A Simple, Safe and Effective Approach to Prevent Postdural Puncture Headache: Epidural Saline Injection

Dural Ponksiyon Sonrası Başağrısının Önlenmesinde Basit, Güvenli ve Etkin Bir Yaklaşım: Epidural Salin Enjeksiyonu

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Abstract

Objective: In this study, we investigated the safety and effectiveness of epidural saline injection to prevent post-dural puncture headache (PDPH) in patients with acute lymphoblastic leukemia (ALL).

Materials and Methods: Thirty-three patients with ALL undergoing induction therapy were accepted for the study. Four to six courses of intrathecal methotrexate therapy were administered to each patient for central nervous system prophylaxis. Patients were divided into two groups. Lumbar puncture (LP) was performed without any additional intervention in the first group (18 cases), whereas 20 mL of isotonic saline was injected into the epidural space in the second group (15 cases). The frequency and severity of PDPH were compared between the two groups.

Results: Thirteen patients from the first group and five patients from the second group experienced at least one PDPH episode. In total, 54 PDPH episodes were reported in both groups. The rate of headache due to the LP was significantly higher in the first group than in the second group (48.8% vs. 16.4%, p<0.001). On the other hand, the severity of pain was also significantly higher in the first group (mean pain scores were 5.6 ± 1.62 vs. 3.07 ± 1.18, p<0.001). Furthermore, two patients from the first group (11.11%) developed generalized convulsion attacks, and one of those patients experienced pulmonary arrest necessitating respiratory support. No serious complications were observed in the second group.

Conclusions: Our study shows that isotonic saline injection into the epidural space after LP is a safe and effective approach to prevent PDPH and related complications.

Keywords: Acute lymphoblastic leukemia, Central nervous system prophylaxis, Epidural saline injection, Post-dural puncture headache

Özet

Amaç: *Bu çalışmada Akut Lenfoblastik Lösemili (ALL) olgularda epidural salin enjeksiyonunun (ESE) Dural Ponksiyon Sonrası Başağrısı (DPSB)' nı önlemede etkinliğini ve güvenilirliğini araştırdık.*

Gereç ve Yöntem: *Remisyon indüksiyon tedavisi uygulanmış 33 ALL hastası çalışmaya kabul edildi. Merkezi Sinir Sistemi (MSS) profilaksisi amacıyla her bir hastaya 4 ile 6 kür İntratekal Metotreksat (İT-MTX) tedavisi uygulandı.. Hastalar iki gruba ayrıldı. Birinci grupta (18 olgu) herhangi bir ek uygulama yapılmaksızın Lomber Ponksiyon (LP) yapılırken, ikinci grupta (15 olgu) epidural mesafeye 20 ml izotonik salin enjekte edildi. İki grup arasında DPSB sıklığı ve şiddeti karşılaştırıldı.*

Bulgular: *Birinci gruptan 13 hasta ve ikinci gruptan 5 hasta en az bir DPSB epizodu yaşadı. Her iki grupta toplam olarak 54 DPSB epizodu gözlendi. Lomber Ponksiyona bağlı başağrısı oranı birinci grupta ikinci gruptan anlamlı olarak daha yüksekti (% 48,80 e karşı % 16,4, p<0,001). Öte yandan birinci grupta ağrının şiddeti de anlamlı olarak daha fazlaydı (ortalama ağrı skorları 5,6 ± 1,62 ye karşı 3,07 ± 1,18, p<0,001). Ek olarak ilk gruptaki iki hastada (%11,11) jeneralize konvülzyon atağı gelişmesine ve bunlardan birinin solunum desteği gerektiren pulmoner arrest ile komplike olmasına rağmen ikinci grupta herhangi bir ciddi komplikasyon gözlenmedi.*

Sonuç: *Bizim çalışmamız, Lomber Ponksiyon sonrası epidural mesafeye izotonik salin enjeksiyonunun DPSB ve ilişkili komplikasyonların önlenmesinde etkin ve güvenli bir yaklaşım olduğunu gösterdi.*

Anahtar Kelimeler: *Akut lenfoblastik lösemi, MSS profilaksisi, Epidural salin enjeksiyonu, Dural ponksiyon sonrası başağrısı*

Introduction

Acute lymphoblastic leukemia (ALL) is a malignant disorder originating from a lymphoid stem cell. It is the most common neoplastic disease in childhood. Treatment for ALL involves remission induction therapy, consolidation therapy, central nervous system (CNS) prophylaxis and maintenance therapy [1]. Although CNS involvement is uncommon at initial diagnosis, most patients will eventually develop overt CNS disease unless CNS preventive therapy is administered. Intrathecal chemotherapy, high dose systemic chemotherapy and cranial radiotherapy can be administered alone or in combination for CNS prophylaxis [1, 2].

Post-dural puncture headache (PDPH) is a common complication of lumbar puncture, which is likely due to the loss of cerebrospinal fluid (CSF) into the epidural space through the dural tear. The reported incidence of PDPH varies from 10% to 40% depending on age, gender and needle size. Characteristically, patients develop a bilateral headache that worsens shortly after assuming the upright position and improves rapidly with recumbence within the first 7 days after lumbar puncture (LP). Although PDPH may persist for six months or longer in occasional cases, most cases resolve within seven days [3, 4].

Several factors contribute to the development of headache after lumbar puncture, including needle size and design, direction of the bevel and number of LP attempts. Namely, using smaller diameter and non-cutting (atraumatic) needles is correlated with a lower incidence of headache after lumbar puncture. Additionally, insertion of the needle with the bevel parallel to the dural fibers facilitates closure of the hole and minimizes cerebrospinal fluid leakage. If these factors are taken into consideration, the incidence of headache can be markedly reduced [5, 6].

The treatment of PDPH consists of conservative measurements such as hydration, analgesics and various medications such as intravenous teophylline and mirtazapine. If these measures fail, an epidural blood patch is administered. Although bed rest after lumbar puncture is generally recommended, several studies have not shown this to effectively prevent PDPH [3-5, 7-9].

This study was designed to evaluate the safety and effectiveness of epidural isotonic saline injection following lumbar puncture for preventing PDPH and related complications.

Table 1: Descriptive information for categorical variables in both groups

Variable	Group 1	Group 1	Difference
Number of cases	18	15	$p>0.05$
Gender	Male: 9	Male: 8	$p>0.05$
	Female: 9	Female: 7	
Mean age	23.9 ± 8.2 (16-44)	24.2 ± 14.2 (15-63)	$p>0.05$
Mean number of IT-MTX therapy	4.6 ± 0.9 (3-6)	5.2 ± 0.7 (4-6)	$p>0.05$
Patients suffered at least 1 PDPH episode	13 (72.2%)	5 (33.3%)	$p<0.05$
Number of PDPH episodes	41/84 (48.8%)	13/79 (16.4%)	$p<0.001$
Mean number of PDPH per case	2.2 ± 1.6	0.8 ± 1.4	$p<0.05$
Mean pain scores	5.6 ± 1.62	3.0 ± 1.1	$p<0.001$
Necessity of EBP	4 (22.2%)	1 (6.6%)	Not performed
Convulsion	2 (11.1%)	0	Not performed
Respiratory arrest	1 (5.5%)	0	Not performed

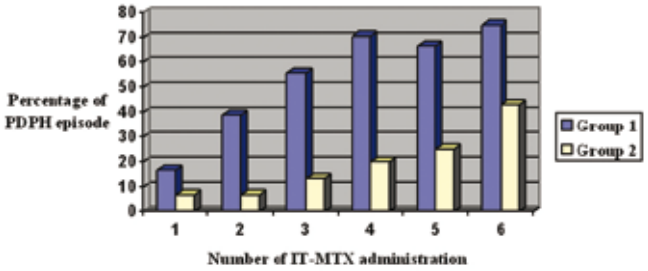

Fig. 1 — Association between the number of intrathecal chemotherapy injections and development of PDPH for both groups

Materials and Methods

Patients:

Thirty-three patients with ALL who had a complete clinical and hematological remission after conventional remission induction therapy were accepted for the study. Seventeen patients were male, and 16 were female. All patients had pre-B ALL and had no clinical or cytogenetic abnormalities related to adverse clinical outcomes.

Patients with CNS leukemia, pre-existing headaches, migraine, sinusitis, flu or other concomitant disease were excluded from the study. A signed consent form was obtained from each patient after he or she was informed about the procedures and the purpose of the study.

Procedures:

For CNS prophylaxis, we planned to administer weekly intrathecal methotrexate (IT-MTX) for 4-6 weeks and high dose systemic chemotherapy in a body surface area-adjusted dose. All lumbar punctures were performed using 22 g spinal needles, and 15 mg of preservative-free MTX was given intrathecally to each patient. In all cases, the cutting edge of the needle was kept parallel to the longitudinal ligament.

Patients were randomized into two groups. The first group consisted of 18 patients who received IT-MTX without any additional intervention, whereas the second group consisted of 15 patients who received 20 ml of isotonic saline injected to the epidural space prior to removing the needle just after the IT-MTX application. Standard procedures such as bed rest in a recumbent position and 2000 ml or more daily hydration were applied to all cases. All cerebrospinal fluid samples were centrifuged and examined for cytological evidence of CNS involvement.

Measures:

Patients were carefully observed for the development of PDPH and related complications. Pain scores were assessed with visual analog scale (VAS) ranging from 0 to 10; 0= no pain, and 10 = most severe pain. Pain scores were compared between the two groups.

Statistics:

All statistical analysis was performed using SPSS 11.5 for Windows. Results were shown as mean ± standard deviation. Comparison between mean ages, mean number of IT-MTX and pain scores for both groups were performed by non-parametric Mann-Whitney-U test. Statistical comparison among groups with regard to development of PDPH was done by Pearson's chi square (χ^2) test. Correlation analysis was carried out by Spearman's rho. $P < 0.05$ were considered to be significant.

Results

Thirty-three patients with a mean age of 24.0 ± 11.1 (range 15 and 63) years were included in the study. Seventeen patients (51.5 %) were male, and 16 (48.5%) were female. There was no significant difference between the mean ages of males and females (p>0.05).

The first group was composed of 18 patients (9 males and 9 females), and the second group had 15 cases (8 males and 7 females). All patients were diagnosed with pre-B ALL. The mean ages were 23.9 ± 8.2 (range 16 and 44) and 24.2 ± 14.2 (range 15 and 63), respectively. There was no significant difference between the mean ages of the groups (p>0.05). All cases were in clinical and hematological remission.

In total, IT-MTX was administered 163 times (84 in the first and 79 in the second groups), averaging 4.93 administrations per patient. The mean number of IT-MTX applications for the groups with and without concomitant isotonic saline injection were 5.2 ± 0.7 (range 4 and 6) and 4.6 ± 0.9 (range 3 and 6), respectively. The difference was not significant (p>0.05).

Thirteen of the patients from the first group (72.2%) and five from the second group (33.3%) suffered at least one PDPH episode. Significantly more patients in the first group experienced PDPH than in the second group (p<0.05).

Fifty-four PDPH episodes were reported in total, with 41 (48.8%) in the first group and 13 (16.4%) in the second group. The difference was highly significant (p<0.001). The mean rate of occurrence of PDPH was also significantly higher in the first group than in the second group (2.2 ± 1.6 and 0.8 ± 1.4, respectively, p<0.05).

The risk for PDPH increased in conjunction with increasing numbers of LP. In the first group, PDPH developed after 16.6% (3/18) of the first, 38.8% (7/18) of the second, 55.5% (10/18) of the third, 70.5% (12/17) of the fourth, 66.6% (6/9) of the fifth, and 75% (3/4) of the sixth IT-MTX applications. In the second group, PDPH developed after repeated IT-MTX applications as follows: 6.6% (1/15) of both the first and second, 13.3% of the third, 20.0% (3/15) of the fourth, 25.0% (3/12) of the fifth and 42.8% (3/7) of the sixth IT-MTX administrations. Comparison between the two groups according to the number of IT-MTX administrations and the occurrence of PDPH is shown in Figure 1.

Pain scores were determined in patients suffering from PDPH and compared between the two groups. The mean pain scores were 5.6 ± 1.6 in the first group and 3.0 ± 1.1 in the second group. Severity of the headache was significantly higher in the first group (p<0.001). Although PDPH development rate increased proportionally with repetitive intrathecal injections, no significant correlation was found between the number of IT-MTX treatments and severity of the pain (p>0.05).

Four patients from the first group (22.2%) and one from the second group (6.6%) had persistent headaches that could not be managed by conventional measures. Epidural blood patch (EBP) application resulted in complete recovery from PDPH in these cases.

In addition to the high rate of PDPH, two patients from the first group (11.1%) developed generalized convulsion attacks as a consequence of lowered intracranial pressure. One (5.5%) was life threatening, and it was complicated by respiratory arrest necessitating respiratory support. Results are summarized in Table 1.

On the other hand, no serious complications were observed in epidural saline injected patients (Group 2). Adverse events related to epidural saline injection (ESI) were limited to local and transient backache in all (100.0%) cases, transient leg pain in 2 (13.3%) cases and short-term paresthesia localized to the lower extremities in 3 (20.0%) cases.

Discussion

ALL is a neoplastic disease that is rapidly fatal if untreated. Current therapy involves a scheduled sequence starting with remission induction therapy followed by intensification, CNS prophylaxis and maintenance therapy lasting 2 to 3 years. CNS prophylaxis is essential in the treatment of ALL. Approximately one-third of adult patients will eventually have CNS involvement as primary site of relapse [1, 2].

Intrathecal chemotherapy is often administered because systemic chemotherapeutic agents do not effectively cross blood-brain barrier. Another approach involves high dose administration of CNS bioavailable drugs such as methotrexate and cytarabine. These approaches should be combined, and cranial irradiation should be considered, because these agents offer poor protection from CNS relapse when administered alone [1, 2, 10].

PDPH is a common complication of LP. Intracranial hypotension due to the loss of CSF through the dural tear has been postulated for pathogenesis. The risk of PDPH always exists in patients who have a lumbar puncture. The symptoms can be severe and may be unbearable. Typically, development of the conditions shows a close relationship with posture. Headache is provoked by upright posture and resolves when a patient reclines [4, 5].

In our study, we found that PDPH developed in 33.1% of patients with respect to the number of IT-MTX administrations. In comparison with the epidural saline-injected group (Group 2),

the group that did not receive ESI experienced a very high rate of PDPH (16.4% vs. 48.8%, respectively). The rate of patients who suffered at least one PDPH episode was also very high in the first group (72.2%) compared to the second group (33.3%). ESI seems to be an effective approach to prevent PDPH.

Although a number of clinical situations such as CNS involvement, migraine, anemia, sinusitis, and viral and bacterial infections can cause headache, all of our cases were in clinical and hematological remission with no co-existing conditions that could be a source of headache. Additionally, in our cases, all pain attacks developed after intrathecal chemotherapy and presented with typical characteristics of PDPH.

On the other hand, intrathecal chemotherapy-associated toxicity characterized by headache, nausea and vomiting should also be taken into account [1, 2]. This condition may explain why the overall incidence of PDPH is higher in our cases than in other reported cases of accidental dural puncture during the administration of epidural anesthesia. However, it is difficult to explain why patients who received ESI had a significantly lower incidence of PDPH. The high incidence of PDPH observed in our cases may be mostly due to the repeated LP applications. In fact, we found that the rate of PDPH attacks increased concordantly with repetitive IT-MTX treatments. These observations suggest that headache in our cases was mostly due to intracranial hypotension as a consequence of cerebrospinal fluid leakage.

Several measurements have been used for preventing and managing PDPH. These include bed rest, hydration, analgesics, caffeine, teophylline, mirtazapine, sumatriptan and methylergonovine maleate [4, 7, 8, 11-13]. However, data are quite limited, and the effectiveness of these measurements needs to be evaluated further.

In our study, we have observed that ESI effectively reduced not only the frequency of occurrence but also the severity of PDPH. Furthermore, EBP became necessary in 22.2% (4 of 18) of patients who underwent IT-MTX therapy without ESI (group 1) compared to only 6.6% (1 of 15) of patients who received ESI (Group 2). Although the sample size was too small to perform a statistical comparison, this approach seems likely to reduce the need for EBP. Further studies on larger series are necessary to confirm this observation.

The EBP is the most effective and widely accepted treatment of choice for PDPH. Rapid recovery from the pain has been reported in 70% to 100% of treated patients [3-5, 14-16]. The technique of EBP is 20 ml of autologous blood injection into epidural space [17].

Although EBP remains the most effective treatment choice for PDPH and is regarded as safe, several complications such as lumbar subdural hematoma and arachnoiditis have been reported following large volume EBP [18]. Furthermore, EBP with autologous blood may increase the risk for iatrogenic seeding of the CNS with leukemic cells in patients with high circulating blast counts [1]. Additionally, Cesur et al reported a case with PDPH and fever. They claimed that EBP using autologous blood should be avoided in order to prevent the development of epidural abscess in case of septicemia, and they successfully used compatible allogeneic blood for patching [19]. However, allogeneic blood use carries important risks such as blood-borne infections. For these reasons, ESI is a safer treatment than both autologous and allogeneic blood patch, especially in leukemic patients.

Although ESI seems to be an effective, simple and safe modality to prevent the development of PDPH, it is not known whether this application has a therapeutic effect when PDPH has already developed. Furthermore, in our study, we demonstrated that ESI significantly reduced the frequency of PDPH, but this technique could not prevent PDPH completely. Although ESI effectively reduces the rate of PDPH, it is likely not as effective as EBP.

In addition to its safety and effectiveness, ESI is easily performed and well tolerated. It is applied during lumbar puncture and does not necessitate additional interventions, so it can be used for the prevention of PDPH, especially in patients who are undergoing more than one lumbar puncture. Our study shows that ESI reduces not only the frequency and severity of PDPH but also life-threatening complications related to intracranial hypotension.

The exact mechanism by which epidural saline injection reduces the frequency of PDPH is poorly understood. One possible explanation is that lumbar injection of saline generates local edema and raises epidural and intrathecal pressure. Reduction in the leak would allow the dura to repair [20].

We believe that ESI is a safe, easy and tolerable modality that effectively reduces the frequency and severity of PDPH with mild and limited adverse events. It also likely reduces the need for EBP. Therefore, it should be used in patients undergoing LP. Further studies on larger series are needed to evaluate its safety and efficacy.

Conflict interest statement The authors declare that they have no conflict of interest to the publication of this article.

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