

USE OF TISSEEL FIBRIN SEALANT IN NEUROSURGICAL PROCEDURES: INCIDENCE OF CEREBROSPINAL FLUID LEAKS AND COST-BENEFIT ANALYSIS IN A RETROSPECTIVE STUDY

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OBJECTIVE: To determine the clinical efficacy and cost effectiveness of using the fibrin sealant (FS) Tisseel (Baxter Healthcare Corp., Deerfield, IL) for patients undergoing anterior cranial base, infratemporal, and retromastoid surgical procedures.

METHODS: A retrospective review was performed, comparing two matched populations of patients who underwent surgical procedures using anterior cranial, infratemporal, or retromastoid approaches to intracranial pathological lesions. The incidences of cerebrospinal fluid (CSF) leaks in matched groups treated with the FS Tisseel or treated without FS were compared. The costs of Tisseel use were examined in comparison with the costs of postoperative management of CSF leaks and/or tension pneumocranium with spinal drainage and occasionally surgical reexploration, when lumbar drainage failed.

RESULTS: Patients who received the FS Tisseel exhibited no detectable postoperative CSF leaks or tension pneumocranium. Patients who did not receive Tisseel demonstrated 4 to 16% incidences of postoperative leaks, depending on the surgical approach used. The costs of treating those leaks far exceeded the costs of using Tisseel, even if it were used indiscriminately for all patients.

CONCLUSION: This retrospective review indicates that the FS Tisseel reduces the incidence of postoperative CSF leaks and tension pneumocranium while reducing overall management costs. Further prospective study is needed to determine which patients can benefit most from FS use.

KEY WORDS: Cerebrospinal fluid leak, Fibrin sealants, Pneumocephalus, Tisseel

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Fibrin sealants (FSs) are two-component biological systems consisting of fibrinogen solution and thrombin, with a calcium cofactor. The resulting seal is based on the final stage of coagulation, specifically the conversion by thrombin, Factor XIII, and calcium of a fibrinogen monomer into a fibrin polymer, to create a hemostatic adhesive clot. In general, FSs are used as adhesives to augment other layers of closure, rather than being relied on as primary sealants. We studied the use of the prepared FS Tisseel (Baxter Healthcare Corp., Deerfield, IL), to determine both its effectiveness in reducing the incidence of cerebrospinal fluid (CSF) leaks in a variety of neurosurgical procedures and its cost-effectiveness.

PATIENTS AND METHODS

This retrospective analysis, based on detailed chart reviews, investigated the use of the prepared FS Tisseel in surgical procedures as an adjunct to initial dural repair. Tisseel was used in cases in which the surgeons considered the patient to be at increased risk for postoperative CSF leaks, because of the nature of the procedure or the quality of the dural closure.

The study group consisted of 72 Tisseel-treated patients and 181 historical control subjects who were treated at a single institution by a single cranial base and microvascular surgical service, consisting of two neurosurgeons and three otolaryngologists. All Tisseel

procedures were performed between May 2000 and September 2000, whereas historical control subjects were treated by the same surgeons between July 1998 and June 2000. Historical control subjects were matched to case patients in a 3:1 ratio when possible. *Table 1* presents the demographic features of the groups, the various surgical approaches, and the pathological conditions treated. Aside from the use of Tisseel, no changes in surgical technique could be identified. The incidences of CSF leaks and tension pneumocranium were determined for each group. Costs for the addition of Tisseel to the procedure (patient costs) were then analyzed, to determine whether the addition of Tisseel was cost-effective. Data analyses were independently performed by a statistician (YFC).

RESULTS

CSF Leaks and Tension Pneumocranium

Table 1 presents the demographic data, surgical approaches, and pathological conditions for the 72 Tisseel-treated patients and the 181 historical control subjects. The age distributions were similar for the two groups ($P = 0.91$), with means of 52.6 years (standard deviation, 15.8 yr) for the Tisseel group and 52.4 years (standard deviation, 15.9 yr) for the control group. This is thought to be an important issue, because there seems to be a strong effect of age on the quality of dura available for closure. The sex distributions were also comparable, with the Tisseel group having a slightly greater number of male patients (48.6 versus 37.6%, $P = 0.11$). Retromastoid craniectomy (RMC) was the most common surgical approach for both groups (Tisseel group, 55.5%; control group, 80.7%).

TABLE 1. Demographic features, surgical approaches, and pathological conditions for the patients who received Tisseel and the historical control subjects^a

	Tisseel	Control
No. of patients	72	181
Age (yr) ^b		
Range	12–86	9–84
Mean \pm standard deviation	52.6 \pm 15.8	52.4 \pm 15.9
Male sex ^b	35 (48.6%)	68 (37.6%)
Approach		
Anterior base	28 (38.9%)	25 (13.8%)
Infratemporal	4 (5.6%)	10 (5.5%)
RMC	40 (55.5%)	146 (80.7%)
Pathological condition		
Tumor	29 (40.3%)	41 (22.7%)
Vascular	36 (50.0%)	137 (75.7%)
Other	7 (9.7%)	3 (1.6%)

^a RMC, retromastoid craniectomy.

^b $P > 0.1$.

Table 2 presents the CSF leak rates for the two groups. Ten control patients (5.5%) experienced CSF leaks, whereas none of the Tisseel-treated patients experienced this complication ($P = 0.067$). The average age of patients with CSF leaks was 49.4 years (range, 9–80 yr), and all underwent either anterior cranial base procedures ($n = 3$) or RMC ($n = 6$). Among patients who underwent anterior cranial base procedures, the control group exhibited a statistically significantly higher incidence of CSF leaks, compared with the Tisseel group (16 versus 0%, $P = 0.04$). This was not observed for the patients who underwent RMC, for whom the CSF leak rates were 4.1% in the control group and 0% in the Tisseel group ($P = 0.34$). With respect to pathological conditions, CSF leaks occurred in 9.8% of tumor cases and 4.4% of vascular cases ($P > 0.1$) in the control group.

Most patients with CSF leaks were treated with a 5-day period of lumbar drainage. Four of the 10 patients, however, required surgical repair after a trial of lumbar drainage failed to seal the leaks.

Table 3 presents the incidences of tension pneumocranium for the two groups. Patients treated with Tisseel demonstrated no incidence of pneumocranium, whereas 1.1% of the patients ($n = 2$) in the historical cohort experienced this complication. Both patients had undergone anterior cranial base procedures for tumor resection.

TABLE 2. Incidence of cerebrospinal fluid leaks, according to surgical approaches and pathological conditions, among Tisseel-treated patients and historical control subjects^a

	No. of patients with CSF leaks	
	Tisseel	Control
Anterior base		
Tumor	0/23	3/22 (13.6%)
Vascular	0/0	1/1 (100%)
Other	0/5	0/2
Subtotal ^b	0/28	4/25 (16%)
Infratemporal		
Tumor	0/3	0/8
Vascular	0/1	0/1
Other	0/0	0/1
Subtotal	0/4	0/10
RMC		
Tumor	0/3	1/11 (9.1%)
Vascular	0/35	5/135 (3.7%)
Other	0/2	0/0
Subtotal	0/40	6/146 (4.1%)
Overall ^c	0/72 (0%)	10/181 (5.5%)

^a RMC, retromastoid craniectomy; CSF, cerebrospinal fluid.

^b $P = 0.04$.

^c $P = 0.067$.

TABLE 3. Incidence of tension pneumocranium, according to surgical approaches and pathological conditions, among Tisseel-treated patients and historical control subjects^a

	No. of patients with tension pneumocranium	
	Tisseel	Control
Anterior base		
<i>Tumor</i>	0/23	2/22 (9.1%)
<i>Vascular</i>	0/0	0/1
<i>Other</i>	0/5	0/2
<i>Subtotal</i>	0/28	2/25 (8%)
Infratemporal		
<i>Tumor</i>	0/3	0/8
<i>Vascular</i>	0/1	0/1
<i>Other</i>	0/0	0/1
<i>Subtotal</i>	0/4	0/10
RMC		
<i>Tumor</i>	0/3	0/11
<i>Vascular</i>	0/35	0/135
<i>Other</i>	0/2	0/0
<i>Subtotal</i>	0/40	0/146
Overall	0/72 (0%)	2/181 (1.1%)

^a RMC, retromastoid craniectomy. All *P* values were >0.1.

Cost Analysis

Cost analysis was performed by examining the cost (system cost) of using Tisseel, compared with the costs (system costs) of lumbar drainage and lumbar drainage plus surgical repair. At our institution, the cost of 2 ml of Tisseel is \$500. The cost of 5 days of lumbar drainage is approximately \$12,100, and the cost of lumbar drainage followed by surgical repair is approximately \$43,117. In this study, none of the Tisseel-treated patients experienced a CSF leak, whereas 10 patients in the control group experienced leaks. Six of those patients were treated with lumbar drainage alone, whereas four required both lumbar drainage and surgical repair. The total cost of additional treatment for those 10 patients was approximately \$245,068. In the RMC subgroup alone, six control patients and no Tisseel-treated patients experienced postoperative CSF leaks. The total cost of CSF leak treatment for those patients was approximately \$165,651 (three lumbar drains and three lumbar drains with surgery).

DISCUSSION

FSs have been widely used for various neurosurgical indications, including dural closure and/or reinforcement, nerve repair, cranioplasty (with mixtures of FS and autologous bone chips), reinforcement of muscle wrapping around aneurysms, hemostasis during tumor resection, and treatment of postopera-

tive subgaleal CSF fistulae, in Europe and Japan for more than 20 years (1–6). FSs are two-component biological systems consisting of a fibrinogen solution and thrombin, with a calcium cofactor. The resulting seal is based on the final stage of coagulation, specifically the conversion by thrombin, Factor XIII, and calcium of fibrinogen monomer to fibrin polymer, thus creating a hemostatic adhesive clot. When applied for augmentation of dural closure, the FS provides a temporary watertight closure and creates an additional barrier to CSF leakage during dural healing and the development of local fibrosis.

The components of FSs can be obtained from autologous cryoprecipitate harvested from single-donor plasma, in combination with currently available bovine thrombin. This use of autologous cryoprecipitate potentially decreases the risk of viral transmission that is associated with pooled donor plasma despite the two viral inactivations in Tisseel manufacture. The risks of viral transmission from bovine thrombin are currently unknown. The primary disadvantages of autologous products are the variable concentrations of each component and the antifibrinolytic agent. Prepared FSs, such as Tisseel, contain an antifibrinolytic agent that yields a more stable clot and thus a more predictable and enduring seal, which provides temporary protection while local healing and fibrosis occur.

In this study, we assessed the efficacy of the FS Tisseel and the costs of using the product. We recognize that the study is limited by both its retrospective nature and its case heterogeneity. Because of those weaknesses, a randomized controlled study is planned. Nevertheless, the current review demonstrates a number of important findings. We think that the use of Tisseel in cases involving anterior cranial base procedures or RMC can reduce the incidence of CSF leaks. The costs of treating such leaks are significant. In the RMC control group alone, the cost of treating CSF leaks was \$165,651. If Tisseel had been used in a shotgun manner for all of the control patients, then patient costs would have been \$90,500. If Tisseel had prevented leaks in this population, then savings of \$75,151 could have been realized. Finally, the increased failure rate in tumor cases may reflect the length of such procedures and the degree of resection of involved dura. These factors may prove, in prospective studies, to be risk factors for CSF leaks and tension pneumocranium, with such criteria becoming part of the selection process for the use of FSs. It is hoped that such selection criteria will reduce overall costs by limiting FS use to patients who will benefit from its application, while minimizing the incidence of leaks.

CONCLUSION

Use of the FS Tisseel in neurosurgical procedures provides clinical and economic benefits, in terms of reducing the risk of postoperative CSF leaks. In our review, anterior cranial base and RMC procedures seemed to exhibit the greatest benefits, with no CSF leaks in the Tisseel group, compared with CSF leak rates of 16 and 4.1%, respectively, for the non-FS-treated group. Infratemporal procedures were associated with no leaks in either group, possibly because of the multilayered

nature of the closure, which can include a thick muscular covering. Although we have demonstrated significant potential cost savings with the shotgun application of Tisseel in all cases involving RMC or anterior cranial base procedures, we think that such savings could be increased on the basis of future studies that reveal which patients in each surgical group are at greatest risk for postoperative leaks or air collections. We think we will be able to significantly reduce our complication rate, while reducing the costs of health care, by selectively using FSs for high-risk populations.

DISCLOSURE

AK is a paid consultant for Baxter Healthcare Corp. The authors acknowledge their affiliation with the Center for the Assessment of Surgical Technology and the Copeland Neurosurgical Laboratories.

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COMMENTS

Cerebrospinal fluid (CSF) leaks can be a frustrating complication of cranial base procedures and, like most complications, are best managed by prevention. I do not routinely use fibrin sealants (FSs), preferring instead to rely on a meticulous, multilayered closure with local tissue as the best means of preventing CSF leaks. The favorable outcome with FS in this retrospective study, however, may encourage me to reevaluate its benefit. Whether Tisseel (Baxter Healthcare Corp., Deerfield, IL) is superior to autologous cryoprecipitate preparations is unknown. Autologous preparations may be equally efficacious while offering the advantage of reduced cost and possibly reduced risk of viral infection, with the only drawback being a less uniformly consistent product.

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This article by Kassam et al. brings to the fore the utility of FSs in preventing CSF leaks after neurosurgical procedures. Tisseel has been commercially available in the United States for

several years but has been used widely in Europe for more than a decade with good results. It has a number of uses and was originally used as an adhesive of sorts. For example, Wullstein first reported its use in nasal septal surgery in 1979 (2). Of interest, nothing further was written about the use of FS until 1987, when a second article, this one by Hayward and Mackay (1), was published. FS also has been used to seal flaps of tissue after performing modified neck dissections, for example. Otolaryngologists have used FS for a number of years to prevent or to repair CSF leaks, most commonly into the nasal cavity. To my knowledge, however, there has been no series reported in the literature in which it has been used routinely as a preventative measure. This article demonstrates the clinical effectiveness and the cost-effectiveness of the routine use of FSs in any setting in which there is significant risk of postoperative CSF leak. The authors have performed an excellent study on the basis of innovative thinking.

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1. Hayward PJ, Mackay IS: Fibrin glue in nasal septal surgery. *J Laryngol Otol* 101:133–138, 1987.
 2. Wullstein SR: Septoplasty without postoperative nasal packing: Mucosal repair of the upper airway with human biological glue [in German]. *HNO* 27:322–324, 1979.

The authors have performed a retrospective analysis of the effect of the FS Tisseel on postoperative CSF leak and pneumocephalus. There was a significant decrease in the incidence of CSF leak but insignificant alteration in pneumocephalus. The data are plain and well presented. The obvious defects of this study are its retrospective nature and the use of historical controls. The problem of changes in factors other than the use of Tisseel cannot be evaluated, thus detracting from the certainty of the conclusions.

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The authors have conducted a study to determine the usefulness of the FS Tisseel in preventing CSF leak. During a 5-month period, no patient in whom FS was used had a CSF leak. The incidence of CSF leak in matched historical control patients during a 1-year period was 5.5%. As the authors remark, the value of this study is limited by its retrospective nature and by the mix of approaches and pathologies studied. In spite of this drawback, the use of fibrin glue seems to be cost-effective by reducing the incidence of CSF leakage. It would be difficult to conduct randomized, controlled trials of the use of this product; therefore, this study is important.

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