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Vivostat®: an autologous fibrin sealant as useful adjunct in endoscopic transnasal CSF-leak repair

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Abstract The benefit of fibrin glue for reduction of postoperative CSF-leaks after endoscopic skull base surgery is not clearly evident in literature. However, its use is supposed to be beneficial in fixing grafting material. As of today there is no specific data available for otolaryngological procedures. A retrospective data analysis at a tertiary care referral center on 73 patients treated endoscopically transnasally for CSF-leaks at the ENT-department Graz between 2009 and 2012 was performed. Primary closure rate between conventional fibrin glue and autologous fibrin glue were analyzed. The Vivostat® system was used in 33 CSF-leak closures and in 40 cases conventional fibrin glue was used. Comparing the two methods the primary closure rate using the autologous Vivostat® system was 75.8 and 85.0 % with conventional fibrin glue. The secondary closure the rates were 90.9 % with Vivostat® 92.5 % with conventional fibrin glue. The Vivosat® system is a useful adjunct in endoscopic CSF-leak closure. Its advantages over conventional fibrin glue are its application system for fixation of grafting material particularly in underlay techniques. Despite this advantage it cannot replace grafting material or is a substitute for proper endoscopic closure which is reflected by the closure rates.

Keywords Autologous fibrin glue · Vivostat · CSF-leak repair · Closure rates · Endoscopic

Introduction

The benefit of fibrin glue for reduction of postoperative CSF-leaks after endoscopic skull base surgery is not clearly evident in literature. However, its use is supposed to be beneficial in fixing grafting material [1].

Over the last decades conventional fibrin glue was used at our department for fixing grafting materials such as cartilage or fascia lata during skull base defect closure. A primary closure rate of nearly 90 % was reached (unpublished data). With the advent of endoscopic skull base surgery, transdural approaches to intracranial lesions became necessary and subsequent defect closure is mandatory. The demand for new closing techniques and adjuncts thus was increasing. Since 2009 an autologous fibrin sealant system produced by Vivostat® is in use.

Autologous fibrin glue is commonly used in general surgery, but until now there is no specific data available for otolaryngological procedures [1–7]. The aim of this study was to compare autologous fibrin glue to conventional fibrin glue, because there is a big difference between the application systems. The common conventional fibrin glue systems are used as a fluid glue compared to the Vivostat system which can be sprayed on longer distances by a special device and create a homogenous layer of fibrin over grafting material or apply distinct droplets of glue on defect margins which helps to fix the grafting material in situ.

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Materials and methods

In a retrospective analysis 73 patients treated endoscopically transnasally for CSF-leaks at our department between 2009 and 2012, were included in this study. Fibrin glue was used as a sealant in each and every case. 40 cases were treated with a conventional sealant and 33 were treated with the Vivostat® system. In 20 out of 33 cases Vivostat® was used in the sphenoid sinus where in 9 cases there was a CSF-leak in the sella and 11 cases were leaks located in the lateral wall of the sinus. The remaining 13 cases were CSF-leaks in the anterior and posterior ethmoid. Conventional glue was used in 24 out of 40 cases in the sphenoid of which in 20 cases CSF-leaks of the sella were sealed and in 4 cases the leak was located in the lateral sphenoid wall. The remaining 16 leaks were in the anterior and posterior ethmoid. The indication to use Vivostat® were iatrogenic leaks in 24 cases, spontaneous leaks in 3 cases and traumatic leaks in 6 cases. Conventional glue was used in 33 iatrogenic CSF-leaks, 5 spontaneous leaks and 2 posttraumatic CSF-leaks. Of the 73 patients, 40 (54.8 %) were women, and 33 (45.2 %) were men. The mean age at time of surgery was 46.9 years with a range from 3 to 78 years. The average BMI was 28.1 with a ranging between 14.2 and 59.3. Primary closure rates as well as secondary or tertiary closure rates between conventional fibrin glue and autologous fibrin glue were analyzed. Primary closure rate means that after one intervention where a CSF-leak was closed, permanent watertight closure was achieved. Secondary closure required a second intervention to close a defect following recurrence after a primary closure attempt. Tertiary closure rates required a third or more interventions after a recurrence of a primary attempt to close a leak.

Fibrin glue

Conventional fibrin glue is composed of fibrinogen and thrombin. In general, the fibrinogen fraction can be gained from single donors, pooled donors or autologous blood donors. The Thrombin fraction is generally derived from bovine origins. When these two main components are mixed together a fibrin clot is produced, following the clotting cascade. The speed of this reaction is depending on the quantity and the concentration of thrombin [1].

In accordance with the literature risks of viral transmissions such as Parvovirus B19, HIV, HCV and HBV can be avoided to a large extend according to the existing modern production regulations. Therefore the existence of these kinds of viral risks remains in theory, with a relative higher risk for a Parvovirus B19 transmission. Because of the long lasting latency periods between the transmission and outbreak of the prion disease, (transmissible spongiform encephalopathy) the fibrin sealant cannot be excluded as a theoretical transmitter of this kind of disease. The highest risk within the use of conventional fibrin sealant is the possibility of anaphylactic shocks or anaphylactoid reactions caused by Aprotinin and other foreign proteins found in this sealant [2–6].

Vivostat®

In order to be able to separate fibrin from the patients' own blood the Vivostat® system was invented. It is fully automated and enables a reliable and reproducible preparation of autologous fibrin sealant. The biotechnological process does neither need cryoprecipitation nor separated thrombin components. Therefore, excellent biocompatibility is described in literature [1, 7–9]. Due to the autologous production the risks of bovine or human borne contaminants, even those which are not identified yet, are eliminated [10]. In comparison to conventional systems the application of Vivostat® can be intermittently applicated during the surgical procedures without a blockage of the process. Physical properties like time to haemostasis, elasticity, adhesion to tissue and impact on tissue are improved compared to conventional fibrin sealants. These results were evaluated in in vitro rheological and tensile tests.

The system consists of three components (processor unit, applicator unit and the disposable set) which enable a fully automated reproducible preparation of autologous fibrin sealant. The result is neither variable due to the concentration of the patient's individual fibrinogen level nor to other external reasons [11] he system allows either applying single drops or spraying fibrin glue over the defect or the grafting material, respectively (Fig. 1). Particularly with the spraying modality the surgeon is enabled to fix the grafting material in the desired position covering it with a homogenous layer of fibrin overlapping the graft with the adjacent bone/mucosa for around 5 mm. Due to the quick clotting of the fibrin glue the material stays in situ and further maneuvers can be performed like applying overlays or hemostyptic material.

Results

During the study period from January 2009 to September 2012, 73 leaks at the anterior skull base were managed with a fibrin sealant. The diagnosis of CSF rhinorrhea was made on the basis of CT and MRI (42 cases), intrathecal sodium-fluorescein (23 cases), clinical history and nasal endoscopy. Of all CSF-leaks, 57 (78.1 %) were iatrogenic, 8 (11 %) occurred spontaneously and 8 (11 %) occurred after trauma. Body mass index was 26.7 in the Vivostat® and 29.4 in the conventional glue group. The primary closure

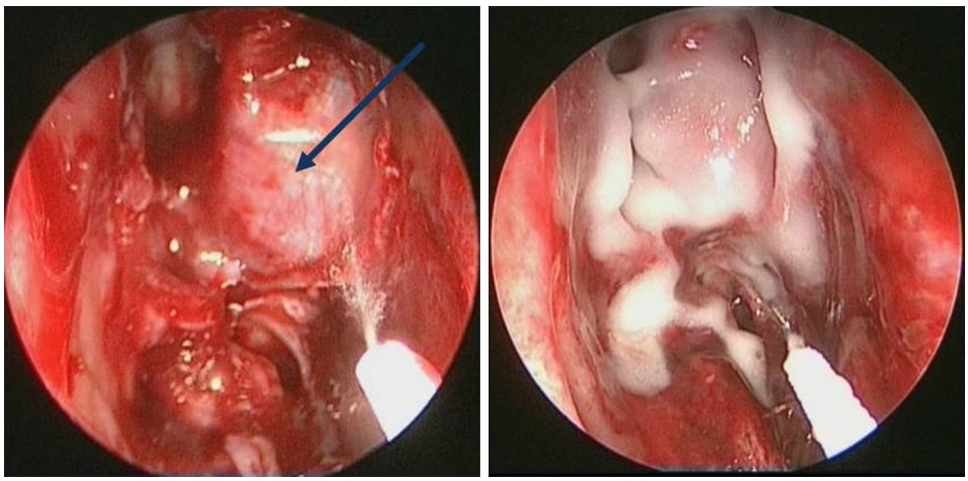
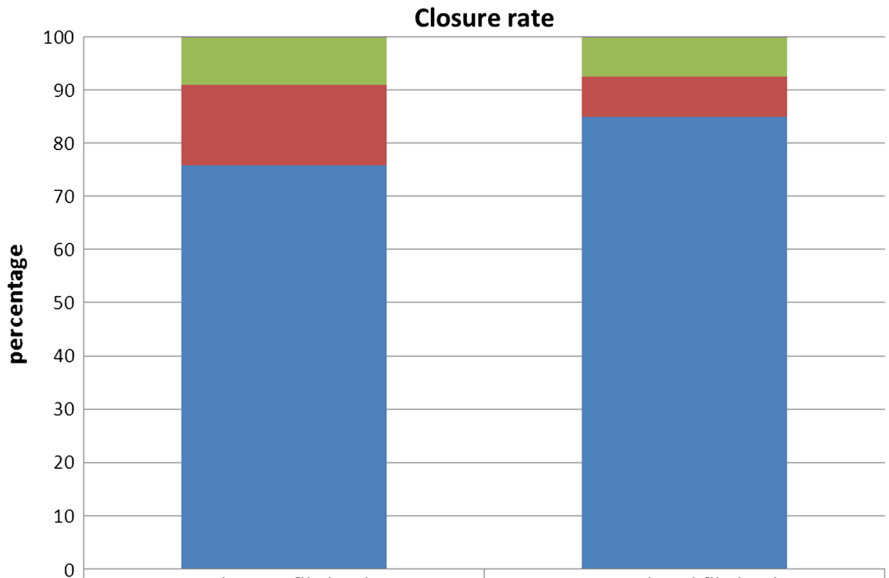


Fig. 1 Intraoperative image of using Vivostat® for fixation of fascia lata at the anterior skull base (*arrow*) in situ (*left*) and final application as spray with homogenous glue layer over the graft (*right*)



	autologous fibrin glue	conventional fibrin glue
Cases	33	40
more than 2	9.09	7.5
Secondary	15.15	7.5
Primary	75.76	85
P-value	0.792	

Fig. 2 Closure rates for Vivostat® and conventional fibrin glue

was achieved in 59 cases (80.8 %) with a secondary closure rate of 91.8 %. Six defects required three or more interventions for permanent watertight closure. The mean follow-up in this study was 31.4 months (Fig. 2).

The Vivostat® system was used in 33 CSF-leak closures and in 40 cases conventional fibrin glue was used. In the Vivostat® group, 17 overlays (54.5 %), 4 underlays (12.1 %) and 9 over- and underlays (33.3 %) were performed. In the conventional group, 12 overlays (32.5 %), 4 underlays (10 %) and 23 over- and underlays (57.5 %) were performed. In all cases of both groups fascia lata was used as grafting material. In 40 % of the Vivostat® group fat plugs were used as additional grafting material compared to 43.6 % in the conventional group (www.vivostat.com).

Comparing the two methods the primary closure rate using the autologous Vivostat® system was 75.8 and 85.0 % with conventional fibrin glue, not reaching statistical significance ($p = 0.792$, Chi-square test). The secondary closure, the rates were 90.9 % with Vivostat® 92.5 % with conventional fibrin glue (Fig. 2).

The closure technique (fascia lata over- and/or underlay), did have an impact on closure rates comparing the two

fibrin sealants, where with Vivostat® the recurrence was higher in cases using an overlay technique only (75 %). Estimated defect sizes in endoscopic skull base interventions were larger when Vivostat® was used. These leaks were created on purpose to get access to intracranial lesions and were located in the sphenoidal plane region.

CSF-leak recurrences typically occurred in the sphenoid sinus (50 %) and at the cribriform plate (27.8 %). Other locations of recurrences were located at the Sternberg's canal (2 cases), the frontal sinus (1 case) and the ethmoidal sinus (1 case).

Discussion

Endoscopic transnasal repair of CSF-leaks at the anterior skull base has become the gold standard over the last decades [1, 12–15]. Various techniques have been established and described in literature as regards overlay and/or underlay techniques and grafting material be it hetero- or autologous [16–20]. Nevertheless, the evidence for the use of fibrin glue as an adjunct to standard closure technique is not clear [1]. Studies describing the application of autologous fibrin glue Vivostat® are rare in literature. Because of its production out of patients' own blood plausible adverse events as infections or anaphylactic reactions are minimized, a clear advantage of Vivostat®. The goal of this study was to focus on the advantages of Vivostat® concerning its application system. However, the better primary closure rates were achieved using the conventional fibrin glue. Explanations for the higher recurrence rate (75 %) were use of an overlay technique only in the Vivostat® group where with conventional glue an over- and underlay technique was used in 23 compared to only 9 in the Vivostat group. A higher BMI (31.16 vs. 25.69) was noted among recurrences than primary closures in the Vivostat® group. Overall the BMI did not differ much between the two groups (26.7 vs. 29.4) with higher BMIs in the conventional group. The most striking reason for the higher recurrences in the Vivostat® group were the larger estimated defects sizes at skull base created to get access to intracranial lesions compared to the conventional fibrin glue which is also true for the higher overall recurrence rate (20 %). Particularly, Sternberg's canal and sella lesions extending to the sphenoidal plane had a worse outcome compared to other regions. Nevertheless, differences in recurrence rate did not reach statistical significance. The shortcoming of this study is its retrospective character compared to randomized trials with matched groups which would have been superior to compare both fibrin sealants.

Despite the higher recurrence rates the advantage of the system is its application technique. The fibrin glue can either be pin-pointed or sprayed over the defect or the grafting material, respectively. This makes the positioning of fascia as an underlay easier particularly when CSF pressure is washing out the graft. Here, the fascia can be "welded" to the bone margins of the defect by applying single drops of glue where desired. The remaining mobile part of the fascia can then be moved between bone and dura without luxation at the primary fixation site. Once the fascia is placed correctly a homogenous layer can be sprayed over it and overlays of fascia or hemostyptic material can be added. The whole reconstruction can then be fixed with another layer of fibrin glue. The rapid clotting and dense consistency of the glue gives another advantage especially since it is not washed away by the CSF as easily as conventional fibrin glue [21, 22]. As reflected by our recurrence rate Vivostat® cannot replace a proper reconstruction technique. The main predictors of recurrence are size of the defects, closure technique and grafting material, where an over- and underlay technique with fascia lata is superior to underlays and/or overlays only. Since the fibrin layer is enzymatically resorbed within a few days a displacement of fascia is possible through CSF-pressure which is underlined by the higher recurrence in overlay technique only. With a combined technique, the CSF-pressure is partially absorbed by the underlay and both layers can heal in at the defect edge and subsequently be covered by mucosa within the time span the fibrin clot takes to be absorbed. A better outcome after secondary recurrence was also noted when an over- and underlay technique was performed compared to overlay only. The benefit of fibrin glue—be it conventional or autologous—remains unclear. However, Vivostat® is a very helpful adjunct for fixation of grafting material in the anticipated position which is technically challenging particularly in high flow CSF leaks.

Conclusion

The Vivosat® system is a useful adjunct in endoscopic CSF-leak closure. Its advantages over conventional fibrin glue are its application system allowing pin-pointing or a homogenous sprayed layer as fixation of grafting material particularly in underlay techniques where CSF washes away the grafts as well as its rapid clotting and consistency. However, proper closure techniques are mandatory for permanent watertight closure of the defects regardless of which fibrin sealant is used as adjunct.

Conflict of interest None.

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