Fibrin glue in initial treatment of epistaxis in hereditary haemorrhagic telangiectasia (Rendu–Osler–Weber disease)

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The purpose of the present study was to evaluate the haemostatic efficacy of fibrin sealant in patients with hereditary haemorrhagic telangiectasia (HHT) or Rendu–Osler–Weber disease suffering epistaxis. A retrospective observational study of patients with HHT who were admitted to an emergency room for anterior or posterior epistaxis during May 2000–March 2003. A total of 24 patients were evaluated, of whom 15 were managed with foam nasal packing during May 2000–March 2002 and another nine were treated during March 2002–March 2003 with 0.3 ml fibrin sealant spray (Quixil; Omrix, Belgium). The immediate and the distant results were compared. Immediate haemostasis was achieved in all seven patients treated with fibrin glue, with good healing of bleeding sites, no secondary bleeding, no inflammation, and no plaque or crists. Twelve months of follow-up monitoring (until October 2003) of atrophic changes of nasal mucosa, bleeding frequency and intensity proved absence of atrophy of nasal mucosa and decreased bleeding frequency. In this group, the bleeding episode duration averaged 2 min 35 s since the moment of admittance. In the nasal packing group, we found local swelling, pain, and slow healing of the bleeding site with accidental atrophy of nasal mucosa and no effect on further bleeding frequency and intensity. Removal of nasal packing frequently initiates secondary bleeding. The rates of these side effects were higher in comparison with the fibrin glue group. The bleeding episode duration was also longer. In patients with HHT suffering profuse epistaxis, fibrin glue is more effective and convenient for the patients as compared with foam nasal packing. It is also safer, since it lacks the complications that usually accompany packing as swelling, atrophy of the nasal mucosa, and secondary bleeding provoked by the removal of the pack. *Blood Coagul Fibrinolysis* 15:359–363 © 2004 Lippincott Williams & Wilkins.

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Introduction

Rendu–Osler–Weber disease, or hereditary haemorrhagic telangiectasia (HHT), is an autosomal dominant inherited disease characterized by systemic vascular dysplasia. Recurrent epistaxis is the most frequent symptom of HHT, occurring in over 90% of patients [1,2]. As William Osler wrote in 1901, "I have reported three cases of chronic recurrent epistaxis in adults associated with remarkable telangiectases of the skin and visible mucous membranes ... There may be an hereditary tendency to it" [3]. HHT is an infrequent disease, but epistaxis is not a rare event, experienced by 5–10% of the population every year [4,5]. That is why the management of epistaxis is similar in HHT and non-HHT patients in most emergency rooms. It involves the use of some form of cautery and/or nasal packing.

Complications of nasal packing, are well recognized and include atrophy, pain [6], dehydration, infections [7], allergy, disturbance of breathing during sleep [8] even with decrease in nocturnal arterial PO_2 [9], dislocation of the pack with possible aspiration (rare), influence on eustachian tube function [10], and altered ventilation. Generally, nasal packing requires administration of antibiotics and/or topical ointment to prevent dryness.

There were several reports about the use of fibrin adhesive for haemostatic needs in otolaryngology [11,12]. The haemostatic properties of fibrin glue are well known [13], and recently we reported benefits of its use in treatment of non-specific epistaxis [14].

The current research was made to prove the second-generation surgical fibrin sealant Quixil to be an effective substitute for nasal packing in management of nosebleeds in patients with HHT when they urgently come to an emergency room. We made a retrospective comparison between two haemostatic methods—previously used nasal packing, and currently using fibrin glue spray—in regard to their effectiveness in treatment of epistaxis. We compared the rates of side effects (local swelling, for example, and especially

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atrophic changes) and rebleeding, time needed for complete stop of haemorrhage, and rate of development of scars.

We did not compare amounts of blood loss since the moment of admittance to the operating room until the moment of complete haemostasis, because the amount of blood loss before the moment of admittance is almost always not known. Therefore, the total blood loss is not known, and the partially known blood loss is of small importance. Second, physiological reactions on blood loss vary significantly among different patients and there is no direct correlation of amount of blood loss with severity of these reactions. In case of HHT, the general condition of a patient and other manifestations of the disease affect the intensity of a nosebleed. Furthermore, easily controlled bleeding, profuse nosebleed, continual haemorrhage, and other types of epistaxis are generally treated with the same devices at the time of admittance to an emergency room.

Methods and materials

Patients

Our series includes 22 patients with anterior epistaxis (bleeding from the anterior area of the septum, like Kiessellbach or Little area) and with posterior epistaxis (bleeding from the posterior and/or superior lateral walls of the nose and septum). Group 1 consisted of 15 patients (mean age, 40.3 years; standard deviation, 10.4), who visited the emergency department of our hospital because of profuse nosebleeds in 2000–2002; Group 2 consisted of nine patients (mean age, 40.9 years; standard deviation, 11.7), who visited the emergency department during the May 2002–August 2003 period. In the first group, epistaxis was initially stopped with nasal packing (Merocel packs), and in the second group epistaxis was initially treated with fibrin glue spray.

Patient data, such as age, sex, etiology and type of bleeding were recorded, and are presented in Table 1. All patients presented active bleeding at the time of admittance. There were no significant differences between the two groups with respect to age, sex, distribution of pathologic condition, and peculiarities of bleeding. All of the patients in both groups had confirmed diagnosis of HHT and prior incidents of epistaxis as a recurrent problem. The diagnosis was based on the following criteria: family history, epistaxis, telangiectases and visceral arteriovenous malformations. The diagnosis was considered definite if three criteria were present.

Materials

The use of fibrin glue was approved by hospital ethics committee (outpatient and inpatient departments) in 2001. Biodegradable surgical adhesive and sealant for wound closure, Quixil (Omrix, Belgium), is made from human plasma cryoprecipitate. It was invented in 1997. Since 1999, it has been licensed in Israel and several other countries, and was approved in the United Kingdom. Based entirely on enzymes and other proteins derived from human blood plasma, Quixil binds itself to severed or damaged blood vessels and tissues, stopping bleeding. Quixil is a surgical sealant whose formulation is based on a concentrate of human clottable proteins (virus-inactivated concentrated cryo) and a highly purified native human thrombin (α-thrombin, 900–1100 IU/ml). Quixil has two liquid components that, when sprayed together on a bleeding site, form an elastic material that mimics natural clotting. There are 1, 2, and 5 ml vials of the components, suitable for almost all occasions.

Currently Quixil is used to facilitate haemostasis and reduce operative and post-operative bleeding and oozing during surgical procedures, including endonasal operations [15,16]. Quixil is sprayed with the help of compressed air onto the bleeding site in short bursts (0.1–0.2 ml) to produce a thin, even layer. If the haemostatic effect is not complete, a second layer should be applied. Quixil is metabolized by the physiological fibrinolytic system and absorbed, in the same way as an endogenous clot. Quixil was applied through a pre-assembled application device featuring the MixJect vital transfer mechanism (Fig. 1). This is a dual-syringe delivery system. The MixJect system is

Table 1 Distribution of patients: age, sex, type of epistaxis, number of emergency room (ER) visits a year because of epistaxis

Patient	Sex	Age (years)	Type of epistaxis	ER visits a year
Group 1				
1	Female	26	Posterior	6
2	Female	40	Anterior	17
3	Female	36	Anterior	21
4	Male	54	Anterior	9
5	Female	28	Anterior	16
6	Male	24	Anterior	12
7	Male	60	Posterior	34
8	Female	44	Anterior	8
9	Male	48	Anterior	19
10	Male	34	Anterior	22
11	Male	39	Anterior	10
12	Female	45	Anterior	8
13	Female	43	Anterior	9
14	Male	56	Anterior	11
15	Male	28	Anterior	7
Group 2				
1	Female	23	Anterior	7
2	Female	45	Posterior	11
3	Female	63	Anterior	12
4	Male	31	Anterior	20
5	Male	30	Anterior	15
6	Female	33	Anterior	8
7	Male	54	Anterior	8
8	Male	46	Anterior	9
9	Female	43	Posterior	7

clog-free and allows for needle-free aspiration of the reagents into the application device, enhancing.

Allergic and neurotoxic reactions to one of the constituents of Quixil may occur. Quixil should not be used in surgical operations where contact with the cerebrospinal fluid or dura mater would occur. Quixil is not known to interact with any other drug. There are concerns about transmission of slow viruses through human-based products. To minimize the risk of transmission of infective agents, stringent controls are applied to the selection of blood donors and donations. In addition, two consecutive virus removal and/or inactivation procedures are included in the glue production process. For clottable proteins this is solvent/detergent (S/D) treatment and pasteurization, and for thrombin this is S/D treatment and virus filtration.

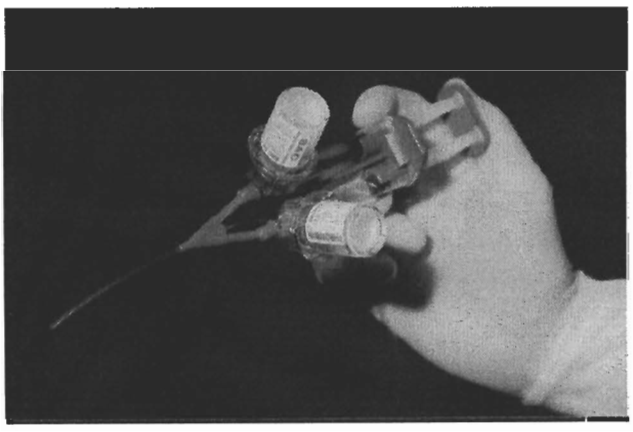
Merocel (Merocel Inc., Connecticut Mystic, CT, USA) foam packing made of polyvinylacetal was used for nasal packing in the Group 1 patients. In the dry state the packs of Merocel are considerably smaller than after hydration at the site of action in the nose. Uptake of blood after intranasal insertion of a pack causes a rapid increase in its volume thus leading to absorption of blood and at the same time to wound compression.

Procedure

Usually patients were assessed while seated bleeding anteriorly into a dish. After clots were evacuated with suction, all patients were examined by anterior rhinoscopy and endonasal endoscopy before treatment.

For Group 1, haemostasis was achieved by nasal packing. For Group 2, haemostasis was achieved by spraying with the Quixil fibrin glue 0.3 ml to each bleeding nostril. Arbitrarily, anterior bleeding sites are those anterior to the maxillary sinus ostium and posterior sites lie behind the ostium. Cases of posterior bleedings were treated under microrhinoendoscopic control. All patients were advised to avoid non-steroidal anti-inflammatory drugs and situations likely to increase blood pressure like hot showers, hot beverages, and vigorous exercises. Follow-up visits were scheduled the next day, the third day, 2 weeks, and 1 month after treatment. After that patients were monitored for another 11 months.

Fig. 1



MixJect—a dual-syringe delivery system for the Quixil fibrin glue. It was used in all types of our endonasal operations.

Results

The results of the treatment were assessed objectively by the surgeon using anterior rhinoscopy and endoscopy of the nasal cavity and assessed subjectively by the patients at the follow-up visits. The results were good in all nine (100%) patients of the fibrin glue group with complete and immediate haemostasis. We found good healing of bleeding sites, no swelling, scars, atrophy, no inflammation, no plaque or crists, related to the glue application. There were no any other complications in this series except only two cases with excessive nasal discharge. Quixil absorbed completely. It did not form plaques, and there was no danger for aspiration of plaques. In Group 2 the bleeding episode duration averaged 2 min 35 s since the moment of admittance. Twelve months' monitoring of atrophic changes of nasal mucosa proved absence of atrophy of nasal mucosa.

In Group 1, where nasal packing was used, we found local swelling, pain, and slow healing of the bleeding site with accidental atrophy of nasal mucosa. The rates of side effects are presented in Table 2. It took 6 min 20 s to stop bleeding. The incidence of post-treatment bleeding (24-h rebleeding) in Group 1 was 60% (nine patients). All these patients returned to the operating room for haemorrhage revision. The incidence of 24-h rebleeding in the fibrin glue group was 0% (0 patients). The incidence of rebleeding is presented in Table 3.

Discussion

Epistaxis is a frequent problem in rhinology and general practice. It presents as an emergency, but for patients with HHT this is a chronic problem of recurrent bleeds. Current practical guidelines for the management of the patient with epistaxis due to HHT are not successful and an innovative approach is essential [17,18].

It is obvious that in cases of recurrent epistaxis or continual haemorrhage nasal packing can cause even more disturbance to a patient than epistaxis itself. In case of HHT, removing nasal packs lacerate nasal mucosa and bleeding resumes. In these cases fibrin glue has obvious advantage because of its painless

Table 2 Incidence of complications and the bleeding episode duration in two investigated groups

	Nasal packing group ($n = 15$)	Fibrin glue group ($n = 7$)
Local swelling	–	0 (0%)
Scars	0 (0%)	0 (0%)
Atrophy of nasal mucosa	2 (13.33%)	0 (0%)
Synechia	1 (6.66%)	0 (0%)
Infection	1 (6.66%)	0 (0%)
Excessive nasal discharge	12 (80%)	2 (28.6%)
Time needed for complete stop of haemorrhage	6 min 20 s	2 min 35 s

Table 3 Incidence of rebleeding in two investigated groups after performed haemostasis

Group	First 24 h	48 h	1 week	2 weeks	1 months	3 months
Nasal packing ($n = 15$)	9	2	4	4	3	5
Fibrin glue ($n = 7$)	0	0	1	2	2	3

method of application by spraying. No anaesthesia is needed before the spraying of fibrin glue. Generally, nasal packing requires administration of antibiotics. This is not a case for fibrin glue treatment.

While groups were small, we cannot make broad statements based on statistics. However, we found statistically significant difference between incidence of complications observed in the Quixil fibrin glue group and nasal packing group of patients (Table 2). Indeed, fibrin glue use did not produce swelling, scars, synechia, infection, or atrophy of nasal mucosa. At the same time, the incidence of rebleeding was much lower in the fibrin glue group (Group 2) than in the nasal packing group (Group 1). The incidence of rebleeding observed in Group 1 (60%) was very high in comparison with the incidence of rebleeding observed in Group 2 (0%).

The absence of side effects after fibrin glue usage is remarkable. Even when opposing septal sites are treated, there is no danger of perforation. Absence of mucosal atrophy or skin necrosis is a very stimulating effect for fibrin glue usage in epistaxis treatment. Dryness is not developed either, and there is no need to apply topical ointment immediately after treatment. In these cases, the ointment was used as a part of continuous management of the patients.

Twelve months of follow-up monitoring of patients in Group 2 revealed some decrease in bleeding frequency and intensity. Some of these patients, however, were treated with tranexamic acid and long-term applications of soft nasal ointment at the same time. While it is known that these drugs can cause a reduction in the frequency of epistaxis [19], we were unable to investigate in detail the similar role of fibrin glue. Additional study is needed to research possible concord in effects of fibrin glue and tranexamic acid on bleeding frequency and intensity.

Finally, we want to underline a limitation of our study. The study was performed to investigate the fibrin glue suitability only as initial therapy of epistaxis in HHT.

Conclusion

Our results indicate that the Quixil fibrin glue application to the bleeding sites in epistaxis due to HHT provides effective haemostasis and sealing. With the help of Quixil we minimized surgical trauma and achieved effective haemostasis at the same time. We completely avoided post-treatment atrophy of nasal mucosa. We found this fibrin glue to be more convenient intranasal haemostatic sealant in comparison with nasal packing for patients who experience repeated, profuse nosebleeds. We suggest that fibrin glue can be used alone or in combination with laser therapy if repeated laser therapy is not indicated. This procedure is less traumatic and can be repeated multiple times. Nasal packing is not a useful treatment for HHT patients and should be avoided.

References

1 Geisthoff UW, Schneider G, Fischinger J, Plikert PK. Hereditary hemorrhagic telangiectasia (Osler's disease). An interdisciplinary challenge. *HNO* 2002, **50**:114–128.

2 Kirchner J, Zipf A, Dietrich CF, Hohmann A, Heyd R, Berkefeld J. Universal organ involvement in Rendu-Osler-Weber disease: interdisciplinary diagnosis and interventional therapy. *Z Gastroenterol* 1996; **34**:747–752.

3 Osler W. *The principles and practice of medicine*, 4th edition. Edinburgh & London: Young J. Pentland; 1901, p. 614.

4 Abelson TI. Epistaxis. In: Paparella MM, Shumrick DA, (editors): *Otolaryngology. Vol. III: head and neck*, 3rd edition. Philadelphia, PA: W.B. Saunders; 1991, pp. 1831–1841.

5 Bingham B., Dingle AF. Endoscopic management of severe epistaxis. *J Otolaryngol* 1991; **20**:442–443.

6 Tierney PA, Samuel D, Patel KS, Thomas DM. Audit of patient acdeptance of nasal surgery as a day case procedure. *Br J Clin Pract* 1996; **50**:357–359.

7 Weber R, Hochapfel F, Draf W. Packing and stents in endonasal surgery. *Rhinology* 2000; **38**:49–62.
8 Kalogjera L, Pegan B, Petric V. Adaptation to oral breathing after anterior nasal packing. *Acta Otolaryngol Stockh* 1995; **115**:304–306.
9 Johannessen N, Jensen PF, Kristensen S, Juul A. Nasal packing and nocturnal oxygen desaturation. *Acta Otolaryngol Suppl* 1992; **492**:6–8.
10 Morgan NJ, Soo G, Frain I, Nunez DA. Do ventilated packs reduce post-operative eustachian tube disfunction? *Clin Otolaryngol* 1995; **20**: 411–412.
11 Moralee SJ, Carney AS, Cash MP, Murray JA. The effect of fibrin sealant haemostasis on post-operative pain in tonsillectomy. *Clin Otolaryngol* 1994; **19**:526–528.
12 Ristic B, Radonjic D, Haralampiev K, Milenkovic L. Fibrin glue in Tympanoplasty. *Vojnosanit Pregl* 1990; **47**:190–193.
13 Radisevich M, Goubran HA, Burnouf T. Fibrin sealant: scientific rationale, production methods, properties, and current clinical use. *Vox Sang* 1997; **72**:133–143.
14 Vaiman M, Eviatar E, Segal S. Fibrin glue treatment for epistaxis. *Rhinology* 2002; **40**:88–91.
15 Vaiman M, Eviatar E, Segal S. Effectiveness of second generation fibrin glue in endonasal operations. *Otolaryngol Head Neck Surg* 2002; 4:388–391.
16 Vaiman M, Eviatar E, Segal S. The use of fibrin glue as haemostatic in endonasal operations: prospective randomized study. *Rhinology* 2002; **40**:185–188.
17 Morales Salas M, Ventura J, Ruiz Carmona E, Munoz F. Management of epistaxis in Rendu–Osler–Weber disease. *An Otorhinolaringol Ibero Am* 2001, **28**:281–291.
18 Byahatti SV, Rebeiz EE, Shapshay SM. Hereditary hemorrhagic telangiectasia: what the otolaryngologist should know. *Am J Rhinol* 1997; **11**: 55–62.
19 Sabba C, Pasculli G, Cirulli A, Gallitelli M, Virgilio G, Resta F, *et al.* Rendu–Osler–Weber disease: experience with 56 patients. *Ann Ital Med Int* 2002; **17**:173–179.