Drug Design, Development and Therapy

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ORIGINAL RESEARCH

The therapeutic efficacy of propranolol in children with recurrent primary epistaxis

This article was published in the following Dove Press journal:
Drug Design, Development and Therapy
28 February 2013
Number of times this article has been viewed

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Abstract: We hypothesized that some characteristics of beta-blockers, including negative inotropic, peripheral vasoconstrictor, and antiangiogenic effects, might be potentially useful in treating children with epistaxis. From June 2010 to March 2012, a total of seven children with recurrent primary epistaxis resistant to conventional management were observed at our institution. An overall effectiveness of propranolol was noted in all seven children when given a dose of 1.5–2 mg/kg/day (divided into three doses) as a second line therapy for terminating epistaxis. Based on our first experience, we believe that propranolol could be a favorable treatment option for patients with primary epistaxis.

Keywords: beta-blocker, epistaxis, children

Introduction

Epistaxis is a common medical problem in the pediatric population, and may generate considerable distress and anxiety among children and their parents. Although in most cases it is mild and self-limiting, a proportion of childhood epistaxis is massive, recurrent, or resistant to conventional management.[1]

At this date, there are still no relevant clinical data concerning the usefulness of nonselective beta-blockers in treating epistaxis.[2] However their antagonistic beta-1, and beta-2 adrenoceptor effects, together with their recently discovered antiangiogenic effect, suggests that nonselective beta-blockers have potentially useful hemostatic abilities.[2–5]

We present a case series of seven children with primary recurrent epistaxis, resistant to conventional management, who were treated with propranolol as a second line agent.

Methods

From June 2011 to March 2012, we saw seven children who were previously diagnosed to have a recurrent (at least one episode per week) and protracted (more than one month of duration) primary epistaxis and were previously unsuccessfully treated with standard therapy (topical antiseptic cream and local vasoconstrictors). Prior to referral to our institution, all children underwent rigid nasal endoscope examinations performed by the same physician (BM) and those that were found to have a specific intranasal pathology (other than prominent vessels on the nasal septum, crusting, or irritation) were excluded from the study. The study was approved by the local ethics committee of the Faculty of Medicine, University of Nis, Serbia No 01-244-2.

The children were started on propranolol if there were no other secondary causes of epistaxis, no history of receiving antiplatelet and/or anticoagulant therapy, and no

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bradycardia, hypotension, or bronchospasm prior to treatment initiation. As part of the initial evaluation, we performed complete blood counts as well as official blood pressure measurements on all our patients.

The dose of propranolol was initiated on an outpatient basis and arbitrarily set at 1.5–2 mg/kg/day, divided into three doses. The treatment duration was also arbitrarily limited to at least two weeks and maximum one month depending on patients' compliance. All the children's families also received standardized instructions regarding home heart rate monitoring, fasting, and signs of hypoglycemia such as sweating, shaking, anxiety, lethargy, hypothermia, or seizures. Occurrence of only one episode of epistaxis within the first month after the last dose of propranolol was considered as a treatment failure. All patients were followed up for six months.

Results

From June 2009 to March 2011, we saw a total of seven children (five boys and two girls, mean age 7.43 ± 2.8 years, age range 4–12 years) who fulfilled our inclusion criteria.

The overall effectiveness of propranolol for terminating epistaxis was successful in all seven children and we did not have any side effects of the treatment. During six months follow-up, only one child (Case 5) had recurrence of epistaxis. His first subsequent bleeding episode occurred for the first time on day 43 after the propranolol initiation and was in the form of minor, self-limiting nose bleeding. During the subsequent follow up period, he had only rare, once or twice a month or even bimonthly episodes of epistaxis. Of note is that prior to referral to our institution, he had almost daily massive nosebleeds, leading him to develop severe hypochromic anemia. For that reason, he also underwent repeated nasal packing to terminate the bleeding and he was considered for transfusion. On the other hand, all other laboratory investigations that were performed (bleeding time, prothrombin time, activated partial thromboplastin time, thrombin time, platelet aggregation, factors I, II, VIII. IX and von Willebrand factor, as well as thrombocyte aggregation, col/ADP, col/epi, and D dimer) revealed normal findings.

Clinical data for all seven children are summarized in Table 1.

Discussion

At this date, there are no relevant clinical data concerning the usefulness of propranolol for treating children with epistaxis.[1,2] This case series provides support for the use of propranolol as a potential treatment option for children with epistaxis.

We would like to emphasize a few important features of propranolol that are potentially hemostatic. By antagonizing beta-1 adrenoceptors, propranolol lowers stroke volume and blood pressure, both of which are frequently elevated in patients with epistaxis.[2] This possibly adverse effect, associated with β_2-adrenergic receptor antagonist activity (peripheral vasoconstriction), is a potentially desirable feature in epistaxis, as well as in a number of other bleeding disorders without signs of hemorrhagic shock.[2,3,6,7]

Recent data also indicate a strong antiangiogenic effect of propranolol.[8,9] Propranolol was shown to have a direct effect on tumor angiogenesis, and has recently been introduced as a novel treatment modality for proliferating hemangiomas and some other solid neoplastic proliferations.[10] Vasoconstriction, decreased expression of basic fibroblast growth factor, matrix metalloproteinase, and vascular endothelial growth factor, and up-regulation of apoptosis of capillary endothelial cells are some of the pathophysiological mechanisms responsible for the antiangiogenic effect of propranolol.[11]

Table 1 Clinical data of all children included in the study

Patient number	Age (years)	Average number of NBE (per week)	Treatment duration (in weeks)	Rhinoscopy findings
1	5	2	2	Bilateral prominent vessels on the anterior nasal septum
2	8	1	4	Normal findings
3	10	5	4	Unilateral crusting
4	12	10	4	Bilateral prominent vessels on the anterior nasal septum
5	7	10	4	Bilateral prominent vessels on the anterior nasal septum
6	6	2	2	Bilateral prominent vessels on the anterior nasal septum
7	4	5	2	Normal findings

Abbreviation: NBE, nosebleed episodes.

Likewise, propranolol might be potentially useful in children with primary epistaxis. After biopsies of the nasal septal mucosa were taken from five children with recurrent epistaxis undergoing nasal cautery, Montague et al found prominent thin-walled arterioles and capillaries with a surrounding inflammatory infiltrate, with no evidence of venous varicosities or arterial microaneurysms. They postulated a mechanism for septal neovascularisation due to chronic low-grade inflammation, as a cause for recurrent epistaxis in children.[12] Of note is that four of the seven of our patients had prominent vessels of the nasal septum.

Recently, the vascular endothelial growth factor inhibitor bevacizumab has shown promise as a medical treatment for epistaxis related to hereditary hemorrhagic telangiectasia. At this point, it is of interest to note the results of experimental study by Albinana et al,[13] who suggested the local administration of propranolol in the nose mucosa as a potential therapeutic option to control epistaxis in patients with hereditary hemorrhagic telangiectasia, as well as the results of clinical study by Olitsky,[14] who suggested topical timolol for the same indication. In our opinion, concerning its lower risk of adverse effects, timolol might also be a rational therapeutic option for children with recurrent epistaxis.

The final possible explanation for the therapeutic effect of propranolol might be related to its potential indirect alpha-1 agonist effect, indirectly provoking systemic veins vasoconstriction.[5,15] We are of the opinion that all these outlined effects are potentially useful in patients with epistaxis and we suggest that this treatment strategy is highly rational in this indication. However, further prospective studies involving large samples and stricter inclusion criteria (eg, nasal cultures) are required to confirm our results.

Acknowledgments

This work has been supported by the Ministry of Science and Technology of the Republic of Serbia by grant No 175092.

Disclosure

The authors report no conflicts of interest in this work.

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