INTRODUCTION

The primary treatment for intracranial hypotension relies on conservative methods such as bed rest, caffeine, and intravenous fluid infusions, but in patients who do not respond to conservative treatment, epidural blood patches (EBP) are commonly used [1–3]. EBPs with autologous blood is now accepted as the gold-standard procedure with low complication rates, but the exact mechanism of the benefit and the details for administration technique have not yet been identified [4,5]. In addition, the success rate of EBPs has exhibited variability [6]. Repeated EBP procedures for patients with persistent symptoms after the first EBP are reported to be common [7]. To predict poor responders to EBP, numerous studies have evaluated relevant factors with respect to clinical presentation, findings on radiologic images, procedural characteristics, and blood laboratory tests [8,9]. However, the factors related to
Factors associated with repeated EBP

One of the challenges in establishing the optimal delivery method and predicting poor responders in EBP is the variety in the etiology of intracranial hypotension as well as the site of cerebrospinal fluid (CSF) leakage. Iatrogenic damage during the procedure is known as the primary mechanism of intracranial hypotension, but the reduction of CSF could also be observed spontaneously with or without an apparent leakage site on imaging studies [4,5]. Since the clinical situations for EBP patients can vary widely, relevant studies require prospectively collected well-controlled data. Unfortunately, this could also act as a barrier in applying study results to daily clinical practice. To cover a broad spectrum of disease and procedural characteristics, a large real-world data analysis of EBP patients may be needed. In the authors’ institution, trained pain physicians have actively performed EBPs under fluoroscopic guidance. In addition to patients who come to the pain clinic for headaches, we also cover patients referred from the Department of Neurology. Using the retrospective data of consecutive patients who underwent EBPs, the authors aim to evaluate factors associated with the requirement of repeated EBPs.

MATERIALS AND METHODS

This study was approved by the Institutional Review Board of the Samsung Medical Center (SMC 2021-07-152). Since the data for this study was retrospectively extracted in de-identified form, written informed consents from individual patients was waived. While conducting this study, we followed the Declaration of Helsinki, and the result was reported according to the Strengthening the Reporting of Observational Studies in Epidemiology guidelines.

1. Data curation & study population

From January 2010 to December 2019, a total of 596 patients underwent EBPs due to headaches related to intracranial hypotension at the Samsung Medical Center, Seoul, Korea. The medical data of these patients were extracted using “Clinical Data Warehouse Darwin-C,” which was built to help investigators search and retrieve de-identified medical records from the electronic archive center. This system provides electronic hospital records of more than 4 million patients with more than 900 million laboratory findings and 200 million prescriptions. Relevant variables were organized by manually reviewing the extracted medical charts. Investigators who reviewed the raw medical charts were independent of the study and were blinded to whether the patient required repeated EBPs or not. Blood laboratory findings were extracted as numbers and units. In the enrolled patients, we identified the patients who required repeated EBPs and conducted separate analyses for subgroups. We analyzed risk factors for repeated EBPs in patients with spontaneous intracranial hypotension (SIH), in those with iatrogenic injury, and in those with available myelographic evaluation.

2. Study endpoint & definition

The study endpoint was to evaluate the factors associated with repeated EBPs. Repeated EBPs were defined as requiring another EBP within 30 days after the first procedure due to persistent or refractory symptoms. Iatrogenic injury was defined as a history of interventional treatment on the dura mater such as spinal tapping, epidural block, spinal/epidural anesthesia, and surgery.

3. EBP procedures

According to the institutional protocol, EBPs were performed under fluoroscopic guidance with 21-gauge Touchy needles. In patients with iatrogenic trauma, the same level with previous dura punctures was primarily chosen. In cases where the same level could not be injected, the adjacent level was chosen at the discretion of the attending clinician. For SIH in which the CSF leakage site was not identified, the level was at the discretion of an attending clinician, and the thoracolumbar junction was also considered. With a patient in the prone position, the injection point for the targeted level was identified under C-arm fluoroscopic guidance. After injecting local anesthetics, the needle was advanced cautiously until the epidural space was identified using the loss of resistance technique. When the epidural space was confirmed with contrast medium, a sufficient amount of blood was withdrawn from the cephalic vein. Autologous blood was injected into the epidural space in a gentle manner. The targeted blood volume was adjusted by the attending physician considering the injection site and disease characteristics. The injection of blood was immediately stopped when the patient complained of back or radicular pain.

4. Statistical analysis

Categorical variables were presented as the number and percentage while continuous variables were presented as the mean ± standard deviation or median with interquartile range (IQR), as applicable. The difference between the groups was compared with the chi-square or Fisher’s exact tests for categorical variables, and the t-test or the Mann-Whitney test for continuous variables. The risk factors of
repeated EBPs were evaluated using the logistic regression analysis. These results were reported by odds ratio (OR) with a 95% confidence interval (CI). Statistical analyses in this study were performed by IBM SPSS 20.0.0 (IBM Co., Armonk, NY). All tests were two-tailed and a P value < 0.05 was considered statistically significant.

RESULTS

1. Baseline characteristics

Of the 592 patients who were treated with EBPs, 125 (21.1%) patients required repeated EBPs within 30 days after the first procedure due to persistent or refractory headaches. Among the patients with repeated EBP, 96 patients underwent two EBP, and 20 patients required three EBPs. The remaining nine patients needed greater number of repeated EBPs, and the maximum number was six. The median number of EBPs performed in the repeated EBP group was 2 (IQR 2–2), and the median number of days between the first and second procedures was 5 (IQR 2–8.5) days. The baseline characteristics of the entire population and each group are presented in Table 1. A single EBP was more frequently required in patients with iatrogenic pathology compared with those with SIH (65.5% vs. 91%).

2. Risk factors of repeated EBPs

The incidences of variables and the associations with repeated EBPs in SIH patients are shown in Table 2. The presence of CSF leakage sites on myelographic images and the leakage sites at the thoracic spine were associated with an increased incidence of repeated EBPs (OR, 2.18; 95% CI, 1.28–3.69; P = 0.004 and OR, 1.34–4.16; P = 0.003, respectively). In the blood laboratory tests, higher international normalized ratio (INR) was shown to increase the risk of repeated EBPs (OR, 1.38; 95% CI, 1.02–1.87; P = 0.043), while high platelet counts were associated with lower risk (OR, 0.95; 95% CI, 0.91–0.99; P = 0.018).

In patients with iatrogenic injury, the site of EBP was associated with repeated procedures. EBP on the cervical and thoracic spine was associated with increased risk of repeated procedures (OR, 6.96; 95% CI, 1.11–43.5; P = 0.042 and OR, 11.24; 95% CI, 2.65–47.68; P = 0.001, respectively), while EBP of the lumbar spine was associated with lower risk (OR, 0.11; 95% CI, 0.03–0.44; P = 0.002) (Table 3).

To accurately evaluate associations between repeated EBP and findings from myelographic images such as a leakage site, we conducted separate analysis limited to those who had available myelographic images. The results in these patients are presented in Table 4. In patients with available myelographic images, the association between repeated EBPs and the presence of leakage sites became marginally insignificant (OR, 1.84; 95% CI, 0.99–3.41; P = 0.052), but the association remained significant for leakage sites at the thoracic spine (OR, 2.21; 95% CI, 1.15–4.23; P = 0.022). The associations with the results on blood laboratory tests were also consistent (OR, 1.83; 95% CI, 1.15–2.89; P = 0.013 for INR and OR, 0.95; 95% CI, 0.90–0.99; P = 0.050 for platelets).

DISCUSSION

In this study, we investigated a large number of consecutive patients who underwent EBPs due to intracranial hypotension and identified variables that may increase the requirement of repeated EBP treatment. According to our results, SIH and high INR were associated with increased...
Aside from the effectiveness of EBPs, there is no firm evidence or guideline regarding the details of the EBP procedure. In our study, the incidence of repeated EBPs was lower for iatrogenic injury, which is in line with previous studies. The primary explanation may be related to the fact that EBPs after iatrogenic injury are more likely to be performed at the same or closer level to the injured site. It is not essential to perform EBPs exactly at the leakage site, and EBPs were shown to be effective in SIH even without determining the leakage site [5]. However, the proposed mechanism for the benefit of EBPs include volume effects that move the dura forward and thecal tamponade with clot formation and incitement of inflammatory processes [10]. Therefore, it is more likely to be effective when the blood is injected closer to the leakage site. Another explanation may be related to the difficulty in properly diagnosing SIH. Without a history of an injury from previous procedures, the broad differential diagnosis of a headache may confuse clinicians and create a high rate of initial misdiagnoses [11]. In fact, the mean time from symptom onset to the diagnosis of SIH is reported to be over a year, which is enormously longer than post-dural puncture headaches [12]. There is no consensus on the optimal timing of EBPs after symptom development, but this may have influenced treatment effectiveness up to this point [13].

We evaluated the results of blood laboratory tests as a risk factor, because the proposed mechanisms of EBPs include clot formation and the inflammatory process. In fact, a recent study where biomedical markers were evaluated regarding the effectiveness of EBPs showed that INR values were higher in the poor responder group [9]. INR is a well-known measurement representing coagulation status [14], and we also demonstrated a significant association between repeated EBPs and INR in patients with SIH. However, it was not significant in patients with iatrogenic injury. In addition, our institutional indications for EBPs do not include patients with increased INRs, considering the risk of complications such as hematoma formation. Therefore, our comparison was made only among patients with normal coagulation status and whether improving the coagulation status of patients could decrease the incidence of repeated EBPs cannot be determined by this study. Moreover, the difference in mean values of INR between the two groups was very small. In a previous study, inflammatory markers were also shown to be associated with poor responses to EBPs, but they could not be adequately evaluated in our study due to a large portion of patients not having full blood laboratory test results.

In SIH patients, the presence of identifiable leakage sites in myelographies and leakage sites at the thoracic spine were shown to be the risk factors of repeated EBPs. It is not yet clear whether the size of the injury on the dura is associated with EBP responsiveness. Although the benefit

| Table 2. Baseline characteristics and associations with repeated epidural blood patch (EBP) in patients with spontaneous intracranial hypotension |
|---|---|---|---|---|
| Characteristic | Single EBP (n = 182) | Repeated EBP (n = 96) | Unadjusted OR (95% CI) | P value |
| Male/Female | 85/97 | 42/54 | 0.89 (0.54–1.46) | 0.642 |
| Age (yr) | 45.3 ± 13.6 | 43.7 ± 14.4 | 0.99 (0.97–1.01) | 0.358 |
| Hypertension | 23 (12.6) | 11 (11.5) | 0.90 (0.42–1.92) | 0.783 |
| Diabetes | 12 (6.6) | 4 (4.2) | 0.62 (0.19–1.96) | 0.409 |
| Current alcohol | 49 (26.9) | 24 (25.0) | 0.91 (0.51–1.59) | 0.734 |
| Current smoking | 25 (13.7) | 7 (7.3) | 0.49 (0.21–1.19) | 0.119 |
| EBP site | | | | |
| Cervical | 50 (27.5) | 25 (26.0) | 0.93 (0.53–1.63) | 0.795 |
| Thoracic | 100 (54.9) | 60 (62.5) | 1.37 (0.82–2.27) | 0.231 |
| Lumbar | 81 (44.5) | 38 (39.6) | 0.82 (0.49–1.35) | 0.427 |
| Amount of injection (mL) | 14.9 ± 5.9 | 14.5 ± 5.7 | 0.99 (0.95–1.03) | 0.587 |
| Myelographic image | 98 (53.8) | 61 (63.5) | 1.49 (0.90–2.48) | 0.123 |
| Cerebrospinal fluid leakage | 45 (24.7) | 40 (41.7) | 2.18 (1.28–3.69) | 0.004 |
| Leakage site | | | | |
| Cervical | 22 (12.1) | 12 (12.5) | 1.04 (0.49–2.20) | 0.923 |
| Thoracic | 33 (18.1) | 33 (34.4) | 2.37 (1.34–4.16) | 0.003 |
| Lumbar | 8 (4.4) | 4 (4.2) | 0.95 (0.28–3.22) | 0.927 |
| Blood lab test | | | | |
| Hemoglobin (g/dL) | 13.5 ± 1.7 | 13.6 ± 1.5 | 1.04 (0.89–1.21) | 0.624 |
| Platelet (×10^12/μL) | 247 ± 62 | 229 ± 55 | 0.95 (0.91–0.99) | 0.018 |
| International normalized ratio | 0.99 ± 0.08 | 1.01 ± 0.09 | 1.38 (1.02–1.87) | 0.043 |
| Neutrophil (%) | 61.5 ± 12.3 | 63.0 ± 11.2 | 1.01 (0.99–1.03) | 0.297 |

Values are presented as number only, mean ± standard deviation, or number (%). OR is estimated for the increase of 0.1 in international normalized ratio and 10 in platelet. EBP at thoracolumbar junction was presented in both thoracic and lumbar site. OR: odds ratio, CI: confidence interval.
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of EBPs also comes from directly blocking leakages, dural defects in SIH are not simply a hole, and the main mechanism of EBPs in SIH is to increase of CSF pressure rather than to seal and repair the injuries [15]. In addition, not all patients with SIH had available myelographic images, and patients without available myelographies were regarded as not having an identifiable CSF leakage site. Considering that myelographies were selectively obtained, patients with available images were more likely to be the ones that did not present typical symptoms of SIH and required a confirmatory diagnosis. This may have affected the results or created selection bias. Therefore, we conducted an additional analysis after enrolling only patients with available myelographic images.

In patients with available myelographic images, the thoracic spine was consistently shown to be associated with repeated EBPs. In fact, the thoracic spine is known to exhibit poor blood circulation and delayed wound healing compared with the other two regions of the spine [16]. The delay in the healing process of the dura mater may lead to higher incidences of repeated EBPs. Additionally, for procedural convenience, selecting a targeted level of EBPs could be different for the thoracic spine. Unlike the other two parts of the spine, EBPs may have been performed in different levels such as the thoracolumbar junction rather than directly at the injured level. Whether performing EBPs at the exact same level or at least a level close to the leakage site could improve outcomes requires further investigation.

In patients with iatrogenic injury, the EBP on the cervical and thoracic spine was associated with repeated EBP. This may be attributed to the fact that the predominant procedure performed on the cervical and thoracic spines is the epidural block, not spinal tapping or neuro-axial anesthesia. The epidural block may cause larger and more serious damage to the dura mater than spinal tapping or neuro-axial anesthesia, which could have increased the incidence of repeated EBP.

Our results should be interpreted considering the following limitations. This study used retrospective data, and there is a possibility for selection bias. As EBPs were mostly performed based on the outpatient department, the results of blood laboratory tests were not fully available. In addition, other unmeasured variables could not be retained in the analysis, such as the number of patients in whom EBP was aborted due to back pain. The procedural

Table 3. Baseline characteristics and associations with repeated epidural blood patch (EBP) in patients with iatrogenic injury

| Characteristic | Single EBP (n = 285) | Repeated EBP (n = 29) | Unadjusted OR (95% CI) | P value |
|----------------|---------------------|----------------------|-----------------------|--------|
| Male/Female    | 72/213              | 6/23                 | 0.77 (0.30–1.97)      | 0.587  |
| Age (yr)       | 36.5 ± 13.4         | 39.0 ± 11.5          | 1.01 (0.99–1.04)      | 0.323  |
| Hypertension   | 16 (5.6)            | 2 (6.9)              | 1.25 (0.27–5.71)      | 0.784  |
| Diabetes       | 11 (3.9)            | 0                    |                       |        |
| Current alcohol| 47 (16.5)           | 5 (17.2)             | 1.06 (0.38–2.91)      | 0.918  |
| Current smoking| 14 (4.9)            | 1 (3.4)              | 0.69 (0.09–5.46)      | 0.732  |
| Previous procedure |             |                      |                       |        |
| Spinal tapping | 78 (27.4)           | 11 (37.9)            | 1.62 (0.73–3.59)      | 0.231  |
| Neuro-axial anesthesia | 184 (64.6) | 14 (48.3)            | 0.51 (0.24–1.10)      | 0.087  |
| Epidural block | 21 (7.4)            | 4 (13.8)             | 2.01 (0.64–6.32)      | 0.231  |
| Spine surgery  | 2 (0.7)             | 0                    |                       |        |
| EBP site       |                     |                      |                       |        |
| Cervical       | 3 (1.1)             | 2 (6.9)              | 6.96 (1.11–43.5)      | 0.042  |
| Thoracic       | 4 (1.4)             | 4 (13.8)             | 11.24 (2.65–47.68)    | 0.001  |
| Lumbar         | 280 (98.2)          | 25 (86.2)            | 0.11 (0.03–0.44)      | 0.002  |
| Amount of injection (mL) | 16.7 ± 4.2 | 15.4 ± 3.9          | 0.93 (0.86–1.02)      | 0.123  |
| Myelographic image | 12 (4.2) | 6 (20.7)              | 5.94 (2.04–17.27)     | 0.001  |
| Cerebrospinal fluid leakage site | 4 (1.4) | 2 (6.9)              | 5.20 (0.91–29.73)     | 0.058  |
| Cervical       | 1 (0.4)             | 2 (6.9)              | 21.04 (1.85–236)      | 0.009  |
| Thoracic       | 1 (0.4)             | 1 (3.4)              | 10.14 (0.62–166)      | 0.112  |
| Lumbar         | 2 (0.7)             | 0                    |                       |        |
| Blood lab test |                     |                      |                       |        |
| Hemoglobin (g/dL) | 12.5 ± 2.0 | 12.9 ± 1.8          | 1.09 (0.90–1.33)      | 0.358  |
| Platelet (×10^9/μL) | 225 ± 76 | 226 ± 57             | 1.00 (0.99–1.01)      | 0.987  |
| International normalized ratio | 0.98 ± 0.07 | 1.00 ± 0.10 | 1.36 (0.86–2.14) | 0.192  |
| Neutrophil (%) | 61.5 ± 13.5        | 59.8 ± 13.7          | 0.97 (0.94–0.94)      | 0.023  |

Values are presented as number only, mean ± standard deviation, or number (%).
OR is estimated for the increase of 0.1 in international normalized ratio and 10 in platelet.
EBP at thoracolumbar junction was presented in both thoracic and lumbar site.
OR: odds ratio; CI: confidence interval.
Factors associated with repeated EBP

In conclusion, repeated EBPs may be more frequently required in patients with SIH and with prolonged INR values. Further studies are needed to determine clinically relevant factors associated with repeated EBP requirements.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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Table 4. Baseline characteristics and associations with repeated epidural blood patch (EBP) in patients with available myelographic image

| Characteristic                       | Single EBP (n = 110) | Repeated EBP (n = 67) | Unadjusted OR (95% CI) | P value |
|--------------------------------------|----------------------|-----------------------|------------------------|---------|
| Male/Female                          | 44/66                | 30/37                 | 1.22 (0.66–2.25)       | 0.526   |
| Age (yr)                             | 43.3 ± 12.8          | 41.9 ± 12.9           | 0.99 (0.97–1.02)       | 0.489   |
| Hypertension                         | 11 (10.0)            | 3 (4.5)               | 0.42 (0.11–1.57)       | 0.197   |
| Diabetes                             | 6 (5.5)              | 0                     |                        |         |
| Current alcohol                      | 25 (22.7)            | 17 (25.4)             | 1.16 (0.57–2.35)       | 0.693   |
| Current smoking                      | 12 (10.9)            | 6 (9.0)               | 0.80 (0.29–2.25)       | 0.682   |
| Iatrogenic pathology                 | 12 (10.9)            | 6 (9.0)               | 0.80 (0.29–2.25)       | 0.682   |
| EBP site                             |                      |                       |                        |         |
| Cervical                             | 26 (23.6)            | 20 (29.9)             | 1.38 (0.69–2.72)       | 0.363   |
| Thoracic                             | 60 (54.5)            | 43 (64.2)             | 1.49 (0.80–2.79)       | 0.209   |
| Lumbar                               | 49 (44.5)            | 23 (34.3)             | 0.65 (0.35–1.22)       | 0.183   |
| Amount of injection (mL)             | 14.2 ± 4.4           | 13.7 ± 4.5            | 0.98 (0.91–1.05)       | 0.512   |
| Cerebrospinal fluid leakage          | 41 (37.3)            | 35 (52.2)             | 1.84 (0.99–3.41)       | 0.052   |
| Leakage site                         |                      |                       |                        |         |
| Cervical                             | 23 (20.9)            | 14 (20.9)             | 0.99 (0.47–2.11)       | 0.990   |
| Thoracic                             | 27 (24.5)            | 28 (41.8)             | 2.21 (1.15–4.23)       | 0.022   |
| Lumbar                               | 8 (7.3)              | 2 (3.0)               | 0.39 (0.08–1.91)       | 0.248   |
| EBP at leakage site                  | 34 (30.9)            | 28 (41.8)             | 1.61 (0.85–3.02)       | 0.142   |
| Blood lab test                       |                      |                       |                        |         |
| Hemoglobin (g/dL)                    | 13.6 ± 1.7           | 13.9 ± 1.4            | 1.12 (0.93–1.35)       | 0.252   |
| Platelet (×10^3/μL)                  | 254 ± 66             | 235 ± 55              | 0.95 (0.90–0.99)       | 0.050   |
| International normalized ratio       | 0.98 ± 0.07          | 1.00 ± 0.07           | 1.83 (1.15–2.89)       | 0.013   |
| Neutrophil (%)                       | 59.9 ± 12.2          | 61.5 ± 11.9           | 1.01 (0.99–1.04)       | 0.385   |

Values are presented as number only, mean ± standard deviation, or number (%). OR is estimated for the increase of 0.1 in international normalized ratio and 10 in platelet. EBP at thoracolumbar junction was presented in both thoracic and lumbar site. OR: odds ratio, CI: confidence interval.
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