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The New Age of Hemangiomas

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Introduction

Infantile hemangioma is the most common soft tissue tumor of infancy[1]. These tumors are benign vascular neoplasms affecting 4–10% of all children less than one year of age and up to 30% of premature babies[1,2]. The demographics of these tumors shows a predilection for females on an order of 4:1 and an increased incidence in Caucasians[3,4].

The natural history of these lesions involves 3 stages: proliferation, stabilization, and involution. Proliferation begins in the first few weeks of life and comprises rapid growth affecting both superficial and/or deep components of the hemangioma. The duration of proliferation ranges from 3 to 24 months[1].

Stabilization follows proliferation, which may begin as early as 3-6 months of age and lasts for a few months. Stabilization is characterized by changes in the superficial appearance of infantile hemangiomas including changes in color from red to grey and decreased firmness to palpation[5]. Involution typically occurs after a few years of life leaving fibro-fatty tissue at the site of the original hemangioma[5].

Regression of infantile hemangiomas has been documented in up to 76% of these lesions by the age of 7 years[6]. Approximately 50% of patients are left with residual changes at the original site including telangiectasia, yellow discoloration, atrophic wrinkling, and alopecia[5].

Typically, 59% of infantile hemangiomas occur in the head and neck, 24% on the trunk, 10% on the lower extremities and 7% on the upper extremities[5]. Most are less than 2.0 cm in diameter and can appear in any range of ways from hypopigmented to "bruise-like" macules[5].

Despite being self-resolving, hemangiomas have the potential for devastating consequences in approximately 10% of cases based on the size, location and sequelae[1]. For instance, hemangiomas growing in high risk areas can require immediate medical intervention and may cause secondary complications such as disfigurement, organ damage, and vision and airway obstruction.

Treatment

Traditionally, corticosteroids have been considered to be the gold-standard treatment of infantile hemangioma. Corticosteroid therapy for hemangiomas decreases the size of hemangiomas in approximately 50% of cases although efficacy rates as high as 84% have been reported with doses of 2.9 mg/kg of prednisone were used[5,7]. Side effects of corticosteroids include cushingoid facies, personality changes, gastric irritation, fungal infection, transient diminished longitudinal growth, transient diminished weight gain, persistent hypertension, hyperglycemia, and hypothalamic-pituitary-adrenal axis suppression[8].

Surgical treatment options are available including laser therapy, cryotherapy, intralesional corticosteroids and excision. Intralesional steroids used to treat

periorbital infantile hemangiomas have been linked to retinal artery occlusion and eyelid necrosis. Pulsed dye laser therapy can be beneficial for superficial hemangiomas but has a limited depth of penetration and cannot treat deep hemangiomas and may lead to ulceration. Surgical excision is indicated in cases with abnormal scarring or excess tissue after natural involution, ulcerated hemangiomas that bleed excessively, or lesions that interfere with development or activities but adverse events such as hemorrhage, subglottic stenosis from tracheotomy, mortality, and prolonged intubation must be considered[5].

Additional treatment options have included vincristine and interferon. Each of these therapies has been accompanied by an associated therapeutic benefit and side-effects. Concerns for sequelae such as hypertension, hepatic toxicity, hypothyroidism, and neuropathy have driven management towards potentially safer options[1].

Propranolol

The discovery of propranolol as a treatment option for infantile hemangiomas was made by a group of French physicians led by Léaute-Labrèze in 2008[9]. This discovery has changed the current management of hemangiomas[5]. The rapid and dramatically effective results of its use, combined with favorable initial safety profile, have led to it to its current place as a new first-line therapy[5]. Propranolol is a well-tolerated, nonselective, B-adrenergic receptor blocker commonly used in children with cardiac indications[1].

Although investigation is ongoing, propranolol effects are attributed to several mechanisms including vasoconstriction, endothelial cell apoptosis, and decreased expression of basic fibroblast growth factor (bFGF) genes and of the vascular endothelial growth factor (VEGF) genes[7]. bFGF and VEGF are proangiogenic factors noted to be involved in the proliferation phase of infantile hemangiomas[10]. There has also been literature supporting the effect of propranolol on the renin-angiotensin system (RAS)[4]. Propranolol is thought to regulate accelerated involution of the proliferating infantile hemangioma by inhibiting the proliferation of CD34þ/VEGFR-2þ endothelial progenitor cells[4].

Multiple subsequent studies and case reports have shown the effectiveness of propranolol. Bertrand *et al* performed a retrospective review on propranolol versus steroids for infantile hemangioma[11]. At 1 month, clinical improvement in the propranolol group was moderate to good in all patients. In the prednisone group, only one patient had moderate improvement, with others showing slight (7/12) or no improvement or stabilization (3/12) from baseline and one case worsening. At 6 months, the propranolol group showed good to excellent response in all cases, whereas nine in the prednisone group showed slight to moderate response[11].

Pre-treatment Evaluation

An electrocardiogram and echocardiogram should be part of the pretreatment evaluation for propranolol. Vital signs including blood pressure and heart rate should be documented. Photographic documentation of patients at all visits is helpful to document the response to therapy.

Treatment initiation monitoring

Patients are generally monitored at the initiation of propranolol therapy. The hospital observation period ranges from 3 days to a minimum of 6 hours[1]. During this time period, heart rate, blood pressure and sometimes blood glucose are monitored. Patients are observed for occurrence of bronchospasm. In the absence of side effects, patients are able to continue therapy on an outpatient basis with initial follow-up appointments up to 10 days post-initiation. Monthly appointments are made to monitor progress.

Dosing regimen

There is variability in propranolol dosing regimen. Starting doses range from 0.16mg/kg/day to 2mg/kg/day. Titration of dosages up to full-treatment dose occurred in some but not all studies and occur over 24 hours to 2 weeks. Typical treatment doses ranged from 1mg/kg/day to 3.5mg/kg/day. The most common dosing used is 2mg/kg/day divided three times daily as in the initial observational study. The original group changed from three times daily dosing to twice daily dosing in their follow-up article stating that the original dosing was used because of concern about the short half-life of propranolol at 3 hours[1].

Adverse effects

The most common side effects observed are hypotension (3.2%) followed by GERD and/or GI upset (2.1%). Traditionally, the most common adverse effects that are attributed to propranolol are hypotension, bradycardia, hypoglycemia, and bronchoconstriction[7]. There have been concerns that using propranolol may mask the clinical signs of early heart failure and diminish cardiac performance. However, this concern is not supported in cases where propranolol was used in patients with pre-existing heart failure who conversely were noted to have improvement of their heart failure with resolution of their hemangiomas using propranolol therapy[12].

Hypoglycemia must be considered, especially in patients who have been on long-term systemic corticosteroid therapy secondary to their deficiency of counter-regulatory hormones, epinephrine and cortisol, because of adrenal insufficiency[13]. Propranolol should be discontinued during illness, especially in the setting of restricted oral intake. In patients whose treatment cannot be interrupted, support with glucose-containing intravenous fluids during periods of decreased oral intake is indicated[14].

Other adverse effects have been noted including diarrhea possibly attributable to osmotic effect from malitol in the formulation of propranolol used in these cases, hyperkalemia, somnolence, gastroesophageal reflux, rash, and respiratory syncytial virus infection exacerbation[12,14].

Conclusions

Infantile hemangiomas are benign neoplasms with potentially devastating side effects, particularly in the head and neck region. The discovery of the effects of propranolol have drastically changed the management of patients with hemangiomas of infancy. While propranolol has undoubtedly been shown to be a safe and effective treatment for infantile hemangiomas, there continues to be a need for more research to develop a standardized treatment and monitoring regimen.

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