Effect of fibrin glue on the prevention of persistent cerebral spinal fluid leakage after incidental durotomy during lumbar spinal surgery

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Abstract Approximately one million spinal surgeries are performed in the United States each year. The risk of an incidental durotomy (ID) and resultant persistent cerebrospinal fluid (CSF) leakage is a significant concern for surgeons, as this complication has been associated with increased length of hospitalization, worse neurological outcome, and the development of CSF fistulae. Augmentation of standard dural suture repair with the application of fibrin glue has been suggested to reduce the frequency of these complications. This study examined unintended durotomies during lumbar spine surgery in a large surgical patient cohort and the impact of fibrin glue usage as part of the ID repair on the incidence of persistent CSF leakage. A retrospective analysis of 4,835 surgical procedures of the lumbar spine from a single institution over a 10-year period was performed to determine the rate of ID. The 90-day clinical course of these patients was evaluated. Clinical examination, B-2 transferrin assay, and radiographic imaging were utilized to determine the number of persistent CSF leaks after repair with or without fibrin glue. Five hundred forty-seven patients (11.3%) experienced a durotomy during surgery. Of this cohort, fibrin glue was used in the dural repair in 278 patients (50.8%). Logistic models evaluating age, sex, redo surgery, and the use of fibrin glue

revealed that prior lumbar spinal surgery was the only univariate predictor of persistent CSF leak, conferring a 2.8-fold increase in risk. A persistent CSF leak, defined as continued drainage of CSF from the operative incision within 90 days of the surgery that required an intervention greater than simple bed rest or over-sewing of the wound, was noted in a total of 64 patients (11.7%). This persistent CSF leak rate was significantly higher ($P < 0.001$) in patients with prior lumbar surgery (21%) versus those undergoing their first spine surgery (9%). There was no statistical difference in persistent CSF leak between those cases in which fibrin glue was used at the time of surgery and those in which fibrin glue was not used. There were no complications associated with the use of fibrin glue. A history of prior surgery significantly increases the incidence of durotomy during elective lumbar spine surgery. In patients who experienced a durotomy during lumbar spine surgery, the use of fibrin glue for dural repair did *not* significantly decrease the incidence of a persistent CSF leak.

Keywords CSF leak · Lumbar spine surgery · Tisseel · Fibrin glue · Incidental durotomy

Introduction

Approximately one million spine surgery procedures are performed in the United States each year [11]. Studies have shown that the most frequent complication of lumbar surgery is an incidental durotomy (ID), or unplanned perforation of the thecal sac, with an incidence ranging from 0.3 to 13% [9, 14, 19, 27]. The reported risk for ID during a microdiscectomy, laminectomy, and redo-microdiscectomy is 1.8, 5.3, and 17.4%, respectively [18]. Three recent studies conducted by the SPORT investigators

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revealed a 2–4% incidence of durotomy for first time microdiscectomy and a 10% incidence for surgical treatment of degenerative spondylolisthesis [24–26]. Prior surgery with the subsequent development of scar tissue, altered anatomy, poor dissection planes, and adherence of tissue to the dura all have been demonstrated to increase the risk of ID [27].

Possible sequelae of ID include the formation of a pseudomeningocele, a cerebrospinal fluid (CSF) cutaneous fistula, arachnoiditis, meningitis, epidural abscess, or deterioration in neurological status [10, 22]. A persistent CSF leak may result in a chronic pain disorder associated with cranial nerve palsies, radiculopathy, and/or postural headaches [1, 2]. A CSF leak also predisposes the patient to poor wound healing and possible wound dehiscence.

Immediate, intraoperative recognition of ID and dural closure may avoid these circumstances if the dural repair is successful and the patient does not continue to experience CSF leakage past the dural barrier. However, the optimal method of intraoperative dural repair remains unproven.

Fibrin glue, a human- or bovine-derived gelatinous matrix combining fibrinogen and thrombin, remains the most frequently used adjuncts to dural repair in the United States. There has been extensive literature, both in vitro as well as in vivo, regarding the use of fibrin glue at multiple sites in the body to augment or primarily close tissue defects [3, 6, 7, 13, 16]. Although the augmentation of dural closure with these products is commonplace, the treatment with fibrin glue increases both the cost and the risk to the patient. This study sought to evaluate unintended durotomies during lumbar spine surgery in a large surgical patient cohort and the impact of fibrin glue usage as part of the ID repair on the incidence of persistent CSF leakage.

Methods

Patients

A retrospective evaluation was performed for all patients undergoing elective lumbar spine surgery by members of the Department of Neurological Surgery at Presbyterian University Hospital of the University of Pittsburgh Medical Center (UPMC), Pittsburgh, PA, USA, between 1994 and 2004. This study was approved by the University of Pittsburgh Institutional Review Board using a certified Honest Broker System to fulfill the regulatory privacy requirements associated with the conduct of retrospective research involving existing health information. All operative notes, clinic notes, inpatient records, and imaging studies were analyzed for the first 3 months of the postoperative period to identify patients experiencing an ID and possible persistent CSF leak.

A durotomy was defined as any unintended perforation of the dura that occurred during surgery. A persistent CSF leak was defined as continued drainage of CSF from the operative incision within 90 days of the surgery that required an intervention greater than simple bed rest or over-sewing of the wound with non-absorbable suture. CSF was differentiated from serous drainage by the use of a *B-2* transferrin assay in all cases if the diagnosis was in question. The *B-2* transferrin assay is a widely employed modality for differentiating serous drainage from CSF, with a sensitivity and specificity of 84 and 100%, respectively [15]. Operative notes, pharmacy records, and billing codes were reviewed to accurately document the use of fibrin glue at the time of open surgical repair of the ID [Tisseel VH fibrin sealant (Duploject System, Baxter Healthcare Corporation, Glendale, CA, USA)]. This system consists of a dual-chambered syringe separating vapor heated, freeze-dried fibrinogen (75–115 mg/ml), and thrombin (500 IU/ml) derived from pooled human plasma [20].

In all cases, an attempt was made at surgery to create a “water-tight” dural closure. Closure was performed with 4-0 dural silk sutures. A simple running or figure-of-eight stitch was the most common methods of suture repair. The use of a fascial or muscle patch over the primary dural repair was utilized at the discretion of the surgeon. A Valsalva maneuver was performed to increase intra-dural pressure for 10 s after dural closure to assess for CSF egress. Fibrin glue was applied over the primary dural repair based on the judgment of the primary surgeon in regards to the location and size of the dural defect, the patient’s history of prior surgery, and the dural integrity. The precise location of the ID, such as midline or lateral, could not be obtained from the operative reports and therefore was not evaluated during the statistical analysis.

After obtaining an acceptable repair of the ID, the lumbar subcutaneous and superficial layers were closed with absorbable sutures. Every attempt was made to oppose muscle so as to eliminate dead space overlying the durotomy. The fascia was meticulously opposed to serve as a barrier to a CSF leak. CSF diversion using a lumbar drainage device was not employed by this patient cohort. The use of a sub-fascial drain was avoided in all cases. The skin layer was approximated with either a running non-absorbable nylon suture or staples. When an ID occurred during surgery, patients were instructed to remain flat in bed for 24–72 h after surgery. Lower extremity serial compression devices with or without the addition of subcutaneous heparin were used to prevent the formation of lower extremity deep vein thromboses in all cases. Postoperative antibiotics were not routinely prescribed as part of the postoperative management of ID. Surgeries

involving planned opening of the dura, such as for intradural tumor resections, were excluded from this study.

Statistical analysis

For statistical analysis, clinical and demographic data were summarized as means and standard deviations for continuous variables and as frequencies for categorical variables. Comparisons of continuous variables such as age, gender, repeat surgeries, use of fibrin glue, and durotomy closure failure as evidenced by a 3-month postoperative leak were done using Wilcoxon two-sample rank sum tests. Chi-square tests were used to evaluate differences in the proportion of durotomy closure failure by gender, first surgery, and use of fibrin glue. A logistic regression analysis was used to model the probability of a persistent 3-month CSF leak by age, gender, need for repeat surgery, and the use of fibrin glue. The Hosmer–Lemshow Goodness-of-Fit test was used to examine the

lack of fit in the final model. Probability values of <0.05 were considered statistically significant. All analyses were performed using SAS software 8.2 (Cary, NC, USA).

Results

There were 4,835 index lumbar spine surgeries reviewed. An ID occurred during 547 procedures with an overall ID incidence of 11.3%. Fibrin glue was used during 278 of these ID cases (50.8%) to augment the dural closure after an ID occurrence. In 128 (23.4%) of these ID cases, the patient had undergone at least one prior lumbar surgery at the operative level or levels. The mean and median ages were 60 and 61 years, respectively (in the range of 17 to 95 years). Men comprised 49% of the cohort. There was no statistically significant relationship between age or gender and the incidence of durotomy (Table 1).

During the first 3-month postoperative period, a persistent CSF leak was documented in 64 (11.7%) cases. This persistent CSF leak rate was significantly higher ($P < 0.001$) in patients with prior lumbar surgery (21%) versus those undergoing their first spine surgery (9%). There was no statistical difference in persistent CSF leak between those cases in which fibrin glue was used at the time of surgery and those in which fibrin glue was not used (Fig. 1).

Treatment of the persistent CSF leak ultimately required open surgical treatment in 44 (69%) patients. Included in this group were three lumbar drains and one blood patch that failed to stop the leak. Surgical treatment varied extensively and included a primary suture closure (10), suture and fat graft (1), suture and muscle graft (6), suture supplemented with Tisseel (20), pericardial graft (1), or Tisseel only (2). In four cases, no dural opening could be

Table 1 Correlation of persistent CSF leakage rate with gender, prior surgery, or fibrin glue usage

Study population	N	CSF leak within 3 months postoperative Number (%)
Men	269	29 (11%)
Women	278	35 (13%)
P-value		0.51
First surgery	419	37 (9%)
Redo surgery	128	27 (21%)
P-value		<0.001
No Fibrin glue	269	31 (11.5%)
Fibrin glue	278	33 (11.9%)
P-value		0.9

Fig. 1 Flow diagram of fibrin glue use and the incidence of a persistent CSF leak in patients undergoing lumbar surgery with a resultant incidental durotomy

Table 2 Logistic regression model for predictors of persistent CSF leakage

Variable	Odds ratio (95% CI)	P-value
Age	1.0 (0.98–1.02)	0.99
Gender	0.74 (0.43–1.29)	0.29
Redo surgery	2.89 (1.65–5.04)	<0.001
Use of fibrin glue	1.03 (0.60–1.76)	0.91

located and nothing was done. Percutaneous procedures were successful in 20 (31%) patients. Eighteen lumbar drains and two blood patches stopped the leak and required no further treatment. Aside from the three lumbar drains and one blood patch, no patient required a repeat procedure to treat the persistent CSF leak.

Logistic models evaluating age, sex, redo surgery, and the use of fibrin glue revealed that prior lumbar spinal surgery was the *only* univariate predictor of persistent CSF leak, conferring a 2.8-fold increase in risk (Table 2). There was no significant difference between the groups receiving fibrin glue and not receiving fibrin glue and the other independent variables.

Of the 547 surgeries in which an ID occurred, 23 (4.2%) cases of postoperative infections presented an average of 17 days after surgery. Eighteen patients required open surgical exploration for irrigation and debridement of the infection. Two superficial infections and three cases of bacterial meningitis were treated non-surgically with antibiotic therapy. There was no significantly increased risk of infection with the use of fibrin glue. However, the risk of infection was significantly increased ($P < 0.01$) for those patients undergoing repeat lumbar surgery (8.5%) compared to first time surgery (2.8%).

There were no complications attributed to the use of fibrin glue. Specifically, no patients experienced infections directly related to the use of fibrin glue, and there were no cases of systemic immunological reactions or hepatitis that developed during the follow-up period. Fibrin glue was not felt to be detrimental to wound healing in any case.

Discussion

The optimal method of intraoperative dural repair during an ID remains unproven. Jones et al. showed that in patients whose durotomy was immediately recognized and repaired primarily, there was no difference in clinical outcome after a mean follow-up of 25 months [2]. There is a general consensus that, if possible, the surgeon should perform a primary suture closure to attain a “watertight” seal, with the option of prolonged, flat bed rest. Other surgical options include placement of topical thrombotic

agents or closure of the dead space dorsal to the durotomy. Biological grafts comprised of fat, muscle, or fascia may be used to augment the dural closure. These may be sutured directly to the defect or simply applied in an “on-lay” fashion. For larger dural defects, allografts such as bovine pericardium may occasionally be necessary.

Cammisa et al. [4] conducted one of the largest prior studies evaluating ID, although their cohort involved both cervical and lumbar spine surgeries. They noted a 3.1% overall incidence of durotomy in 2,144 patients. Revision surgery was associated with a higher incidence of durotomy (8.1%). Repair always involved direct suturing of the defect. The decision to augment in this case series of 68 repairs was made based on intraoperative findings, and included 44 repairs that were augmented with locally harvested muscle, fat grafts, fibrin patches, or fibrin glue. Bed rest was required for 3–5 days. After a mean follow-up of 22.4 months, no patient whose durotomy was noted and repaired during surgery had a persistent CSF leak. Of note, five of six patients with durotomies not identified during surgery and one patient whose durotomy was noted but not repaired required re-exploration and dural repair.

Wang et al. [23] reviewed another large cohort of patients who sustained a dural tear during lumbar spine surgery. They reported a 14% overall incidence of durotomy in 641 consecutive patients. Eighty-six of the 88 dural tears were repaired primarily with interlocking suture and gelfoam. One ventral tear could not be repaired and one large tear required a fascial graft. Of interest, all patients received a subfascial-closed suction wound drain with no obvious sequelae, in contradistinction to recommendations espoused by prior literature [5]. Bed rest was maintained for an average of 2.9 days. Only 2 of the 88 patients required repeat surgery due to a persistent CSF leak. Both patients had five or more prior surgeries that included spinal instrumentation.

Fibrin glue is a sterile, virally inactivated preparation of purified human fibrinogen and thrombin [25]. Fibrin glue bypasses the clotting cascade by catalyzing the conversion of fibrinogen into fibrin to immediately produce activated clotting factors. It was approved in the United States in 1998 for use as an adjunct to attain hemostasis in cardiothoracic or intra-abdominal surgeries when conventional methods proved ineffective [16]. Although it is a potent hemostatic agent, the instantaneous fibrin cross-linking made this product a natural choice as a sealant. Initially used for bowel anastomosis, fibrin glue gained popularity in neurosurgical procedures for repair of dura during intra-cranial surgery. Sawamura et al. [17] reported a significant decrease in the risk of intracranial CSF leaks by using an aerosol derivative of fibrin glue. Perhaps their histological review of the resultant fibrin glue scar is of greater interest. They documented an

evolution of the fibrin plug into a mature, physiological collagenous granulation tissue.

There are several concerning issues regarding the use of fibrin glue in the setting of lumbar spine surgery. From a practical standpoint, the approximate 20-min preparation time can be relatively significant when approaching the end of an operation. Once applied, the coagulum needs 3–5 min to attain optimal adherence and 2 h to reach its ultimate strength. The feasibility of providing appropriate setting conditions during bleeding, irrigation, building intradural pressure, and movement remains questionable. There is also concern regarding the effect of fibrin glue on bone formation. Although some studies have shown fibrin glue to be a successful scaffold for bone growth when combined with osteoinductive or osteoconductive substances, multiple animal studies have raised concern that fibrin glue may inhibit bony fusion, even when using recombinant bone morphogenetic proteins [8, 13, 21, 28]. Finally, there is an issue regarding the cost of the product. In 1996, the total annual cost for the surgical use of fibrin sealants in Japan was approximately 160 million U.S. dollars [18]. At our institution, the smallest volume provided (2 cc) costs \$1,836.75, with a 5 cc volume costing \$4,592.00.

In the current series of a 10-year compilation of elective lumbar spine surgery, prior lumbar spinal surgery was the most significant predictor of the occurrence of an ID and of a persistent CSF leak. Furthermore, in patients with an ID, repair with fibrin glue did not reduce the incidence of a persistent CSF leak. One possibility for this negative finding of the benefit of fibrin glue usage is that in this series only the most “severe” durotomies were repaired with the use of fibrin glue and had a higher risk of subsequent leakage. After careful review of all operative notes in which an ID occurred, no correlation could be found between the length and complexity of the dural tear and use of fibrin glue. There was a lack of selection bias for the use of fibrin glue for such dural tears. Surgeons tended to use fibrin glue on all dural repairs or avoid its use completely. Furthermore, there were no significant differences between the ages or sex of the groups receiving or not receiving fibrin glue. The precise location of the ID relative to the thecal sac could not be evaluated from this retrospective review.

Based on the findings of this study and the results of prior large reviews, every attempt should be made to repair in a primary fashion known dural openings. Direct suturing of the defect is the method of choice. Augmentation with muscle, fat, fibrin glue, or graft should be considered when the dural closure is sub-optimal. In this study, the use of fibrin glue did not significantly decrease the incidence of subsequent CSF leakage. Considering the risk of fusion inhibition, operative time consumption, and added expense,

our findings do not support the prophylactic use of fibrin glue when a primary repair is deemed adequate.

Conclusion

This study evaluated the incidence of durotomy during elective lumbar spine surgery and the potential efficacy of fibrin glue for augmenting dural repair. Prior lumbar surgery was the only variable found to increase the likelihood of the occurrence of an ID. The incidence of persistent CSF leakage after ID was not found to be decreased by the addition of fibrin glue to the dural repair. These results will help guide the spine surgeon when obtaining informed consent for elective lumbar spine surgery and in choosing the most effective, economic closure method of a durotomy.

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