Failure to repair native dura after neurological surgery remains a significant source of morbidity for many neurosurgical procedures. Closure of the dura serves as a mechanical and biological barrier to both the egress of cerebrospinal fluid (CSF) and the ingress of infectious organisms. In many cases, primary closure remains difficult, if not impossible, because of the inherent pathology or the insufficiency of native dura. Since the first report of duraplasty using natural latex in the late 19th century, surgeons and engineers have pursued alternatives for dural substitution, including autograft, allograft, xenograft, and synthetics (1–8, 10, 14, 16–19, 21–25, 32–34, 37). Despite decades of research, the incidence of CSF leak (fistula or pseudomeningocele) after craniotomy remains as high as 10% (10, 13). In this report, we present our outcomes and experiences with matrix grafts manufactured from reconstituted type I bovine collagen. This includes use of these grafts in combination with cranioplasty material and dural sealants. In a subsequent report, we will present our institutional experience with the effects of dural sealants on postoperative dural integrity and infection.
a collagen sponge was used during closure of nontrauma cranial operations was performed. The primary goal was to compare the incidence of postoperative CSF leak and infection between 2 types of commercially available collagen sponges. We hypothesized that the bilayer (BL) sponge would have a lower incidence of CSF leak and infection compared with the monolayer (ML) sponge. In secondary analyses, we also examined the impact of nonautologous materials (e.g., biological glues, dural grafts, and cranioplasty material) on the incidence of CSF leak and infection when used in conjunction with collagen sponges. Finally, in an effort to predict which patients are most likely to benefit from the use of these products, we examined correlates of CSF leak and infection in this large patient series.

**PATIENTS AND METHODS**

**Patient Population**

The study was performed at Oregon Health & Science University, a quaternary care academic hospital, and was approved by its Committee on Human Research. A retrospective search of surgical and billing records between January 2004 and August 2006 identified 523 operations in 480 patients in which collagen duraplasty (DuraGen, DuraGenPlus, or Suturable DuraGen; Integra LifeScience Corp., Plainsboro, NJ) was performed. We then confirmed use of a collagen graft by reviewing the surgeon’s operative report, and the circulating RN’s implant record. All patients were 18 years of age and older. Data were collected using a double-entry method. A flow chart of case inclusion is presented in Figure 1. Cases were excluded for the following reasons: 1) product was billed, but according to the operative record, not implanted, (0.6%); 2) incomplete records or loss to follow-up (1.9%); 3) spinal or transphenoidal operation (5.2% and 0.8%, respectively); 4) death within 24 hours of operation because of underlying causes (0.6%); and 5) excessive number (n = 47) of previous operations (0.2%). In total, 475 cases were evaluated.

**Clinical Material and Methods**

ML (DuraGen or DuraGen Plus) sponges or BL sponges (Suturable DuraGen) were implanted in the patients at the attending surgeon’s discretion and based on product availability. During the study period, the first use of DuraGen Plus was July 2004, and the first use of the sutureable sponge was February 2005. Before availability of the sutureable product, the collagen sponge was used exclusively in an onlay fashion, with edges overlapping the dural defect. The sutureable sponge was used in 1 of 2 fashions: as either an onlay or an inlay/underlay. In the case of an inlay, the graft was sized larger than the defect and then sutured to the dural edge with a running 4-0 braided nylon suture to prevent migration. In addition to collagen sponge, foreign materials used (at the surgeons discretion) included bovine pericardial patch (Lyoplant; Aesculap, Inc., Center Valley, PA), calcium phosphate cranioplasty (Norian CRS; Synthes, West Chester, PA), and dural sealant, either fibrin glue (Tisseel; Baxter, Westlake Village, CA) or polyethylene glycol (PEG) hydrogel (DuraSeal; Confluent Surgical, Waltham, MA). Per our standard of care, calcium phosphate was impregnated with vancomycin before implantation.

**Statistical Methods**

Two exposure groups were defined, ML (DuraGen and DuraGen Plus) or BL (Suturable DuraGen), with secondary exposure to dural sealant (Tisseel or DuraSeal) or cranioplasty (Norian CRS). The ML products were grouped together based on the assumption that the manufacturing differences between the 2 products do not significantly affect in vivo performance. Primary endpoints were defined as CSF leak (including fistula and clinically diagnosed pseudomeningocele) and infection (including wound infections, abscess, and meningitis). For the purpose of our analyses, both fistula and pseudomeningocele were defined as CSF leak because, in our opinion, either outcome represents a primary failure of dural closure. Pseudomeningocele evident solely on postoperative imaging, which did not come to the patient’s or surgeon’s attention on postoperative examination, was not included as a complication. Infections were classified according to Centers for Disease Control and Prevention criteria for surgical site infection, although we use the term deep instead of organ space (15).

Pearson’s $\chi^2$ test and analysis of variance were used to compare characteristics of exposure groups. Association of categorical exposure(s) and outcome(s) was assessed using Pearson’s $\chi^2$ test or, when expected counts were small, Fisher’s exact test. The rank-sum test was used to determine the significance of differences in event curves. Odds ratios (ORs) are reported with 95% confidence intervals. All P values were calculated at the 0.05 significance level in 2-sided tests.

The univariate relationship between independent variables and outcome(s) was assessed using crude ORs from simple logistic regression. Because of sample size constraints, some categorical variables were compressed to binary form. Multivariate logistic regression models of CSF leak and infection status were constructed using backward, stepwise methods. In each case, effects were allowed to enter the model if the univariate association was significant at a P value of 0.2 or less. Interaction effects between significant predictors and outcome(s) were explored. All analyses were conducted using SPSS (version 14; SPSS Inc., Chicago IL) and STATA (version 9; StataCorp, College Station, TX).
RESULTS

Baseline Characteristics

ML collagen (DuraGen or DuraGen Plus) was used in 61.5% (292/475) of the cases. Groups were well matched with respect to important characteristics, with the exception of surgery duration and length of follow-up (Table 1). The length of follow-up in the ML group was significantly longer than that in the BL group (203 versus 116 days, respectively; \( P < 0.001 \)). The length of operation was significantly longer in the ML group compared with the BL group (175 minutes versus 144 minutes, respectively; \( P = 0.005 \)). This difference in operation length persisted as a strong trend after stratifying by convexity versus cranial base approaches (\( P = 0.08 \)).

Overall, 325 supratentorial (68.4%) and 150 infratentorial (31.6%) operations were evaluated. The 3 most common surgical approaches were frontal craniotomy (41%), suboccipital/retrosigmoid craniotomy (27%), and temporal craniotomy (12%). The most common indication for surgery was tumor resection (221 of 475; 47%) (Fig. 2).

Causes of Death

Overall mortality during the follow-up period was 12.3% (36/292) in the ML group and 9.8% (18/183) in the BL group (\( P = 0.46 \)). Two deaths (0.4%) are particularly notable as complications of surgery and potentially the implantation of a collagen sponge. One death was caused by fatal meningitis that developed secondary to a persistent postoperative CSF leak, despite diversion (lumbar drain) and operative revision. This leak developed after a combined craniofacial resection of a nasopharyngeal adenocarcinoma that had eroded from the sinuses, through the orbit, into the anterior cranial fossa. In this case, BL collagen was used to reconstruct the dura of the cranial base of the anterior fossa and was tacked in place with sutures without obtaining a watertight closure. This was the third recurrence of the tumor, and the patient had previously received radiation to the field, precluding the use of a vascularized pericranial graft.

Two notable deaths were caused by septic multisystem organ failure that seems to have originated as an orbital cellulitis after bifrontal craniotomy for olfactory groove meningioma. After resection of the meningioma, a 2-layered reconstruction of the floor of the anterior fossa was performed, consisting of BL collagen and a vascularized pericranial graft.

CSF Leak

The overall frequency of postoperative CSF leak was 6.7% (32 of 475). This included 23 CSF fistulae and 9 pseudomeningoceles. As described above, we consider these complications synonymous, although their management is different; both outcomes represent a failure of dural integrity. Although we noted a somewhat lower incidence of CSF leak in the BL group than the ML group (5.5% versus 7.5%, respectively), this difference was not significant (\( P = 0.4 \)) (Fig. 3A; Table 3). However, we did note a significantly higher incidence of CSF leak in infratentorial (11.3%) versus supratentorial (4.6%) operations (odds ratio [OR], 2.3; 95% CI, 1.3–5.5). There were no significant differences in the incidence of leak between patients who had never had a previous operation and patients undergoing a reoperation (6.8% versus 6.6%, respectively; \( P = 0.9 \)). Furthermore, the lack of evidence of a significant difference based on reoperation status held when stratifying by type of graft implanted or the addition of dural sealant.

Three of the pseudomeningoceles were managed expectantly and resolved without further intervention. Of the remaining CSF leaks, 34% (11 of 32) were managed with operative explo-

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**TABLE 1. Baseline Characteristics of Cohort by Exposure**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Monolayer (n = 292)</th>
<th>Bilayer (n = 183)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>52.2 ± 16.2</td>
<td>53.4 ± 15.0</td>
<td>NS</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>126 (43)</td>
<td>70 (38)</td>
<td>NS</td>
</tr>
<tr>
<td>Smoking status</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>158 (54.1)</td>
<td>107 (58.5)</td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>75 (25.9)</td>
<td>41 (22.4)</td>
<td></td>
</tr>
<tr>
<td>Previous</td>
<td>59 (20.0)</td>
<td>35 (19.1)</td>
<td></td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>28.4 ± 6.9</td>
<td>29.0 ± 6.2</td>
<td>NS</td>
</tr>
<tr>
<td>Diabetes</td>
<td>NS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>269 (92.1)</td>
<td>160 (87.4)</td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>1 (0.4)</td>
<td>1 (0.6)</td>
<td></td>
</tr>
<tr>
<td>Type 2</td>
<td>22 (7.5)</td>
<td>22 (12.0)</td>
<td></td>
</tr>
<tr>
<td>Previous CNS surgery</td>
<td>101 (35)</td>
<td>66 (36)</td>
<td>NS</td>
</tr>
<tr>
<td>Length of operation, min</td>
<td>175.3 ± 81.5</td>
<td>145.3 ± 79.0</td>
<td>&lt;0.005</td>
</tr>
<tr>
<td>Length of follow-up, d</td>
<td>203 ± 256</td>
<td>116 ± 149</td>
<td>&lt;0.005</td>
</tr>
</tbody>
</table>

\( ^a \) NS, not significant; BMI, body mass index; CNS, central nervous system. Mean ± SD or number (%).

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**FIGURE 2. Case distribution. Vascular category includes emergent neurosurgical cases such as ruptured aneurysm or nontraumatic hematoma evacuation. Congenital/Acquired category includes anatomic defects (congenital or iatrogenic) producing a cerebrospinal fluid fistula or pseudomeningocele requiring repair.**
RATION/REVISION, 16% (5 of 32) with lumboperitoneal shunting, 9% (3 of 32) with ventriculoperitoneal shunting, and the remaining 31% (10 of 32) with lumbar drainage without operative wound revision.

Infection

The overall frequency of postoperative infection was 4.2% (20 of 475). There were 14 superficial surgical wound infections and 6 deep (i.e., meningitis or abscess) infections. Two cases of meningitis were preceded by development of a CSF fistula with a subsequent superinfection. There was no significant difference in the incidence of infection in the BL and ML groups (4.9% versus 3.8%, respectively; \( P < 0.05 \)) (Fig. 3B; Table 3). The most common isolates from infections were Staphylococcus aureus in 11 cases (78.6%), an additional 3 cases of methicillin-resistant S. aureus, 1 case of Serratia marcescens, 1 case of Propionibacterium acnes, and 1 polymicrobial infection that included P. acnes, Escherichia coli, Lactobacillus, and Enterobacter cloacae (Table 2).

Despite the significant difference in CSF leak between the supratentorial and infratentorial cases, there was no significant difference in infection rates (4.9% versus 2.7%, respectively; \( P = 0.3 \)). Among all cases of postoperative infection, there was a 65% reoperation rate (i.e., operative débridement, removal of bone flap, and/or removal of implant).

Additional Complications

There were 2 cases of aseptic meningitis in the cohort. In both cases, implantation of collagen graft was performed as part of a reoperation to repair an existing CSF leak. In both cases, patients had symptoms (headache, nausea, photophobia) preoperatively. Because we were unable to establish a clear temporal association between implantation and then development of aseptic meningitis, we omitted these complications from analysis. There were no cases of postoperative seizures after implantation of the collagen graft.
Effects of Nonautologous Materials

In approximately 33% of cases (155 of 475), collagen sponge (either ML or BL) was used in combination with a gel sealant (fibrin glue or PEG hydrogel) in an attempt to achieve a watertight duraplasty. There was no significant difference in the prevalence of sealant use between the ML and BL groups (35.3% versus 28.4; \( P = 0.1 \)), which held true after stratifying by type of operation (\( P = 0.2 \)). Fibrin glue was used in the majority (66%) of these cases, most commonly with ML collagen. In contrast, PEG hydrogel was most commonly used in combination with BL collagen.

Postoperative CSF leak was significantly more frequent in cases in which sealant was applied than in cases in which sealant was not used (11.6% versus 4.4%, \( P = 0.01 \)). There was no significant association between incidence of leak and type of sealant used (Fig. 4A; Table 4).

The overall incidence of postoperative infection was significantly lower when sealant was applied than when it was not (1.2% versus 5.6%; \( P = 0.02 \)). There were 2 infections in the sealant group, both of which were associated with use of PEG hydrogel. There were no postoperative infections with fibrin glue use. The small number of patients in whom an infection developed after application of sealant made statistical tests of differences between sealants inappropriate (Fig. 4B; Table 4).

Among all cases, approximately 31% (147 of 475) required calcium phosphate cranioplasty for repair of a calvarial defect after implantation of a collagen sponge. The overall incidence of CSF leak in this group was 11.5% (17 of 147), significantly greater than the 4.6% rate of CSF leak seen when no cranioplasty was performed (\( P = 0.02 \)). There was no significant difference in rates of infection with or without cranioplasty (2.0% versus 5.2%; \( P = 0.3 \)) (Table 5).

Early in our institutional experience, collagen sponge was used in an onlay fashion to cover the suture line between the dura and a bovine pericardial patch graft. Post hoc subgroup analysis revealed 38 cases in which ML collagen was combined with bovine pericardium. There was no significant difference between the incidence of CSF leak in these cases compared with those in which ML collagen was used alone (12.2% versus 6.2%). These analyses also suggest a lower incidence of CSF leak when BL collagen was used alone compared with the combination of ML and pericardium (5.6% versus 13.2%; \( P = 0.15 \)). There was no significant difference in rates of postoperative infection with ML and pericardium versus BL collagen alone.
Incidence of postoperative complications with the combined use of a collagen sponge and cranioplasty:

<table>
<thead>
<tr>
<th>Complication</th>
<th>% (no.)</th>
<th>Pvalue</th>
</tr>
</thead>
<tbody>
<tr>
<td>CSF leak</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cranioplasty</td>
<td>4.6 (15)</td>
<td>0.02</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>11.5 (17)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No cranioplasty</td>
<td>5.2 (17)</td>
<td>NS</td>
</tr>
<tr>
<td>Calcium phosphate</td>
<td>2 (3)</td>
<td></td>
</tr>
</tbody>
</table>

*a CSF, cerebrospinal fluid; NS, not significant.

Predictors of Performance for Collagen Sponge Duraplasty

Multivariate regression models were constructed to identify potential risk factors for the development of a CSF leak or postoperative CSF infection. Because of significant confounding, separate models were developed for CSF leak in the supratentorial and infratentorial groups.

In the supratentorial group, use of any sealant (PEG hydrogel or fibrin glue) significantly increased the risk of the development of a postoperative CSF leak (OR, 4.1; 95% CI, 1.4–11.7). Among infratentorial cases, the type of collagen sponge, but not the use of sealant, was a significant predictor of the development of a postoperative CSF leak. Specifically, use of BL collagen was associated with a significantly lower incidence of CSF leak (OR, 0.09; 95% CI, 0.01–0.7).

With respect to multivariate analysis of complication development, we found that application of sealant was associated with a reduced risk of infection (OR, 0.2; 95% CI, 0.05–0.9). Although the number of adverse (infectious) outcomes in the sealant subgroup was too small to determine an association with a particular type of sealant, it is notable that there were no infections associated with use of fibrin glue (Table 6).

DISCUSSION

Use of non-native material to restore dural integrity after cranial surgery is a calculated risk, balancing the benefit of immediate restoration of dural integrity with the risk of a foreign graft. In the case of dural substitutes, the specific risks include graft failure (i.e., development of a CSF fistula or pseudomeningocoele), infection, foreign body reaction, graft rejection, allergic reaction, adhesions, and even delayed hemorrhage (9, 12, 23, 26, 35). Working with allograft, nonhuman xenograft, and, most recently, synthetics, a significant amount of research effort has been spent on nonautologous materials to meet the needs of a dural replacement (1–8, 10, 14, 16–19, 21–25, 27–30, 32–34, 37).

There are at least 5 goals that should be met when engineering a dural substitute. First, the implant should serve to temporarily or permanently assume the function of the native tissue that it replaces (in this case, separating and sealing the subdural compartment from the epidural space). Second, the implant should induce host cells to differentiate and repair/replace those lost during tissue resection (i.e., meningotheilal induction). Third, the implant should facilitate infiltration and implantation of such cells (i.e., meningotheilal conduction). This characteristic is a direct function of the 3-dimensional structure of the graft. Fourth, if possible, the implant should include cellular components capable of regenerating the native tissue (i.e., meningotheilogenesis). Fifth, one must take into consideration surgical handling of the material. What surgeons consider handling falls into 2 characteristics of the graft: ductility, the ability to conform to a surgical defect without deforming the surrounding tissues, and tensile strength, which is inversely proportional to the density of the graft and translates to the ability of the graft to hold suture under tension. Some of these characteristics are mutually exclusive. For example, ductility and conductivity tend to come at the expense of tensile strength (37).

Purely synthetic absorbable dural grafts (i.e., polyglactin), which are engineered to be conductive and/or inductive, often induce a vigorous inflammatory reaction that inhibits wound healing and increases the risk of wound infection (11, 21, 23). In contrast, nonabsorbable grafts are neither inductive nor conductive and act only as a mechanical barrier. Unlike absorbable grafts, they heal primarily by encapsulation with a neomembrane, which forms in continuity with the cut edge of the dura. Although a nonabsorbable graft may rapidly assume the barrier function of dura, its mechanical stability under tension comes at the cost of pliability and conductivity. Because of neomembraneous healing, such grafts do not permit restoration of native tissues over time.

One dural substitute that has been proven safe and effective in both animal and clinical studies is the acellular dural grafts derived from type I collagen. This 3-dimensional matrix of collagen fibers acts as a scaffold for the healing of a dural tear (18, 21, 37). Such matrix grafts have the advantage of direct absorption of CSF, which may leak through a suture line, decreased meningocebral adhesions at the site of surgery, and direct hemostatic effect with no apparent increase in postoperative infection (7). In our opinion, their principal advantage is that the structure allows both fibroblast migration and neovascularization, setting up a reaction that allows the implant to be replaced by native tissue within 2 to 3 months (20, 31). Although they are not impermeable, the collagen grafts are sufficient until native tissues are restored (21).
In this retrospective study, we compared homogeneous ML collagen graft with a more recently developed BL collagen graft. The BL sponge was approved as a “substantially equivalent design” to previous collagen matrix dural grafts without clinical demonstration of equivalence (or lack thereof) to previous implants (36). Thus, we believed that a large retrospective cohort study was a reasonable design with which to examine the association of this newer graft with CSF leak and infection. Furthermore, this cohort provided the opportunity to examine the common practice of simultaneous implantation of a sponge with other materials focusing on potential interactions between implants.

Our overall incidence of postoperative CSF leak was 6.7%, well within the reported range (10, 13, 31). We found that fistulae developed in a smaller proportion of the patients receiving BL collagen duraplasty and that this difference was significant when performing procedures in the posterior fossa. It is likely that the ability to hold a suture under tension allows the surgeon to better approximate the graft to the defect in the face of increased hydrostatic pressure, even when only a few tacking sutures are placed. When closing dura in the posterior fossa, the data suggest that BL collagen is at least as effective as a non-absorbable patch graft combined with a sponge over the suture line. It may be that the mutually exclusive healing pathways for these 2 types of grafts (encapsulation versus incorporation) result in diminished efficacy when the 2 types of dural grafts are combined.

With regard to the common practice of combining sponges with other foreign material during closure, our findings suggest that there may be an increased risk of CSF leak in the supratentorial space when a sealant and/or cranioplasty is used in combination with collagen sponge. At this point, the reason for this is not entirely clear. It may be that implantation of multiple products for dural closure represents the surgeons’ recognition of a situation with an inherently higher risk of postoperative CSF leak. Conversely, the use of a sealant may reduce the efficacy of the graft over time, likely by impairing conductivity, which would lead to graft decay without replacement by native tissue. Although these are undoubtedly important findings, conclusions related to differences between sealants and/or cranioplasty will require further study.

Additionally, in multivariate modeling predictors of leak or infection, we found that intrinsic patient characteristics such as nicotine exposure (smoking), diabetes, and patient age were not significant factors. Surgeons should not hesitate to implant a graft in procedures performed in the elderly, those with diabetes, or smokers; the advantage of dural closure seems to outweigh the risks of a foreign body implant in patients with impaired wound healing.

CONCLUSION

This study examined our institutional experience with the safety and efficacy of type I collagen sponges for duraplasty. Compared with ML sponges, BL collagen sponges are associated with a reduction in postoperative CSF leak (fistula or pseudomeningocele), especially in posterior fossa surgery. There is no increased association with infection when implanting the BL sponge, and it can be safely combined with other non-native closure materials. Under most circumstances, the BL sponge provides sufficient restoration of dural integrity and requires significantly less operative time to implant.

Patients who require additional nonautologous materials to effect closure of the craniotomy site, such as dural sealants and cranioplasty materials, are at increased risk of postoperative CSF leak. No conclusions should be drawn regarding causality, merely that there is a strong association between the use of multiple products and the development of a post-operative leak. Nonetheless, such patients should be counseled regarding their risks of CSF leak and the steps that may be taken to manage it. In the next report, we will further examine our institutional experience with fibrin glue and PEG hydrogel as dural sealants.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or devices described in this article.

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Acknowledgments
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COMMENTS
Itvack et al. present a complex retrospective review of a large series of patients. As one might expect, when a large group of patients is treated by multiple surgeons, it may be difficult to reach conclusions about cause and effect. For example, as the authors note, why was the risk of cerebrospinal fluid leak increased in patients who received dural sealants and/or cranioplasty in addition to collagen sponges for dural closure? Is it likely that such patients were recognized during surgery to have a higher risk of cerebrospinal fluid leak, and, thus, extra steps were taken by the surgeon to try to prevent postoperative cerebrospinal fluid leakage. A retrospective review cannot provide definitive answers to these questions. Nevertheless, the descriptive data in this article and the thoughtful Discussion should be of interest to all neurosurgeons.

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