dose oral propranolol.

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Introduction

Infantile Haemangiomas (IH) are the most common benign tumors of infancy, affecting 5-10% of all infant.[1] And up to 30% of premature babies.[2] They can be differentiated from vascular malformations by their dynamic growth and spontaneous regression. It is usually pinkish or reddish in color, present with a well defined mass, doughy feeling and compressible. It is a benign vascular tumor that appears soon after birth and usually involutes spontaneously within 6 years of age. A small number of IH can grow very large with destruction of surrounding tissue and organ and may become even life-threatening.[3] Infantile haemangioma is characterized by rapid proliferation during infancy (proliferative phase-12 months of age), followed by slow spontaneous involution (involuting phase up to 5 years with continued improvement up to 12-years of age (involuted phase).[4.5]

Although 85-90% of all IH eventually undergo spontaneous involution, they can still cause disfigurement and serious complications depending on their location (obstruction of airways and vision), size (cardiac insufficiency, hypothyroidism), and speed of regression, which can be associated with painful ulcerations and haemorrhage. Standard treatment options for complicated haemangiomas include oral steroids,, laser surgery, cryosurgery, or vincristine, interferon or cyclophosphamide in life-threatening cases.[6-8] Each of these options has its restrictions and/or side effects. In 2008, Leaute -Labre'ze et. described their serendipitous observation of an antiproliferative effect of propra-nolol on IH.[9] Propranolol has since then become the first choice of therapy for complicated 1H.

Case reports

Two girls, aged two months and six months, received propranolol for the treatment of haemangiomas. Parents provided informed consent in all cases. Thorough cardiologic (clinical examination, electrocardiogram and echocardiography) and respiratory evaluation were carried out prior to initiation of treatment. Additionally, all patients had full blood count, biochemistry profile, urine dipstick for glucose, abdominal ultrasonography. Parents were encouraged to feed their children frequently and anticipatory guidance was provided regarding symptoms and signs of hypoglycaemia, bradycardia and hypotension. In accordance to treatment protocols, the patients remained in hospital for 48 hours under close cardiorespiratory monitoring.[10] Propranolol was given every 8 hours with the dose of 2-3mg/kg/day.[3]

Case no-1

The first child, Tasnim 6 months of age had a large ulcerated and painful capillary hemangioma (Fig-1) on the lower part of the dorsum of the left hand and wrist extending to fingers below and lower part of the forearm above encircling almost whole circumference. At first mother noticed a small pink colored lesion on the dorsum of the left wrist on the 3rd day of baby's birth. It became very rapidly increasing in size, and rose from skin surface. Central necrosis and ulceration

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developed. The baby was clinically evaluated having no other congenital anomalies or heart disease. Further evaluation with imaging e.g.

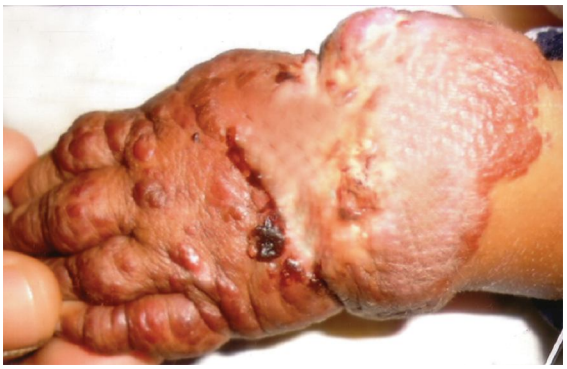

Figure-1. Before propranotol therapy (Case 1)

ultrasonography and echocardiography was done to exclude visceral hemangiomas and cardiac problems. Parents were duly counseled and admitted in the pediatric surgery ward in Khulna Medical College Hospital on 04/10/14 for close monitoring while initiating propranolol therapy. We started with propranolol 2 mg/kg body weight.

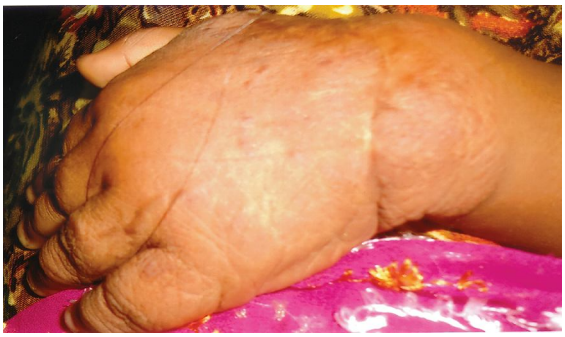

Figure-2. Six months after propranotol therapy (Case 1)

Oral antibiotics cephradin was given to control infection of the ulcerated lesion. Heart rate and blood pressure was monitored closely for 24 hours. On the third day of initiation of propranolol, the color of the lesion was changed from intense red to purple, and was softened. We discharged the child on the third day and advised to continue the drug in the same dose. When the child came on follow up visit one month later, the lesion was further reduced in size and almost flat. Six months later, we observed that the lesion completely disappeared (Fig-2). Propranolol was discontinued. The baby is still under follow-up.

Case no-2

The second child Baishakhi, two months of age, had a painful, ulcerated and discharging hemangioma on her left inguinal region. -Mother gave the history of a very small pink colored spot that appeared on the 3rd day of birth on the baby's left inguinal region. It was gradually increasing in size. On her 1st visit on 25/07/14, it was 4cm X 3cm in size (Fig. 4), raised, circular but irregular margin and compressible. Again, the baby was evaluated both clinically and with imaging studies. The patient was treated with propranolol.

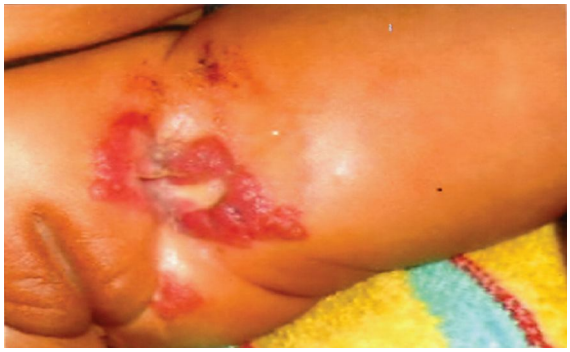

Figure-3. Before propranolol therapy (Case 2)

Antibiotics and pain killer was also added. On the third day after the initiation of treatment the hemangioma was changed from intense red to purple, and was softened. Pain and discharge became reduced. One month later, the surface of the lesion became flat and reduced in size (Fig-4). Treatment is being continued.

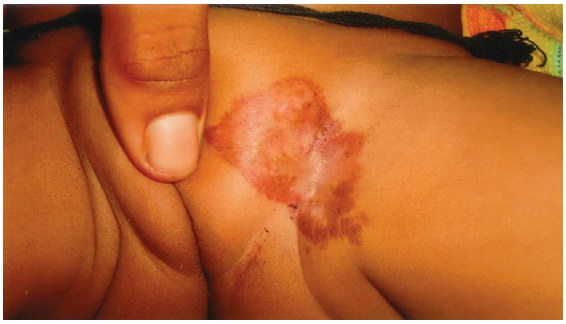

Figure-4. One month after propranolol therapy (Case 2)

Discussion

In order to increase consensus in the field and to provide guidance for the most appropriate treatment, the ISSVA (International society for the study of vascular anomalies 1996) classification categorizes all vascular anomalies in two major groups: (1) vascular tumor and (2) vascular malformations. Hemangiomas are vascular tumors that grow rapidly during the first year of life and usually regress spontaneously over 1 to 8 years of life. In contrast, vascular malformations are developmental defects resulted from failure of proper formation of vascular tree.[3]

Infantile hemangiomas are composed of a complex mixture of clonal endothelial cells associated with pericytes, dendritic cells, and mast cells. Regulators of hemangioma growth and involution

are poorly understood. During the growth phase, two major proangiogenic factors are involved: basic fibroblast growth factor (bFGF) and vascular endothelial growth factor (VEGF). Histologic studies have shown that both endothelial and interstitial cells are actively dividing in this phase-" The striking effect of propranolol on growing IH can be attributed to three molecular mechanisms: vasoconstriction, inhibition of angiogenesis and induction of apoptosis. They correspond to early (brightening of haemangioma surface), intermediate (growth arrest), and long-term (regression) clinical observations.[12]

Molecular processes in IH that may be affected by propranolol have recently been depicted. Control of vascular tone: Beta adrenergic agonists lead to vasodilation via release of NO. Conversely, beta-adrenergic antagonists like propranolol lead to vasoconstriction (through inhibition of NO synthesis and NO release). Angiogenesis: Beta-adrenergic agonists stimulate the synthesis of proangiogenic factors [growth factors (VEGF and bFGF) and matrix metalloproteinases (MMP-2 and MMP-9)] and activate proangiogenic cascades (ERK/MAPK cascade) thereby promoting angiogenesis. In contrast, beta blockers like propranolol lead to a down regulation of these proangiogenic proteins and to an inhibition of the ERK/MAPK cascade thus suppressing angiogenesis. Apoptosis: Beta-adrenergic agonists, inhibit apoptosis via src/MAPK. In contrast, beta blockers induce apoptosis.[12,14]

About 5% of cuteneous hemangiomas cause local complications such as hemorrhage, spontaneous epithelial breakdown, ulceration, and necrosis. Ulceration and necrosis may cause pain and may lead to scars that are difficult to repair. Obstruction of a vital organ and high output cardiac failure due to diversion of a large amount of blood can be fatal complications. Most of the hcmangiomas do not necessitate intervention. Only the deforming, destructive, obstructing lesions are treated with pharmacotherapy or resection.[3,15]

After getting written informed consent from the parents, propranolol was given to both the children. About 24 hours after the initiation of treatment, we observed a change in color of the hemangioma from intense red to purple; this change was associated with softening of the lesion. Both the patients were closely monitored hemodynamicaly. After these initial changes, the hemangiomas continued to improve until they were nearly flat. Both the patients are still under follow-up. In a study of five girls (age range 2 months to 12 years), oral propranolol with satisfying results. Researchers found no major side effect of the drug and all haemangiomas were begun to lighten shortly after onset of treatment.[13] Serial photographs of patients were taken during the course of treatment. Response rate in color and size of the lesions were the indicators of resolution. Both the patients were considered to show excellent response. No side effects of propranolol were noted.

Given the limitation of small number, further study is undertaken with larger sample size to find out the validity of the findings of the present study. Propranolol appears to be a very simple and cost effective for the treatment of infantile hemangioma.

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