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Review Article

Propranolol treatment of subglottic hemangiomas: a review of the literature

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Abstract: Subglottic hemangiomas (SGH), which are rare benign tumors of the airway, are potentially life-threatening conditions that may require intervention. Propranolol appears to be an effective treatment for these tumors and should therefore be a first-line treatment for SGH that require intervention. This review presents the clinical presentation and diagnosis of SGH and discusses current knowledge regarding the use of propranolol for the treatment of SGH.

Keywords: Hemangiomas, larynx, propranolol, child

Introduction

Infantile hemangiomas (IH) are the most common tumors of infancy, affecting nearly 1 in 10 children [1]. Approximately 60% of IH are located in the head and neck regions [2]. In contrast, subglottic hemangiomas (SGH) are rare benign tumors of the airway, accounting for only 1.5% of all congenital laryngeal anomalies [3]. SGH are a well-recognized but rare cause of stridor. In SGH cases, stridor typically manifests within the first several months of life; in particular, 85% of SGH cases present with stridor by six months of age, with a female to male ratio of 2:1 [4]. SGH symptoms consist of inspiratory or biphasic stridor, which may be exacerbated by excitement, feeding or upper respiratory tract infections and can lead to respiratory difficulty. Other symptoms may include a barking cough, hoarseness, cyanosis, hemoptysis, dysphagia, and failure to thrive. In total, 50% of SGH patients have an accompanying cutaneous lesion; 1-2% of patients with a cutaneous hemangioma also have a subglottic lesion [5].

Medical and surgical interventions for SGH have been thoroughly described in the literature. These interventions include steroids, chemotherapy agents (such as vincristine and alpha-interferon), laser treatment, surgical excision, tracheostomy, or a combination of these therapies. The spectacular effect of propranolol on cutaneous IH was first described in 2008 by Léauté-Labrèze et al. [6]. These researchers successfully treated 11 cases and observed a change in hemangioma coloration in all of the examined children as early as 24 hours after the initiation of treatment.

Clinical presentation

Patients with SGH are typically asymptomatic during the first several weeks of life. In the proliferative stage, which occurs at approximately 6 to 12 weeks of age, the symptoms of biphasic (inspiratory and expiratory) stridor and respiratory distress become noticeable. An infant with an SGH typically has a normal voice and no difficulty in swallowing but frequently exhibits difficulty in feeding because the infant struggles to breathe and suck at the same time. Due to variations in size, shape, and behavior, SGH in children may present with a broad spectrum of clinical features and can range from well-tolerated, asymptomatic tumors to life-threatening lesions. SGH patients are commonly misdiagnosed with croup, a much more common pediatric condition that causes edema in the subglottic region. A child with an SGH frequently has a cough that mimics the barking cough of croup. Two features that differentiate croup and SGH are the lack of fever and rhinorrhea in children with SGH. Hemangiomas decrease in size when treated with typical anti-croup agents,

such as nebulized epinephrine, inhaled steroids, and systemic steroids; thus, the clinical picture for SGH patients can initially be misleading. Because the short duration of therapy for croup only produces transient effects on SGH, the recurrence and gradual worsening of stridor and respiratory distress typically occur in SGH patients who are treated for croup. Thus, recurrent croup in the neonatal period is a "red flag" for the presence of an SGH [7].

Cutaneous hemangiomas can be associated with SGH, particularly in cases involving cutaneous lesions distributed in a "beard" pattern across the preauricular areas, chin, anterior neck, and lower lip. The biological basis for this association is unknown. It appears that a more extensive "beard" of cutaneous hemangiomas is associated with a higher likelihood of a symptomatic airway hemangioma [7].

If left untreated, SGH, similarly to other hemangiomas, undergo proliferation for approximately 1 year, followed by slow, spontaneous involution in most cases. According to Bruckner [8], complete resolution occurs in 50% 70%, and 100% of cases by the ages of 5, 7, and 10-12 years, respectively.

Diagnosis

A high-kilovolt plain neck X-ray is typically the first procedure performed to diagnose SGH. This X-ray alone may reveal asymmetric subglottic narrowing. Based on a patient's clinical history and examination results, the presentation of an SGH must then be differentiated from the presentation of a subglottic cyst, stenosis or a papilloma. A flexible laryngoscopy in the office may be sufficient to reveal that a hemangioma is the cause of a patient's respiratory symptoms. However, the mainstay of SGH diagnosis is rigid endoscopy under general anesthesia after laryngomalacia and vocal cord paralysis have been excluded by transnasal flexible laryngoscopy. An SGH appears as a reddish smooth mass; most SGH are located in the left posterolateral subglottis and extend cranially to the underside of the vocal cords. Right-sided, posterior and bilateral SGH are also frequently observed. The tumor mass is spongy and compressible, allowing for easy intubation with an Endotracheal tube with no risk of major hemorrhage.

A CT scan using intravenous contrast medium can easily reveal abnormal vessels narrowing the trachea without requiring the sedation of an infant patient [9]. Three-dimensional (3D) reconstructions of the laryngotracheal airway offer useful information regarding the location, extent and severity of the obstruction. However, virtual endoscopy cannot replace conventional laryngotracheal bronchoscopy. In particular, virtual endoscopies provide no information regarding mucosal quality (cicatricial versus inflammatory). Furthermore, trapped secretions below the stenosis may misleadingly exacerbate the extent to which a patient's trachea is constricted. In cases involving the total obstruction of the airway, virtual endoscopy is helpful for visualizing the distal portion of the airway [10]. CT with contrast can also reveal unrelated anomalies present in addition to an SGH, such as a vascular ring; either an SGH or an unrelated anomaly can cause stridor [11].

Once a patient's airway has been established, an MRI of the neck and brain is useful to ensure that the hemangioma has not extended into the neck or skull. SGH appear as solid tissues of intermediate intensity on T1-weighted spin-echo images and of moderate hyperintensity on T2-weighted spin-echo images [12].

Propranolol treatment of SGH

Since the initial report in 2008 describing the use of propranolol for treating IH, there has been a flurry of case reports and case series describing propranolol's efficacy and potential side effects in this context. The first report addressing this drug's efficacy for alleviating respiratory symptoms due to SGH was published in May 2009 [13]. In particular, this report describes the cases of two infants with SGH who had been subjected to several unsuccessful regimens of corticosteroid treatment, one of whom had also experienced unsuccessful vincristine treatment; these infants responded spectacularly to 2-3 mg/kg/day of propranolol. Propranolol is a systemic nonselective β-blocker that has been used for decades in pediatric patients with cardiovascular disease at standard doses of 0.5 to 4 mg/kg/day. There are no US Food and Drug Administration (FDA)-approved agents for the treatment of IH; thus, at present, IH treatments are based on expert opinions and observational studies [14].

The proposed mechanism of action of propranolol in cases of IH includes rapid vasoconstriction, which may be responsible for the change in tumor color from pink to violet that is typically observed during the first 1 to 2 days of therapy. The inhibition of angiogenesis via the downregulation of proangiogenic growth factors, including vascular endothelial growth factor, basic fibroblast growth factor, and matrix metalloproteinases 2 and 9, appears to play a role in arresting tumor growth. Furthermore, studies have proposed that propranolol's hastening of the induction of apoptosis in endothelial cells, which is known to occur during natural involution, may stimulate the regression of IH [15, 16]. In addition to propranolol, nadolol and atenolol have been suggested as alternative systemic-blockers for IH [17].

Before initiating propranolol therapy, patients should be screened for risks associated with propranolol use. Relative contraindications include cardiogenic shock, sinus bradycardia, hypotension, second- or third-degree heart block, heart failure, bronchial asthma, and hypersensitivity to propranolol hydrochloride. The prescribing physician should perform standard cardiovascular and pulmonary examinations and obtain the patient's cardiovascular and pulmonary history (or acquire current documentation providing the patient's relevant history and examination results). Key elements of the patient's history include poor feeding, dyspnea, tachypnea, diaphoresis, wheezing, heart murmur, or a family history of heart block or arrhythmia. Examinations should include determinations of HR and BP as well as cardiac and pulmonary assessments. Routine ECG screening before the initiation of propranolol treatment has been advocated, although the utility of ECG screening for all children with hemangiomas prior to initiating propranolol therapy is unclear [14].

Inpatient hospitalization for propranolol initiation is suggested for children with SGH. The patient's baseline pulse and blood pressure should be recorded prior to treatment. The large majority of propranolol-treated SGH patients have received a dose of 2 mg/kg/day, although optimal doses and dose-related efficiency for propranolol have not yet been determined. In most studies that have reported details regarding dosing regimen and titration, the initial dose of propranolol was between 0.5 and 1 mg/kg/day and was increased to the goal dose over the course of days to weeks. The peak effects of oral propranolol on HR and BP occur 1 to 3 hours after administration. Patients' HR and BP should be measured at baseline, at 1 and 2 hours after receiving the initial dose of propranolol, after a significant increase in dose (0.5 mg/kg/day), and after the target dose has been achieved.

The response of SGH to propranolol should be assessed by serial endoscopic examinations. The first endoscopy will typically be performed six weeks after the commencement of treatment to assess whether an SGH has responded. Follow-up endoscopies are performed at three-month intervals. With respect to treatment duration, Denoyelle et al. suggested that propranolol therapy could be stopped before the age of spontaneous hemangioma regression; however, further studies are needed to confirm the validity of this approach [13]. After treatment, children are weaned off propranolol in a manner subject to their endoscopic responses and symptoms. Propranolol should be stopped by reducing the dosage over four weeks; in particular, the dose should be halved at the start of this period and then halved again after two weeks [18].

The most serious known adverse effects of propranolol include bradycardia, hypotension, hypoglycemia and bronchospasm [19]. The most commonly reported non-potentially life-threatening complications of propanol treatment are sleep disturbances, including nightmares; somnolence; cool or mottled extremities; diarrhea; and gastroesophageal reflux/upset. Severe, life-threatening hyperkalemia has also been reported as a side effect complicating the propranolol treatment of IH [20].

However, when a patient does not appear to respond to therapy or when treatment fails, a biopsy should be performed to obtain pathological confirmation of a diagnosis of IH by histology and by immunohistochemical staining for GLUT-1 [21]. Proliferative vascular tumors other than IH include pyogenic granulomas (lobular hemangiomas), tufted angiomas, kaposiform hemangioendotheliomas, rapidly involuting congenital hemangiomas, and noninvoluting congenital hemangiomas [22]. Among proliferative vascular tumors, only IH are positive for GLUT-1.

Despite the great efficiency of propranolol, recurrence can occur after the early interruption of propranolol treatment, and secondary resistance is also possible. Patients who experience recurrence may require prolonged propranolol therapy that continues at least until spontaneous SGH regression, which typically occurs after 18 months of age [23]. Laryngeal surgery at the tumor site, performed either endoscopically or with an external approach, can be used to treat these resistant cases.

Conclusion

SGH are a rare but potentially life-threatening disease. A high index of suspicion is vital for the early, accurate diagnosis of this disease. Propranolol treatment has many advantages: it is non-invasive; it exhibits a rapid onset; it allows for the avoidance of a tracheostomy, prolonged steroid therapy, the manipulation of subglottic tissues, and prolonged periods of intubation; it has a low complication rate; and it is inexpensive. There are few disadvantages of this treatment. Thus, we propose the use of propranolol as a first-line treatment for SGH.

Disclosure of conflict of interest

None.

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