



# Comparison of the Effects of Propofol and Midazolam Sedation on Post-dural Puncture Headache

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## Abstract

**Background:** Post-dural puncture headache (PDPH) is a common side effect after spinal anesthesia.

**Objectives:** This study aimed to compare the sedative dose of propofol and midazolam in reducing headaches after spinal anesthesia.

**Methods:** In order to conduct this study, 80 candidates for spinal anesthesia were divided into two groups, A and B. Both groups received spinal anesthesia with marcaine. In group A, propofol was infused slowly at a dose of 30  $\mu$ g per minute, and in group B, 1 mg midazolam was injected intravenously. In the two groups, the incidence and intensity of headaches were measured using the VAS pain scale. Data were analyzed using Mann-Whitney and t-tests at a significance level of 0.05.

**Results:** In this study, 65% (52) were male and 35% (28) were female. There was no significant difference between the two groups in terms of demographic information ( $P > 0.05$ ). In the propofol group, the incidence and severity of headaches were significantly lower than in the midazolam group ( $P < 0.01$ ).

**Conclusions:** This study's results indicated that administering low-dose propofol as a sedative during spinal anesthesia may be more effective in reducing PDPH than midazolam.

**Keywords:** Midazolam, Propofol, Spinal, Headache, PDPH

## 1. Background

Anesthesia and analgesia are inseparable parts of surgery that are used in various ways according to the patient's condition. One of the most common methods of anesthesia for surgery is a neuraxial block, which subcategories include spinal anesthesia. In this method, an anesthetic is injected into the spinal space to cause numbness and immobility in the lower parts of the injected surface by affecting the nerves. This method is widely used and has advantages such as a faster effect, greater depth of anesthesia, and reducing the possibility of infection for the patient (1, 2). Among the side effects of spinal anesthesia, we can mention shivering during surgery, nausea, and vomiting (3), as well as neurological damage such as cauda equina syndrome, low

blood pressure, decreased heart rate, and unexplained cardiac arrest. Additionally, headaches are one of the most common side effects caused by this procedure (2).

The probable mechanism of post-dural puncture headache (PDPH) is due to the loss of cerebrospinal fluid, which leads to tension and pressure on the brain tissue and dilation of blood vessels (2). Risk factors for this type of headache include sudden cessation of caffeine consumption, previous headache history, dehydration, spinal needle diameter, number of dural punctures, and previous history of spinal headaches. The diagnosis of PDPH, in the case of ruling out other factors, is in the form of pain that is aggravated by moving the head and gets worse when standing and better when lying down (2, 3). An increase in headaches in the

standing position is a necessary condition for diagnosing PDPH (4). The treatment of this headache includes narcotics, reducing auditory and visual stimulation, and caffeine consumption (5). If there is no response to the continuation of the treatment, an epidural blood injection is performed (6).

At the same time as spinal anesthesia, various drugs are used to make the patient fall asleep and calm down, among which midazolam and propofol are mentioned (7, 8). On the other hand, studies have shown that propofol can be effective in the treatment of migraine headaches by acting on the beta-1 gamma-aminobutyric acid receptor (9, 10).

Midazolam is also a benzodiazepine drug that is used in anesthesia for most patients for sedation and amnesia (8).

In some studies, intraspinal injection of midazolam increased the time of postoperative analgesia (11).

Considering that patients undergoing spinal anesthesia require sedative drugs for calmness and sleep, and commonly used sedatives are midazolam and propofol, proper selection of sedative drugs by an anesthesiologist can have a significant impact on preventing post-spinal anesthesia headaches, improving the patient's recovery, and reducing hospital costs.

## 2. Objectives

The lack of definitive prevention methods for this type of headache, the results of previous studies on the effect of propofol on treating mild and migraine headaches, and the weakness of previous studies in this regard caused the researchers to conduct this study to compare the effect of the sedative dose of propofol and midazolam on PDPH during lower abdominal and lower limb surgeries.

## 3. Methods

This double-blind clinical trial study was conducted in 2015 at 15 Khordad Hospital in Gonabad City after receiving the ethical code IR.GMU.REC.1394 and IRCT code IRCT2015120712312N3, on 80 patients aged 25 to 75 who were candidates for surgery and underwent spinal anesthesia. The aim was to compare the effect of propofol sedative drug dose with midazolam on PDPH.

The inclusion criteria were patient consent, no coagulation problem, no history of headaches, no skin infection at the site of spinal anesthesia, ASA class one and two patients, and no history of seizures. In addition, more than 2 punctures in the dura for spinal anesthesia drug injection, the need for narcotic drugs during surgery, and the need for general anesthesia after spinal anesthesia were the exclusion criteria from this study.

After obtaining informed consent and if they met the inclusion criteria, the patients were divided into 2 groups, A and B, using the permutation block randomization technique.

In both groups, 6 mL/kg of Ringer's fluid was given as a compensatory volume. Then, the patient was placed in a sitting position; the skin was prepared with 10% betadine, and under sterile conditions, Quincke No. 25 spinal needles were used to enter the subcutaneous tissue parallel to the spinal cord fibers. After entering the dura and removing the cerebrospinal fluid, 2 cc of spinal marcaine was injected. The needle was removed, and after dressing the patient's skin, he was placed in a supine position. After obtaining anesthesia and maintaining the anesthesia level, in group A, propofol was infused slowly at a dose of 30  $\mu\text{g}/\text{min}$ . In group B, midazolam was injected intravenously at 1 mg. Also, in both groups, in case of blood pressure dropping more than 30% of the initial amount, 5 mg of ephedrine was used intravenously.

The main variable investigated in this study was the headache of the patient after spinal anesthesia and the severity of the headache of the patient after the operation was recorded by a trained nurse immediately after entering the recovery room and in the ward for up to 24 hours based on the VAS pain criterion in the checklist that was prepared for this purpose. In the case of headaches in patients, the usual treatments include complete rest, hydration, and the use of analgesics, which in this research included acetaminophen, codeine 300 mg every 6 hours, and the use of an abdominal binder.

### 3.1. Statistical Analysis

The data analysis was performed using the statistical analysis software SPSS version 20. Descriptive statistics (determining the indices of central tendency and dispersion and drawing frequency tables) were used to determine pain intensity and examine demographic variables. The non-parametric Mann-Whitney test was used to compare pain intensity in two groups. The difference between the groups in terms of other demographic variables according to their type was investigated with *t*-test and chi-square tests. Data analysis was considered at a 5% significance level and 80% statistical power.

## 4. Results

In this clinical trial study, 80 patients under spinal anesthesia were compared with each other in terms of the amount and severity of headaches caused after spinal anesthesia, using 2 sedation methods: Propofol

and midazolam. In this study 65% (52 people) of the participants were men and 35% (28 people) were women. In the group receiving midazolam, 42.5% (17 people) of the participants performed hernia repair surgery and 57.5% (23 people) for orthopedic surgery in the lower limb, and in the group receiving propofol, 40% (16 people) for hernia repair surgery and 60% (24 people) were subjected to spinal anesthesia for orthopedic surgery in the lower limb. The chi-square test did not show a significant difference between the two groups ( $P = 0.82$ ).

Additionally, the results of demographic analysis using the *t*-test showed no significant difference between the 2 groups in terms of demographic information such as height, weight, and BMI (Table 1).

**Table 1.** The Mean and Result of the *t*-test in Relation to Demographic Information

Variables	Propofol; Mean $\pm$ SEM	Midazolam; Mean $\pm$ SEM	P-Value
Weight (kg)	76.92 $\pm$ 1.1	79.15 $\pm$ 1.2	0.19
Height (cm)	173.15 $\pm$ 1.0	173.78 $\pm$ 1.0	0.66
BMI	25.60 $\pm$ 0.2	26.14 $\pm$ 0.1	0.07

Examining the data related to the incidence of headache after spinal anesthesia in the midazolam group showed that 16 of the participants reported no headache, 24 reported the occurrence of headache, 16 of them had a mild headache, 6 had moderate and 2 were severe. In the propofol group, 27 people did not have headaches, and 13 people had headaches after spinal anesthesia. Among them, 10 people reported mild headaches, and 3 people reported moderate headaches. None of the people in this group had a severe headache. Finally, the results obtained from the analysis of the data related to the incidence of headaches in the patients participating in the two groups using the chi-square test showed that the two groups differed from each other in terms of the occurrence of headaches after spinal anesthesia ( $P = 0.01$ ) so that in the subjects receiving propofol, the incidence of headache was lower than the participants in the group receiving midazolam.

Also, the severity of headache in two groups was compared using the Mann-Whitney test, and the results of data analysis showed that the two groups had a significant difference in terms of the severity of the headache caused by the operation, so that the severity of the headache was higher in the midazolam group. ( $P = 0.01$ ) (Table 2).

**Table 2.** Result of the Mann-Whitney Test Regarding Pain Intensity in 2 Groups

Group	N	Median $\pm$ IQR	Z	P-Value
midazolam	40	1.00 $\pm$ 2.00	-2.47	0.013

## 5. Discussion

This clinical trial study was conducted to compare the effect of propofol and midazolam on headaches after spinal anesthesia. The results showed that propofol, as a sedation drug combined with spinal anesthesia, was more effective than midazolam in reducing the incidence and severity of headaches caused after spinal cord rupture. However, midazolam was also effective in reducing headaches; in the studies conducted, researchers introduced midazolam as an effective drug to reduce pain after spinal anesthesia (12). However, in another study that used two different doses of half and one milligram of midazolam combined with lidocaine injected into the spinal space, the results showed that intraspinal midazolam does not affect postoperative headaches (13).

On the other hand, propofol is also used as a suitable drug for the treatment of headaches with different origins, so in 2021, Vosoughian et al. used it as an effective drug for the treatment of migraine headaches, and in 43.1% of the participants in this study Treatment with propofol successfully controlled migraine headaches (14). However, migraine headaches are different from PDPH in terms of the mechanism of occurrence. In this regard, the results of Gulfam et al.'s study on cesarean section patients were conducted to compare the effect of propofol in reducing headaches after spinal anesthesia with the control group (15). In line with our study, it confirms the effect of propofol on headaches after spinal anesthesia. Also, in another study in Egypt, propofol was compared with aminophylline, and the results showed that propofol has a greater effect than aminophylline on reducing the intensity and duration of PDPH (16). The researchers in a case report study reported the treatment of PDPH in 2 patients with propofol injection (17).

Zhao et al., in a meta-analysis study after reviewing 22 clinical trial studies regarding drugs used to reduce PDPH after spinal anesthesia in cesarean surgery, stated that different drugs such as aminophylline, dexamethasone, gabapentin, ondansetron, propofol, hydrocortisone, etc. are used; but among these drugs, propofol, ondansetron, and aminophylline had a better effect on reducing it (18).

### 5.1. Conclusion

Based on the results of the current study, compared to midazolam, propofol is more successful at reducing headaches after spinal anesthesia and is introduced as a more effective drug. Therefore, the use of this drug in low doses is recommended for the prevention and treatment of headaches after spinal anesthesia in patients who undergo this method of anesthesia for surgery.

## Footnotes

**Authors' Contribution:** Study concept and design, M.KH and A.T and M.S; Acquisition of data, M.S; Analysis and interpretation of data, M.S and M.T; Drafting of the manuscript, FP M.KH and R.M; Study supervision, and critical revision of the manuscript for important intellectual content, all of the authors; Statistical analysis, M.S; Administrative, technical, and material support, A.T and M.T.

**Clinical Trial Registration Code:** IRCT2015120712312N3

**Conflict of Interests:** The authors confirm that there was no conflict of interest when conducting this research.

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**Informed Consent:** Informed consent was obtained.

## References

- Pardo M. *Miller's Basics of Anesthesia*. Philadelphia, USA: Elsevier Health Sciences; 2022.
- Elia N, Culebras X, Mazza C, Schiffer E, Tramer MR. Clonidine as an adjuvant to intrathecal local anesthetics for surgery: systematic review of randomized trials. *Reg Anesth Pain Med*. 2008;**33**(2):159-67. [PubMed ID: 18299097]. <https://doi.org/10.1016/j.rapm.2007.10.008>.
- Vagharfard J, Rastgarian A, Rahmanian M, Pourmokhtari M, Damshenas MH, Taban S, et al. [The effect of fentanyl addition to bupivacaine on shivering and vomiting nausea in patients undergoing femoral fracture surgery by spinal anesthesia: A double-blind randomized clinical trial]. *Pars J Med Sci*. 2022;**18**(4):9-16. Persian. <https://doi.org/10.52547/jtmj.18.4.2>.
- MacArthur C, Lewis M, Knox EG. Accidental dural puncture in obstetric patients and long term symptoms. *BMJ*. 1993;**306**(6882):883-5. [PubMed ID: 8490410]. [PubMed Central ID: PMC1677341]. <https://doi.org/10.1136/bmj.306.6882.883>.
- Weber JG, Klindworth JT, Arnold JJ, Danielson DR, Ereth MH. Prophylactic intravenous administration of caffeine and recovery after ambulatory surgical procedures. *Mayo Clin Proc*. 1997;**72**(7):621-6. [PubMed ID: 9212763]. [https://doi.org/10.1016/S0025-6196\(11\)63567-2](https://doi.org/10.1016/S0025-6196(11)63567-2).
- Choi PT, Galinski SE, Takeuchi L, Lucas S, Tamayo C, Jadad AR. PDPH is a common complication of neuraxial blockade in parturients: a meta-analysis of obstetrical studies. *Can J Anaesth*. 2003;**50**(5):460-9. [PubMed ID: 12734154]. <https://doi.org/10.1007/BF03021057>.
- Soleimanpour H, Taheraghdam A, Ghafouri RR, Taghizadieh A, Marjany K, Soleimanpour M. Improvement of refractory migraine headache by propofol: case series. *Int J Emerg Med*. 2012;**5**(1):19. [PubMed ID: 22587626]. [PubMed Central ID: PMC3514246]. <https://doi.org/10.1186/1865-1380-5-19>.
- Khanderia U, Pandit SK. Use of midazolam hydrochloride in anesthesia. *Clin Pharm*. 1987;**6**(7):533-47. [PubMed ID: 3319363].
- Drummond-Lewis J, Scher C. Propofol: a new treatment strategy for refractory migraine headache. *Pain Med*. 2002;**3**(4):366-9. [PubMed ID: 15099247]. <https://doi.org/10.1046/j.1526-4637.2002.02034.x>.
- Mendes PM, Silberstein SD, Young WB, Rozen TD, Paolone MF. Intravenous propofol in the treatment of refractory headache. *Headache*. 2002;**42**(7):638-41. [PubMed ID: 12482216]. <https://doi.org/10.1046/j.1526-4610.2002.02151.x>.
- Bharti N, Madan R, Mohanty PR, Kaul HL. Intrathecal midazolam added to bupivacaine improves the duration and quality of spinal anaesthesia. *Acta Anaesthesiol Scand*. 2003;**47**(9):1101-5. [PubMed ID: 12969103]. <https://doi.org/10.1034/j.1399-6576.2003.00186.x>.
- Piraccini E, Albarello R, Biagini C, Novi A, Agnoletti V, Gambale G. Spinal anesthesia plus ketamine-midazolam sedation for pediatric orthopedic surgery in a developing country. *HSR Proc Intensive Care Cardiovasc Anesth*. 2012;**4**(3):176-8. [PubMed ID: 23439924]. [PubMed Central ID: PMC3485388].
- Talebi H, Yazdi B, Alizadeh S, Moshiry E, Nourozi A. [Effects of adding two Doses of Midazolam to Lidocaine for Spinal Anesthesia on Post-operative Pain Severity in Patients undergoing Inguinal Herniorrhaphy]. *Anesth Pain*. 2010;**1**(3):53-62. Persian.
- Vosoughian M, Saeedi N, Moshari M, Dabir S, Dahi M, Tabashi S, et al. The Effect of Propofol Anesthesia on the Pain Severity and Frequency of Migraine Attacks in Patients with Chronic Migraine Headache over a Six Month Follow Up: An Observational Study. *Iran J Pharm Res*. 2021;**20**(4):415-21. [PubMed ID: 35194456]. [PubMed Central ID: PMC8842614]. <https://doi.org/10.22037/ijpr.2021.115243.15266>.
- Jafari RM, Golfam P, Yari M, Rezaei M, Farhadi K, Lahoopour A. The effect of intravenous propofol on the incidence of post-dural puncture headache following spinal anesthesia in cesarean section. *J Kermanshah Univ Med Sci*. 2016;**20**(2). e69698. <https://doi.org/10.22110/jkums.v20i2.3262>.
- Mohamed AG, Refky MA, Sayouh EF, Abdelnaby SM. The Effect of Intravenous Infusion of Propofol or Aminophylline on Incidence and Severity of Post-dural Puncture Headache in Elective Cesarean Section. *Egypt J Hosp Med*. 2021;**84**(1):2646-54. <https://doi.org/10.21608/ejhm.2021.189610>.
- Vosoughian M, Dabir S, Dahi M, Moshari M. Low-dose Propofol for the Treatment of Severe Postpartum Post-dural Puncture Headache: A Case Report. *Case Rep Clin Pract*. 2021. <https://doi.org/10.18502/crcp.v6i4.7860>.
- Zhao G, Song G, Liu J. Efficacy of pharmacological therapies for preventing post-dural puncture headaches in obstetric patients: a Bayesian network meta-analysis of randomized controlled trials. *BMC Pregnancy Childbirth*. 2023;**23**(1):215. [PubMed ID: 36991366]. [PubMed Central ID: PMC10053677]. <https://doi.org/10.1186/s12884-023-05531-7>.