Postoperative Cerebrospinal Fluid Leakage Associated With Total En Bloc Spondylectomy

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abstract

Cerebrospinal fluid (CSF) leakage is a serious postoperative complication associated with total en bloc spondylectomy. The authors examined the risk factors for CSF leakage after this procedure. A total of 72 patients underwent total en bloc spondylectomy at the authors’ institution between May 2010 and April 2013. Postoperative CSF leakage was observed in 17 of the 72 patients (23.6%). The results of univariate analysis suggested that age 54 years or older, preoperative surgical site irradiation, resection of 3 or more vertebral bodies, and dural injury were significant risk factors for postoperative CSF leakage after total en bloc spondylectomy. Multivariate analysis showed that preoperative surgical site irradiation was the only significant risk factor for postoperative CSF leakage (adjusted odds ratio, 5.22; 95% confidence interval, 1.03-26.45, P=.046). The authors also assessed the course of treatment for postoperative CSF leakage in each patient. Of 17 patients with postoperative CSF leakage, 13 recovered without further complications, but 4 required reoperation (2 for wound dehiscence, 1 for surgical site infection, and 1 for severe intracranial hypotension). All 4 patients who required reoperation had a history of surgical site irradiation. Thus, this study suggests that careful consideration should be given to postoperative CSF leakage in patients with a history of surgical site irradiation. These findings may contribute to the management of postoperative CSF leakage associated with total en bloc spondylectomy and supplement the information given to the patient in the process of obtaining informed consent. [Orthopedics. 2015; 38(7):e561-e566.]
Total en bloc spondylectomy is a procedure performed to completely resect spinal tumors, including primarily malignant, aggressive benign, and metastatic tumors (Figure).\(^\text{1,2}\) Intervention with total en bloc spondylectomy reduces local tumor recurrence and improves prognosis.\(^\text{3-5}\) However, because of its highly invasive nature and its use in patients who often have complicated medical backgrounds (eg, cancer), the incidence of complications in total en bloc spondylectomy is high compared with that in other spinal surgeries.\(^\text{6}\) Cerebrospinal fluid (CSF) leakage is a serious postoperative complication associated with spinal surgery and can lead to surgical site infection, pyogenic meningitis, intracranial hypotension, and prolonged hospitalization. During total en bloc spondylectomy, the dura mater is dissected circumferentially, creating a large dead space. Therefore, great care must be taken to prevent CSF leakage after this procedure. However, the incidence of postoperative CSF leakage after total en bloc spondylectomy is high. To the authors’ knowledge, no reports on the incidence and risk factors associated with postoperative CSF leakage after total en bloc spondylectomy have been published. This study examined the risk factors in a single-center, retrospective study.

**Materials and Methods**

This study was approved by the ethics committee of Kanazawa University. Written informed consent for the surgery and entry into the research study was obtained from all 73 patients. When the patient was a minor, informed consent was obtained from the parent or legal guardian.

**Patient Characteristics**

Candidates for total en bloc spondylectomy included patients with primary malignant, aggressive benign, or solitary metastatic tumors and life expectancy of at least 2 years. Between May 2010 and April 2013, a total of 73 patients underwent total en bloc spondylectomy performed by the same surgeon (H.M.) at the authors’ institution. Surgery was performed because of neurologic deficit, intractable pain, or spinal instability caused by the tumor. One patient with an osteosarcoma who underwent total en bloc spondylectomy with transection of the spinal cord was excluded because of tumor invasion. A retrospective review of prospectively collected data was performed for the remaining 72 patients. The study population included 39 men and 33 women, with a mean age of 53.5 years (range, 16-75 years) at the time of surgery.

Of the 72 patients, 65 had metastatic tumors and 7 had primary tumors. Of the 65 patients with metastatic tumors, the primary tumor was located in the kidney in 15 patients, the breast in 12 patients, the thyroid in 9 patients, the lung in 3 patients, the colon in 3 patients, other organs in 19 patients, and unknown locations in 4 patients. Of the 7 patients with a primary tumor, 4 had giant cell tumors and the remaining patients had synovial sarcoma, pleomorphic carcinoma, or chordoma.

**Surgical Procedure**

Preoperative embolization of the bilateral segmental arteries at 3 levels (embolization of bilateral segmental arteries of the tumor and the adjacent caudal and cephalic vertebrae) was performed within 72 hours before surgery in all 72 patients. During surgery, en bloc laminectomy and corpectomy were performed with circumferential dissection of the dura mater and transection of the spinal nerve roots, as necessary. Spinal reconstruction was performed with posterior instrumentation and anterior bone grafting using a titanium cage (Figure). All intraoperative dural injuries were sutured primarily and were covered with fibrin glue spray. In all cases, a submuscular negative pressure drainage system was used after surgery.

**Evaluation Items**

In this study, postoperative CSF leakage was defined as drainage of colorless liquid observed in the negative pressure drainage system. The authors examined the incidence of postoperative CSF leakage and its association with the following parameters: age (mean age, <54 or ≥54 years), sex, smoking status, body mass index (<20, 20-25, or >25 kg/m²), diabetes, tumor histology, previous spinal surgery, preoperative surgical site irradiation, preoperative chemotherapy, surgical level of the spine (thoracic or lumbar), surgical approach (posterior only or combined anterior and posterior), number of resected vertebrae (<3 or ≥3), transection of the nerve roots, and intraoperative dural injury. The authors also assessed the course of treatment for postoperative CSF leakage in each patient.

**Statistical Analysis**

Univariate methods were used to detect differences between the incidence of postoperative CSF leakage and risk factors. Contingency tables were used to...
assess the association with Pearson’s chi-square or Fisher’s exact test. Statistical significance was set at $P<.05$. For multivariate analysis, multivariable stepwise logistic regression was used to identify independent risk factors. The variables with univariate value of $P \leq .3$ were considered candidates for multiple logistic regression. The Mann-Whitney $U$ test was used to compare differences.

Statistical analysis was performed with SPSS statistical software version 19 (SPSS, Chicago, Illinois).

### RESULTS

#### Incidence of Postoperative CSF Leakage

Postoperative CSF leakage was noted in 17 of the 72 patients (23.6%).

#### Risk Factors for Postoperative CSF Leakage

The results of univariate analysis (Table 1) suggested that age 54 years or older, preoperative surgical site irradiation, resection of 3 or more vertebral bodies, and dural injury were significant risk factors for CSF leakage associated with postoperative total en bloc spondylectomy. Multivariate analysis showed that preoperative surgical site irradiation was the only significant risk factor for postoperative CSF leakage (Table 2).

#### Course of Treatment for Postoperative CSF Leakage

All 17 patients with postoperative CSF leakage were treated with natural gravity drainage and intravenous administration of Factor XIII concentrate (24 mL/d×5 days). As necessary, a spinal drainage system was placed.
Additional Examinations

This study also examined the association between postoperative CSF leakage and the details of preoperative irradiation, including total radiation dose and the interval between the end of irradiation and surgery.

Of the 72 patients, the 22 patients who had preoperative irradiation were divided into 2 groups, those with (11 patients) and those without (11 patients) postoperative CSF leakage. When the 2 groups were compared, total radiation dose was a mean of 40.1 Gy (range, 30-64 Gy) in those with postoperative CSF leakage and 40.6 Gy (range, 28-60 Gy) in those without postoperative CSF leakage. The interval between the end of irradiation and surgery was a mean of 26.9 months (range, 1-161 months) in those with postoperative CSF leakage and 30.9 months (range, 2-101 months) in those without postoperative CSF leakage. There were no significant differences. The Mann-Whitney U test was used to compare the differences.

DISCUSSION

Although several studies examined the incidence and associated risk factors for dural injury during spinal surgery, few reports focused on postoperative CSF leakage. Most postoperative CSF leakage resolves spontaneously. However, it is sometimes troublesome and can cause severe complications, particularly after surgery that creates large dead spaces, such as total en bloc spondylectomy. Therefore, assessing the risk factors for postoperative CSF leakage is extremely important. In the current study, the incidence of dural injury during total en bloc spondylectomy was 8.3%, similar to the incidence previously reported.7-9 However, a high rate of postoperative CSF leakage, without apparent dural injury during surgery, was also noted. This may be because evidence of dural injury was not obvious during surgery. Dural injury is likely to occur because of the extensive dura mater dissection that is characteristic of total en bloc spondylectomy. Baker et al10 also reported that more invasive surgery is a significant risk factor for dural injury. In the current univariate analysis, resection of 3 or more vertebral bodies was also a risk factor for postoperative CSF leakage. Surgical invasiveness naturally increases with greater exposure, and it is higher when 3 or more vertebral bodies are resected than when 2 or fewer are resected. Additionally, changes in the structure of the dura mater itself, such as weakening or increased permeability as a result of aging and irradiation, may contribute to postoperative CSF leakage.

Aging was assumed to be a significant risk factor for dural injury.9 Pearce and Grimmer10 reported that the amount of elastin in tissues decreases with age and that reduced elastin content significantly affects biomechanical strength. McEllistrem et al11 reported that age-related structural changes to the dura mater may account for the increased dural permeability. Hence, degenerative changes to the dura mater may induce weakening or increased permeability. Therefore, in elderly patients, care must be taken to prevent CSF leakage both during and after total en bloc spondylectomy.

Several studies showed that irradiation leads to wound complications, such as delayed union, dehiscence, and infection. Ghogawala et al12 reported that the rate of major wound complications was 32% in patients who underwent irradiation before surgical decompression for metastatic spinal cord compression, which was 3 times higher than the rate reported in patients who did not undergo irradiation. Demura et al13 reported that the rate of surgical site infection after surgery for spinal metastasis was 31.8% in patients who underwent irradiation, much higher than that in those who did not undergo irradiation (1.1%). Likewise, in spinal surgery after irradiation, dural injury and CSF leakage appear to occur frequently. However, no studies have reported a re-

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### Table 2

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Standard Error</th>
<th>Significant Probability</th>
<th>Adjusted Odds Ratio</th>
<th>95% Confidence Interval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age: ≥54 y</td>
<td>0.80</td>
<td>0.150</td>
<td>3.18</td>
<td>0.66-15.34</td>
</tr>
<tr>
<td>Sex: female</td>
<td>0.82</td>
<td>0.264</td>
<td>2.49</td>
<td>0.50-12.33</td>
</tr>
<tr>
<td>Diabetes: yes</td>
<td>1.05</td>
<td>0.292</td>
<td>3.03</td>
<td>0.39-23.83</td>
</tr>
<tr>
<td>Previous spine surgery: yes</td>
<td>1.37</td>
<td>0.724</td>
<td>1.62</td>
<td>0.11-23.91</td>
</tr>
<tr>
<td>Preoperative surgical site irradiation: yes</td>
<td>0.83</td>
<td>0.046</td>
<td>5.22</td>
<td>1.03-26.45</td>
</tr>
<tr>
<td>No. of resected vertebral: ≥3</td>
<td>0.77</td>
<td>0.091</td>
<td>3.65</td>
<td>0.81-16.39</td>
</tr>
<tr>
<td>Intraoperative dural injury: yes</td>
<td>1.82</td>
<td>0.283</td>
<td>7.08</td>
<td>0.20-251.75</td>
</tr>
</tbody>
</table>
The dura mater is mostly composed of collagen fibers, similar to the composition of the skin and subcutaneous tissues. Therefore, the adverse effects of irradiation can be assumed to be similar, including acute and chronic effects.14,15 The chronic effects, such as fibrosis and poor wound healing, may be the result of fibroblast dysfunction.16-18 Bentzen et al reported that fibrosis begins after approximately 6 months and reaches a steady state within approximately 3 years. Fibrosis leads to adhesions between tissues and may cause tissue injury, such as dural injury, during surgery. Therefore, postoperative CSF leakage with dural injury may frequently occur in patients with chronic postirradiation effects, and great care must be taken during dissection. Despite primary suturing of dural injuries during surgery, postirradiation fibroblast dysfunction may increase the chance of postoperative CSF leakage. The current study also noted that postoperative CSF leakage was observed in cases of relatively acute radiation injury. The acute effects of radiation lead to inflammatory reactions and apoptotic cell death, and endothelial cell apoptosis and slow regenerative proliferation result in increased vascular permeability.14,20,21 Through a similar mechanism, increased permeability of the dura mater may also occur. The authors are studying this with an experimental animal model.

In the current study, preoperative surgical site irradiation was a strong risk factor for CSF leakage after total en bloc spondylectomy. Patients with preoperative irradiation were 7 times more likely to have postoperative CSF leakage than those without preoperative irradiation. Postoperative CSF leakage is likely to occur regardless of total irradiation dose or timing. Hence, careful consideration should be given to patients receiving preoperative irradiation and, whenever possible, preoperative irradiation should be avoided in patients with indications for total en bloc spondylectomy. However, radiation therapy is widely performed as a standard treatment for spinal metastases. Therefore, total en bloc spondylectomy is inevitably needed in some patients receiving radiation therapy. With current treatment methods, including primary suturing of dural injuries and the use of fibrin glue spray, postoperative CSF leakage may not be completely prevented and may lead to severe complications. Therefore, prompt implementation of a spinal drainage system seems to be necessary for patients receiving preoperative irradiation, regardless of intraoperative dural injury. Although Factor XIII can encourage wound healing because of its proangiogenetic and fibroblast proliferation effects,22,23 its use for postoperative CSF leakage has only been noted in case reports. Randomized controlled trials are needed to conclusively identify the effects of Factor XIII. Additionally, recent studies have suggested that some agents can reverse human chronic radiation injury. Delanian et al reported that application of combined pentoxifylline and tocopherol in patients with radiation-induced fibrosis elicited a 70% reduction in fibrotic volume; the authors are planning to use these agents. However, because current treatments are insufficient, careful operative indications and adequate informed consent are very important for patients receiving preoperative irradiation.

**Limitations**

The current study had several limitations, including its retrospective design, small sample size, and patient diversity. In addition, although the same surgeon performed total en bloc spondylectomy, dural injury is still considered an iatrogenic complication. However, this was the first study to identify risk factors for postoperative CSF leakage associated with total en bloc spondylectomy through multivariate analysis, with a focus on preoperative irradiation. The study findings will contribute to the management of postoperative CSF leakage associated with this procedure.

**Conclusion**

Postoperative CSF leakage is a frequent complication associated with total en bloc spondylectomy. Preoperative irradiation at the surgical site is a strong risk factor for postoperative CSF leakage, and treatment of this complication is time consuming.

**References**


