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BRIEF COMMUNICATION

Clinical observations on propranolol use for paediatric airway hemangiomas

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KEYWORDS
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Abstract
Treatment of subglottic hemangiomas in children has traditionally been characterized as a challenging situation with multiple therapeutic options without consensus as to which one is the best and with risks of severe side effects. Recent reports on the experience of propranolol use in the treatment of paediatric airway hemangiomas suggest favourable reasons for this use due to the rapid improvement and its lack of severe side effects. In this paper we report the experience with 6 children having symptomatic airway hemangiomas treated with propranolol. All children improved their respiratory symptoms dramatically and did not need additional interventions.

PALABRAS CLAVE
Propranolol;
Hemangioma subglótico;
Beta-bloqueantes

Observaciones clínicas sobre el uso de propranolol en hemangiomas de vía aérea infantil

Resumen
El tratamiento del hemangioma subglótico infantil tradicionalmente se ha caracterizado por presentar multitud de técnicas terapéuticas, tanto médicas como quirúrgicas, sin existir consenso sobre cuál es la mejor opción y con la desventaja de potenciales efectos adversos muy severos. Trabajos recientes informan de mejorías sintomáticas significativas con el uso de propranolol en estos pacientes concluyendo que puede ser una alternativa eficaz a los tratamientos clásicos sin el inconveniente de tan graves efectos secundarios. Se presenta la experiencia de 6 casos de niños con hemangiomas sintomáticos de vía aérea tratados con propranolol. Todos ellos permanecieron asintomáticos respiratoriamente sin necesidad de tratamientos adicionales.

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Introduction

The natural history of subglottic hemangiomas is characterised by a mortality rate around 50% if not treated.[1] Approximately 2/3 manifest an obstruction of the airways of about 70%.[1,2] Histologically, the majority are capillary hemangiomas.[2]

They are often associated with a segmental distribution of cutaneous hemangiomas in the mandibular region.[1,3] The PHACE syndrome associates malformations of the posterior fossa, hemangiomas, cardiovascular abnormalities with aortic and ocular coarctation.[3,4] Up to 5% of subglottic hemangiomas manifest concomitant skin lesions and 1%2% of cutaneous cases present subglottic lesions.[4]

A limited efficiency of traditional methods is suggested by the variability of treatment options depending on the health centre, the absence of consensus on clinical guides[1] and the basis on expert opinions about the best therapeutic decision. The vast array of techniques usually employed, from the use of corticosteroid therapy to open surgery procedures, has been associated with important side-effects.[1,3]

In 2008, Léaute-Labrèze[5] reported the accidental discovery of rapid improvement in children with cutaneous hemangiomas, one of them with a subglottic lesion, treated with propranolol due to concomitant heart problems. This finding led to the possibility of studying the efficiency of propranolol to improve traditional options.

In this article, we describe our experience with 6 children with symptomatic laryngeal hemangiomas who were treated with propranolol.

Patients and method

Retrospective review of children with symptomatic laryngeal hemangiomas who were treated with propranolol as the main therapeutic option, seen in the paediatric ENT service since June 2008.

A total of 6 children with stridor were studied (5 female, 1 male), with airway hemangiomas identified through laryngotracheobronchoscopy with a rigid optic under general anaesthesia. The clinical, endoscopic and radiological characteristics prior to treatment are described.

The most important adverse effects attributed to propranolol are hypotension, bradycardia, hypoglycaemia and bronchoconstriction. A pre-treatment protocol was used to minimise these side-effects. The protocol included:

- Consultation with cardiology, electrocardiogram, echocardiogram.
- Hospital admission for 48 hours to monitor blood pressure, heart rate and blood glucose and to perform a paediatric assessment.
- Propranolol administration was started at 0.5km/kg/day (divided into 3 doses) and was incremented to 2mg/kg/day on the 2nd day of hospitalization.
- Informed consent for compassionate use was required (obligatory in our healthcare system).
- Cardiological reassessments were carried out at the end of the first month of treatment and from then on, every 2 months.

The drug was administered through the use of commercially-available 10 mg propranolol pills, which were dissolved in milk preparations.

Improvements in signs and symptoms during clinical exploration were considered as criteria of effective response towards the treatment.

Results

Table 1, Figure 1, Figure 2, and Table 2 respectively describe the clinical characteristics of patients and studies carried out before starting treatment with propranolol, pre-treatment endoscopic images of patients 1-4, imaging findings in patients 1-4, and the clinical evolution and incidences during treatment.

All cases presented a resolution of respiratory signs and symptoms during treatment with propranolol.

Discussion

The two traditional treatment options and their potential unwanted side-effects can be divided into 2 groups[1,2,6]:

- Pharmacological (corticosteroids, α-interferon, vincristine): Cushing, neurological disorders. Not all hemangiomas have a good response to systemic corticosteroids (only about 50%), and subglottic lesions show worse responses.
- Surgical (laser, cryotherapy, tracheotomy, intralesional corticosteroids, open surgery): subglottic stenosis, mortality, prolonged intubation, paediatric intensive care techniques.

Experiences with the use of propranolol in subglottic hemangiomas appear to show a high degree of efficiency in improving clinical symptoms without the disadvantage of severe side-effects compared to conventional treatments. This would be an argument in favour of the inclusion of propranolol as a therapeutic alternative. A reduction in size has been proven starting on the first day of treatment.[6-8] These effects are attributed to several mechanisms[5]: vasoconstriction, endothelial cell apoptosis, decreased expression of fibroblast growth factor genes and of the vascular endothelial growth factor genes.

In case number 1, the unfavourable evolution of the child, scheduled for tracheotomy, despite previous treatment attempts and having passed the theoretical age of the involution phase (around 2 years), treatment with propranolol produced spectacular results in the first doses. These circumstances are similar to those described in other cases.[7] However, the patient had a clinical recurrence after medication was temporarily suspended. This was solved by the first doses of beta-blocker after restarting the treatment.

In case number 2, the patient had a predominantly supraglottic component with minimal subglottic involvement, which justified the moderate clinical manifestations. Considering the type of laryngeal lesion this girl suffered, traditional treatment would have normally resulted in recurring episodes of moderate respiratory

Table 1 Description of patient characteristics before treatment with propranolol

Patient No.	1	2	3	4	5	6
Age/DB	3 m/February 2007	9 m/December 2007	1 m/ 7 d June 2008	2 m/15 d January 2008	1 m/15 d February 2009	1 m/12 d February 2009
Motive of remission	Dyspnoea from 2 m	Stridor from 1 m	Stridor dyspnoea	Stridor from 2 weeks	Neonatal stridor	Stridor from 48 h
Hemangiomas in 1st endoscopic airway	01-06-2007 Circumferential subglottic 70% obstruction. Planes in trachea	15-10-2008 Epiglottis, arytenoid, aryteno-epiglottic fold, left band and ventricle.	07-07-2008 Circular subglottic (1.5 mm aerial lumen). Planes in trachea	03-04-2008 Subglottic left and posterior. Aerial lumen 3 mm	Not prior to treatment with propranolol	24-03-2009 Left subglottic and posterior commissure. Aerial lumen 3 mm
Other cutaneous hemangiomas	Left submental. Occipital. Superior subcutaneous thorax	Sacrum region	Lower lip, free edge of tongue	Left cheek and cervical	Preauricular, cheek, left lower lip and tongue	Left maxillary and cervical
Affectation in imaging techniques (CT and/or MRI)	Maxillary, submental, presternal and left paratracheal.	Left hemi-supraglottis	Giant hemangiomas surrounding airway from oropharynx to carina	Left parotid and left posterior cervical triangle	Left parotid and subglottis with lumen of 3.2 mm	Left parotid, subglottis
Treatment prior to propranolol	SCC 2nd month CO_2 laser+ intralesional CC Weighted delay Consideration of tracheotomy	SCC	Urgent with CO_2 laser+intralesional CC SCC	SCC Cushing	No	SCC

CC indicates corticoids; DB, date of birth; SCC, systemic corticoids.

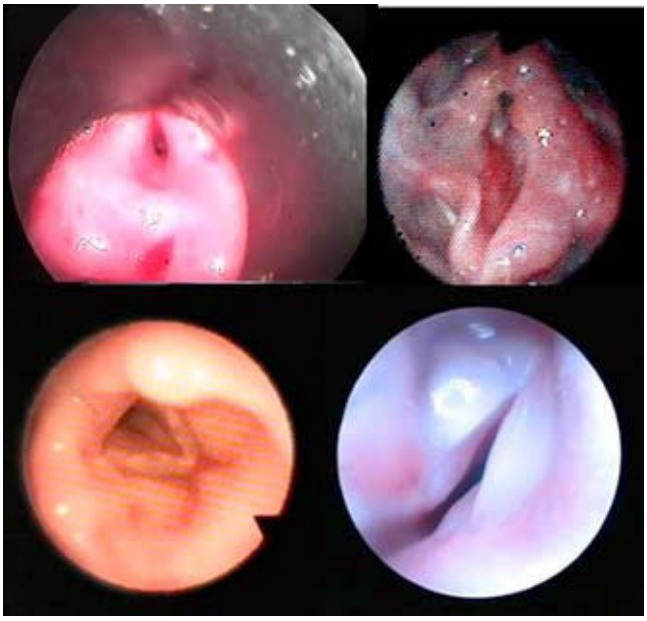

Figure 1 Endoscopic images of cases 1, 2, 3, and 4 (from left to right and from top to bottom), pre-treatment with propranolol.

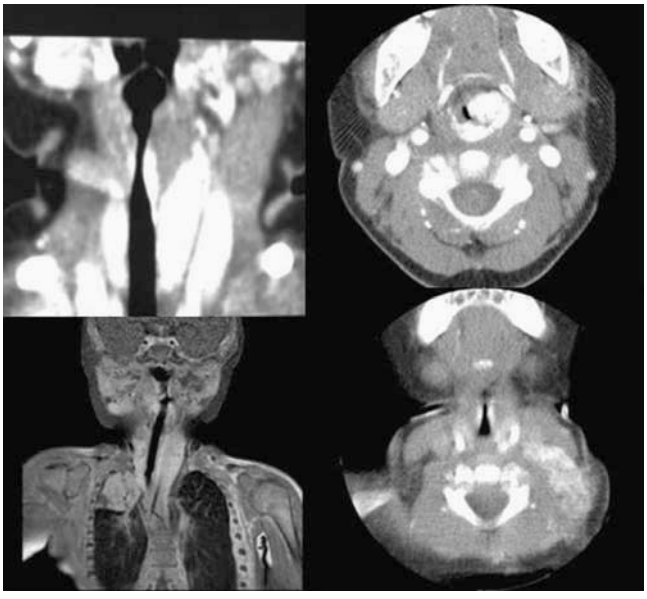

Figure 2 Imaging techniques for cases 1, 2, 3, and 4 (from left to right and from top to bottom), pre-treatment with propranolol.

distress, controllable through corticosteroids until the phase of involution, with the classical, associated side-effects.

In case number 3, the patient presented a giant extraluminal haemangioma around the airway from pharynx to carina, with a severe subglottic obstruction. Despite the emergency treatment to remove obstruction, the definitive resolution of symptoms would not be expected, but rather the need for further treatment.

In cases 4, 5, and 6, the patients presented mild respiratory symptoms with typical left subglottic lesions but with a moderate restriction of airway calibre. The prognosis with standard treatments would probably be based on systemic corticosteroids for nearly 1 year.

Although in all cases the use of beta-blocker was crucial in the improvement from the clinical point of view, the methodologically ideal alternative would be to document the potential therapeutic effects of propranolol evaluating 3 indicators: clinical, radiological and endoscopic.

It was not possible to systematically obtain evidence of improvement in all patients through the use of imaging techniques. In our hospital, CT is performed initially because of increased availability and better assessment of the air calibre. To assess the extraluminal component, an MRI is more useful. Controversy may persist about which cases this study should be requested for.

As with imaging techniques, it was complicated to obtain systematic post-treatment endoscopic explorations. In some cases, parents were reluctant to allow an exploration because of the need for general anaesthesia when the infant had been asymptomatic and without side-effects for some time. It would be necessary to carry such explorations out systematically for cases of clinical trials with an appropriate design.[9]

Tolerance to propranolol was good, both in the initial phase and in the maintenance phase, following the recommended protocols.[10] The following incidents took place:

- Case number 2 presented, 2 months after treatment, a case of pallor without loss of conscience, attributed by the emergency service to a possible vagal reaction. Cardiac and neurological studies during the episode and subsequently were negative. The patient continued with the same doses of propranolol without other incidents.
- Case number 4 suffered a crisis of bronchospasm with fever after 7 months of treatment. Propranolol administration was suspended. The patient did not present new episodes of stridor or asthma during the following 6 months.

Nevertheless, these incidents were easier to control than the possible adverse effects of classical treatments: stenosis, Cushing and reoperation under general anaesthesia.

As to adjusting for the most effective doses, the studies published on airway hemangiomas in infants used a dose of 2mg/kg/day, as described in the original report by Léaute-Labrèze. With regard to how and when to reduce the dosage, it is normally maintained[7] until the phase of proliferation has theoretically ended (around the age of 12 months), reducing it every 2 or 3 weeks and monitoring the possibility of regrowth with symptomatic recurrence.

In all cases except for number 3, the regression of cutaneous lesions was observed, along with simultaneous respiratory improvement.

None of the children included in this study required additional treatment for the control of their airways.

Despite the possible secondary effects attributable to beta-blockers found, the rapid symptomatic improvement and the manageable control of those effects suggest that the use of propranolol may be more beneficial than traditional treatments for the resolution of the process and for the control of adverse effects. Although further studies are needed to confirm safety and results, propranolol appears to be an acceptable alternative in the compassionate treatment of symptomatic airway hemangiomas.

Table 2 Clinical characteristics of patients after treatment with propranolol

Patient No.	1	2	3	4	5	6
Start with propranolol	27-06-2008 Decrease SCC	16-10-2008 No simultaneous SCC	08-07-2008 Decrease SCC	17-06-2008 Decrease SCC	15-04-2009	25-03-2009
Initial evolution with propranolol	17-8-2008 No dyspnoea No CCS	13-11-2008 No stridor	13-08-2008 No stridor No dyspnoea	18-07-2008 No stridor	17-04-2009 No stridor	10-06-2009 No stridor
Post-treatment endoscopies	18-08-2008 50%obstruction	13-11-2008 Only in free edge epiglottis	13-08-2008 3 mm of subglottic lumen	15-08-2008 No subglottic affectation	17-04-2009 No subglottic affectation	10-06-2009 Subglottic lumen of 5 mm
Follow-up	Asymptomatic	Episode of paleness in December 2008, with no syncope with normal cardiological and neurological evaluations	Asymptomatic	Episode of bronchospasm, stop PRP.	Asymptomatic	Asymptomatic
Subsequent months	Reduction to 1 mg/kg/d February 2009 Stop of PRP August 2009 Stridor in September 2009 with restart of PRP and disappearance of symptoms after 2 days	Reduction in size in MRI Stop of PRP June 2009. Asymptomatic	Stopping PRP		Continues with PRP	Continues with PRP

PRP indicates propranolol; SCC, systemic corticoids.

Conflict of interest

The authors declare no conflict of interests.

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