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The effect of pregabalin on postdural puncture headache among patients undergoing elective cesarean section: A randomized controlled trial

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ABSTRACT

Introduction: Post-dural puncture headache (PDPH) is one of the most common problems of cesarean section. The present study aimed to evaluate the effect of pregabalin on PDPH among patients undergoing elective cesarean section.

Materials and methods: This double-blind clinical trial was performed on 136 patients undergoing elective cesarean section referred to Shahid Motahari Teaching Hospital in Urmia in northwestern Iran from February 1 to December 20, 2020. Patients were selected by convenience sampling method and randomly divided into two groups of intervention and control (N = 68 people each group). The presence of PDPH and its severity were recorded in the checklist based on the VAS, and conventional treatments were prescribed in the case of occurrence of the PDPH. The PDPH severity was also assessed by the patient using the 10-cm Visual Analog Scale (VAS).

Results: The mean age of participants was 27.82 years. A total of 29 people suffered from hypotension. Regarding pain severity, the mean pain score in the intervention group was significantly lower than the control group ($p = 0.01$). Results also showed that the frequency of PDPH in the intervention group was significantly lower than the placebo group (4.4% vs. 11.8%; $p = 0.019$). There was no significant difference between intervention and control groups in terms of demographic characteristics ($p > 0.05$).

Conclusion: Results of the present study showed the use of oral pregabalin at night before spinal anesthesia in patients undergoing elective cesarean(C-) section had a preventive effect on the severity and incidence of PDPH.

1. Introduction

Today, the cesarean section is one of the most popular methods of delivery. Recent studies show that more than 21% of deliveries occur by cesarean section worldwide. Spinal anesthesia is mostly used during C-section [1]. Because this anesthesia is easier to perform and local anesthetics are less dangerous than epidural anesthesia in terms of risk of preeclampsia and is effective in controlling pain and reducing postoperative nausea and vomiting [2]. Spinal anesthesia is one of the local anesthesia methods, which is associated with complications such as neurological complications (paraplegia, cauda equina syndrome), PDPH, and cardiovascular complications (hypotension, bradycardia, and cardiac arrest) [3].

PDPH is a common complication of spinal anesthesia, as a meta-analysis study shows that the prevalence of PDPH is between 1.5% and 11.2% [4]. Severe PDPH occurs frequently and is felt in the forehead or back of the head while standing. Overall, these factors can reduce the quality of life of individuals [5]. Factors such as age, sex, needle size, and frequency of use can alter the prevalence of PDPH.

Despite the high prevalence and importance of this complication, there has been no definitive treatment for these complications and most treatments are supportive and symptom-based. Supportive treatments include complete rest in a supine position, fluid therapy, and the use of analgesics (acetaminophen, codeine, nonsteroidal anti-inflammatory drugs, narcotics) [6,7]. Pregabalin is one of the drugs used, which is an anticonvulsant and acts by inhibiting the entry of calcium [8]. Pregabalin has been used in different populations to reduce pain in different patients, including epilepsy [9], chronic pain [10], and improvement of anxiety disorders [11]. Despite studies on different populations, few studies have investigated the effect of pregabalin on PDPH [12].

Also, since PDPH, apart from its physical and psychological effects, causes delays in hospital discharge and imposes further costs on the health system, and the one hand, and there has been no definitive treatment, and there have been few studies with contradictory Results,

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on the other hand, the present study aimed to evaluate the effect of pregabalin on PDPH among women undergoing elective C-section.

2. Methods

2.1. Study design

This double-blind clinical trial was performed on 136 patients undergoing elective C-sections referred to DپDMotahari Teaching Hospital in Urmia in northwestern Iran from February 1 to December 20, 2020. Inclusion criteria included patient consent to participate in the study. Exclusion criteria also included the history of migraine, patients with ASA III ASA IV, patients with a history of dural puncture more than once, patients with an indication for emergency C-section, previous history of PDPH, contraindications of spinal anesthesia, block failure, or patients who need adjuvant injection due to incomplete block, patients with surgical complications such as atony and heavy bleeding or hysterectomy, patients who do not complete the 3-day follow-up period for any reason.

2.2. Instruments

Data collection was carried out using a questionnaire, which consisted of two parts. The first part included demographic and underlying characteristics including age (year), hypotension (yes/no), bradycardia (yes/no), hypoxia (yes/no), nausea and vomiting (yes/no), ephedrine use (yes/no), atropine use (yes/no), and oxygen saturation (%). The second part checked pain (yes/no) and pain severity (VAS). VAS was used to assess the pain severity. In this scale, visual scoring was explained to the patients so that no pain and the worst pain ever experienced were represented by 0 and 10, respectively. On the scale, scores 0, 1–3, 4–6, and 7–10 indicate no pain, mild pain, moderate pain, and severe pain, respectively [13]. The validity and reliability of this instrument have been confirmed by Williamson and Hoggart [14].

2.3. Intervention and data collection

In this study, the sample size was estimated at 136 people (N = 68 people per group) according to the study by Mortazavi et al. (2018) [15], based on previous studies considering the difference between means of 0.89 and the variance (σ) = 10 using Power and Sample Size software to determine the Type I error = 5% and power = 80%. After coordination with the hospital and operating room authorities, all possible patients were found. Then the patients were evaluated for the inclusion criteria. Initially, 136 people were selected using the convenience sampling method, and then, patients were given assigned numbers ranging from 1 to 68 using a simple random number table. Then, patients with odd numbers were placed in the intervention group (pregabalin) and patients with even numbers in the control group (Placebo). Sampling continued until reaching 68 individuals in each group of patients. Pregabalin was prepared from Zahravi Pharmaceutical Company in Tabriz, Iran. Patients of the intervention group received pregabalin at a dose of 150 mg the night before spinal anesthesia. Patients of the placebo group also received a placebo the night before spinal anesthesia. After transferring patients to the operating room, standard monitoring was performed for all patients, including pulse oximetry, electrocardiography, non-invasive blood pressure measurement, and heart rate control. After creating two safe intravenous routes by 18 gauge IV needles, Ringer serum was prescribed at a rate of 5–10 ml/kg (maximum 1000 ml). To ensure the double-blind nature of the study, the project executor, patients, and the person who recorded the study Results were unaware of the patient grouping. In both study groups, spinal anesthesia was performed by an anesthesiologist by injecting 10 mg of 0.5% bupivacaine solution into the intervertebral space L3-L4 or L4- L5 using a 25 gauge Quincke spinal needle in a sitting position. Immediately, the patients were placed in a supine position and the patient's bed was rotated 15° to the left to maintain hemodynamic stability and prevent compression of inferior vena cava syndrome (IVCS). A face mask was used to administer oxygen 6 L per minute for patients. The sensory block level was checked with a pinprick test and recorded in the checklist preoperatively. In case of a severe decrease in systolic blood pressure to more than 20% of basal blood pressure or drop in heart rate below 50 beats per minute, therapeutic interventions were performed using 5–10 mg ephedrine or 0.5–1 mg atropine. Pain and PDPH were monitored since admission in the room recovery until three days after surgery, and the patient reported any headache whenever occurred (Fig. 1).

2.4. Ethical considerations

This study has been approved by the Ethics Committee of XXXX University of Medical Sciences under the Ethics code of IR.UMSU.REC. 1398.341. The study protocol has been registered in the Iranian Registry of Clinical Trials (IRCT20170516033992N4). Written and oral consent was obtained from all participants in the study. Participants were assured that their information will remain confidential. The CONSORT checklist was used to report the study [16].

2.5. Data analysis

Data analysis was carried out using SPSS Ver. 22. Descriptive statistical tests (quantitative (mean, standard deviation, frequency, and percentage) and analytical tests (chi-square) were used to describe the demographic characteristics of the participants. Kolmogorov–Smirnov test was also used to evaluate the data distribution Independent *t*-test and chi-square were used to compare pain between the intervention and control groups. P-value$<$0.05 was considered as the statistically significant level.

3. Results

A total of 136 patients entered the final phase of the present study. The mean age of participants was 27.82 years. A total of 29 people suffered from hypotension. The prevalence of bradycardia was higher in the intervention group than in the control group. The most common site of spinal anesthesia was T5 (n = 114). The prevalence of nausea and vomiting was higher in the intervention group (25%). The prevalence of PDPH was 4.4% in the intervention group and 11.4% in the control group. The mean VAS score was 3.3 in the intervention group and 5 in the control group. There was no significant difference between intervention and control groups in terms of demographic characteristics ($p > 0.05$) (Table 1).

Regarding pain severity, the mean pain score in the intervention group was significantly lower than the control group ($p = 0.01$). Concerning the frequency of PDPH, the frequency of headache in the intervention group was significantly lower than the placebo group (4.4% vs. 11.8%; $p = 0.019$) (Fig. 2)

4. Discussion

The present clinical trial investigated the effect of pregabalin on PDPH. Patients were evaluated in intervention and control groups. In the present study, the frequency of PDPH was significantly lower in the intervention group (pregabalin) and the mean PDPH severity was also lower based on VAS scoring. Recent studies have shown that PDPH is one of the most common complications of spinal anesthesia [17]. In some cases, PDPH is associated with nausea, vomiting, and vision disorders. Some cases of nausea and vomiting were also observed in the present study. Vandam and Dripps reported that the prevalence of PDPH is about 70% among candidates for spinal anesthesia during the first 7 days after surgery [18]. In contrast to existing invasive therapies for PDPH, effective non-invasive therapies such as rest, hydration, analgesics, caffeine, theophylline, sumatriptan, and adrenocorticotropic

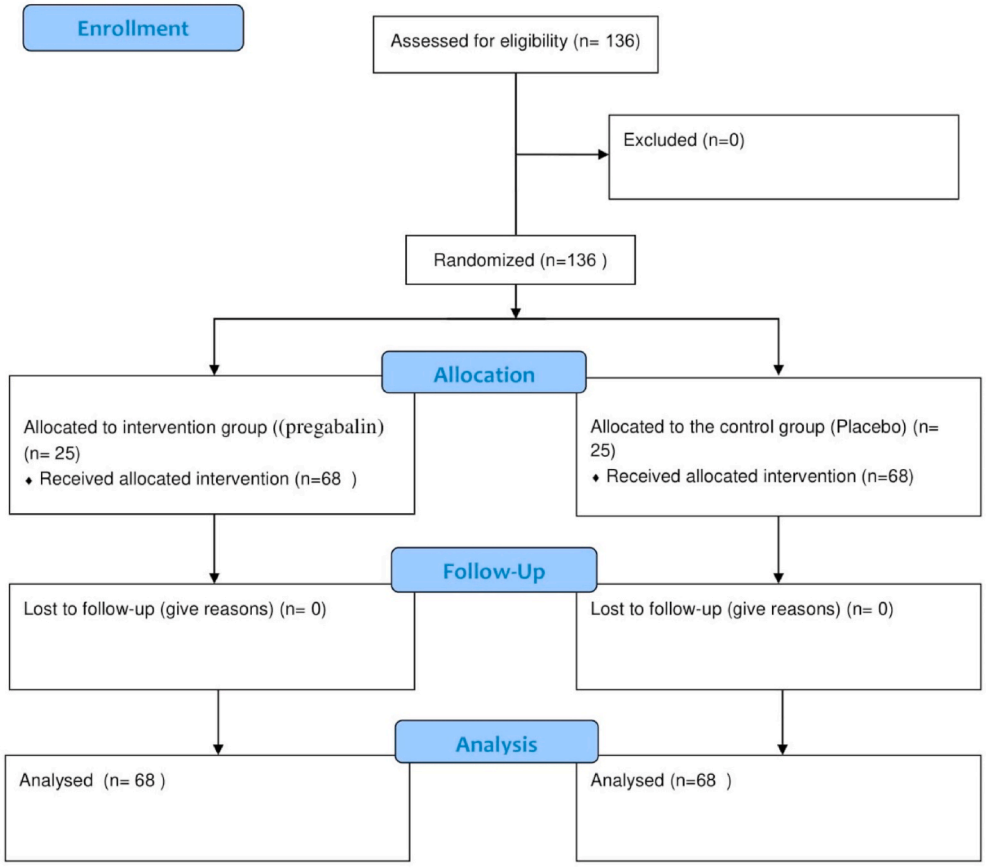

Fig. 1. CONSORT 2010 flow diagram.

Table 1
Demographic characteristics, pain extent, and severity among participants.

Group Variable	Intervention (n = 68)	Placebo (n = 68)	Total (n = 136)	P-value
Age (years)	28.50 ± 5.78	27.15 ± 5.73	27.82 ± 5.77	0.173
Hypotension	16 (23.5)	13(19.1)	29(21.3)	0.338
Bradycardia	18 (26.5)	12(17.6)	30(22.1)	0.151
Level of spinal anesthesia				0.481
L4- L5	1 (1.5)	0	1(0.7)	
L5	58 (85.3)	56(82.4)	114 (83.8)	
> L5	9(13.2)	12(17.16)	21(15.4)	
Nausea and vomiting	17(25)	14(20.6)	31(22.8)	0.342
PDPH	3(4.4)	8(11.8)	11(8.1)	0.019
VAS (positive case for headache)	3.33 ± 0.57	5 ± 0.81	4.50 ± 1.08	0.012
Use of atropine	12 (17.6)	18(26.5)	30(22.1)	0.151
Use of ephedrine	13(19.1)	16 (23.5)	29(21.3)	0.338

hormones are used to manage patients with PDPH [19,20]. On the other hand, the above-mentioned non-invasive treatments are not enough in cases where the treatment is temporary and may have other side effects [21]; therefore, to minimize the use of invasive treatments for PDPH management, pharmacological therapies are being developed.

In a study by Huseynoglu et al. (2011), patients with PDPH were divided into intervention and placebo groups. Patients in the intervention group received pregabalin for 5 days at a dose of 300 mg daily for 3 days and then 150 mg daily for 2 days. Consistent with the present study, this study also showed that the VAS score was significantly lower in the intervention group than the control group on the second day after PDPH [22]. Consistent with the present study, in their study on the incidence and chronic PDPH among FMS patients, Morsy et al. showed that the incidence of PDPH was higher in the fibromyalgia group (n = 18 patients, 25.7%) than in the control group (n = 10 patients, 14.3%). PDPH persisted for 7 or more days in 8 patients in the fibromyalgia group (11.4%) of 2.86% of control patients. PDPH persisted for more than 3 months in 2 patients in the fibromyalgia group (2.86%) [23]. Overall, it can be stated that pregabalin is effective in improving PDHD symptoms on voltage-dependent calcium channel subunit alpha-2/delta-1. Pregabalin is also chemically similar to gamma-aminobutyric acid (GABA) and it has been shown that pregabalin activity does not involve GABAergic mechanisms [24]. A review study by Taylor et al. showed that pregabalin has a sufficient and effective analgesic effect considering its molecular binding to voltage-dependent calcium channels alpha-2-delta subunit, which has also been mentioned in two animal model studies.

In our study, patients of the intervention group received 150 mg of oral pregabalin each day. Other studies have investigated other pregabalin doses as follows. In a recent study, patients received a dose of 300 mg/daily for the first 2 days and 150 mg/daily for the next 3 days, and Results were consistent with the present study [22]. In another study, patients received oral pregabalin (900 mg/day), which significantly reduced the VAS score in patients compared to the placebo group [25]. Lin et al. showed that patients with PDPH who were still undergoing a non-invasive routine continued, were recovering after receiving pregabalin (400-mg/day) for 3 days [26]. In general, the results of the present study are consistent with the above studies and the superiority of the study included administration of the lowest dose and better effectiveness. In another study, Mahoor et al. compared the effectiveness of pregabalin, gabapentin, and acetaminophen in the treatment of PDPH in patients undergoing spinal anesthesia. Patients received the drug for three days every 8 h. The results showed that the VAS score in the

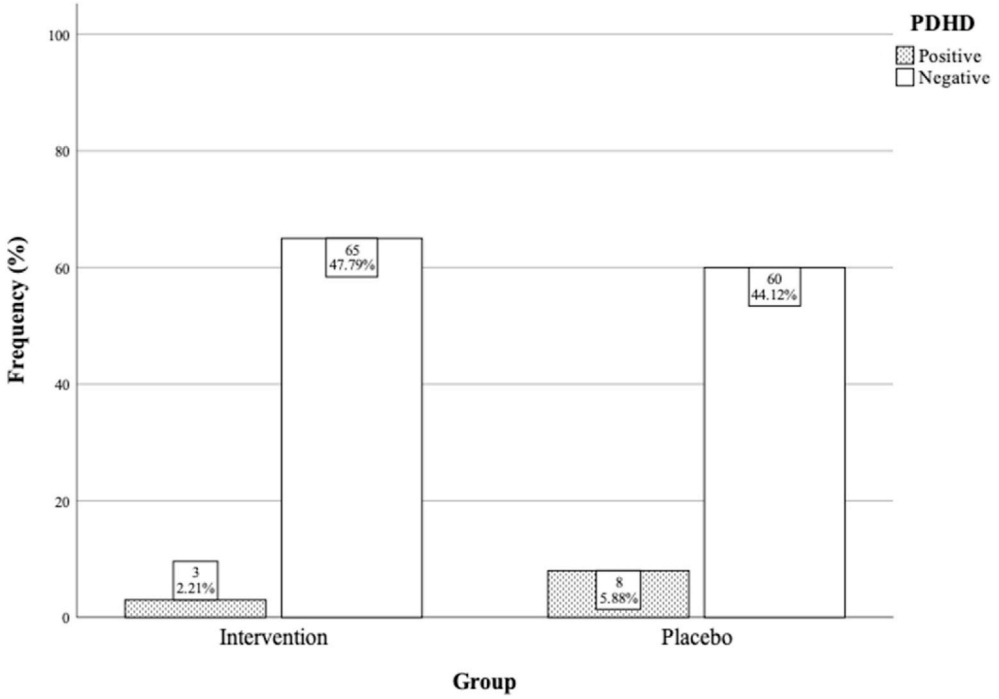

Fig. 2. Frequency of PDHD among the studied patients.

pregabalin group was significantly lower than the other two groups 24, 48, 72 h after the study. Also, no side effects were observed in this study, which is consistent with the results of the present study [27].

The most important limitations of the present study included a low sample size, which may limit the generalizability of the Results, therefore, it is advised to carry out a relevant study on patients with larger sample size.

5. Conclusion

The Results of the current study showed that pregabalin in patients undergoing elective cesarean section can have a preventive effect on the severity and incidence of PDPH. It is suggested that to investigate patients' pain daily in future studies. It is also recommended to compare the effects of other NSAIDs with pregabalin in a clinical trial.

Declaration of competing InterestCOI

None.

Sources of funding

None.

Ethical approval

This study has been approved by the Ethics Committee of Urmia University of Medical Sciences under the Ethics code of IR.UMSU.REC. 1398.341. The study protocol has been registered in the Iranian Registry of Clinical Trials (IRCTID: IRCT20170516033992N4). Written and oral consent was obtained from all participants in the study. Participants were assured that their information will remain confidential. The CONSORT checklist was used to report the study.

Consent

Approved.

Author contribution

Dr. Tohid Karami and Hadi Hoshyar: conceptualized and designed the study, drafted the initial manuscript, and reviewed and revised the manuscript.

Amin Farid Jafari, and Hadi Hoshyar: Designed the data collection instruments, collected data, carried out the initial analyses, and reviewed and revised the manuscript.

Registration of research studies

1.Name of the registry: Iranian Registry of Clinical Trials (IRCT)
2.Unique Identifying number or registration ID: IRCT20170516033992N4
3.Hyperlink to your specific registration (must be publicly accessible and will be checked): https://en.irct.ir/trial/52261

Guarantor

Tohid Karami.

Provenance and peer review

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