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The use of propranolol in the treatment of subglottic hemangiomas: A literature review and meta-analysis

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ABSTRACT

Objectives: 1) Describe the origins of the use of propranolol in the treatment of subglottic hemangiomas, 2) Perform meta-analysis of all case reports and series in which propranolol was used to treat subglottic hemangiomas.
Study design: Literature review and meta-analysis.
Methods: A total of 61 cases were identified from 19 scholarly articles. Cases were assessed by parameters including age at diagnosis, presence of other hemangiomas, percent airway obstructed, dose of propranolol, treatment duration, age at therapy termination, use of steroids, and treatment failure. Treatment failure was defined as: 1) Need for surgery after initiation of propranolol, 2) Return of symptoms, or 3) Endoscopic worsening/recurrence of hemangioma. All data was subjected to comprehensive statistical analysis.
Results: Though not statistically significant, a trend was noted towards a decreased treatment failure rate with increasing doses of propranolol ($p = 0.0563$). The use of concurrent steroids was associated with a higher failure rate ($p = 0.0487$). Notably, no associations were observed between the presence of additional hemangiomas, prior surgery, or increased initial percent airway obstruction with treatment failure.
Conclusion: Propranolol is rapidly becoming the standard of care in the treatment of subglottic hemangiomas. Despite widespread adoption, the rarity of this condition has limited previous studies to case reports and small series. No evidence-based guidelines exist for proper dosing of propranolol. The results of this meta-analysis suggest a benefit to higher doses of propranolol (3 mg/kg/day), though further investigation is needed.

1. Introduction

A subglottic hemangioma (SGH) is a benign tumor of infancy that can cause severe obstruction of the airway. Infantile hemangiomas, in general, are the most common head and neck tumor in children, affecting 4–5% of the pediatric population [1]. Subglottic growths, however, only account for 1.5% of congenital abnormalities [2]. This rarity, coupled with a mortality rate of close to 50% when left untreated [3], means that SGHs present a great challenge to clinicians evaluating children with respiratory distress. From an epidemiologic standpoint, SGHs have been linked to low birth weight and prematurity [4]. As with infantile hemangiomas of other parts of the body, SGHs follow a well-described pattern of proliferation beginning in the first one to three months of life, followed by involution by about one year of age [5,6]. It is during the proliferative phase that patients with SGHs become symptomatic, developing characteristic biphasic stridor which may progress to respiratory distress as the tumor grows. In this early stage, a SGH is often mistaken for croup, even presenting with a similar "barking" cough in some instances [6]. In patients with SGH, however, conservative interventions such as racemic epinephrine and steroids are only transiently helpful [6]. Though SGHs often occur in isolation, the presence of cutaneous hemangiomas, especially in the "beard distribution" (chin, anterior neck, preauricular region and lower lip), may certainly suggest the presence of a SGH in children with respiratory distress [7].

Treatments for SGH have been steadily evolving over time.

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These treatment modalities include systemic corticosteroids [8], intralesional steroids [9], carbon dioxide laser [8], tracheostomy, and open surgical resection [10–12]. Systemic corticosteroids were long seen as a mainstay of treatment, as 25% of lesions respond to this method, despite the risk of unwanted side effects [8]. In one 1997 study, intralesional steroids demonstrated 82% effectiveness in relieving airway obstruction but required a mean of six procedures and 37 days of intubation to achieve success [9]. Likewise, laser treatment has produced success rates as high as 89% but with a high rate of complications, limiting their use to smaller, non-circumferential lesions [8]. Tracheostomy may also be employed, as SGHs will spontaneously involute after about 1 year of life, but this may lead to tracheal stenosis or tracheocutaneous fistulae following decannulation. Open surgical excision is often seen as the gold standard for definitive management of SGH, achieving success rates as high as 94% with a relatively low complication rate using modern airway reconstruction techniques [8,10,11]. In 2008, however, a landmark "letter to the editor" published in the New England Journal of Medicine observed that two infants being treated with propranolol for unrelated cardiac conditions had both exhibited rapid regression of large infantile hemangiomas within days of initiating treatment [12]. In both cases, this had also followed failed trials of corticosteroids for the treatment of the hemangiomas [12]. A subsequent randomized clinical trial showed that infants who received propranolol showed statistically significant reduction in the thickness of their hemangiomas as compared to a placebo group [13]. Propranolol has since become the first-line treatment for infantile hemangiomas, including those of the subglottis, producing excellent results in a number of case reports and retrospective series [4,5,14–30].

Side effects of propranolol are rare, but may include bradycardia, hypotension, and hypoglycemia [18]. Other potential side effects include bronchospasm, fatigue, nightmares, heart failure and peripheral vasoconstriction [18]. The benefits of propranolol therapy, however, are generally considered to outweigh its risks, as compared to surgical morbidity and the systemic effects of steroids.

Despite the growing acceptance of propranolol as a leading treatment modality for subglottic hemangiomas, no clear treatment guidelines exist. A wide range of starting doses and final doses exist in the literature, along with an equally broad range of treatment durations [4,5,14–30]. The Great Ormond Street Hospital recently released a proposed protocol for the use of propranolol based on their experiences, but this has not seen widespread adoption [18]. This absence of clear treatment guidelines is partially based on the rarity of this condition coupled with a lack of true randomized clinical trials. In this study, we perform a systematic literature review and meta-analysis of the existing case reports and series to better elucidate the efficacy of propranolol in the treatment of SGHs.

2. Materials and methods

This study was designed as a literature review and meta-analysis. A search was first performed for case reports, retrospective case series, and randomized clinical trials pertaining to the use of propranolol in the treatment of SGHs. This search was conducted using PubMed and Google Scholar, employing the phrases "propranolol subglottic hemangioma", "subglottic hemangioma AND propranolol" and "subglottic hemangioma." The search was narrowed by looking for articles published in 2008 or later, as this is when propranolol was first used to treat infantile hemangiomas. The search concluded in January 2015 at the end of our study period. Additionally, the reference sections of suitable sources were searched for related papers. Through these methods, 19 scholarly articles were identified, containing a total of 61 cases in which propranolol was used to treat a SGH.

Once these cases were identified, all text and figures were carefully assessed for relevant data. Cases were assessed by parameters including age at diagnosis, presence of other hemangiomas, percent airway obstructed, propranolol dose, treatment duration, age at therapy termination, use of steroids, adverse effects and treatment failure. Treatment failure was strictly defined as: 1) Need for surgery after initiation of propranolol, 2) Return of symptoms after use of propranolol, or 3) Endoscopic worsening/recurrence of hemangioma after use of propranolol. Data was only included in our study if it was explicitly defined in its original paper. All data had been previously de-identified according to IRB guidelines at their respective authors' institutions.

The collected data was then entered into a database for statistical analysis. Basic clinical demographics, type of hemangiomas, percent airway obstructed before and after propranolol, starting and final propranolol doses, duration of therapy, time to effect, prior and concurrent use of steroids, treatment failure, surgery, and adverse effects, were summarized by basic descriptive statistics. Various logistic regression models and the Fisher's exact method were used to access whether or not there were any potential risk factors associated with treatment failure. Various linear regression models were used to test whether or not there were any potential risk factors associated with the % change in airway before and after the propranolol treatment. All hypothesis testing was two-sided and a p-value of less than 5% was considered to be statistically significant.

3. Results

A total of 61 subjects were obtained from 19 articles through literature review (Table 1). The results were studied carefully to identify clinically relevant trends within the data. All variables were assessed as they relate to the outcome measures of success/failure or percent change in airway following propranolol.

The first variable examined was the presence of other hemangiomas. Of the 49 subjects in which the presence of hemangiomas was addressed, 24 (49.0%) had other hemangiomas at the time of diagnosis, with the head and neck being the most common location (Table 2).

Next, we analyzed whether age at diagnosis played a role in the success or failure of treatment with propranolol. The mean and median ages at diagnosis were 2.56 months and 2.0 months respectively, with a range of 0.7–9 months. No association was found between age at diagnosis and the failure rate of treatment ($p = 0.7336$) or the change in airway ($p = 0.6394$).

One key question in determining the efficacy of propranolol in a variety of situations is whether it is effective in patients who have already undergone surgery. Our study found that there was no statistically significant relationship between prior surgery and the failure rate ($p = 0.7071$) or percent change in airway (0.7771).

Statistically, there was no correlation between use of steroids *prior* to propranolol and the failure rate ($p = 0.3277$) or airway change ($p = 0.8206$). This indicates that a failed trial of steroids seems to have no correlation with the future efficacy of propranolol. When examining the use of *concurrent* steroids with propranolol, however, a statistically significant association was found with the failure rate ($p = 0.0487$). This suggests that patients receiving steroids during propranolol treatment may be more likely to experience treatment failure than patients receiving propranolol alone.

One of the greatest areas of interest in our study related to starting and final doses of propranolol. In assessing starting doses of propranolol, it was found that, in the 49 patients in whom the starting dose was explicitly stated, doses ranged from 0.16 to 6.0 mg/kg/day. No associations were found between starting dose