Case report

A self-controlled comparative clinical trial to explore the effectiveness of three topical hemostatic agents for stopping severe epistaxis in pediatrics with inherited coagulopathies

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Objective: The aim of this study was to assess the effectiveness of localized treatments to persistently stop epistaxis in patients with inherited bleeding disorders.
Methods: In a self-controlled comparative clinical trial, to offer the best solution to stop epistaxis at home (within 10 minutes), patients with inherited bleeding disorders were treated using three different topical hemostatic agents, including Tranexamic acid impregnated tampon, EpiCell tampon prepared from oxidized regenerated cellulose pad, and ChitoHem tampon (reinforced with chitosan). The results of using these different products on three groups of randomly selected patients were ultimately compared using the χ^2 and Fisher's exact test statistics.
Results: A total of 31 patients, 5 females and 26 males with a mean age of 5.6 years, were included in the study. Twenty-three patients had Glanzmann disease, four had von-Willebrand disease, two had Bernard soulier syndrome, two had activated factor VII deficiency, and one patient had impaired secretion of adenosine deaminase. The study exhibited that statistically there was no significant difference between EpiCell tampon and Tranexamic acid impregnated tampon treatments with respect to the hemostasis duration. However, ChitoHem tampon was more efficient than Tranexamic acid impregnated tampon (P value <0.001) and EpiCell tampon (P value < 0.05).
Conclusion: ChitoHem tampon, the chitosan-reinforced product, was the best therapy solution to stop epistaxis. We recommend further research on the use of other hemostatic agents for localized bleeding in patients with inherited bleeding disorders.

Keywords: Local hemostatic agents, Inherited blood coagulation disorders, Epistaxis, Hemostasis

Introduction

Epistaxis or nosebleed is a common complaint and a significant concern among individuals with inherited coagulopathies. In some cases in epistaxis, the bleeding is so frequent that it may lead to anemia. Some patients are injected with coagulation factors or platelets, which in addition to side effects it can significantly affect the patient's quality of life due to recurrent hospital admissions and also impose a great burden to the health services system. Therefore, it is important to be able to find effective topical hemostatic treatments to stop bleeding in epistaxis cases for individuals with inherited coagulopathies.

There exists a considerable body of evidence indicating the role of some topical hemostatic agents in stopping epistaxis. The first major category is chitosan-based products, which are traditionally derived from shrimp's shell and that of other crustaceans.[1] Based on their cationic characteristics, these compounds have hemostatic properties. Furthermore, they reportedly have anti-bacterial and anti-fungal characteristics.[2–6] They have also received the approval

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of the Food and Drug Administration as well as European health authorities to be used in bondages and other hemostatic agents, and are therefore, being used in American and British army.[7,8]

Tranexamic acid, another hemostatic agent, belongs to the category of antifibrinolytics, hindering the bonding of plasminogen and plasmin with fibrin which in turn prevents dissolution of hemostatic platelets.[9,10] Antifibrinolytics are effective in stopping epistaxis by holding fibrinolysis. They are also effective in decreasing the need for coagulation factors in individuals with inherited coagulopathies.[11] Tranexamic acid is also effective in patients with lack of alpha anti-plasmin[12] in epistaxis in patients with inherited Telangiectasia,[13,14] and in decreasing the need for surgery in case of gastrointestinal bleeding.[15,16]

Finally there is oxidized regenerated cellulose (ORC), which has hemostatic properties through a variety of mechanical and chemical effects on decreasing pH, which can accelerate the cascade of coagulation and clot formation.[17] The most frequent use of ORC is for controlling the oozing from large surfaces; however, it can also be used to control bleeding from small coronary arteries.[18]

Although the effectiveness of the above mentioned hemostatic agents has been widely assessed in the literature,[19–27] there is no previously conducted studies evaluating and comparing their effectiveness in epistaxis. Therefore, this work sought to investigate and compare the effectiveness of the aforementioned topical hemostatic agents, i.e. chitosan-based products, Tranexamic acid impregnated gauze, and ORC-based products in to stop nasal bleeding in patients with inherited coagulopathies.

Methodology

Study design

In this work, patients referred to Mofid Pediatrics Hospital, Tehran, Iran, during the year 2012 for inherited coagulopathies and repeated epistaxis were considered for eligibility in a Self-Controlled Comparative Clinical Trial. The inclusion criterion was the existence of coagulopathies and epistaxis, which could not have been controlled with simple localized pressure or ice compress in 10 minutes. If the bleeding in treatment cases continued following the removal of the tampon, it was considered unsuccessful. However, patients with other acquired bleeding disorders or those who were receiving other coagulation factors at the time of admission were excluded.

Study procedure

In this work, three separate epistaxis episodes were considered for each patient, each of which was randomly treated using one of the hemostatic agents mentioned below:

- The commercially available Tranexamic acid purchased from Rasht Company, Iran. (Tranexamic acid impregnated tampons were the same size as other tampons used).
- The commercially available ORC tampon, trade named 'EpiCell', purchased from ChitoTech Company Inc., Iran.
- The commercially available chitosan impregnated tampon, trade named 'ChitoHem', purchased from ChitoTech Company Inc., Iran.

The parents of patients admitted to Mofid Pediatrics Hospital were asked to have their children to be included in the study. Provided the patients met the eligibility criteria, their parents signed the informed consent before being included in the study. The parents of eligible participants were then given the required devices and were instructed, by a trained pre-instructed nurse, to randomly use one of the hemostatic agents in the study procedure. In addition, the pre-instructed nurse was constantly in contact with the parents of patients monitoring the use of the products and recording all the findings. Patients' parents who were trained by the nurse inserted the tampons. The same pre-instructed nurse also treated participants, who were admitted to the hospital for controlling their bleedings, based on the study protocol. For either case, a data collection form was filled out, recording the patient's disorder, age, and gender, effectiveness to stop epistaxis (cessation of epistaxis episode in less than 10 minutes) and non-stanching.

Ethical considerations

Before being included in the study, the parents of eligible participants accepted to sign the informed consent. Each participant was allowed to withdraw from the study whenever they desired. All the treatment devices were provided for the participants free of charge. Finally, all of the patients' information was classified and the findings were reported anonymously.

Statistical analysis

The McNamara test was used to compare the therapeutic effects of the three hemostatic agents two by two. In order to eliminate the effect of multiple comparisons, a P value of less than 0.017 was considered as significant.

Results

A total of 31 patients complied with the eligibility criteria and were included in the study. The result for each patient was compared with themselves in three different epistaxis episodes. In five cases, patients did not use all three agents; therefore, their results were not compared in three groups.

Table 1 The absolute and relative frequency of epistaxis episodes stopped in <10 and >10 minutes by each of the localized treatments

The time required for stanching epistaxis	<10 minutes number (percent)	>10 minutes number (percent)
Tranexamic acid	6 (20.7%)	23 (79.3%)
EpiCell tampon (ORC)	12 (41.4%)	17 (58.6%)
ChitoHem tampon (Chitosan impregnated)	24 (80%)	6 (20%)

The average (±SD) age of the participants was 6.5 ± 2.6 years, generally in the range of 2–14 years. Five patients (16.1%) were female, while 26 patients (83.9%) were male. With respect to the type of disorder, 22 patients (71%) had Glanzmann disease, 4 patients (13%) had von Willebrand disease, 2 patients (6.5%) had Bernard-soulier disease, 2 patients (6.5%) had factor 7 deficiency, and 1 patient (3%) had impaired platelet granule secretion.

Table 1 presents the absolute and relative frequency of epistaxis episodes stopped in <10 minutes and >10 minutes by each of the localized treatments. Considering the results, there existed statistically significant differences between chitosan-based product and Tranexamic acid ($P < 0.0001$), and between chitosan-based product and ORC ($P = 0.013$). However, no significant difference was observed between Tranexamic acid and ORC tampons ($P = 0.125$). There was no report of any other complications using the above-mentioned products.

Discussion

This study was conducted aiming to explore the effectiveness of three topical hemostatic agents, a chitosan-based tampon, ORC tampon, and Tranexamic acid tampon, in stopping epistaxis in patients with inherited coagulopathies in a Self-Controlled Comparative Clinical Trial. Results from this study indicated that ChitoHem® tampon was capable of faster hemostasis in patients compared to EpiCell® tampon (ORC) and Tranexamic acid impregnated tampon. However, there was no difference in the effectiveness of ORC and Tranexamic acid in stopping epistaxis. In fact, in most cases (i.e. 80%), ChitoHem® tampon could stop the nose bleeding in less than 10 minutes, while for ORC and Tranexamic acid, only in 41.4 and 20.7% of the cases, respectively, the epistaxis could be stopped in less than 10 minutes.

Although the effectiveness of the three hemostatic agents has been evaluated in previous studies, none of them had sought to compare their effectiveness in a single study. Among the three hemostatic agents, chitosan-based products have been most extensively studied for their effectiveness in stopping epistaxis. For example, Brown *et al.*[18] conducted a clinical trial to explore the effectiveness of bandage with chitosan-based compounds in hemostasis. Results indicated that normal bandage could not stop bleeding; however, bandaging with chitosan-based compounds could stop approximately 75% of the bleeding cases in less than 3 minutes. In another study conducted by Cox *et al.*,[20] it was found that bandaging with chitosan-based compounds could stop bleeding in 97% of the cases without having side effects. Other studies have also confirmed the relatively high efficacy of chitosan-based compounds in hemostasis.[21,22,27]

Few studies have been conducted to explore the effectiveness of ORC and Tranexamic acid in stopping epistaxis and their results have been rather controversial. For example, Ramström *et al.*[26] reported that Tranexamic acid can prevent the postsurgical bleeding in oral surgeries. However, in another study by Tibbelin *et al.*,[28] the hemostatic effect of local application of Tranexamic acid was evaluated in patients with nose bleeding in a double-blind, multicenter trial. The results indicated no significant difference between the efficacies of this treatment compared to that of the placebo group existed. With respect to ORC, Rossmann and Rees[29] indicated that the application of this hemostatic agent was less efficient and had more side effects than other agents in stanching the bleeding after a surgery. These findings are somewhat consistent with those from this study, indicating the higher efficacy of chitosan-based compounds that ORC and Tranexamic acid in stanching bleeding.

This work was the first comparative study exploring the effectiveness of three topical hemostatic agents in stopping epistaxis. In addition, it was the largest study, with respect to the sample size, focusing on patients with inherited coagulopathies. Furthermore, the results of this study are of great importance for a better quality of life for patients by decreasing hospital admits and intravenous injection of coagulation factors, for clinical practitioners and for health policy makers in countries with limited resources due to the significantly less cost of treatments of local hemostatic agents compared with systemic treatments.

Conclusion

According to the results from this study, it can be concluded that ChitoHem tampon (chitosan reinforced) is more effective than EpiCell tampon (ORC based) and Tranexamic acid impregnated tampon in accelerating hemostasis of epistaxis in patients with inherited coagulopathies. Therefore, patients were able to quickly and efficiently stop bleeding without the need to be admitted to the hospital and injected with other coagulation factors. This can also be translated as the high efficacy of chitosan-based products in stopping epistaxis among patients with inherited bleeding disorders.

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