Online First

Choice of Graft Material and Postoperative Healing in Endoscopic Repair of Cerebrospinal Fluid Leak

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Objective: To compare the postoperative healing profiles of graft materials used for endoscopic repair of cerebrospinal fluid (CSF) leak.

Design: Retrospective cohort study with 1 to 21 months of follow-up.

Setting: Tertiary referral, academic medical center.


Intervention: Endoscopic repair of CSF leak with acellular dermis, collagen matrix, or sinonasal mucosal grafts. Graft success, time to full graft mucosalization, and duration of graft or donor site crusting were assessed during the postoperative period.

Results: Forty repairs were performed on 37 patients: 17 with mucosal grafts, 10 with acellular dermis, and 13 with collagen matrix grafts. The mean follow-up time was 5.3 months (range, 0.5-21.0 months). Two patients had partial graft loss; none had a recurrence of CSF leak. There was a significant difference in time to mucosalization with acellular dermis (11.7 weeks) when compared with collagen matrices (6.6 weeks) or mucosa (4.9 weeks) ($P<.001$). Graft crusting was more prolonged with acellular dermis (9.4 weeks) than with collagen matrices (5.1 weeks) ($P=.04$). No patients with mucosal grafts had graft crusting. Donor site crusting was present only in the mucosal group, with an average duration of 6.5 weeks (range, 1.0-20.0 weeks).

Conclusions: Mucosal grafts, acellular dermis, and collagen matrices have similar success rates in endoscopic repair of CSF leak. Acellular dermis grafts have longer time to mucosalization and more weeks of crusting than mucosal or collagen matrix grafts.


DESCRIPTIONS OF SURGICAL repair of cerebrospinal fluid (CSF) leak have been published in the literature since 1926, when Dandy first described a successful intracranial repair technique. Over the past 80 years, the preferred method of repair has evolved as new instruments, imaging modalities, and repair materials have become available. After Wigand first described successful transnasal endoscopic repair of CSF leak in 1981, multiple authors have confirmed the excellent success rates and relatively benign morbidity profile associated with this closure method.3-13

The details of operative technique vary widely; successful repairs have been described with methods both simple and complex and with materials ranging from endogenous tissues to allografts, xenografts, and engineered matrices. Despite significant progress, a consensus on how to provide the best outcomes for patients has yet to be reached. To date, there are few comparative data available to help surgeons differentiate among available graft materials. This study was designed to assess early postoperative healing after repair of CSF leak with 3 different graft materials. Specifically, we compared weeks of graft crusting, time to graft mucosalization, and rate of recurrent CSF leak in patients undergoing endoscopic repair of CSF leaks with acellular dermis, collagen matrices, and sinonasal mucosal grafts.

METHODS

DATA COLLECTION

A retrospective review of sequential patients undergoing endoscopic repair of CSF leak at a tertiary care referral center from March 2007 through May 2009 was undertaken. Patients were identified from the operative records of the 2 primary rhinologists (S.K.W. and J.M.D.) at the institution, who performed all surgical...
Table 1. Demographic Information

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mucosal Graft (n=17)</th>
<th>Acellular Dermis (n=10)</th>
<th>Collagen Matrix (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age, y</td>
<td>49.4</td>
<td>49.0</td>
<td>49.8</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Female</td>
<td>12</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Site of leak</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethmoid sinus</td>
<td>8 (47)</td>
<td>2 (20)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Sphenoid sinus</td>
<td>5 (29)</td>
<td>4 (40)</td>
<td>2 (15)</td>
</tr>
<tr>
<td>Cribriform plate</td>
<td>4 (24)</td>
<td>4 (40)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>Sella</td>
<td>0</td>
<td>0</td>
<td>6 (46)</td>
</tr>
<tr>
<td>Cause of leak</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>10 (59)</td>
<td>4 (40)</td>
<td>4 (31)</td>
</tr>
<tr>
<td>FESS</td>
<td>5 (29)</td>
<td>1 (10)</td>
<td>0</td>
</tr>
<tr>
<td>TSA</td>
<td>0</td>
<td>3 (30)</td>
<td>5 (38)</td>
</tr>
<tr>
<td>Trauma</td>
<td>1 (6)</td>
<td>0</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (6)</td>
<td>2 (20)</td>
<td>3 (23)</td>
</tr>
<tr>
<td>Adjunctive measures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar drain/shunt</td>
<td>3 (17)</td>
<td>5 (50)</td>
<td>7 (54)</td>
</tr>
<tr>
<td>Bone graft/implant</td>
<td>6 (35)</td>
<td>1 (10)</td>
<td>2 (15)</td>
</tr>
</tbody>
</table>

Abbreviations: FESS, functional endoscopic sinus surgery; TSA, transsphenoidal adenectomy.

procedures. Patient selection was limited to a 2-year period when all 3 graft materials were in routine use to ensure comparable size of study groups. Demographic data and information on the site and pathogenesis of the CSF leak were collected on all patients. Defect size was recorded based on endoscopic examination and radiographic findings. Some defects were created intraoperatively (e.g., during transsphenoidal adenectomy), and detailed size information was not available. Careful inspection of graft and donor site(s), if applicable, was undertaken at each follow-up visit. The patients were seen at 2, 5 to 6, and 10 to 12 weeks after surgery. Subsequent follow-up visits occurred at 2- to 3-month intervals and were determined on an individual basis. Primary outcomes included weeks of graft crusting, time to mucosalization of graft, and rate of recurrence of CSF leak. All complications related to instrumentation on the day of surgery were recorded. The institutional review board of Emory University, Atlanta, Georgia, granted approval for this study.

SURGICAL TECHNIQUE

Grafts were composed of native sinonasal mucosa, acellular dermis (Alloderm; LifeCell Corp, Branchburg, New Jersey), or collagen matrix (Duraform; Codman & Shurtleff Inc, Raynham, Massachusetts; and DuraGen; Integra Lifesciences Corp, Plainsboro, New Jersey). The choice of graft material was left to the primary surgeon. Closures consisted of a single layer of study material supported by bone graft or multiple layers of study material. No cartilage grafts were used. Fibrin glue and absorbable packing were used to secure and bolster all grafts. The use of additional measures to support graft healing, such as nonabsorbable nasal packing or lumbar drains, was left to the discretion of the primary surgeon.

STATISTICAL ANALYSIS

Data were entered into an Excel spreadsheet (Microsoft, Seattle, Washington) and analyzed using SPSS version 11.0 statistical software (SPSS Inc, Chicago, Illinois). Data on recurrent leaks were not analyzed, as no patient had a recurrence of CSF leak during the postoperative assessment period. Univariate analysis of variance with Tukey post hoc testing was used to analyze time to graft mucosalization. An independent samples t test was used to compare weeks of crusting in the acellular dermis group and the collagen matrix groups. Because no patients in the mucosal graft group had graft crusting, this group was not included in this portion of the analysis. Statistical significance was defined at P < .05. Complications did not occur with sufficient frequency or variability to support valid statistical analysis.

RESULTS

Forty patients underwent 43 eligible procedures during the study period. In patients undergoing repairs at multiple sites, each skull base defect was assessed as a separate case (3 patients each had 2 anatomically separate sites of skull base defect repair). Three eligible patients had incomplete records and were excluded, leaving a study group of 37 patients (40 total procedures). Seventeen repairs were performed with mucosal grafts, 10 with acellular dermis, and 13 with collagen matrix–based materials. The characteristics of each group are shown in Table 1. The average follow-up time was 5.3 months (range, 0.5-21.0 months). Precise measurements of defect size were not available for all patients. In general, defect sizes were similar among patients receiving acellular dermis and collagen matrix grafts and tended to be smaller in the mucosal graft group. Concern for donor site morbidity limited the use of mucosal grafts in the repair of large defects. There was a significant difference in time to mucosalization with acellular dermis (11.7 weeks) when compared with collagen matrices (6.6 weeks) or mucosa (4.9 weeks) (P < .001), with a large effect size (η² = 0.55). Mucosa and collagen matrix grafts were not significantly different from each other (P = .19).

Graft crusting was more prolonged with acellular dermis (9.4 weeks) than with collagen matrices (5.1 weeks) (P = .04). At the first postoperative evaluation, no patients with mucosal grafts had graft crusting. Representative photographs of each graft type at the 6-week postoperative visit are shown in Figure 1. Donor site crusting was only present in the mucosal group, with an average duration of 6.5 weeks (range, 1.0-20.0 weeks). Donor site crusting at 4 weeks is shown in Figure 2.

Complications are shown in Table 2. Any complication requiring further procedural intervention was designated as a major complication. Eighteen patients (48%) reported a complication or adverse effect from surgery. Of these, 16 (88%) had minor complications, and 2 (5%) had complications that required procedural intervention. One patient in the collagen matrix group had a retained portion of a lumbar drain catheter and was taken to the operating room for uncomplicated image-guided retrieval of the catheter tip. One patient in the mucosal graft group had postoperative epistaxis that required nasal packing and embolization of the sphenopalatine artery on the operative side. The most common complication was formation of synechiae, which occurred in 5 patients (4 in the mucosal graft group; 1 in the acellular dermis graft group).
A survey of the core otolaryngologic and neurologic surgery journals yields dozens of articles pertaining to repair of CSF leak. Multiple successful techniques for repair have been described, ranging from simple endoscopic local mucosal flaps to complex free tissue transfer with microvascular anastomosis. Fixation of grafts with suture, fibrin adhesives, fibroblast growth factor, and laser tissue welding has been documented. Similarly, myriad graft materials have been used in endoscopic repair of the skull base. Autologous tissue, in the form of mucosa, bone, fascia, fat, or muscle, has been used extensively because of its availability, low cost, and biocompatibility. Processed tissues such as decellularized human dermis, bovine pericardium, or equine Achilles tendon have been used to add structural support or when local tissues are limited. Advances in tissue engineering have also made synthetic collagen matrices and dural substitutes available for routine use. Reported benefits include a microstructure that has been optimized for fibroblast and blood vessel ingrowth, rapid incorporation into surrounding tissue, and minimal inflammatory reaction in the surrounding native tissue.

Studies have been published showing the efficacy of all the materials mentioned herein, but there continues to be a paucity of comparative evidence supporting one material over another. To date, the literature has defined success with a single outcome: repair with no recurrence of CSF leak. The narrow scope of this definition is somewhat problematic; in experienced hands, most techniques and materials yield similar results, with 90% to 97% of repairs considered successful on first attempt. Such parity does little to guide decision making for today’s endoscopic surgeon and suggests that consideration of multiple outcomes may be necessary to determine best practice standards in repair of CSF leak.

This study addresses the postoperative phase of surgical treatment of CSF leak.

Figure 1. Intranasal photographs at the 6-week follow-up visit. A, Acellular dermis graft in the central anterior skull base. B, Collagen matrix graft in the sphenoid roof. C, Mucosal graft in the posterosuperior sphenoid sinus.

Figure 2. Nasal septal graft harvest site at 5-week follow-up visit before (A) and after (B) debridement.
operations. In an attempt to characterize postoperative healing objectively in this study, time of graft crusting, time to mucosalization of the grafts, and time to failure of the grafts were measured. No grafts failed during the follow-up period. One patient in the collagen matrix group and 1 patient in the acellular dermis group had partial graft loss without recurrence of leak. These results correlate well with previously published excellent success rates in endoscopic repair of CSF leak.

Postoperative crusting in the nose hinders mucosalization, inhibits surveillance of the operative site(s), and contributes to symptoms of nasal obstruction. During the postoperative period, in-office debridement of crusts is necessary to ensure proper healing of the underlying tissue. These debridements can be uncomfortable for the patient and time consuming for all parties involved. Removal of crusting directly over the graft site also carries the risk of graft dislodgment. Our results indicate that acellular dermis grafts have significantly longer periods of postoperative crusting than mucosal or collagen matrix grafts. Mucosal grafts were incorporated rapidly into the surrounding mucosa with no crusting observed but carried the unique morbidity of donor site crusting. Total weeks of crusting were comparable in the mucosal and collagen matrix graft groups.

Mucosalization of the graft and adjacent surgically treated tissue provides physical evidence of the healing process. It is also essential for return of normal nasal function. Tissue that heals with granulation or scar may exhibit abnormal mucociliary clearance, which can lead to recurrent sinus disease. A competent mucosal barrier also helps protect the graft site from intranasal insults such as mechanical trauma and infection. Our results showed that acellular dermis grafts had a significantly longer time to mucosalization than collagen matrix or mucosal grafts. This longer time may be attributable to the need for processed tissues, such as acellular dermis, to be remodeled by host fibroblasts and angiogenic factors. Matrix graft materials are purposefully constructed for rapid incorporation into host tissue and do not contain unnec-

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**Table 2. Complications Related to Surgical Intervention**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mucosal Graft (n=17)</th>
<th>Acellular Dermis Graft (n=10)</th>
<th>Collagen Matrix Graft (n=13)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Minor complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epistaxis requiring intervention</td>
<td>1 (6)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent CSF leak</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retained portion of lumbar drain catheter</td>
<td>0</td>
<td>0</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Synchiae</td>
<td>4 (24)</td>
<td>1 (10)</td>
<td>0</td>
</tr>
<tr>
<td>Septal perforation</td>
<td>1 (6)</td>
<td>0 (10)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Infection</td>
<td>1 (6)</td>
<td>2 (20)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Partial graft loss</td>
<td>0</td>
<td>1 (10)</td>
<td>1 (8)</td>
</tr>
<tr>
<td>Numbness of upper incisors</td>
<td>1 (6)</td>
<td>0</td>
<td>2 (15)</td>
</tr>
</tbody>
</table>

Abbreviation: CSF, cerebrospinal fluid.

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Our study is limited by its small sample size and retrospective design, both of which introduce the possibility of selection bias. A degree of selection bias based on defect size could not be avoided, as some defects were simply too large to be repaired with local mucosal flaps. Defect size could also affect healing time and would be expected to be most significant when comparing the mucosal graft group (which generally had smaller defects) with the groups requiring exogenous graft materials for closure. However, the duration of the crusting at mucosal donor sites was comparable to that of the crusting seen with acellular dermis grafts. Also, defect size was similar among patients receiving acellular dermis and collagen matrix grafts and is therefore unlikely to fully explain the differences in healing time between these groups. Crusting and mucosalization were determined by a single, unblinded evaluator (the primary surgeon: S.K.W. or J.M.D.), which could potentially lead to assessment bias. To minimize assessment bias, enrollment in the study was limited to a period during which all 3 graft materials were in routine use.

Despite the limitations, several important conclusions can be drawn from the results of this study. The above-mentioned data show that graft materials are associated with different postoperative healing profiles. Specifically, acellular dermis grafts appear to have prolonged healing when compared with mucosal and collagen matrix grafts. How, and if, these differences affect nasal functioning, graft stability, and overall success of the procedure remains unclear without further investigation. It is clear, however, that the results of comparative effectiveness research will play an increasing role in guiding medical decision making in the near future. Graft materials that require more complex surgery, more frequent follow-up, or more postoperative intervention may fall out of favor as the cost and efficiency of health care delivery fall under greater scrutiny. In conducting further research, treatment “success” may need to be redefined to incorporate the entire surgical care experience, rather than focusing on the single surgical outcome of preventing recurrent CSF leak.

In conclusion, repairs using sinonasal mucosa, acellular dermis, and collagen matrices are equally effective in preventing recurrent CSF leak. Acellular dermis grafts have a longer time to mucosalization and longer periods of postoperative crusting than mucosal or collagen matrix grafts. Further study of the postoperative healing expected with different graft materials may help determine the best surgical strategy for endoscopic management of CSF leak.

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Author Contributions: All authors had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Wise and DelGaudio. Acquisition of data: Wise and DelGaudio. Analysis and interpretation of data: Pickett, Wise, and DelGaudio. Drafting of the manuscript: Pickett and Wise. Critical revision of the manuscript for important intellectual content: Wise and DelGaudio. Administrative, technical, and material support: Pickett and DelGaudio. Study supervision: Wise.

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Additional Contributions: Justin C. Wise, PhD, assisted with statistical analysis.

REFERENCES