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First Step Monotherapy with Lower Dosage of Propranolol at Complicated Infantil Hemangiamo

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Abstract

Hemangiomas are the most common tumors of infancy. They are mostly benign and self-limited however some with side effects such as ulceration, bleeding, massive growth, cosmetic disvisualities and disfunctions. The complicated hemangioma cases are commonly via ınvolvement face, airway, anogenital area, skin, periorbital and ear [1,2]. These cases frequently require treatment to prevent side effects and sustain well cosmetic outcomes.

Treatment protocols for infatil hemangiomas are still in research and there is no approved systematic theraphy. Previously oral steroids such us prednisolone considered to be effective in treatment approach for complicated infantile hemangioma however there are conflicts due to potential side effects, risk for variable response and diffuculties at follow up. There are some other options at monothearpy for infantil hemangioma like vinciristine, interferon alpha and cyclophosphamide while they seem unuseful of their severe side effects [3,4]. Also there is a review introducing propranolol plus dye laser concurrent therapy more effective while propranalol alone seem to be near-complete effective [5].

Propranolol as mono therapyat infantil hemangioma has been recently stuided in various series and mostly documenting good improvement responses [6]. Via these knowledge's in this study also we suggest propranolol as firstline therapy in infantil hemangioma cases.

Keywords: Infantil Hemangioma; Propranalol

Introduction

In infantile hemangioma; currently systematic or intralesional corticosteroid first step monotherapy is preferred in literature but side effects such as hyperthropic cadiomyopathy, arterial abnormalities, cardiac disorders, eye disorders, external genital malformations, lipomyelomeningocel, vesicarenal abnormarmalities, imperforated anus and high output heart failure can be in sight [7]. The other current treatment options for problematic hemangiomas include systemic or intralesional corticosteroids, chemotherapeutic agents (vincristine, alpha-interferon), laser, surgery, or a combination of these therapies [8,9]. Unfortunately, each treatment option has limited therapeutic benefit with its own side-effect profile and risks. Non-selectif beta-blocker agent Propranolol is being popular of being first step treatment in İnfantile hemangioma as its lower side effect profile and cost rates than other therapeutic options. Recently, Leaute-Labreze and colleagues reported the serendipitous finding that hemangiomas regress in newborns treated with propranolol, a known nonselective beta-blocker used in treating infants with cardiac and pulmonary conditions [10]. This finding has been supported by a few additional case reports [11,12]. In our study we presented two cases of infantil hemangioma treated with Propranalol. The first case with right frontal head localated 6*6*2 cm diameter circuler shaped hemangioma and the second case with first right gluteal located 2*2*0.5 cm diameter and the second upper sternal localated 4*4*1 cm diameter of hemangioma. Both two cases responded with involution and degradation in diameter and vascular shining. Although recent literature refers propranalol 3 mg/kg/ per day dosage for best response, in our study we refer 2 mg/kg/per day dosage with less side effect tendency and similar effectivity in infantil hemangioma treatment.

Case 1

13 month aged girl patient has applied to outpatient clinic of pediatrics with the complaint of hemorrhage and up growth of right frontal head localated 6*6*2 cm diameter circular shaped hemangioma. She complained of hemorrhage and ulceration when wear

up and take off clothes especially last 2 months. Medical history of patient introduced that the tumor is visible from birth to now and progressed in volume in time. The hemorragies started in last one month and ulceration occurred at once. At first examination a 6*6*2 cm diameter of hemangioma obtained bleeding mild so a local compression needed. On physical examination vital findings were in normal values. (Body temperature: 37,1, Blood pressure: 92/59 mm/hg, Pulse: 87/min.). Laboratory findings were WBC (white blood cell): 10, 87 /mm, Hb (hemoglobulin): 11,7 g/dl, TROMBOCYTE: 437000/mm. Electrocardiogram was in normal pattern and lung radiogram obtained normal either. Patient had hospitalized to evaluatethe medical therapy and to follow up local hemorrhage of cutaneous infatil hemangioma. Non-selectif beta blocker agent Propranalol with an oral dosage of 1mg/kg/day divided with two times a day (TID) was begun. In two day follow up vital findings were stabil so the dosage increased to 2mg/kg/day TID. The hemorrage of hemangioma was stopped by local compresions and after a three days hospitalizition; there was no side effect or markable complication. The patient diccharged and advised to continue Propranalol by 2mg/kg/dosage TID to 6 months. Per month the patient had examined of control tests including labaroutary tests and electrocardiogram. No marginal side effects of Propranalol obtained. After 6 months oral proranalol therapythe diameter and volume of the tumor regressed to 3*2*1 cm and the volume to its 2/3 volume similarly. Also vasculer shining and the complications especially hemorrage diminished. The Figure 1 shows the view of hemangioma after a 3 months oral propranalol therapy.

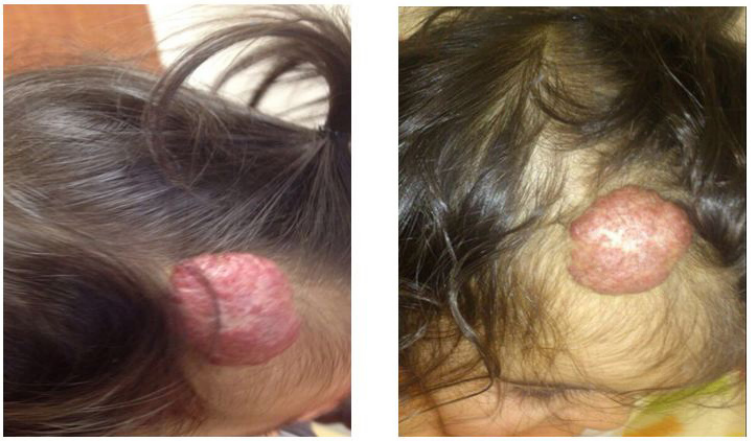

Figure 1: (A) Before the inition of thearphy; **(B)** After 3 months of oral poropranolol therapy, the involution and the degradation of vasculer shing is markable

Case 2

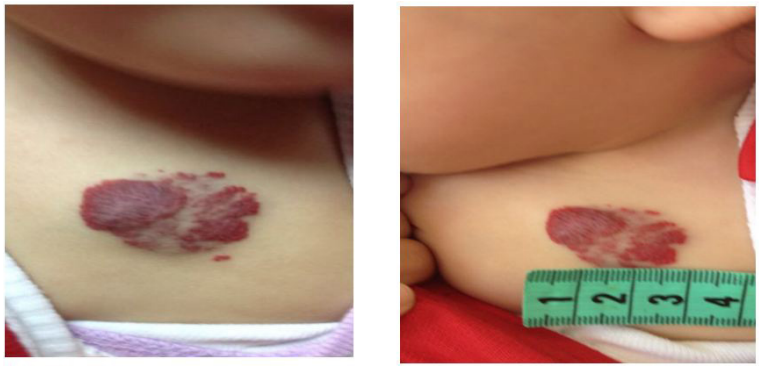

Figure 2: (A) Before the inition of therapy; **(B)** After 3 months of therapythe hemangioma diameter degraded from 4*4*1cm to 2,5*1.5*0.5 cm.

14 month aged girl patient has applied to outpatient clinic of pediatrics with the complaint of hemorrhage and up growth of substernal located 4*2*1 cm diameter separated hemangioma and a second one perianal located 3*3*1 cm diameter ciculer hemangioma. She complained of hemorrahage of sternal hemorrage when wear up and take off clothes and fidgetiness during defecation of perianal hemangioma. Medical history of patient introduced that the two tumors is visible from birth to now and progressed in volume and complicated in time. The hemorragies of sternal and perianal tumor increased in last weeks. At first examination a 4*2*1 cm diameter of sternal hemangioma obtained bleeding mild so a local compression and treatment needed. And perianal tümor 3*3*1 cm diameter circular hemangioma with no acute complication. But the lesion seemed fragil and tend to bleed. On physical examination vital findings were in normal values. (Body temperature: 36, 9, Blood pressure: 90/57 mm/hg, Pulse: 88/min.). Laboratory findings were WBC: 7,9/mm, Hb: 11,8 g/dl, TROMBOCYTE: 422000/mm. Electrocardiogram was in normal pattern and lung radiogram obtained normal either. Patient had hospitalized to evaluate the medical theraphy and to follow up local hemorrage of cutaneous infatil hemangioma. Non-selectif beta blocker agent Propranalol with an oral dosage of 1mg/kg/day divided with two times a day (TID) was begun. In two day follow up vital findings were stabil so the dosage increased to 2mg/kg/day TID. The hemorrage of hemangioma was stopped by local compresions and after a three days hospitalization; there

was no side effect or markable complication. The patient discharged and advised to continue Propranolol by 2mg/kg/dosage TID to 6 months. Per month the patient had examined of control tests including laboratory tests and electrocardiogram. No marginal side effects of Propranolol obtained. After 6 months oral propranolol therapy the diameter and volume of the sternal tumor regressed to 2, 5*1*0.5 cm and the volume to its 1/3 volume and the perianal tumor 2*1*0.5 cm similarly. Also vascular shining and the complications especially hemorrhage diminished. The fragile vascular view of perianal tumor turned to pale. The Figure 2 shows the view of sternal hemagioma after a 3 months oral propranolol therapy.

Discussion

Hemangiomas are the most common benign tumor in infancy [13,14]. Although the majority has little impact on childhood health, some head and genital hemangiomas can progress to problamatic state. These hemangiomas require intervention to control growth and complications to prevent functional and cosmetic deformities [2]. Propranolol was recently found to reduce the size of hemangiomas during the proliferative phase of development [10]. The mechanism of action and pathophysiology behind this discovery remains unclear. Theories suggesting that propranolol impacts hemangioma growth through the induction of apoptosis and anti-angiogenic activity are gaining support. Nevertheless, several case studies have further provided evidence of the dramatic effect of propranolol on massive, proliferating, life threatening, and involuting lesions [11,12,15].

Although propranolol has been used for several decades to treat hypertension, ischemic heart disease, arrhythmias, endocrine and neurologic disorders, and eye disorders; the safety and effectiveness in pediatric patients have not been established. Alternative treatments for alarming infantil hemangioma include systemic corticosteroids, vincristine, interferon alpha, cyclophosphamide, and surgical excision, therapies that all carry significant risks. We present two patients to report examples of the dosage needed and safety of usage of beta-blockers in the treatment of infantil hemangioma. Propranolol is the non-selective beta blocker. It antagonizes both b1 and b2 receptors equivocally [16]. These receptors when activated by epinephrine or norepinephrine result in a variety of actions in a wide variety of tissues. Responses have been much well-studied in adults than in children. In Liver, where glycogen phosphorylase is activated, and in heart where calcium influx and sequestration increase. When these receptors are blocked, effects including bradycardia, hypotension, and hypoglycemia may occur. Clinical signs of these adverse effects include lethargy, restlessness, difficulty breathing, and cool clammy skin, delayed capillary refill, and decreased appetite. Propranolol given orally shows significant first pass metabolism with peak absorption at 1-3 hours in adults. The half-life is reported between 3.5 and 6 hours in adults, but effects often last longer than predicted. The mechanism of action for beta-blockers in treating hypertension, ischemic heart disease, arrhythmias, endocrine and neurologic disorders eye disorders and also in infantil hemangioma is not clear. Propranolol's effects on placenta have been demonstrated when used to treat pre-eclampsia [17]. Perhaps beta-blockers induce apoptosis by antagonizing Glut-1 receptors or act through other pathways to inhibit growth of the infantil hemangioma. The pharmacologically optimal dosing interval for propranolol is every 6 hours, but compliance is easier if the medication is given every 8 to 12 hours. At our institutions, hospitalized infants receive a starting dose of 1mg⁄kg/day given at 12-hour (TID) intervals [18]. Vital signs and blood glucose are monitored 1 hour after each dose, corresponding with peak absorption time. If the first two doses are tolerated, the amount is doubled to 2 mg⁄kg⁄dose/day TID next 48 hours. This is the equivalent of 2.0mg⁄kg⁄day, the dose utilized in most patients by Leaute-Labreze *et al.* [19] Maximum daily doses of up to 5.0 mg⁄kg have been reported for infants with arrhythmias, but ratio of risk-to-benefit for higher doses is unclear for infants with infantil hemangiomas. Like in our cases the patients over 6 month of age we recommend a starting dose of 1 mg⁄kg with vital signs and blood glucose checked 1 hour after the first dose. If vital signs and glucose are stable, the dose is generally doubled every 2 days with monitoring after every dose increase. Recently; Przewratil *et al.* studied propranolol treatment in infantil hemangiomas may inhibit angiogenesis and induce apoptosis. To investigate this claim, they study to analyze the serum and tissue profiles of VEGF and VEGRR1/2 in patients treated with propranolol. As a result this studied referred only VEGF and VEGFR1 expression in mRNA studies may prove the proposed theory of antiangiogenic properties of propranolol. Other results will not confirm it and remain inconsistent with the fantastic clinical response to this medication [20]. In our cases we demonstrated at 2mg/kg/day dosage is safe in range to lower the even tissue and side effects and for most effectivity and rapid response to treatment more studies may be needed to identify in increased dosage safety ranges. Also after hospitalization, to provide treatment persistnace of families, prescribing physicians should educate parents and staff about the importance of continue therapy.

In our cases we demonstrated Propranalol of initially 1mg/kg/dosage with TID ın hospital and after 24 hours monetarizition of blood glucose, electrocardiogram and vital signs (blood pressure, pulse, saturation oxygen, body temprature per hour), 48 hours later dosage increased to 2mg/kg/dosage. On 4 day follow up there was no side effects obtained. The regimen planned to continue peroral 6 months treatment by 2mg/kg TID dosage and the patients discharged at 4th day. Every month the patient's lesions are noted in diameter showing regressions in tumors. İn this study we mainly present the details of a treatment protocol to minimize the risk of adverse events until additional data are available on safety and efficacy of propranolol in the treatment of infantil Hemangiomas.

Conclusion

Infantil Hemangiomas are the most common tumor of ınfants and previously the studies demonstrated the Propranalol mono therapies most simple, usable and cost effective option in the treatment options. Although recent literature refers propranalol 3 mg/kg/ per day dosage for best response, in our study we refer 2 mg/kg/per day dosage with less side effect tendency and similar

effectivity in infantil hemangioma treatment.

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