Retrospective Evaluation

Epidural Blood Patch for the Treatment of Spontaneous and Iatrogenic Orthostatic Headache

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Background: The cerebrospinal fluid (CSF) leakage could be happened spontaneously or related to the procedures such as spinal anesthesia, epidural anesthesia, CSF tapping, intrathecal chemotherapy or other spinal procedures. The leakage of CSF leads to intracranial hypotension of which distinguishing clinical feature is orthostatic headache. The epidural blood patch is a gold-standard treatment for intracranial hypotension-related orthostatic headaches.

Objective: We conducted this study to compare the efficacy and number of epidural blood patches for spontaneous and iatrogenic orthostatic headaches.

Study Design: Retrospective study.

Setting: University hospital inpatient and outpatient referred to our pain clinic.

Methods: Sex, weight, height, cause of orthostatic headache, leakage site evaluation test, epidural blood patch injection level, number of administered epidural blood patches, and pain intensity data were collected. We classified patients into two groups according to the cause of orthostatic headache: spontaneous (Group S) and iatrogenic (Group I). Patients with myelograms were also divided into 2 groups: multiple cerebrospinal fluid (CSF) leakages and no multiple leakages.

Results: Overall, 133 patients (162 procedures) were managed using epidural blood patches. Groups S and I included 34 and 99 patients, respectively. In Group I, 90.9% of the patients achieved complete recovery following a single procedure, whereas 44.1% of Group S patients required repeated procedures. The average number of administered epidural blood patches was significantly higher in Group S (1.48 ± 0.64) than in Group I (1.11 ± 0.35; $P = 0.007$). Among 23 patients evaluated via myelography, 12 had multiple CSF leakages. Patients with multiple leakages required a significantly higher number of epidural blood patches, compared to patients without multiple leakages ($P = 0.023$).

Limitations: This retrospective study reveals several limitations including insufficient evaluation of CSF leakage site by myelogram and the retrospective nature of the study itself.

Conclusions: Most patients with iatrogenic orthostatic headache required a single epidural blood patch, although most did not undergo a myelogram or similar test. Patients with spontaneous orthostatic headache or multiple CSF leakages were more likely to require a repeated epidural blood patch.

Key words: CSF leakage, dural puncture, epidural blood patch, intracranial hypotension, orthostatic headache, spinal headache

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A rent of the dura mater that leads to cerebrospinal fluid (CSF) leakage may occur spontaneously or in association with procedures such as spinal or epidural anesthesia, CSF tapping, intrathecal chemotherapy, or other spinal procedures. The cause of headache in the former is called spontaneous intracranial hypotension, and the cause in the latter is called iatrogenic intracranial hypotension, or postdural puncture headache (1,2). CSF leakage that causes a decrease in the intracranial CSF volume is called intracranial hypotension, the distinguishing clinical feature of which is orthostatic headache. Orthostatic headache is characterized as a headache aggravated by an upright or standing position and relieved by lying down.

Two types of treatments are available for orthostatic headache: conservative treatment and epidural blood patch. Conservative treatment includes bed rest, oral or intravenous fluid administration, and first-line medications such as caffeine, non-steroidal anti-inflammatory drugs (NSAIDs), opioids, and/or steroids (3,4). The autologous epidural blood patch is administered when conservative treatment fails and has become a standard treatment for orthostatic headache (1,5-7).

Many studies have compared the epidural blood patch and conservative treatment with respect to efficacy. Sandesc et al and Oedit et al stated that the epidural blood patch was more effective than conservative treatment for post-dural puncture headache, regardless of the etiology (1,6). Similarly, Sencakova et al and Berroir et al reported a higher symptom relief rate with the epidural blood patch than with conservative treatment (8,9). However, almost all of these studies compared the efficacies of the epidural blood patch and conservative treatment for either spontaneous or iatrogenic orthostatic headache. Therefore, we decided to conduct a retrospective study to compare the efficacy and number of epidural blood patches required for complete recovery for spontaneous and iatrogenic orthostatic headaches.

Methods

We performed a retrospective study after receiving approval from our institutional review board. All patients aged 19 – 80 years who received an epidural blood patch to treat orthostatic headache at our hospital from March 2011 to December 2014 were included in this study. All epidural blood patches were administered via C-arm fluoroscopically guided injection by a single practitioner with an experience of over 8,000 C-arm fluoroscopically guided procedures. A total of 20 mL of autologous blood was injected via a 20-G Tuohy needle regardless of the spinal level.

Data concerning gender, weight, height, cause of orthostatic headache, CSF leakage site evaluation test, epidural blood patch injection level, number of epidural blood patches required for complete recovery (defined as no additional treatment or symptoms for more than one month after blood patch administration), the time interval between onset of symptoms and the first epidural blood patch, and that between the first and repeat patch, post-injection complications, and baseline and post-treatment pain intensities were collected by reviewing patients' medical records. Pain intensities were measured using a visual analogue scale (VAS; 0 = pain and 10 = most severe pain imaginable) before, immediately after (day of procedure), and one day after epidural blood patch treatment.

We classified patients into 2 groups according to the cause of orthostatic headache: spontaneous (Group S) and iatrogenic (Group I). These groups were compared with respect to demographic data, the cause of CSF leakage, number of epidural blood patches required for complete recovery, levels of epidural blood patches, and pain intensities before and after epidural blood patch treatment.

Among patients who had undergone computed tomography (CT) or magnetic resonance imaging (MRI) myelography, the number of epidural blood patches was compared between patients with multiple CSF leakages (multiple leakage group) and those with no multiple leakages (no multiple leakage group).

SPSS, version 17 (SPSS, Inc., Chicago, IL, USA) was used for the statistical analyses. Student's t-test was used to analyze differences between the groups with respect to weight, height, age, pain intensity, and number of conducted procedures. A paired t-test was used to analyze changes in pain intensity before and after the procedure within each group. The chi-square test was used to analyze differences in gender and injection level. Mean differences among patients who underwent myelography were analyzed using the Mann–Whitney U test. In patients who received multiple epidural blood patches, the mean time intervals between the first and second trials and between the second and third trials were analyzed using the Mann-Whitney U test. Statistically significant differences were identified by an exact P value of ≤ 0.05.

Results

A total of 133 patients (162 epidural blood patch treatments) with orthostatic headache were managed using epidural blood patches from March 2011 to December 2014. Thirty-four patients received the epidural blood patches for spontaneous orthostatic headache (Group S), and 99 patients received epidural blood patches to treat iatrogenic orthostatic headache (Group I).

No differences were observed between the groups with respect to demographic data (e.g., age, height, weight, gender; Table 1).

The average time interval from onset of orthostatic headache to the first epidural blood patch showed no significant differences between Group S and Group I (4.91 ± 5.89 days vs. 6.66 ± 5.07 days; $P = 0.15$).

Nineteen patients (55.9%) in Group S and 90 patients (90.9%) in Group I achieved complete recovery from their symptoms with a single procedure. The remaining patients complained of continuing symptoms or relapse after epidural blood patch treatment and underwent repeated epidural blood patch treatments. The average number of epidural blood patches required for complete recovery was significantly higher in Group S than in Group I (1.48 ± 0.64 vs. 1.11 ± 0.35; $P = 0.007$; Table 2).

Among 133 patients, 24 received multiple blood patches and the maximum number of epidural blood patches received by a single patient was 3. The mean time interval between the first and second epidural blood patches was 4.48 ± 2.52 days, and was 10.0 ± 4.06 days between the second and third patches. The mean time interval between the second and third epidural blood patches was significantly longer than that between the first and second patches ($P = 0.006$).

In Group S, 18 patients received an epidural blood patch at the targeted level indicated via myelography; the remaining patients received epidural blood patches at the cervico-thoracic junction, which is known as the most frequent area of spontaneous CSF leakage (2,4,10,11). In Group I, 5 patients received epidural blood patches at the targeted level according to imaging analysis; the remaining patients received epidural blood patches at the level associated with iatrogenic CSF leakage.

In Group I, the most common causes of CSF leakage were the CSF tapping test (35.3%) and spinal anesthesia (16.5%; Table 3).

The most common injection site was the lumbar spine (133 patients, 71.4%). In Group S, the most common injection site was the cervico-thoracic junction (38.2%), followed by the thoracic level (29.4%). In Group I, the most frequent injection site was the lumbar spine (90.9%), followed by the cervico-thoracic junction (6.1%). The difference in injection levels between Groups S and I was statistically significant ($P < 0.001$; Table 4).

Table 1. *Demographic characteristics.*

	Group S (n=34)	Group I (n=99)	*P* value
Age	41.00 ± 12.34	37.65 ± 12.08	0.18
Height (cm)	164.65 ± 8.57	165.94 ± 8.24	0.45
Weight (kg)	61.25 ± 10.73	62.81 ± 11.47	0.48
Gender (M:F)	12:22	40:59	0.60

M, male; F, female; Group S, spontaneous orthostatic headache group; Group I, iatrogenic orthostatic headache group

Table 2. *Number of conducted epidural blood patches required for complete recovery.*

	Average	*P* value
Group S (n = 34)	1.48 ± 0.64	0.007
Group I (n = 99)	1.11 ± 0.35	

Group S, spontaneous orthostatic headache group; Group I, iatrogenic orthostatic headache group

Table 3. *Causes of orthostatic headache in Group I.*

Epidural A	Operation	Spinal A	CSF tapping	Other procedures
8	2	22	47	20

Group S, spontaneous orthostatic headache group; Group I, iatrogenic orthostatic headache group; Epidural A, epidural anesthesia; Spinal A, spinal anesthesia

In Group S, the average pain intensity (5.65/10) before the procedure was significantly higher than that (2.28/10) after the procedure. Similarly, in Group I, the average pain intensity (5.11/10) before the procedure was statistically higher than that (2.23/10) after the procedure. However, no differences in the average pain scale scores before and after the procedure were observed between the groups. In Group S, the pain intensities immediately (postVAS) and one day after the procedure (POD#1 VAS) were lower than that before the procedure (preVAS) ($P < 0.001$), and the POD#1 VAS was significantly lower than the postVAS ($P = 0.029$). Similarly, in Group I, the postVAS and POD#1 VAS were both significantly lower than the preVAS ($P < 0.001$), and the POD#1 VAS was significantly lower than the postVAS ($P < 0.001$; Tables 5, 6).

There were no major complications reported after the blood patch such as compressive radiculopathy, repeat dural puncture, meningitis, cauda equina syndrome, or neuraxial hematoma. All patients reported

Table 4. *Levels of conducted epidural blood patches.*

	Level							Total number	P value
	CT	CT, T	CT, L	T	TL	L	T, L		
Group S	13	3	1	8	2	5	2	34	< 0.001
Group I	6	0	0	2	1	90	0	99	
Total	19	3	1	10	3	95	2	133	

Group S, spontaneous orthostatic headache group; Group I, iatrogenic orthostatic headache group; CT, cervico-thoracic junction; T, thoracic; L, lumbar; TL, thoraco-lumbar junction

Table 5. *Pain intensity before and after the epidural blood patch.*

	Group	Pain intensity	P value
PreVAS	Group S	5.65 ± 2.37	0.203
	Group I	5.11 ± 2.09	
PostVAS	Group S	2.28 ± 1.73	0.887
	Group I	2.23 ± 1.51	
POD #1 VAS	Group S	1.60 ± 1.14	0.554
	Group I	1.15 ± 1.06	

Group S, spontaneous orthostatic headache group; Group I, iatrogenic orthostatic headache group; PreVAS, pain intensity before the epidural blood patch; PostVAS, pain intensity within 24 hours after the epidural blood patch ; POD#1 VAS, pain intensity one day after the epidural blood patch

Table 6. *Comparison of pain intensity between Group S and Group I.*

	P value	
	Group S	Group I
PreVAS – PostVAS	< 0.001	< 0.001
PreVAS – POD #1 VAS	< 0.001	< 0.001
PostVAS – POD #1 VAS	0.029	< 0.001

Group S, spontaneous orthostatic headache group; Group I, iatrogenic orthostatic headache group; PreVAS, pain intensity before the epidural blood patch; PostVAS, pain intensity within 24 hours after the epidural blood patch; POD#1 VAS, pain intensity one day after the epidural blood patch

spinal discomfort or mild to moderate pain at the injection site for 1 – 4 days after the procedure.

The average number of epidural blood patches was significantly higher in patients evaluated via CT or MRI myelography (1.83 ± 0.72) than in patients who were not evaluated with imaging modalities (1.09 ± 0.30, $P < 0.001$).

Eighteen patients in Group S and only 5 patients in Group I were examined via CT or MRI myelography. Among the 23 patients evaluated via CT or MRI myelography, 12 had multiple CSF leakages. The most common multiple leakage level was the thoracic spine (41.7%), followed by the cervico-thoracic junction and thoracic level (25%; Table 7).

The multiple leakage and no multiple leakage groups did not differ significantly with respect to demographic data. The number of administered epidural blood patches was significantly higher in the multiple leakage group (mean rank which was calculated using the Mann–Whitney U test: 15.08; mean number of epidural blood patches: 2.17 ± 0.58) than in the no multiple leakage group (mean rank: 8.64; mean number of epidural blood patches: 1.45 ± 0.69, $P = 0.023$; Tables 8, 9).

Discussion

According to our results, Group I required a significantly lower number of epidural blood patches for complete recovery, compared with Group S. We consider this outcome to be associated with differences in the of dural tear characteristics between the groups. Most iatrogenic CSF leakages were created by a needle puncture through the dura mater, and CSF leakages were therefore thought to occur precisely at the needle entry point (12-15). However, the etiology of spontaneous CSF leakage is often unidentified. Spontaneous CSF leakage is thought to occur in fragile areas of the

Table 7. *Sites of CSF leakage in patients with myelogram data.*

Level	Multiple leakage		Total	*P* value
	(-)	(+)		
CT	5	1	6	0.02
CT, T	0	3	3	
CT, L	0	1	1	
T	1	5	6	
L	2	0	2	
TL	0	2	2	
TL	3	0	3	
Total	11	12	23	

CT, cervico-thoracic junction; T, thoracic; L, lumbar; TL, thoraco-lumbar junction

Table 8. *Patients with myelogram data in Group S and Group I.*

	Multiple leakage		Total	*P* value
	(-)	(+)		
Group S	7	11	18	0.06
Group I	4	1	5	
Total	11	12	23	

Group S, spontaneous orthostatic headache group; Group I, iatrogenic orthostatic headache group

Table 9. *Number of epidural blood patches required for complete recovery in patients with myelogram data.*

	Mean rank	Average	*P* value
Multiple leakage group (n = 12)	15.08	2.17 ± 0.58	0.023
No multiple leakage group (n = 11)	8.64	1.45 ± 0.69	

Mean rank was calculated using the Mann–Whitney U test.
Multiple leakage group, patients had multiple CSF leakages according to computed tomography (CT) or magnetic resonance imaging (MRI) myelography; No multiple leakage group, patients had no multiple CSF leakages on CT or MRI myelography

dura mater, and these spontaneous tears tend to have a larger diameter than those caused by iatrogenic needle injuries (16,17). Dural tears in cases of spontaneous intracranial hypotension are thought to correlate with connective tissue disorders, meningeal diverticulum, and similar conditions (18-20). According to Sakurai et al and Bonetto et al, imaging tests such as CT or MRI myelography or radionuclide cisternography tend to reveal multi-level CSF leakages throughout the spine (mostly at the cervico-thoracic junction) in patients with spontaneous intracranial hypotension, and can easily detect sites of CSF accumulation in the epidural space (21,22). However, in patients with iatrogenic intracranial hypotension, imaging tests tend to identify an exact CSF leakage level that corresponds with the needle entry point (12-14). In Group I, 90.9% of patients made a complete recovery after a single epidural blood patch, and a mean of 1.11 epidural blood patches was required for complete recovery. This suggests that spontaneous orthostatic headache is an important factor predictive of the need for a repeated epidural blood patch. Therefore, patients with spontaneous orthostatic headache should be advised that multiple epidural blood patches might be required for symptom resolution.

The epidural blood patch is widely considered the treatment of choice for orthostatic headache caused by intracranial hypotension (5-7,9,23,24). Intracranial hypotension is defined as an orthostatic headache associated with a low CSF volume (2,20,22). CSF leakage can lead to reduced CSF pressure and consequent stretching of pain-sensitive brain structures, resulting in orthostatic headache, nausea, vomiting, dizziness, tinnitus or hearing impairment, abducens nerve palsy, and diplopia, among other phenomena (9,16,23,25).

The mechanisms by which epidural blood patches treat orthostatic headaches can be explained in 2 stages. In the earlier stage, pressure in the epidural space is elevated by the injection of autologous blood, leading to an elevation in CSF pressure and redistribution of the CSF volume and consequently relieving the orthostatic headache (1,26,27). This mechanism is known as the hydrostatic or mass effect. In the later stage, the injected autologous blood forms an organized blood clot to seal the CSF leakage site, thus preventing further leakage. This is known as the sealing effect. (1,26,27). We injected the same volume of blood regardless of spinal level. Therefore, the mass effect of an epidural blood patch might be slightly different in injections at different spinal levels. Considering the relationship between the dural leak site and the effect of gravity, lumbar dural leaks are associated with higher CSF pressures than cervical or thoracic dural leaks because of the effect of gravity on the CSF column. From this, we could assume that the epidural blood patch in the lumbar spinal area may have a risk of relapse. In the lumbar spine, the higher pressure of CSF may be related to a tear of the epidural blood patch seal as compared with the lower pressure of CSF in the cervical or thoracic spine.

Despite this negative factor in Group I, Group S needed significantly more epidural blood patches for complete recovery. We assumed that multi-level leaks in Group S may be the major factor leading to repeated epidural blood patching, compared with lumbar level leaks in Group I. Investigation of the association between the spinal level of the leak site and the effectiveness of epidural blood patching will be needed.

Arai et al (28) reported that in patients with spontaneous orthostatic headache caused by multiple CSF leakages, at least 2 epidural blood patches per each leak site are needed to achieve a complete recovery. Lee et al and Park et al also reported that patients with multiple CSF leakages achieved symptomatic relief after more than 3 epidural blood patch treatments (29,30). According to our results, the mean number of epidural blood patches required for complete recovery in patients with multiple CSF leakages was 2.17. Among patients who underwent myelography, the number of epidural blood patches required for complete recovery was higher in the multiple leakage group than in the no multiple leakage group. Therefore, the presence of multiple CSF leakage sites is another important factor associated with repeated epidural blood patch treatment.

Although the epidural blood patch is considered a gold-standard treatment for orthostatic headache, the epidural blood patch administration method (treatment level or fluoroscopic guidance) and treatment efficacy are debatable. According to many reports, an epidural blood patch for intracranial hypotension treatment can be performed at the lumbar level, regardless of the actual CSF leakage level or target level identified using image modalities such as CT or MRI myelography or radionuclide cisternography (3,31,32). In contrast, Wang et al and Schievnick et al demonstrated that targeted epidural blood patches more effectively treated cervical and upper thoracic CSF leakages than did lumbar epidural blood patches (10,32). Cho KI et al and other research groups further reported fluoroscopic guidance was more effective than a blind technique for administering an epidural blood patch (32-35). In the present study, we used C-arm fluoroscopic guidance for epidural blood patch treatment, and the treatment injection levels were the injection site responsible for the iatrogenic injury in Group I and the myelographically confirmed leakage site or cervico-thoracic junction in Group S. A comparison of the average number of epidural blood patches between patients evaluated with imaging modalities and those without showed that patients evaluated with imaging needed significantly more blood patches for complete recovery. However, among 133 patients enrolled in this study, only 23 were evaluated with a CT or MRI myelogram, and 78.3% (18 patients) were in group S. It is well known that spontaneous orthostatic headache tends to be associated with multiple CSF leaks. Therefore, this result shows that it is difficult to verify the effectiveness of imaging modalities for accomplishing complete recovery with fewer epidural blood patches.

Although only 5 patients in Group I underwent imaging evaluations, all patients in this group reported significant reductions in pain intensity after epidural blood patch treatment. In Group I, 90.9% of orthostatic headaches were resolved with a single epidural blood patch, and this group required a lower average number of epidural blood patches to achieve complete recovery, compared with Group S. Accordingly, we estimate in a patient with iatrogenic orthostatic headache and a prior history of an epidural or spinal procedure, the epidural blood patch can be injected into the same spine level in which an earlier procedure had been performed immediately prior to symptom onset. Furthermore, epidural blood patch was found to be a highly effective treatment for iatrogenic orthostatic headache.

Our study had a few limitations. First, the retrospective design led to an imbalance in the number of patients allocated to each group. Second, not all patients who received an epidural blood patch had undergone imaging evaluations to identify the exact CSF leakage site. In Group I, most patients (94/99) did not undergo imaging, and epidural blood patches were instead administered at the level expected to contain a CSF leakage site resulting from a previous procedure. In Group S, 18 patients underwent imaging to determine the CSF leakage site and received epidural blood patch treatments at the indicated sites. The remaining patients in Group S received epidural blood patches at the cervico-thoracic junction, where spontaneous CSF leakages most frequently occur. In other words, 16 Group S patients received epidural blood patches at the empirically most probable leakage site. However, in these patients, we could not determine whether the cervico-thoracic junction was the actual CSF leakage site. This discrepancy might explain why patients in Group S more often required repeated epidural blood patch treatment, compared with those in Group I. Despite the lower rate of myelographic CSF leakage site confirmation in Group I, this group required a lower number of epidural blood patches to achieve complete recovery, compared with Group S. These results suggest that iatrogenic orthostatic headache is not indicative of a requirement for repeated epidural blood patches for complete recovery. Third, we could not analyze the effect of spinal leakage level on epidural blood patching because we did not evaluate the leakage site by myelogram in all patients. There may be an association between spinal level of leakage site and the effectiveness of epidural blood patching. However, to our knowledge, this is the first study comparing spontaneous intracranial hypotension and idiopathic intracranial hypotension. Generally, as in the results of this study, most cases of iatrogenic orthostatic headache originate in the lumbar spine at the cervical, thoracic, or cervicothoracic junction level (1,2,4,7,10,11). Therefore, we cannot regard the level of leakage site and the cause (iatrogenic vs. spontaneous) of orthostatic headache as separate.

Conclusion

In conclusion, most patients with iatrogenic headache required a single epidural blood patch for complete recovery from orthostatic headache, although most of these patients did not undergo imaging tests such as CT or MRI myelography to identify CSF leakage sites. However, patients with spontaneous orthostatic headache or multiple CSF leakages were more likely to require repeated epidural blood patches.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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