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Original Study

Efficacy and Safety of Intranasal Medical Management in Pediatric Patients with Idiopathic Recurrent Epistaxis

İdiyopatik Rekürren Epistaksisli Pediyatrik Hastalarda İntranazal Medikal Tedavinin Etkinliği ve Güvenliği

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Ethics Committee Approval: This study was approved by the Istanbul Medeniyet University Goztepe Training and Research Hospital, Clinical Studies Ethics Committee, 21 March 2018, 2018/0099.
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ABSTRACT

Objective: *The goal of the study was to verify the efficacy and safety of topical medical treatment in idiopathic recurrent pediatric epistaxis patients by intranasal usage of both an antimicrobial and a moisturizing agent as a first-step management modality.*
Method: *Sixty-seven out of 326 pediatric patients with idiopathic recurrent epistaxis selected on a chart review of follow-up were enrolled in the study. The study was designed as an analysis of two groups: one group included 35 individuals (52.2% of the total cohort) having a hyperemic nasal mucosa and the second group included 32 individuals (47.8% of the total cohort) having a hypervascular nasal mucosa on physical examination before treatment.*
Results: *The study was performed with a total of 67 children (age range 3-17 years) including 36 males (53.7% of total cohort) and 31 females (46.3% of total cohort). The mean age was 9.78±4.09 years. There was not any statistically significant difference between the groups in terms of age, duration of follow-up and recurrence time of epistaxis (p>0.05). Recurrence of epistaxis was seen in 22.9% (8/35) of hyperemic nasal mucosa group and in 34.4% (11/32) of hypervascular nasal mucosa group (p>0.05).*
Conclusion: *We advise the use of both an intranasal antimicrobial ointment and a mucosal moisturizing gel as an effective, noninvasive and easily applicable medical treatment option for pediatric patients with idiopathic recurrent epistaxis before more invasive methods of epistaxis control.*

Keywords: *Recurrent epistaxis, idiopathic, child, tonimer, terramycin*

ÖZ

Amaç: *Çalışmanın amacı, idiyopatik rekürren pediyatrik epistaksis hastalarında topikal tıbbi tedavinin etkinliğini ve güvenliğini hem antimikrobiyal hem de nemlendirici bir ajanın intranazal uygulanmasının birinci basamak tedavi yöntemi olarak incelemektir.*
Yöntem: *İzlemin hasta kayıtlarının gözden geçirilmesiyle seçilen idiyopatik tekrarlayan burun kanaması olan 326 pediyatrik hastanın 67'si çalışmaya dahil edildi. Çalışma iki grubun analizi olarak tasarlanmıştır: bir grupta hiperemik burun mukozasına sahip 35 pediyatrik hasta (toplam kohortun %52,2'si) ve ikinci grupta hipervasküler burun mukozasına sahip 32 pediyatrik hasta (toplam kohortun %47,8'i) tedaviden önce fizik muayeneleri yapılmış uygun hastalar olarak seçilmiştir.*
Bulgular: *Çalışma 36 erkek (toplam kohortun %53,7'si) ve 31 kadın (toplam kohortun %46,3'ü) olmak üzere toplam 67 çocuk hasta (3-17 yaş arası) ile gerçekleştirildi. Yaş ortalaması 9,78±4,09 idi. Gruplar arasında yaş, takip süresi ve burun kanaması nüks süresi açısından istatistiksel olarak anlamlı fark yoktu (p>0,05). Hiperemik nazal mukoza grubunun %22,9'unda (8/35) ve hipervasküler nazal mukoza grubunun %34,4'ünde (11/32) burun kanaması nüksü görüldü (p>0,05).*
Sonuç: *Daha invaziv epistaksis kontrol yöntemlerinden önce, idiyopatik tekrarlayan epistaksisi olan pediyatrik hastalar için hem intranazal antimikrobiyal merhem hem de mukozal nemlendirici jelin birlikte kullanımının etkili, invaziv olmayan ve kolayca uygulanabilir bir tıbbi tedavi seçeneği olarak kullanılmasını öneriyoruz.*

Anahtar kelimeler: *Rekürren epistaksis, idiyopatik, çocuk, tonimer, terramycin*

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INTRODUCTION

Epistaxis is one of the leading causes of otorhinolaryngology and pediatric emergencies in pediatric population. Epistaxis affects up to 64% of those aged 11-15 years, 56% of those aged 6-10 years and 30% of those aged 0-5 years[1,2]. Rare causes of recurrent pediatric epistaxis include coagulopathy disorders, nasal trauma, nasal polyp, juvenile nasopharyngeal angiofibroma, hereditary hemorrhagic telangiectasia[3], and bacterial biofilms[2]. In most cases, the cause of recurrent pediatric epistaxis is unclear[1-3].

The majority of cases of nosebleeds can be controlled simply by clearing blood clots in nostrils followed by digital compression. However in some cases, these methods are not enough to control bleeding[3]. The characteristic features of pediatric epistaxis are attacks of nosebleeds at varying time intervals, bleeding from the anterior septal region (Little's area)[4], and commonly without any well-defined cause [so called as "idiopathic recurrent epistaxis" (IRE)].

In these patients results of laboratory tests performed to detect coagulopathy are within normal reference range and they have an unremarkable medical history for coagulation disorders except for recurrent attacks of epistaxis at highly variable time intervals. In these children, attacks of epistaxis can take place spontaneously or with minimal nasal trauma which is self-trauma as nasal itching or external trauma such as ball hit.

Noninvasive treatment options of idiopathic epistaxis are bidigital compression and intranasal application of antibacterial ointments with/without nasal hydration with saline gels and creams[1-7]. Chemical cauterization with silver nitrate in 75% or 95% concentrations in the form of a fused tip as potassium nitrate on thin plastic or wooden applicators is widely used as a minimally invasive therapeutic option[4]. Anterior packing with different nasal packing materials is also needed in some cases. More invasive intervention in uncontrolled bleedings and bleeding recurrences is electrocauterization of clearly visible vessels[3].

In children, epistaxis from anterior nasal mucosa generally occurs following a trauma such as scratching the nose, and this mucosal region which also heals with formation of a scab as in other wound healing processes[1,7-9]. During this healing process, the coagulated blood elements trapped under scabs, and the warm and moist nasal mucosa, creates a favorable milieu for the pathogenic bacteria to settle and proliferate. With the effect of this mild chronic inflammation nasal scabs enlarges even more, and when these scabs fall out bleedings recur, and thus a vicious cycle forms. In order to break this vicious cycle, nasal moisturizing creams and gels are also needed. For this purpose, seawater gel is used as a nasal moisturizer in addition to antibacterial cream in our patients.

In the current study, we aimed to verify the effectiveness and safety of topical medical management with oxytetracycline plus polymyxin B (*Terramycin®* cream, Pfizer Corp. Istanbul/Turkey) ophthalmic ointment and sterile isotonic seawater solution (*Tonimer®* Gel, Istituto Ganassini S.p.A., Milan/Italy) gel in pediatric patients with IRE as a first step noninvasive therapeutic management option.

MATERIALS and METHODS

This retrospective study was carried out in pediatric patients with idiopathic recurrent epistaxis who received local intranasal medical management between January 2015 and December 2018 in our Otorhinolaryngology outpatient clinic. The study was approved by the Institutional Review Board of our Hospital, with approval number of 2018/0099.

Medical records of the patients were retrieved from electronic outpatient chart review in a tertiary care center. Retrospective reviews of outpatient charts of these patients were analyzed, and

all patients who underwent any prior invasive intervention for management of epistaxis such as chemical cauterization with silver nitrate and/or electrocauterization were excluded from the study. Patients having other clinical conditions that can lead to nosebleeds such as allergic rhinitis, nasal septal deviation, upper respiratory tract infections and sinusitis were also excluded from the current study. Patients whose laboratory test results of whole blood cell counts (WBC), activated Partial Thromboplastin Time (aPTT), prothrombin time (PT/INR) performed to diagnose possible coagulation abnormalities that were abnormal or missing were also excluded from the study.

This was a retrospective study in which patients had already been treated when they were identified and recruited to the study. Data collection and follow up proceeded prospectively until a minimum 6 months of follow-up period was complete in all cases. Eligible patients were called by phone for control examination, and medical and family histories of the patients regarding epistaxis were obtained from at least one of the parents of the patients. Patients having a family history/medical history of suspect coagulation disorders and/or medications affecting the coagulation cascade were excluded from the study. Information about recurrence and the timing of recurrence were also obtained from the parents of the patients. All of the patients were younger than 18 years old, and all patients followed-up for at least 6 months. The patients who were followed up for less than 6 months, the follow-up time was extended up to a minimum of 6 months.

Only patients who received first-step treatment with intranasal application of Terramycin® 3.5 gr. 5 mg/1gr and *polymyxin* B 10.000 U/1gr) ophthalmic ointment twice per day (morning and evening) and Tonimer® saline gel (with algae extracts) nightly for two weeks were included in the study. The patients who were given solely Terramycin® 3.5 gr. (oxitetracycline 5 mg/1 gr and *polymyxin* B 10.000 U/1 gr) ophthalmic ointment or Tonimer® saline gel (with algae extracts) were excluded from the study.

We divided the patients into two groups according to anterior nasal mucosal examination findings where the recurrent epistaxis had taken place. Patients were categorized as having hyperemic (Figure 1) or hypervascular (Figure 2,3) mucosa with or without crusting. These two groups were compared.

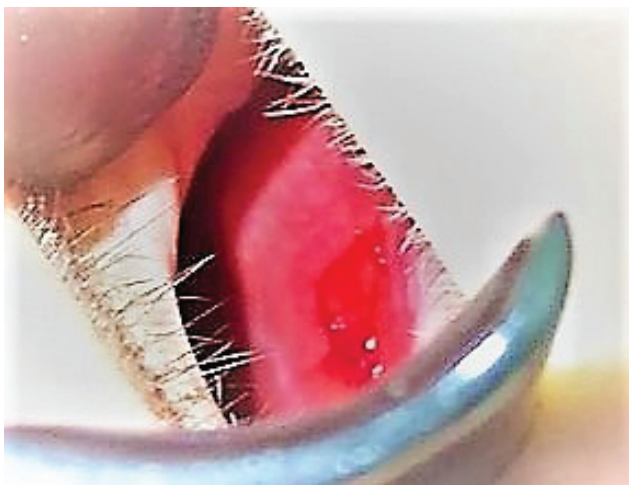

Figure 1. The right anterior septal hyperemic mucosa with a centrally located (Little's area) fresh coagulum due to epistaxis attack in a pediatric patient who had a complaint of right sided recurrent epistaxis is seen before treatment.

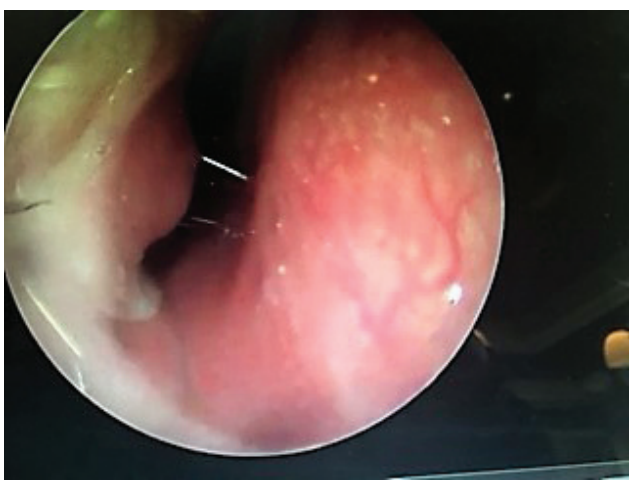

Figure 2. The right anterior septum with prominent vascular framework (hypervascular) mucosa (with a mild mucosal hyperemia) due to recurrent epistaxis attacks who had a complaint of bilateral recurrent epistaxis is seen before treatment.

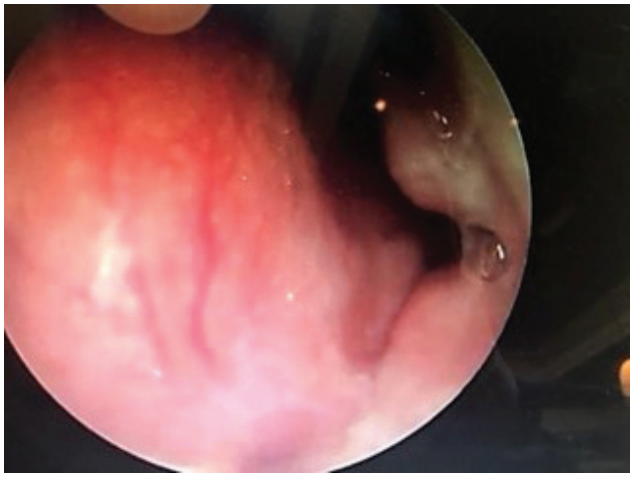

Figure 3. The left anterior septum with prominent vascular framework (hypervascular) mucosa (with a mild mucosal hyperemia) of the same patient who had a complaint of bilateral recurrent epistaxis is seen before treatment.

Statistical Analyses

IBM SPSS Statistics 22 (IBM, SPSS) software was used for analyzing data obtained from the study. The suitability of the parameters for normal distribution were evaluated by Shapiro-Wilk test. During analysis, besides descriptive statistical methods (mean, standard deviation, frequency), Student t test was used for comparison of parameters showing normal distribution, Mann-Whitney U test was used for those not showing normal distribution in the comparison of quantitative data between two groups. Chi-square test with Yates continuity correction was used in comparison of qualitative data. Level of significance was accepted as $p<0.05$.

RESULTS

Sixty-seven (36 males and 31 females) out of 326 eligible pediatric patients with IRE were enrolled in the study. The study was performed with a total of 67 children whose ages ranged from 3 to 17 years, including 36 (53.7%) males and 31 (46.3%) females. The mean age of all children was 9.78±4.09 years which was 9.8±4.35 years for hyperemic and 9.75±3.86 years for hypervascular group. The study was conducted as an analysis of two groups, one of which included 35 individuals (52.2%) with hyperemic nasal mucosa and the other 32 individuals with hypervascular nasal mucosa.

There was no statistically significant difference between the groups in terms of age, date of examination, duration of follow-up, and recurrence time of epistaxis ($p>0.05$) (Table 1).

In the hyperemic nasal mucosa group 51.4% of the patients were males and 48.6% of them were females, and in the hypervascular nasal mucosa group 56.3% of them were males and 43.8% of the were females, without any statistically sig-

Table 1. Comparison of study parameters and epistaxis recurrences between the groups.

	Groups			
	Patients with hyperemic nasal mucosa ***(Min-Max)-(Mean±SD)***	**Patients with hypervascular nasal mucosa** ***(Min-Max)-(Mean±SD)***	**Total** ***(Min-Max)-(Mean±SD)***	**p**
Age	(3-17)-(9.8±4,4)	(3-17)-(9.75±3,86)	(3-17)-(9.78±4,09)	[1]0.961
Follow-up duration (months)	(6-24)-(14.69±6,04)	(6-24)-(13.41±5,33)	(6-24)-(14.07±5,71)	[1]0.363
Epistaxis Recurrence duration (weeks)$_{(median)}$	(2-16)-(6.25±4.23 (5.5))	(3-24)-(8.45±7,17 (6))	(2-24)-(7.53±6,07 (6))	[2]0.800
Gender n (%)				
Males	18 (%51.4)	18 (%56.3)	36 (%53.7)	[3]0.881
Females	17 (%48.6)	14 (%43.8)	31 (%46.3)	
Epistaxis recurrence n (%)				
Yes	8 (%22,9)	11 (%34.4)	19 (%28.4)	[3]0.439
No	27 (%77,1)	21 (%65.6)	48 (%71.6)	

[1]Student t test, [2]Mann whitney U test, [3]Continuity (yates) correction

nificant difference between both groups (p>0.05) (Table 1).

Recurrence of epistaxis was seen in 22.9% (8/35) of hyperemic nasal mucosa group and in 34.4% (11/32) of hypervascular nasal mucosa group, without any statistically significant difference between both groups (p>0.05) (Table 1).

As a result, we observed that topical medical management with Terramycin® ointment and Tonimer® gel as first line treatment in pediatric patients with IRE successfully stopped epistaxis attacks in 71.6% (48/67) of all cases over at least 6 months of follow up (range: 6-24 months). In a follow-up period of at least 6 months, attacks of nosebleeds resolved in 48 patients (71.6%) without any need for additional intervention.

DISCUSSION

Nose bleeding in pediatric patients is mainly originates from the anterior part of the septum, almost always from Little's area (Kisselbach plexus), and due to mostly benign conditions which differ from adult patients[4-9]. A rich blood supply with a delicate network of blood vessels exists on Little's area covered with thin mucosal septum that can be easily destroyed and lead to bleeding even with minor trauma[9]. Pediatric IRE is defined as recurrent nose bleeding attacks with varying time intervals in pediatric patients. Although epistaxis may be an alarming event for parents, the majority of cases are self-limited and can be easily controlled by bidigital compression. In the current study, we found that local endonasal application of Terramycin® ophthalmic antimicrobial ointment and Tonimer® gel nasal moisturizer in pediatric patient with IRE is an effective first-line therapeutic option, stopping nose bleeding attacks in 71.6% of patients over six months. The difference in the frequency of epistaxis between the hypervascular and hyperemic nasal mucosa groups was not statistically significant which were 34.4% (11/32) and 22.9% (8/35), respectively.

In a study performed by Elden et al.[10] including 47 pediatric patients having IRE who were resistant to medical treatment, the authors found that 15 of them had abnormal coagulation tests and 5 of those were diagnosed to have bleeding diathesis based on pediatric hematology consultation results. Five of their 47 patients who had hemostasis disorder, they stated that the probability of having bleeding diathesis was more likely especially in pediatric patients having IRE who were resistant to medical treatment. In our study, exclusion of the patients with abnormal coagulation test results explains high success rates of local medical therapy given as a noninvasive treatment method for pediatric patients having IRE.

During anterior rhinoscopic examination of pediatric patients with IRE, crusting with/without prominent vessels, hyperemia, blood clots on the anterior septal region (Little's area) and normal looking mucosa have been detected [8]. As a cause of IRE in pediatric patients it has been recently reported that this inflammatory irritation induced by bacterial colonization of the anterior nasal mucosa might result in crusting and bleeding[8,9]. Additionally, this colonization leads to new vessel formation[8]. Effectiveness of intranasal application of antimicrobial agents to stop IRE attacks in pediatric patients explains this proposed causative effect of bacterial colonization on the anterior nasal mucosa[11-14]. Terramycin® which is originally an ophthalmic ointment is a locally effective antimicrobial agent used mainly by ophthalmologists. It has been widely used for treatment of trachoma[15]. Tube designing of the ointment by the manufacturer which has a tapered considerable long tip is an ergonomic form to facilitate the application of the ointment to the eye. This tip design also facilitates application of ointment to the nasal mucosa through the nostrils especially of pediatric patients who have smaller nares.

The limitation of this study is its retrospective design. Additionally, the use of only one type of treatment modality in the comparison of two

groups of patients according to anterior rhinoscopy findings is the other limitation of the study. On the other hand, assessment of the prevention of attacks of epistaxis in pediatric IRE patients during a considerable long time period ranging from 6 to 24 months is the strength of this study.

Ozmen S and Ozmen OA[16] concluded that chemical cauterization of anterior nasal mucosa with a 75% silver nitrate stick was not superior to intranasal application of Terramycin® as an antimicrobial ointment for the management of pediatric IRE patients so as to stop recurrences up to three months with a success rate of 62% and 48%, respectively. We also used Terramycin® for the management of our pediatric IRE patients who were not managed with any invasive methods such as chemical cauterization and electrocauterization. Our success rate of stopping recurrences of nosebleeds was higher (71.6%), and we believe that this higher success rate in our study was due to additional usage of Tonimer® gel which prevents nasal crusting by its moisturizing effect, and promotes wound healing/protective effect on mucosa via ingredient of dexpanthenol.

Use of local ointments for hydrating, moisturizing nasal mucosa and local antimicrobial ointments have been found to be effective in 65.2%-91% of pediatric IRE patients[5-14] which was compatible with our results (71.6%). On the contrary, Robertson and Kubba[17] found that in 65% of pediatric epistaxis patients treated with cream with/without cautery for long periods of five years nasal bleeding persisted, and the rate was highest (77%) in patients treated with combined application of cautery and cream. The rates of complete resolution of nose bleeding during 8 weeks of follow-up period using 75% and 95% concentrations of silver nitrate stick were found to be 98% and 90%, respectively[4]. Chemical cauterization of nasal mucosa with silver nitrate is a minimal invasive intervention but it potentially has some complications such as mucosal synechia, tattooing and septal perforation as well. Complication(s) due to intranasal application of ointments and saline spray and/or gels have not been pointed out in the literature yet, although it would be expected to cause local drug reactions at least. We detected only a mild short-lasting burning sensation reported in 8 patients (11.9%; 8/67) after intranasal application of Tonimer® gel which did not preclude drug usage.

Tonimer® gel is produced by conversion of diluted seawater into isotonic solution by electrodialysis technique and contains active particles coming from seawater which protect cells and promotes healing (sea algea extract = algea extract, hyaluronic acid and panthenol)[18]. It is in a format of high viscosity gel and when applied intranasally it provides long-lasting moisturization by forming a protective layer on mucosa. It has been shown that dexpanthenol found in Tonimer® gel, which is an active substance similar to panthenol, decreased nasal congestion, rhinorrea, conchal hypertrophy and nasal mucosal hyperemia by promoting wound healing with its epithelial protective effect[19]. Ercan et al.[18] found that the use of Tonimer® gel along with isotonic nasal spray was superior to the use of isotonic nasal spray alone in promoting healing and improving patient comfort by decreasing scabbing on nasal mucosa after endonasal surgery. The ameliorating effect of Tonimer® gel on scabbing together with its promoting effect on healing of scabbing on the anterior nasal septal mucosa in pediatric patients with IRE, exerts a positive impact by breaking the vicious cycle.

We found that intranasal treatment with Terramycin® as an antimicrobial ointment and Tonimer® gel as a mucosal moisturizing gel in pediatric patients with IRE is an effective, reliable, noninvasive, reproducible, safe, straightforward and easily applicable first-line treatment method. Local medical management seems to be a cost-effective noninvasive treatment modality. Therefore, we advise to use topical medical treatment option for pediatric patients with IRE as a first-line treatment before more invasive methods.

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