A Novel Impermeable Adhesive Membrane to Reinforce Dural Closure: A Preliminary Retrospective Study on 119 Consecutive High-Risk Patients

Paolo Ferroli, Francesco Acerbi, Morgan Broggi, Marco Schiariti, Erminia Albanese, Giovanni Tringali, Angelo Franzini, Giovanni Broggi

OBJECTIVE: Postoperative cerebrospinal fluid (CSF) leak in neurosurgery remains a significant source of morbidity. TissuePatchDural (TPD), a novel impermeable adhesive membrane, can be used to reinforce dural closure in cases considered at high risk to develop postoperative CSF leak.

METHODS: A retrospective, single-center, clinical investigation was conducted on 119 patients who underwent elective neurosurgical procedures between January and June 2010. Inclusion criteria included adult patients undergoing clean elective surgeries where a primary watertight closure was not possible. Three groups of patients were considered: 1) infratentorial, 67 cases; 2) supratentorial, 34 cases; and 3) spinal, 18 cases. All these patients received TPD to reinforce dural closure. Preoperative (long-term corticosteroid therapy, previous surgery and radiotherapy), intraoperative (site of procedures and size of dural gap), and postoperative (early and late hydrocephalus) conditions were analyzed as possible risk factors associated with CSF leakage.

RESULTS: The mean follow-up was 7.14 months (range 6–12 months). CSF leak was detected in 11 of 119 cases (9.2%). The presence of pre- and postoperative risk factors was associated with a higher percentage of CSF leakage: 8 of 22 cases (36.3%) vs. 3 of 97 cases (3.1%) ($P < 0.0001$). All leaks could be conservatively treated and no patient required readmission or second surgery. No TPD-related adverse or allergic effects were observed.

CONCLUSIONS: TPD seems to be a safe tool to be used to reinforce dural closure in patients with a high risk of developing CSF leaks.

INTRODUCTION

Cerebrospinal fluid (CSF) leakage is one of the most common and potentially dangerous complications in neurosurgery. Current first line treatment aims to promote wound healing by reducing CSF pressure (CSF lumbar drainage or repeated spinal taps) and to prevent infections by administering intravenous antibiotics to the patient. Failure of these treatments eventually leads to further surgical procedures. However, in spite of all these treatments, an infection of the CSF itself or of the brain can complicate the postoperative course (8). Although technologic advances in neurosurgical techniques reduced the occurrence of this complication, postoperative CSF leakage is still a serious unsolved problem whose incidence can be as high as 42% (2, 3, 5, 7, 9, 11, 13, 14, 18, 24-27, 29, 30, 33-35, 37, 41).

TissuePatchDural (TPD) (Tissuemed Ltd., Leeds, United Kingdom) is a sterile, self-adhesive, absorbable surgical sealant indicated for adjunctive prevention of CSF leakage in neurosurgery (12). In this retrospective, non-randomized, single-center study, the authors aimed to evaluate the safety and to obtain initial data about the effectiveness of this novel sealant as an adjunct to standard dural closure during neurosurgical procedures at high risk of developing a CSF fistula.

MATERIALS AND METHODS

Patient Population

This study is a retrospective, single-center, clinical investigation conducted on 119 patients who underwent elective neurosurgical procedures in a 6-month period (January-June 2010). Informed consent was obtained from all patients. Preoperative inclusion criteria included adult patients undergoing clean elective surgeries. Previous radiotherapy, previous surgery, or long-term corticosteroid therapy were not considered exclusion criteria. Intraoperative inclusion criteria included wide cisternal and/or ventricular opening and the failure to obtain a watertight primary closure with a standard dural microsuture (leakage evidenced by subdural irrigation of the surgical cavity before tying the last stitch, followed by Valsalva maneuver to test the last stitch). These patients received TPD to reinforce dural closure. In the period between January and June 2010, a total of 123 consecutive patients treated at the authors’ institution were selected as meeting the inclusion criteria described above. Three patients were excluded because of hemorrhagic or ischemic complications that required early reoperation and subsequent TPD removal. One patient was excluded because of a technical problem during the intraoperative application of TPD. In total, 119 patients, 64
All patients underwent daily postoperative wound examination in order to assess the occurrence of subgaleal CSF collection, incisional CSF leak, any inflammatory reaction or wound infection. An early, usually day 1, postoperative brain or spine computed tomographic scan was performed to detect the development of hydrocephalus or spinal soft tissues CSF collection. In case of clinical uncertainty, a biochemical testing for transferrin leakage was performed in order to confirm CSF leak. The wound was then examined at two weeks and at two and six months after surgery. In addition, in the period from 2 weeks to 2 months, patients were instructed to contact the hospital in case of wound leakage and/or subgaleal or spinal collection. Demographic data, operative and outcome data were collected and analyzed.

In this study the term “CSF leak” was used for both pseudomeningocele and incisional CSF leak. The etiology of these complications is the leak of the CSF from the subarachnoid space to the extradural compartment. When the skin incision has adequately healed, a pseudomeningocele may develop; otherwise, an incisional CSF leak can also occur. However, both situations should be considered as a failure of the dural sealant to prevent CSF from leaking to the extradural compartment (38).

TissuePatchDural

TPD is a sterile, self-adhesive, absorbable surgical sealant and barrier available in four different sizes ranging from 25 × 50 mm to 10 × 100 mm (Figure 1). It is a multilayered device comprising alternate layers of poly(lactide-co-glycolide) and a proprietary adhesive Terpolymer. Poly(lactide-co-glycolide) is a resorbable membrane that provides reliable strength for temporary wound support (12).

According to the product instructions for use provided by the manufacturer (Tissuemed Ltd.), the material is adhesive by virtue of the initial tack provided by both poly(acrylic acid) and poly(vinyl pyrrolidone) functional groups and longer term adhesion via nucleophilic substitution reaction between N-hydroxysuccinimide and amine/thiol groups. TPD re-

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### Table 1. Surgical Site and Number of Cerebrospinal Fluid Leakage in the 119 Cases Operated at the Fondazione IRCCS Istituto Neurologico Carlo Besta of Milano, Italy, Between January and June 2010, where TissuePatchDural was Used

<table>
<thead>
<tr>
<th>Number of Cases (%)</th>
<th>Number of CSF Leaks (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infratentorial craniotomies</td>
<td>67 (56.3)</td>
</tr>
<tr>
<td>Supratentorial craniotomies</td>
<td>34 (28.6)</td>
</tr>
<tr>
<td>Spinal cases</td>
<td>18 (15.1)</td>
</tr>
<tr>
<td>Total</td>
<td>119</td>
</tr>
</tbody>
</table>

CSF, cerebrospinal fluid.

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### Table 2. Comparison of Studies with Different Types of Dural Sealant Including the Present

<table>
<thead>
<tr>
<th>Author</th>
<th>Sealant</th>
<th>No. of Patients</th>
<th>% of Leakage</th>
<th>% High-Risk Patients</th>
<th>Site</th>
<th>Follow-Up Period (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Boogaarts et al., 2005 (4)</td>
<td>DuraSeal</td>
<td>46</td>
<td>4.9% (out of 41 patients)</td>
<td>High- and low-risk procedures</td>
<td>26 supratentorial 18 infratentorial 2 spinal</td>
<td>3</td>
</tr>
<tr>
<td>Cosgrove et al., 2007 (8)</td>
<td>DuraSeal</td>
<td>111</td>
<td>4.5%</td>
<td>High- and low-risk procedures</td>
<td>58 supratentorial 53 infratentorial</td>
<td>3</td>
</tr>
<tr>
<td>Than et al., 2008 (38)</td>
<td>DuraSeal</td>
<td>100</td>
<td>2%</td>
<td>Not specified</td>
<td>Posterior fossa</td>
<td>2.9</td>
</tr>
<tr>
<td>Kumar et al., 2003 (22)</td>
<td>Bioglue</td>
<td>210</td>
<td>0.93% (in two posterior fossa approach)</td>
<td>Not specified</td>
<td>114 supratentorial 53 infratentorial 41 transsphenoidal 8 spinal</td>
<td>1.5</td>
</tr>
<tr>
<td>Jankowitz et al., 2009 (21)</td>
<td>Tissuemed</td>
<td>278</td>
<td>11.9%</td>
<td>Not specified</td>
<td>Spine</td>
<td>3</td>
</tr>
<tr>
<td>Ferroli et al., 2011 (current study)</td>
<td>TissuePatchDural</td>
<td>119</td>
<td>9.2% (11 of 119) 38.5% (8 of 22) of high-risk cases* 3.1% (3 of 97) of normal-risks cases†</td>
<td>All patients with wide cisternal or ventricular opening. 22 of 119 (18.5%) high-risk cases*</td>
<td>67 infratentorial 34 supratentorial 18 spinal</td>
<td>6</td>
</tr>
</tbody>
</table>

*Patients with preoperative (previous surgery, radiotherapy, and long-term corticosteroid therapy) and postoperative (early and late hydrocephalus) risk factors.
†All the other patients.
mains in position while it slowly degrades until substantially reabsorbed in approximately 50 days facilitating tissue ingrowth and wound healing. Risks associated with TPD include allergic reaction to the device and local, mild inflammatory reaction leading to encapsulation by inflammatory cells with some fibrosis. Therefore, it should not be used on patients with a known allergy or sensitization to its constituent components.

**Technique**

TPD was used after the standard microsuture technique of dura mater, when subdural irrigation and Valsalva maneuver confirmed the presence of a clear CSF leakage (Figures 2 and 3). When air-filled cavities within cranial bones were opened, for example frontal sinus or mastoid air cells, muscle or wax were used as a sealant. Small dural gaps (<5 mm in diameter), when present, were plugged with muscle, when available, or collagen sheet (Condress, Abiogen Pharma S.p.A., Ospedaletto [PI], Italy) before the application of the TPD in order to create a barrier to CSF leak and to avoid the adhesion of the film to the cerebral tissue. In six cases, a large defect in the dura mater (>5 mm) was present at the end of the procedure and required reconstruction with various dural substitutes (Duraf orm, Codman & Shurtleff, Inc., Berkshire UK; Duragen, Integra LifeSciences Corporation, Plainsboro, NJ, USA; Tutopatch, Tutogen Medical GmbH, Neunkirchen, Germany). Care was taken to keep the dural surface as dry as possible without excessive blood or fluid in order to avoid premature activation and facilitate attachment of the TPD to the tissue surface. In addition, the material was handled with dry instruments. During placement moist cottonoids/swabs were used to help in softening the film and enhance its conformability. Gentle digital pressure for at least 60 seconds enabled the film to adhere properly to the tissue surface.

Following application of the device, patients were reassessed for intraoperative CSF leakage through the sealed durotomy with a second Valsalva maneuver for 10 seconds. The objective was to obtain an intraoperative wa-

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**Table 3. Preoperative, Intraoperative, and Postoperative Risk Factors in the 101 Patients Submitted to Surgical Procedures for Infratentorial (67 Cases) and Supratentorial (34 Cases) Pathologies**

| Risk Factors                                      | Number of Patients | Site              | Number of Leaks |  
|--------------------------------------------------|--------------------|-------------------|-----------------|---
| Preoperative                                     |                    |                   |                 |---
| Previous surgery                                 | 15                 | 9                 | 6               | 2/9 (22.2%) | 3/6 (50%) |
| Prior radiation                                  | 7 (all submitted to previous surgery) | 6 | 1 | 2/6 (33.3%) | 1/1 (100%) |
| Long-term corticosteroid therapy                 | 6 (all submitted to previous surgery) | 6 | 0 | 2/6 (33.3%) | 0/0 |
| Postoperative                                    |                    |                   |                 |---
| Early hydrocephalus                              | 7 (3 submitted to previous surgery) | 2 | 5 | 1/2 (50%) | 5/5 (100%) |
| Delayed hydrocephalus                            | 3                  | 0                 | 3               | 0/0 |
| Preoperative and postoperative risk factors      | 22                 | 11                | 11              | 3/11 (27.2%) | 5/11 (45.4%) |
| No preoperative or postoperative risk factor     | 79                 | 23                | 56              | 0/23 (0%) | 1/56 (1.8%) |
| Intraoperative                                   |                    |                   |                 |---
| No dural gap (CSF leak only after Valsalva)      | 57/101 (56%)       | 13                | 44              | 0/13 (0%) | 1/44 (2.25%) |
| Small gap <0.5 cm (plugged with muscle or Condress) | 38/101 (37%)       | 10                | 28              | 1/10 (1%) | 4/28 (14.2%) |
| Large gap >0.5 cm (sutured dural substitute)     | 6/101 (6%)         | 4                 | 2               | 2/4 (50%) | 1/2 (50%)  |

CSF, cerebrospinal fluid.

**Figure 1.** TissuePatchDural film (50 × 50 × 0.04 mm) before (left side) and after activation and adhesion to the sutured dural surface in a supratentorial craniotomy (right side).
tight closure in all patients. The wounds were closed in layers. A subgaleal or subfascial drain was placed as deemed necessary only in spinal procedures, and prophylactic antibiotic therapy was administered during and after surgery as usual.

Statistical Analysis
Statistical analysis was completed using Prism 4 version 4.0a (GraphPad Software, Inc.). Durotomy site (supratentorial, infratentorial, spinal) was studied as a variable possibly influencing the rate of CSF leak. In addition, in patients submitted to surgical procedures for infratentorial or supratentorial pathologies, a range of variables were analyzed. Specifically, 1) preoperative risk factors, including (a) long-term corticosteroid therapy, (b) previous surgery, and (c) radiation therapy; 2) intraoperative risk factors, including (a) size of dural gap (CSF leakage only on Valsalva maneuver, small gap plugged with muscle or collagen, need for duroplasty); 3) postoperative risks factors, including (a) early and (b) late postoperative hydrocephalus were evaluated. Proportions were compared using chi-square test, with a value of P < 0.05 being considered significant.

RESULTS
Overall, TPD was used in 119 surgeries. The mean follow-up was 7.3 months (range 6–12 months). Tables 2 and 3 provide baseline patient data including preoperative (long-term corticosteroid therapy, previous surgery, radiation therapy), intraoperative (size of dural gap), and postoperative risk factors (early or delayed hydrocephalus). CSF leakage was found in 11 of 119 cases (9.2%). All these leaks were evident at the short-term follow-up of 2 weeks. CSF leakage presented as subgaleal CSF collection and spinal subfascial collection in 9 (6 infratentorial and 3 supratentorial approaches) and 2 cases respectively (Table 1).

Both patients with subfascial lumbar CSF collection were successfully treated with two needle aspirations and pressure bandage. Resolution of the subgaleal collection was also obtained in all patients; one fully recovered after a single lumbar puncture and pressure bandage, whereas two were treated over a period of 3 days with a lumbar CSF drain and pressure bandage. Six patients developed hydrocephalus. Five of them underwent ventriculoperitoneal shunt with resolution of the CSF leakage. In the remaining case, an endoscopic third ventriculostomy was performed before tumor removal and the leak recovered after 5 days of lumbar drainage; the hydrocephalus then slowly resolved.

TPD reabsorbs in approximately 50 days; therefore, it was decided to perform a medium-term follow-up 2 months after surgery, close to the product reabsorption period, and a long-term follow-up 6 months after the surgical procedure. No patient contacted the hospital in the period from 2 weeks to 2 months postoperatively for the appearance of wound leakage and/or subgaleal or spinal collection. In addition, at the 2- and 6-month follow-ups, all wounds appeared well healed and no late postoperative leakage was observed; no patient required readmission and second surgery.

Three cases (2.3%) of wound infection were observed: two in immunocompromised glioblastoma multiforme affected patients under long-term corticosteroid therapy. Both patients were successfully treated with antibiotics. The other wound infection occurred in a young patient affected by acne that required repeated surgery because of extradural empty-
should verify that the dura is pulsating without any fluid leak during the Valsalva maneuver. The film was found to stick to the bone surface, and often the TPD used was oversized, over the bone edges.

**DISCUSSION**

CSF leak after neurosurgical procedures can occur in 0.9% to 42% of cases. This high variability depends on many factors such as surgical approach and location, general and local conditions (previous radiotherapy, immunodepression, corticosteroid therapy, uncontrolled diabetes, renal or hepatic dysfunction, etc.), surgical technique, and CSF leak diagnostic methods (radiologic or clinical diagnosis) (2, 3, 5, 7, 9, 11, 13, 14, 18, 24-27, 29, 30, 33, 35, 37, 41). CSF leak remains a potential life-threatening complication because of the risk of meningitis. Other risks include non-healing wounds and prolonged hospitalization. The medical costs in such cases have been estimated to be 141% greater than in uncomplicated cases (18). No comparative cost analysis was performed, but we found the cost of TPD comparable to other commercially available sealant products.

Since the early days of neurosurgery, watertight dural closure has been recommended in order to avoid CSF leakage (10). Although recently it has been advocated that watertight dural closure is not mandatory in supratentorial procedures (4), direct watertight suturing of the dural defect is generally attempted in every neurosurgical procedure (8). Unfortunately, the dura matter, when opened, tends to shrink because of dehydration and sometimes necessary bipolar coagulation. In the elderly, it can be particularly fragile and bone adherent. Its biochemical features make it an elastic membrane where needle piercing creates pinholes. In addition, when a dural excision is necessary because of infiltration of a tumor, a primary closure cannot be obtained (15, 16). In such circumstances, plastic re-reconstruction could be considered (21, 23, 28, 40). To assist in the sealing of dural closures under problematic conditions when a watertight closure is desirable but difficult to achieve, different materials have been used alone or in combination (4, 6, 8, 21, 22, 32, 36, 38, 39, 42-44). Even if different studies have shown a reduction in terms of CSF leakage, the results in high risk patients and procedures are still questionable.

We began using TPD in late 2009 and in this study we reported the results of a retrospective evaluation of 119 cases treated in our Institution in the period January–June 2010. The primary objective of this study was to evaluate product safety and to obtain initial data about the effectiveness of this novel sealant as an adjunct to standard dural closure during neurosurgical procedures at high risk of developing a CSF fistula.

As TPD is an artificial membrane, the risk of a foreign graft has to be considered. In the case of dural substitutes, risks include graft failure, infection, foreign body reaction, graft rejection, allergic reaction, adhesions, and even delayed hemorrhage (17, 20, 29, 31, 42). In addition, purely synthetic absorbable dural grafts often produce a vigorous inflammatory reaction that inhibits wound healing and increases the risk of wound infection (19, 27, 29). In this series, no such device-related complications occurred. Three patients presented postoperative wound infection, but this was not related to TPD.

With regards efficacy in preventing CSF leaks, the results are encouraging. All patients presented with ventricular or wide cisternal opening; furthermore, patients with pre- and postoperative risk factors were included in the analysis (Table 3). Taking this into consideration, the percentage of 0.2% (11/119 cases) of CSF leakage is comparable with previous studies involving adjunctive treatments, where the percentage of high-risk cases was not specified (Table 2).

Interestingly, the presence of preoperative and postoperative risk factors seems to be one of the factors negatively influencing the total results. In fact, in the 22 patients where pre- (long-term corticosteroid therapy, previous surgery, and radiation therapy) and/or postoperative (early and late hydrocephalus) risk factors were present, 8 developed a CSF leak (36.3%). In comparison, in the remaining cases without pre- and/or intraoperative risk factors (97), only 3 patients developed a CSF leak (3.1%) (Tables 2 and 3). Moreover, size of dural gap at the end of dural closure was another factor related to the appearance of CSF leakage, with better results in the group where TPD was applied if CSF was evident intraopera-

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**Analysis of Specific Risk Factors**

No significant statistical difference in CSF leakage rate could be found among patients submitted to different approaches (infratentorial/supratentorial/spinal, *P* = 0.688). In comparison, the presence of pre- (long-term corticosteroid therapy, previous surgery, and radiation therapy) or postoperative (early and late hydrocephalus) risk factors was associated with the appearance of CSF leakage (*P* < 0.0001). Specifically, 15 patients were submitted to previous surgery, 7 and 6 of them also received radiotherapy and long-term corticosteroid therapy respectively. In addition, 7 patients presented with early hydrocephalus (3 of them had been also submitted to previous surgery) and 3 with late hydrocephalus. Therefore, a total of 22 patients presented pre- and/or postoperative risk factors. Eight of these developed a CSF leak (36.3%). In the remaining cases without pre- and/or intraoperative risk factors (97), only 3 patients developed a CSF leak (3.1%) (Tables 2 and 3).

Considering the size of dural gap (CSF leakage only on Valsalva maneuver, small gap <5 mm plugged with muscle or collagen, large gap >5 mm needing a duroplasty), the absence of a clear dural gap after microsuture was associated with a prevention of CSF leakage after TPD application (*P* = 0.0095) (Table 3).

**Feasibility of TPD Application**

The application of TPD was found to be sometimes difficult because of its fragility when bended. This was particularly true when TPD had to be applied in deep and narrow spaces. TPD could be cut to the required shape and size. The dural surface requires some preparation before TPD application, to ensure the area is free of excess fluid (both CSF and blood). Delicate digital pressure for 60–120 seconds allows the TPD to adhere to the dura. Thereafter, one...
CONCLUSIONS

TPD seems to be a safe product for use as an adjunct to standard dural closure in high-risk cases of postoperative CSF leak. CSF leakage seems to be associated with a number of pre- and postoperative risk factors. Furthermore, the size of the dural gap is another factor influencing the results. Further prospective, randomized, multicenter studies are necessary in order to show the utility of this sealant for reducing postoperative CSF leaks in high-risk neurosurgical procedures.

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