CASE SERIES

Use of propranolol in infantile haemangiomas: report of five cases and review of the literature

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Abstract

Infantile haemangiomas are common benign tumours that do not require treatment unless they cause significant functional impairment or disfigurement. We report our experience with the off-label use of propranolol in 5 children with haemangiomas and review the relevant literature. Hippokratia 2011; 15 (1): 81-83

Key words: haemangioma, propranolol, vascular anomaly, beta-blocker

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Infantile haemangiomas (IH) are the most common vascular tumours of childhood[1]. Usually their course is self – limiting. Albeit that, a significant minority requires treatment due to dramatic cosmetic impact or functional impairment[2]. The efficacy of propranolol for the treatment of IH was recently, serendipitously discovered by Leaute-Labreze et al[3]. Since then, there has been a great interest in this off-label use of propranolol[4]. In this paper, we report our experience with this novel treatment and review the limited literature available.

Cases' report

Five girls, aged two months to twelve years, 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 and ultrasonography of the IH treated. 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 other treatment protocols[5], patients remained in hospital for 48 hours under close cardiorespiratory monitoring; finger stick blood glucose was checked every three hours.

Propranolol was given every 8 hours, with an initial dose of 0.16mg/kg/dose per os. The second day the dose was doubled and the third day the full dose of 0.66mg/kg/dose per os was reached (total dose of 2 mg/kg/day)[6].

- **Case No 1 (Figures 1a & 1b)**

A four month old girl presented with a 6cm x 5cm large sharply-bordered red tumour with central ulceration of her right forearm. The mother reported that the lesion was barely evident at birth and that it grew rapidly in size and thickness since then. She also mentioned fre-

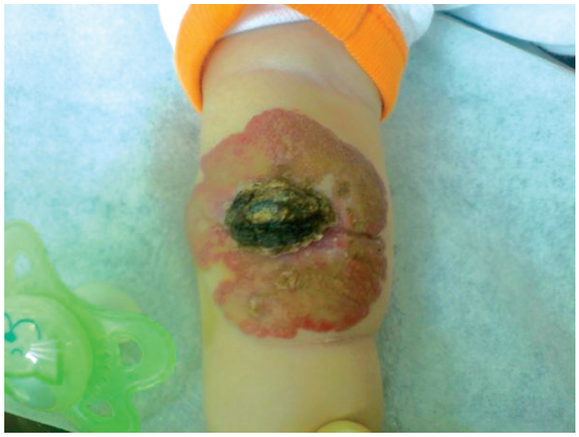

Figure 1a: Case No 1 prior to initiation of treatment with propranolol.

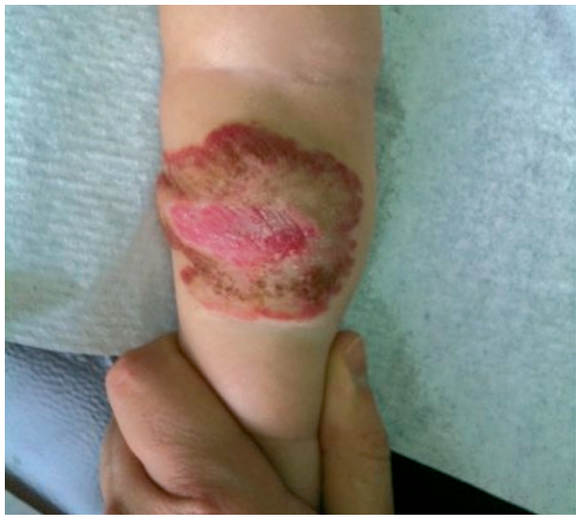

Figure 1b: Case 1 on the 2nd week of treatment with propranolol.

quent blood staining of the infant's clothes. Initiation of treatment with propranolol resulted in discolouration of the lesion, initially noted by the mother on day 2. The central ulceration healed rapidly and the lesion became flatter and decreased in size. She is currently on her 3rd month of treatment with no side effects and the plan is to gradually taper the dose over two weeks after a follow up ultrasound in 3 months time.

- **Case No 2 (Figures 2a & 2b)**

A seven month old girl presented with a 3 cm x 2.5 cm haemangioma of her right labium major. The mother

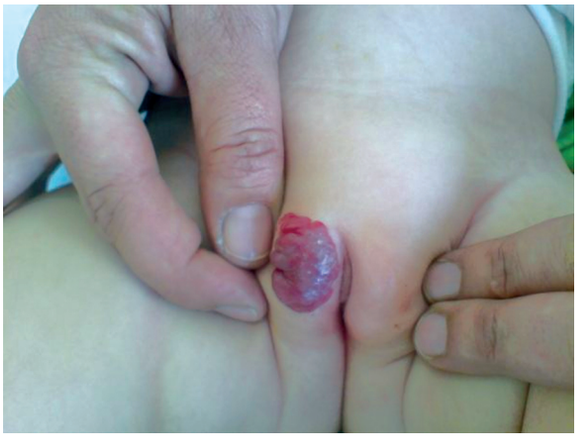

Figure 2a: Case No 2 prior to initiation of propranolol.

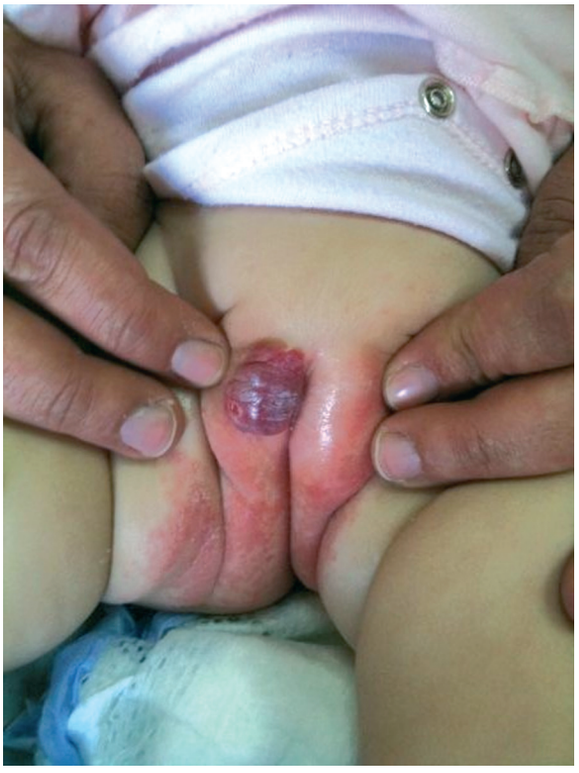

Figure 2b: Case 2 on day 15 of treatment with propranolol. The patient also had diaper dermatitis.

reported occasional bleeding and was very unhappy with derogative comments by family members. On the first day of treatment there was slight discolouration and on day 15 the haemangioma had shrunk to 2/3 of the original size. Parents were very happy with the result. She is now on day 45 of treatment with no side effects and follow up is due in 15 days.

- **Case No 3**

A twelve year old girl was referred by a paediatric surgeon because of an enlarging mass of her right forearm. It was initially noted just before her first birthday; Family started seeking medical advice 3 months prior to referral because the lesion had enlarged. At presentation the lesion was palpable and ultrasonography revealed a spindle – shaped cavernous haemangioma measuring 7cm x 1.4 cm. She received propranolol according to the aforementioned protocol. Forty five days later, a follow – up ultrasound showed dramatic reduction of the lesion to less than half of its original size. No side effects were reported.

The patient is currently on propranolol for 6 months and mother is delighted with the result. The plan is to review the patient in 3 months and to discontinue the medicine over a 2 weeks period.

- **Case No 4**

A two month old girl presented with a haemangioma of her right cheek, uvula and her right upper eyelid. Bronchoscopy was not performed since there was no stridor. MRI of the central nervous system ruled out PHACE syndrome (Posterior fossa brain malformation, Haemangiomas of the face, Arterial anomalies, Cardiac abnormalities, Eye abnormalities, Sternal cleft defects). On follow up echo one week post initiation of treatment the lesion's size had slightly decreased. The plan is to review the patient in 3 months.

- **Case No 5**

A 3.5 year – old girl with a haemangioma at the tip of the nose was treated with propranolol. The lesion became visible at the age of 40 days and had grown to the size of an olive by her first birthday. The family pushed for treatment because their girl was bullied at kindergarten due to this minor lesion. The lesion was noted to be less red from the first day of treatment; after 2 weeks the haemangioma was considerably reduced in size. Parents and the little girl were thrilled with the result. No side effects were reported.

Discussion

Infantile haemangiomas(IH) are the most common benign tumours of infancy[2]. They often are inapparent at birth and have a period of rapid growth during early infancy followed by gradual involution[7]. Given the natural history of involution, watchful waiting is the best management. In cases where the haemangioma involves a vital structure causing a func-

tional problem (e.g. subglottic, nasal or orbital IH) or causes significant disfigurement, treatment should be sought. Ulceration can also justify treatment of IH, since it can be very painful and virtually always results in scarring[1].

Therapeutic options available are not robustly evidence-based and have significant side-effects[8]. Systemic steroids are currently the mainstay of treatment for endangering IH[9], but their safety profile is far from being ideal and rebound growth can occur upon cessation of treatment[10]. Other therapeutic options include vincristine, cyclophosphamide, interferon α and imiquimod[8]. All of these have well known side effects and their effectiveness has only been shown in small case reports. Laser treatment and surgical excision also have several drawbacks.

Recently, Leaute-Labreze et al reported dramatic improvement of IH with the use of propranolol. This serendipitous discovery prompted many clinicians to adopt the off-label use of this oral non-selective β – blocker[2,5,11-14].

In our series, 5 girls (age range 2 months to 12 years) received oral propranolol with satisfying results. No other treatment was used. No major side effects were noted. All haemangiomas begun to lighten shortly after onset of treatment, possibly due to vasoconstriction[12]. Proposed mechanisms[3] of action also include induction of apoptosis[15] and down-regulation of angiogenic factors such as VEGF and bFGF[16].

Potential side effects of propranolol include bradycardia, hypotension, hypoglycaemia without jitteriness, concealment of clinical signs of early cardiac failure, bronchospasm, hypersomnolence, reflux, rash and failure to thrive[10,17]. All the aforementioned side effects emphasize the need for rigorous monitoring and a multidisciplinary team approach. Special attention should be paid in patients that are in high risk for high-output cardiac compromise, such as children with very large or diffuse haemangiomas[17] and children with PHACE syndrome[18].

Conclusions

Propranolol appears to be effective in the treatment of infantile haemangiomas. Its use should be judicious, at least until large multicenter well designed studies verify its effectiveness and above all its safety.

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