The Effect of Midazolam on Prevention of Post-Dural-Puncture Headache

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Abstract: Objective: Post-dural-puncture headache (PDPH) is the most common side effect associated with a lumbar puncture (LP). The present study aims to evaluate the effect of midazolam on the prevention of PDPH.

Methods: This single-blind randomized clinical trial study was performed on 120 patients aged 18-60 years who were candidates for diagnostic LP in 2017-2018. In the intervention group (n=30), 3 mg of midazolam was injected intravenously for two minutes 5-10 minutes before LP, and the control group received normal saline as placebo. Patients in both groups were evaluated and compared with each other in terms of incidence, onset, severity, and duration of PDPH.

Results: The incidence of PDPH was lower in the midazolam group, but the difference was not significant (P>0.05). Mean severity, onset time, and duration of PDPH were not significantly different between the two groups (P<0.05). All patients in the intervention group and 75% of patients in the control group with PDPH had a history of headache. There was no significant difference between gender, mean age, BMI, pressure and CSF volume in patients with PDPH (P>0.05). The mean age of patients with PDPH was significantly lower in both groups, and the percentage of women with PDPH was considerably higher than that of men (P<0.05).

Conclusion: Although there was no significant difference between the parameters studied in the two groups, patients with less age, history of headache, lower CSF pressure, and female gender were more likely to develop PDPH.

Keywords: Lumbar puncture, Headache, Midazolam.

INTRODUCTION

Lumbar puncture (LP) is a diagnostic, therapeutic, and anaesthetic intervention [1]. The most common side effect of LP is post-dural puncture headache (PDPH) [2], which occurs in up to 40% of patients [3]. According to the International Classification of Headache Disorders (Beta version), PDPH is defined as a headache that develops within 5 days after the LP, with no other diagnostic reason [4]. 90% of them occur within 3 days and 66% within the first 48 hours [5,6]. PDPH remits spontaneously within 2 weeks, or after sealing of the leak with the autologous epidural lumbar patch [5]. The pathophysiology of this headache is not fully described, but a decrease in cerebrospinal fluid volume may drive pain-sensitive structures down and lead to headaches. Loss of cerebrospinal fluid, on the other hand, increases blood flow, dilates the arteries and veins, and creates post-dural puncture headache. Another justification for the development of PDPH involves the role of substance P and regulator of neurokinin receptors [6]. Many studies focus on treatment after the onset of PDPH symptoms, including conservative measures such as bed rest and prescribing pain. However, prevention of this headache is also an important issue [6-8].

On the other hand, LP is a very stressful event for most patients, and the prediction of pain itself increases the sensitivity to pain. Prescribing painkillers to the patient can counteract this increase in adrenergics and pain sensitivity. Benzodiazepines with sedative-hypnotic effects are good options for this purpose [9, 10]. The purpose of this study was to evaluate the efficacy of midazolam administration on reducing PDPH incidence and decreasing its severity and duration.

METHOD

After being approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Code of Ethics: IR.AJUMS.REC.1397.138), this single-blind randomized clinical trial (IRCT code: IRCT20180205038631N1) was performed on 120 patients aged 18-60 years who were candidates for the diagnostic LP referred to Golestan Hospital of Ahvaz in 2017-2018. All patients were candidates for LP based on indications from the American Academy of Neurology. Exclusion criteria included any chronic pulmonary disease, known allergy to benzodiazepines, current or previous drug abuse disorder, and consciousness disorder. Patients were randomly divided into two groups of intervention and control (n= 60) by block randomization, and patients in both groups were not aware of the way of grouping. Patients were equalized for age, gender, CSF pressure, BMI. In the

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intervention group, 3 mg of midazolam was injected intravenously for two minutes 5-10 minutes before LP, and the control group received normal saline as placebo with the same volume. After topical anaesthesia with intradermal injection of 1 cc of lidocaine 2% for patients in both groups, LP was carried out with 20-gauge needle Quincke in sterile conditions and lateral position. The procedures were performed by specialists with similar work experience. All patients were hospitalized for at least 6 hours. Patients in both groups were evaluated and compared with each other in terms of incidence, onset, severity, and duration of PDPH. Headache severity was measured using the Visual Analogue Scale and shortly after the onset of headache.

Statistical Analysis

Quantitative data were presented as mean and standard deviation and qualitative data as frequency and percentage. Independent t-test was used to compare quantitative data, and Chi-square test was used for qualitative data. Data were analyzed using SPSS 22 software. Significance level was considered less than 0.05.

RESULTS

The demographic and clinical data of the two groups were not statistically significant (Table **1**).

Although PDPH was lower in the intervention group than that in the control group, the difference was not statistically significant (P >0.05) (Table **2**).

There was no statistically significant difference between mean PDPH severity in the two intervention and control groups (P >0.05). Frequency of patients with pain score 7-8 was higher in both groups (Table **3**).

Table 1: The Demographic and Clinical Data of the Two Groups

Variables		Midazolam (n=60)	Control (n=60)	P-value
Gender (N, %)	Female	41 (68.3%)	38 (63.3%)	0.094
	Male	19 (31.67%)	22 (36.67%)	
Age (year)(Mean±SD)		37.05±10.48	37.68±9.68	0.732
BMI (kg/m^2)(Mean±SD)		25.46±2.77	25.95±4.79	0.501
CSF pressure (mmHg) (Mean±SD)		16.01±4.8	16.16±5.97	0.880
Cause of LP (N, %)	CNS infection	13 (21.67%)	4 (6.67%)	0.197
	Cranial nerve palsy	3 (5%)	5 (8.33%)	
	Headache	15 (25%)	19 (31.67%)	
	Demyelinating disease	14 (23.33%)	11 (18.33%)	
	Myelopathy	4 (6.67%)	5(8.33%)	
	Neuropathy	6 (10%)	13(21.67%)	
	Optic Neuritis	4 (6.67%)	1 (1.67%)	
	Other	1(1.67%)	2 (3.33%)	
History of Headache	Yes	9 (15%)	11 (18.3%)	0.590
	No	51 (75%)	49 (81.67%)	
Number of try for LP	One	41 (68.33%)	43 (71.67%)	0.492
	Two	14 (23.33%)	11 (18.33%)	
	Three	3 (5%)	2 (3.33%)	
	Four and more	2 (3.33%)	4 (6.67%)	

Table 2: Comparison of PDPH Incidence in Two Groups

Presence of Headache	Midazolam (n=60)	Control (n=60)	P-value
Yes	12 (20%)	16 (26.67%)	0.388
No	48 (80%)	44 (73.33%)	

Table 3: Comparison of PDPH Severity in Two Groups

Severity of Headache		Midazolam (n=12)	Control (n= 16)	P-value
VAS Score (Mean±SD)		6.83±2.03	6.81±1.93	0.978
VAS Score (N, %)	3 - 4	2 (16.67%)	2 (12.5%)	0.112
	5 - 6	3 (25%)	5 (31.25%)	0.075
	7 - 8	4 (33.33%)	6 (37.5%)	0.088
	9 - 10	3 (25%)	3 (18.75%)	0.072

Table 4: Comparison of PDPH Duration in Two Groups

Duration of headache until recovery		Midazolam (n=12)	Control (n= 16)	P-value
Time (Day)(Mean±SE)		4.33±0.72	4.12±0.91	0.899
Time (Day) (N, %)	≤1	4 (33.33%)	5 (31.25%)	0.891
	2 - 5	4 (33.33%)	7 (43.75%)	0.092
	6 - 10	3 (25%)	2 (12.5%)	0.075
	≥11	1(8.33%)	2 (12.5%)	0.525

There was no statistically significant difference between the mean duration of PDPH incidence (days) in the two groups (P>0.05), and in both groups, the majority of patients recovered in less than 5 days (Table **4**).

Although the mean PDPH onset time (hours) was higher in the intervention group patients, there was no statistically significant difference between the two groups (P>0.05). Also, although the frequency of patients in the intervention group was greater than 24 hours, there was no statistically significant difference in the distribution of patients based on headache time (less than 24 hours) in the two groups (P>0.05) (Table **5**).

There was no significant difference between the mean age of patients with PDPH in the intervention and control groups (P>0.05). In contrast, the mean age of patients without PDPH was significantly higher in both groups, indicating a higher incidence of PDPH in younger individuals.

There was no significant difference between the mean of BMI in patients with PDPH in the two groups (P>0.05). Also, in both groups, the mean BMI of patients without PDPH was not significantly different from those with PDPH (P>0.05).

There was no significant difference between the mean of CSF pressure of patients with PDPH in the two groups (P>0.05). In the intervention group, there was a significant difference between mean CSF pressure in patients with PDPH incidence and non-incidence of PDPH (P <0.05).

The mean CSF volume in PDPH patients was not significantly different between the two groups. There was no significant relationship between CSF volume and PDPH in the intervention group, but in the control group, CSF volume was significantly higher in patients with PDPH (P <0.001).

There was no significant difference between the two groups regarding the gender distribution of the patients with PDPH (P>0.05). Frequency of PDPH in both men and women was evaluated intra-group and accordingly, in both groups the percentage of women with PDPH was significantly higher than that of men (P <0.0001) (Table **6**).

Table 5: Comparison of PDPH Onset Time in Two Groups

	Onset of Headache	Midazolam (n=12)	Control (n= 16)	P-value
Time (hours) (Mean±SE)		22.50±14.27	19.93±16.65	0.672
Time (hours) (N, %)	<24	4 (33.33%)	7 (43.75%)	0.084
	>24	8 (66.67%)	9 (56.25%)	

Table 6: Comparison of Age, Gender, BMI, Pressure and CSF Volume of Patients with PDPH in Two Groups

Variables	Status	Midazolam	Control	P-Value
Age (year) (Mean±SE)	With Headache	33.58±10.61	32.31±6.12	0.692
	Without Headache	37.92±7.53	39.64±8.12	0.212
	P-Value	<0.0001*	<0.0001*	-
BMI(kg/m^2) (Mean±SE)	With Headache	24.83±2.33	26.31±5.95	0.424
	Without Headache	25.62±2.88	25.82±3.41	0.951
	P-Value	0.542	0.487	-
CSF Pressure (Mean±SE)	With Headache	13.75±2.89	15.63±8.57	0.475
	Without Headache	16.58±3.89	16.36±5.42	0.954
	P-Value	0.002*	0.815	-
CSF Volume (Mean±SE)	With Headache	8.33±2.52	9.69±2.63	0.425
	Without Headache	9.37±1.57	5.18±2.09	<0.001*
	P-Value	0.408	<0.001*	-
Gender (N, %)	Male	2 (10.53%)	3 (13.64%)	0.501
	Female	10 (24.39%)	13 (34.21%)	
	P-Value	<0.001*	<0.001*	-

In the intervention group, all patients and the control group, 75% of the patients with PDPH had a history of headache, and there was a significant relationship between the history of headache in patients with PDPH (P <0.001).

DISCUSSION

In the present study, although PDPH was lower in the intervention group than in the control group (20% vs. 26.67%), there was no statistically significant difference between the two groups (P >0.05). In the study of Khlebtovsky *et al*., 27.6% of patients under diagnostic LP developed PDPH, which was similar to that in the control group but was higher than our intervention group [1]. In the study of Vilming *et al*., 37% of 239 patients under diagnostic LP had PDPH, which was higher than the groups of the present study [11]. In the study by Park *et al*., 8.72% of patients under diagnostic LP had PDPH, which was lower than the groups of the present study [12]. In the study of Almeida *et al*., 5.6% of patients with PD developed PDPH, which was lower than the groups of the present study. The reason for the differences in the last two studies may be due to differences in the number of patients studied with the present study. The needles used in the previous two studies were also different from the present study, which may have influenced the results [13]. There was no significant difference between the meantime of onset and duration of PDPH after LP until recovery in the two groups (P>0.05). Mean age of patients without PDPH in both intervention and control groups was significantly higher than that in patients with PDPH, indicating a higher incidence of PDPH in younger subjects. In the study by Khlebtovsky *et al*., the age of patients with PDPH was significantly lower [1]. In the study by Park *et al*., patients with PDPH were younger and had a lower mean age [12]. In van Oosterhout *et al*. study, patients with PDPH were younger [14]. However, in the study of Vilming *et al*., there was no significant relationship between PDPH in patients under diagnostic LP [11]. In the present study, although there was no significant difference in the gender distribution of headache patients between the two groups, an intra-group study in each gender showed a higher percentage of female patients with PDPH than men (P <0.0001). In the study by Khlebtovsky *et al*. on PDPH patients, the number of women was significantly higher than that of men [1]. In the study of Vilming *et al*., the incidence of PDPH in women was considerably higher than in men [11]. However, there was no significant relationship between gender and PDPH in the study of Almeida *et al*. [13]. The mean BMI of patients with and without PDPH was not significantly different in both intervention and control groups (P >0.05). In the study of Khlebtovsky *et al*., the mean BMI in individuals with and without PDPH was not significantly different [1]. In the study of Park *et al*., patients with PDPH had lower body mass index [12]. In the study of Oosterhout *et al*., BMI significantly

increased the risk of PDPH [10]. The results of the study by Almeida *et al*. reported a BMI of less than 25 as one of the major risk factors for PDPH [13]. There was no significant relationship between BMI and PDPH incidence after diagnostic LP in the study of Vilming *et al*. [11].

The mean CSF pressure in both groups was lower in patients with PDPH. In the study of Park *et al*., CSF pressure was lower in patients with PDPH [12]. However, in the Study by Khlebtovsky *et al*., CSF pressure was significantly higher in patients with PDPH [1]. There was no significant difference between the two groups in the mean CSF volume in PDPH patients. There was no significant relationship between CSF volume and PDPH in the intervention group, but in the control group, CSF volume was significantly higher in patients with PDPH (P <0.001). In the intervention group, there was no significant relationship between CSF volume and PDPH, but in the control group, CSF volume was significantly higher in patients with PDPH (P <0.0001). In the study of Almeida *et al*., the incidence of PDPH was not significantly correlated with the volume of CSF removed [13].

All patients in the intervention group and 75% of the patients in the control group with PDPH had a history of headache. In the study of Khlebtovsky *et al*., history of headache was significantly higher in patients with PDPH [1], but in the study of Oosterhout *et al*. there was no significant relationship between migraine history and PDPH incidence [14].

CONCLUSION

According to the results, although there were no significant differences between the parameters studied in the two groups, similar to the results of several studies conducted on the risk factors of PDPH incidence after diagnostic LP, in the present study also patients with lower age, history of headaches, lower CSF pressure, and female gender were more likely to develop PDPH.

DECLARATION

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethics code: IR.AJUMS.REC.1397.138), and all patients provided written informed consent before enrollment.

Consent for Publication

This manuscript has not been published and is not under consideration for publication elsewhere in whole or in part. No conflicts of interest exist in the submission of this manuscript, and the manuscript has been approved for publication by all listed authors.

Availability of Data and Material

The data used to support the findings of this study are available from the corresponding author upon request.

Competing Interests

None of the authors has any financial and personal relationships with other people or organizations that could potentially and inappropriately influence this work and its conclusions. Authors declared no competing interest in publishing this paper.

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