

ORIGINAL RESEARCH

Subglottic hemangioma—prevalence, clinical presentation and treatment

Mihail Basa¹, Predrag Minic^{1,2}, Bojana Gojsina¹, Aleksandar Sovtic^{1,2,*}

¹Department of Pulmonology, Mother and Child Health Care Institute of Serbia, 11000 Belgrade, Serbia

²School of Medicine, University of Belgrade, 11000 Belgrade, Serbia

***Correspondence**

aleksandar.sovtic@med.bg.ac.rs
(Aleksandar Sovtic)

Abstract

This retrospective study aimed to investigate the clinical features and treatment of pediatric subglottic hemangioma (SH), identify risk factors for treatment-induced adverse effects, and identify a strategy for timely therapy discontinuation in children diagnosed with SH at the national pediatric center. Medical records of patients presented with stridor from 2010 to 2020 were retrieved and assessed, the diagnosis of SH was established *via* flexible bronchoscopy, and the patients were treated using propranolol with a subsequent gradual dose increase to 3 mg/kg body weight daily. A two-week oral steroids trial was added for those with circumferential lesions. Early indicators of a good therapeutic response included decreased stridor and primary lesion size on follow-up bronchoscopy performed one week after propranolol commencement. Duration of therapy, tailored individually based on bronchoscopy findings, and at least twelve months of treatment were the two main criteria for deciding therapy termination. Outpatient visits were arranged at least every three months. Our results showed that SH was the third most frequent cause of stridor (15/137 patients), and biphasic stridor was uniformly present as a typical symptom. Both clinical improvement and bronchoscopy findings confirmed the efficacy of the treatment. The mean therapy duration was 17 months. The only significant adverse event observed was hypoglycemic seizures in one infant. Contributory factors were all prematurity, high propranolol dose (3 mg/kg) and poor oral intake. Collectively, defining a safe and timely protocol for therapy cessation and avoidance of risk factors for adverse effects is the mainstay of SH treatment.

Keywords

Subglottic hemangioma; Propranolol; Hypoglycemic seizures

1. Introduction

Chronic stridor is a hallmark symptom of subglottic hemangioma [1]. Infantile hemangiomas (IH) are the most prevalent type of benign tumor in infancy and the most common vascular tumor in childhood, accounting for up to 5% of all cases [2, 3]. They usually manifest in the first few weeks of life, a subsequent phase of intensive growth during early infancy, with 80% of IH reaching maximum size by the age of three months [4]. Then, a stage of spontaneous gradual involution occurs, which can vary, but is completed in most cases by the age of four years and requires no treatment [5]. However, specific therapy is reserved for patients with significant functional and potentially life-threatening complications, such as subglottic localization of hemangioma [2, 3].

Propranolol, a non-selective β -blocker, is the first-line treatment for most patients with proven efficacy. It has replaced previous mainstays of treatment such as systemic steroids, interferon alpha and vincristine for steroid-refractory lesions [6]. In recent years, there has been a shift toward using more selective β -antagonists to minimize the potential adverse

effects of propranolol. These newer agents have less potential for hypoglycemic events previously reported in patients diagnosed with infantile hemangioma outside the airways [7, 8]. However, studies investigating serious adverse effects, such as hypoglycemic seizures, in patients with subglottic hemangioma taking propranolol remain limited.

In this study, we conducted an overview of all patients with chronic stridor and confirmed diagnosis of subglottic hemangioma to identify potential risk factors of treatment-induced adverse events and determine the time for therapy discontinuation.

2. Materials and methods

This was a retrospective analysis based on the medical records of patients with chronic stridor and eventually diagnosed with subglottic hemangioma from June 2010 to June 2020 at the Department of Pulmonology of the Mother and Child Health Institute of Serbia, a national pediatric center and referral center for pediatric bronchology.

Bronchoscopy was performed using a standard or ultra-thin

pediatric flexible bronchoscope according to widely accepted clinical practice by two experienced bronchoscopists with a cumulative experience of more than 50 years [3]. The patients underwent topical anesthesia and analgesedation by benzodiazepines. Of note, general anesthesia was not employed in any of the cases investigated in this study. After inspecting the upper airways *via* the nasal route, the procedure was continued through the vocal cords to the lower airways, as previously described [9]. Subglottic stenosis was considered critical if an ultra-thin flexible bronchoscope (distal end outer diameter, 3.1 mm) could not pass through. The stenosis severity was graded as moderate when one-third to half of the subglottic area was obstructed, and graded as severe when the obstruction was more than half. All procedures were completed successfully without complications. According to local protocol, propranolol was initiated immediately at a total dose of 2 mg/kg body weight (BW), administered three times daily, and increased to 3 mg/kg BW daily during the first week. Continuous monitoring of heart rate, blood pressure and regular blood glucose measurements upon awakening and before meals were mandatory for each child until discharge. Both a gradual decrease in stridor and hemangioma's volume on follow-up bronchoscopy at the end of the first week of treatment were considered indicators of good initial response. We firmly believe that direct visualization of the primary lesion one week after therapy commencement is valuable for reliable estimation of treatment effectiveness. In addition, reevaluation every six months to document the lesion size helps decide on eventual earlier therapy discontinuation. In addition, therapy duration, tailored individually based on normal bronchoscopy findings, and at least twelve months of treatment were the two main criteria for deciding therapy termination. If both criteria were met, the therapy was stopped.

Follow-up visits were scheduled on a monthly interval during the first three months after the initial discharge, then at least every three months. More frequent early-stage appointments aimed to monitor the initial proliferative growth of IH and adjust treatment dose according to the patient's weight while also reviewing adherence to therapy. In addition to clinical examination, the parents were informed about the importance of regular feeding to avoid potential hypoglycemic events.

Statistical data were analyzed using the IBM SPSS v25 software (Armonk, NY, United States of America) for Windows. Differences between non-normally distributed variables were analyzed using the Mann-Whitney U test. Statistically significant differences were considered for *p* values < 0.05.

3. Results

Of the 137 patients who presented with chronic stridor, subglottic hemangioma was the third most frequent cause of stridor (15/137 patients) in our cohort after laryngomalacia and vascular compression on the airways, with a prevalence of 11.2%. Their demographic data and outcomes are shown in Table 1.

Biphasic stridor was the most prominent clinical feature in each patient. Typically, stridor becomes apparent in the second or third month of life, followed by gradual intensification. Initially, it occurred during crying and later progressed to harsh

TABLE 1. Demographic data and outcomes in pediatric patients with subglottic hemangioma.

| Demographic data and outcomes—the summary | |
|---|----------------------------------|
| Sex (male:female) | 8:7 |
| The mean age at diagnosis | 5 mon (min–max range 1.5–12 mon) |
| Additional multiple cutaneous hemangiomas | 3/15 (20%) |
| Critical subglottic stenosis | 10/15 (66%) |
| The mean duration of the therapy | 17 mon (IQR* 13.5–18.5 mon) |
| Serious adverse events during the treatment | 1/15 (7%) |
| Medical treatment failure | None |

*IQR**: interquartile range (25%–75% values).

sounds during sleeping. While stridor was the only symptom in 12/15 patients, two had croup in the first six months of life, and one had partial responsive croup in the second half of the first year accompanied by facial hemangioma. Additionally, three out of fifteen patients had additional superficial cutaneous hemangiomas, of whom two were located in the head/neck region and one on the trunk above the skeletal prominence. None of the children had other respiratory symptoms related to subglottic hemangioma. Also, none of the presented cases were associated with clinical syndromes related to hemangioma but were exclusively isolated.

The distribution of primary lesions was found to be non-uniform. Specifically, four children (27%) had circumferential subglottic lesions, while the rest (11/15 or 73%) had either right or left-sided hemangiomas (six on the left and four on the right-sided subglottic wall). Fig. 1 depicts a representative initial bronchoscopy finding in one of the investigated patients.

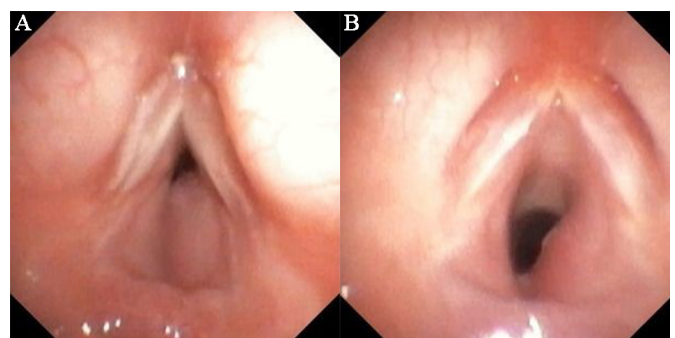


FIGURE 1. Evolution of bronchoscopy finding upon the therapy with propranolol. (A) Initial bronchoscopy: confirmed diagnosis of subglottic hemangioma. (B) Significant improvement at the end of the first week in the same child.

In 10/15 cases, subglottic space was significantly reduced, resulting in critical subglottic stenosis. Surprisingly, despite appreciably increased breathing, there were no blood gas abnormalities in the patients, and no ventilatory support was needed, even in patients with critical subglottic stenosis. Rapid response to propranolol led to favorable outcomes. There were

no additional structural abnormalities in the airways. The lower airways of each child were examined at the first bronchoscopy whenever possible. In those with critical subglottic stenosis, the lower airway structure was assessed no earlier than one week after starting propranolol.

Propranolol therapy alone was effective, demonstrating successful initial response in all the treated patients. The mean time for reduced stridor was 18 days, ranging from one to five weeks. All children with the circumferential lesions had received an additional two-week oral prednisolone concomitantly with propranolol (1 mg/kg BW). However, the initial clinical response was not superior to the propranolol monotherapy regimen in terms of time for stridor diminishing (p -value 0.358, Table 2). None of the examined cases required tracheostomy tube placement. Due to the adequate evaluation of IH morphological features on bronchoscopy and good initial response on propranolol, none of the patients were assessed with other imaging modalities. The therapy lasted from a minimum of 12 months to a maximum of 24 months, with a mean duration of 17 months. We found that the initial concomitant use of prednisone led to a shorter long-term therapy duration. The mean duration was 18 months with propranolol alone and 14 months with the addition of prednisone (p -value = 0.02).

TABLE 2. Initial clinical response to therapy with and without additional steroid treatment.

| Therapy | Stridor cessation (in days) | | | p -value |
|--------------------------------------|-----------------------------|------|---------|------------|
| | Minimum | Mean | Maximum | |
| Propranolol alone (11 cases) | 7 | 17 | 35 | 0.358 |
| Propranolol + prednisolone (4 cases) | 8 | 12 | 22 | |

During initial hospitalization, none of the patients experienced adverse drug reactions, including hypoglycemic events, systemic arterial hypotension or heart rate disturbances. Nevertheless, the only significant adverse event occurred two months after discharge in a 10-month-old premature-born girl taking propranolol at a total daily dose of 3 mg/kg BW. Although there were no symptoms of concomitant acute infection, her calorie intake on the day before the event was poorer than usual. During the morning routine, the child became unconscious and flabby and had profound sweating and generalized seizures. Consequently, the patient was admitted to the pediatric intensive care unit due to status epilepticus. Laboratory findings revealed severe hypoglycemia (0.33 mmol/L) and positive urinary ketones, following which she was administered hypertonic glucose solution and quickly recovered. Repeated laboratory findings were within the normal range. As a result, her total daily dose of propranolol was reduced to 1.5 mg/kg BW daily. Before discharge, the parents were instructed on essential measures to take if similar situations were to occur and to ensure regular feeding of the girl to avoid prolonged fasting. More frequent outpatient visits were also arranged for the

patient. As there was no clinical turbulence in the further course, her treatment was continued for the next 12 months. The follow-up bronchoscopy performed one week after the initiation of treatment showed significant improvement at the former lesion site (Fig. 1).

None of the patients experienced asphyctic episodes, ulceration or bleeding. Due to the complete resolution of symptoms, bronchoscopy was not performed in any child once the therapy was stopped. Follow-ups were continued for at least one year after the termination of the treatment.

4. Discussion

Subglottic hemangiomas can be life-threatening due to airway obstruction unless timely treated [2, 3]. The mechanism *via* which propranolol leads to the reduction of infantile hemangiomas includes vasoconstriction, inhibition of angiogenesis and induction of apoptosis. These effects are mediated by both β -1 and β -2 receptors [10]. Although the standard reported dose in most studies is 2 mg/kg/day (range: 0.5–3.0 mg/kg/day), the resolution of symptoms is known to become more prominent with higher doses [6, 11].

Besides certain short and long-term benefits of propranolol, some concerns have been expressed regarding adjuvant steroid treatment. Although additional use of steroids may not result in better outcomes in some centers, we tended to use an adjuvant course of steroids in circumferential lesions and observed rapid recovery in all of our four selected patients [12]. Although this finding might be clinically significant, this study cannot recommend adjuvant systemic corticosteroid therapy in selected cases as a standard part of the local protocol due to our small sample size. Thus, studies with larger cohorts of patients using prospective settings are required to confirm these findings.

As recommendations on the duration of treatment remain debatable, an individualized approach is often adopted. [13]. While official recommendations provide a general guideline for treatment duration, their applicability to individual cases is limited due to a potential rebound growth of the primary lesion irrespective of the duration of the treatment [13]. However, we adopted a more cautious approach, where therapy was continued for at least 12 months, with the decision to discontinue treatment based on clearly normal bronchoscopic findings. This strategy yielded good results, as there was no observed primary lesion regrowth in this present study. Following the decision to terminate the propranolol treatment and obtaining normal bronchoscopic findings, in cases where treatment is discontinued, a one-month dose-tapering approach can be employed to minimize the potential for hemangioma regrowth, with the dose halved twice in the first and third weeks before discontinuation [14, 15]. Therapy was terminated only if a child remained asymptomatic for four weeks. Nonetheless, reliance on endoscopic images for treatment decisions is not without limitations, as evidenced by the prolonged treatment duration in one girl (24 months) with this approach.

Adverse effects significantly contribute to treatment discontinuation in this disease, particularly regarding propranolol-induced hypoglycemic episodes. Propranolol may impair glucose homeostasis in patients diagnosed with hemangioma by inhibiting gluconeogenesis, glycogenolysis

and lipolysis through the activation of β -2 receptors [8]. In addition, both higher (4–12 mg/kg) and lower doses (0.5–2 mg/kg) might pose a risk for hypoglycemia [8, 16]. Propranolol can also potentially lead to severe hypoglycemia by masking early adrenergic signs such as tachycardia and profound sweating [17].

Notably, the important contributing factors in infancy are lower glycogen storage and higher glucose utilization during fasting [18]. Furthermore, accessorial predictive factors for propranolol-induced hypoglycemic events previously identified in the literature are prematurity, low birth weight and low body weight [19].

There is still no recommendation for therapy after serious events such as hypoglycemic seizures [2, 3]. As mentioned above, abrupt and permanent termination of propranolol therapy is not recommended due to the potential rapid regrowth of the primary lesion [13]. Propranolol replacement using the selective β -1 blocker atenolol, which is at least equally efficient and safer, could be a reasonable option, but this assertion has not been widely accepted [20]. In this present study, we found that reducing the total daily dose, frequent follow-ups and propranolol intake during or immediately after feeding led to favorable outcomes. However, more investigations and randomized controlled trials are needed to determine the optimal therapeutic strategy.

5. Conclusions

Presently, propranolol remains the primary therapy for treating hemangioma. Accordingly, future efforts could aim to establish a protocol for the safe and timely discontinuation of this treatment while minimizing potential adverse effects. In this regard, discontinuing treatment after hypoglycemic events is not recommended because of possibly fatal consequences in untreated patients and the high risk of rapid tumor regrowth using short-term therapy. In such cases, a reduction in the administered dose and avoiding risk factors, such as prolonged fasting and low body weight, are preferred approaches.

AVAILABILITY OF DATA AND MATERIALS

The data presented in this study are available on reasonable request from the corresponding author.

AUTHOR CONTRIBUTIONS

MB and AS—designed the study; PM—contributed to the conception and design of this study; MB and BG—collected data; MB, BG and AS—analyzed data; MB and AS—wrote the manuscript; AS—critically reviewed the manuscript and supervised the whole study process. PM and AS—gave technical support and conceptual advice. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Informed parental consent was obtained for each patient. The study was conducted in compliance with the Declaration of Helsinki. The Ethics Committee of the Mother and Child Health Care Institute of Serbia approved the study protocol in 2021 (decision number 8/31).

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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