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Original Article

The effect of intravenous propofol on the incidence of post-dural puncture headache following spinal anesthesia in cesarean section

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Abstract

Introduction: Post Dural puncture headache is still a common complication among young women undergone cesarean section, although use of small size spinal needles reduced its prevalence. Several methods have been suggested for prevention and treatment of this side effect; such as complete bed rest, hydration, non-opioid analgesics, caffeine, codeine, which none of them proved to be totally effective. The last option would be epidural blood patch, if headache persist. The aim of this study was evaluation the efficacy of intravenous propofol on post dural puncture headache incidence after cesarean section.

Methods: In a randomized clinical trial 120 patients aged 18-45 years old in American Society of Anesthesiologist (ASA) class I or II, who had no history of headache, analgesic consumption, substance abuse and drug addiction, candidate for elective cesarean section, were randomly assigned into intervention (propofol) and control groups. The anesthesia method for both groups was precisely the same. After spinal anesthesia in the first group 30µg/kg/min of intravenous propofol have been infused slowly. Then at 1, 6, 18, 24 hours and 2nd to 7th days after surgery, anesthesiologist asked groups for presence or absence of headache. The data analyzed with SPSS 16.0 software.

Results: Headache incidence rate in the group who receiving propofol was significantly reduced (P.V=0.001).

Conclusion: This study showed that 30µg/kg/min of intravenous propofol caused reduced the incidence of post spinal headache in young women undergone elective cesarean section.

Introduction

Spinal anesthesia has numerous advantages such as elimination of the risks of general anesthesia, shortening the patient's hospitalization, and controlling postoperative pain (1, 2). This method is possible to be used in many kinds of surgeries. In common surgeries like cesarean, owing to reducing intubation, bleeding, and aspiration, it can decrease the mortality rate by 1/16 compared with general anesthesia and is considered a less risky procedure. Despite these advantages, spinal anesthesia has side effects like acute postoperative headache, mainly due to the puncture of dura and pressure reduction of cerebrospinal fluid, with an incidence rate of approximately 1-50%. Generally, the symptoms of this lesion occur few hours after the puncture of dura and continue to seven days.

Since young age and female gender are the risk factors in post-dural puncture headache (PDPH), this lesion is more prevalent among the pregnant women undergoing spinal anesthesia due to vaginal delivery or cesarean section. Because of the tendency for shorter hospitalization after cesarean, it may recur after discharge from hospital or it may postpone the patient's discharge from the hospital (3). Two interpretations have been expressed for PDPH, none of which is certain. One is the loss of cerebrospinal fluid (CSF) within dura which leads to the stretching of pain-sensitive structures within the skull, and the other is dilation of cerebral arteries due to initial compensation of reduced intrahepatic cholestasis of ***pregnancy*** (ICP) and loss of CSF (1).

Artemin is a member of glial cell line-derived neurotrophic factors, which is a vessel-derived growth factor regulating the migration of sympathetic neuroblasts and sympathetic innervation targeting. Recent evidence supports the role of Artemin in cold-oriented and inflammatory pain. There is a functional interaction between Artemin, sympathetic regulation, and catechol-aminergic transmission in the nerves of cranial dura, which may provide the ground for the incidence of PDPH (2). The post-dural puncture headache is usually generalized and is sometimes felt at the back of the head. It is intensified while sitting and dwindled while sleeping, and is occasionally followed by diplopia. Diplopia occurs as a result of stretching of

the sixth cranial nerve. Acute tinnitus and hearing loss may also occur (1).

Some risk factors increasing the incidence of PDPH include pregnancy, female gender, younger age, more frequency of puncture, larger size needle, lower body mass index (BMI), lack of smoking, higher height, history of migraine headache, using catheter for continuous spinal anesthesia, and needle bevel not parallel with neuraxial longitudinal axis (2).

Cerebrovascular vasodilation is the major cause of migraine, and there are a lot of data showing propofol involvement in migraine (5). Further, sub-hypnotic doses of propofol affect the central pains not neuropathic pains; for example, in chronic intractable headaches, maximum 400 mg propofol is required every 3-4 minutes. Given the similar mechanism of migraine headache and PDPH, propofol was selected to be analyzed in the current study. The major complications of propofol are hypotension and apnea, which are rarely seen in sub-anesthetic doses. The less common side effects include rash, arrhythmia, and bradycardia (6).

The common treatments of PDHP often reduce the pain insufficiently, and treatment-resistant or untreated PDPH may reduce the efficiency of a person's life and lead to frequent hospitalization (4). It seems that none of the treatments is ideal. Considering the psychological problems and lack of a definitive prevention method for this headache, the present study was aimed to determine the effect of intravenous propofol on the incidence of post-dural puncture headache following spinal anesthesia in cesarean section. There is not adequate evidence to support the treatment of PDPH with propofol and the current ambiguities require a more comprehensive analysis of the potential effects of propofol.

Materials and methods

All pregnant women with homogenous obstetric indications and demographic characteristics referring to Imam Reza hospital –Kermanshah for elective cesarean in the first two months of 2014 were included in this study in the case of fulfilling the required qualifications and signing the informed consent. The samples were selected through convenient sampling. The inclusion criteria consisted of ASA CLASS I and II, age range of 18-45, BMI of 23-27, and height of 160-170. The exclusion criteria, however, comprised of history of headache, history of using analgesics, drug and tobacco addiction, presence of cardiac, respiratory and mental diseases, diabetes, other diseases requiring therapeutical measures (e.g. preeclampsia), patients with more than one attempt for needle insertion into dura, and patients with more than 1 Lit (20%) bleeding during surgery (6).

There was no similar study performed based on the investigations. The sample size in each group was calculated according to the statistical computations as well as the results of pilot study conducted prior to the main study. Assuming the improvement ratio of 70% and 90% in both groups and according to the sample size calculation formula for comparison of both ratios, with 95% confidence and 80% power, a total of 60 samples were calculated to be included in each group.

A total of 120 patients, homogenized in terms of demographic variables, were randomly assigned to an intervention group (propofol) and a control (no drug administration) group. The study procedures were explained to the patients and informed consent was taken from them. Both groups were given ringer solution as a compensatory volume. The patients were then placed in a sitting position and their skin was prepared with 10% Betadine, and under sterile conditions 2 cc 2% lidocaine was injected to anesthetize the skin and subcutaneous tissue. Using 25 G Quincke spinal needle once at L3-L4 parallel with spinal cord fibers and penetrating into dura, the cerebrospinal fluid was extracted and 2.8 cc 0.5% hyperbaric bupivacaine was injected into spinal space and the needle was extracted. The skin was dressed and the patient was placed in the lying position. Anesthesia was confirmed at T4 dermatome. Then, the liquid deficit was administered. For one mL bleeding, 3 mL ringer solution was injected and in the case of abnormal bleeding more than 1 Lit (20%), the patient was excluded from the study. Skin was dressed and the patient was placed in sleeping position. Anesthesia was confirmed in T4 dermatome. Then, liquid deficit was administered. For one mL bleeding, 3 mL ringer liquid was injected and in the case of abnormal bleeding over 1 Lit (20%), the patient was excluded from the study. In the case blood pressure drop more than 30% of primary amount, single or repeated dose of 5 mg intravenous ephedrine was used to maintain a hemodynamic condition.

In the first group, propofol infusion (30 30μg/kg/min) was administered by a pump through green angiocath after extracting the infant. In the control group, however, propofol was not administered. The BP, PR, RR and ECG monitoring as well as consciousness level of patient were evaluated according to responses to verbal orders of the researcher. The headache severity of the patients was measured after surgery by a second anesthesiologist immediately after entering recovery 1, 6, 12, 18, and 24 hours after discharge from operation room. The patients were under control for seven days after surgery with regard to the presence and severity of headache. The patients were given the visual analogue scale (VAS) according to which they reported the onset of headache, time of final pain, and severity and time of pain relief. The follow-up was performed at hospital as visits by the physician and by phone after discharge from hospital. The side effects of propofol were taken into account and recorded in the case of occurrence.

To evaluate the pain severity according to VAS, a figure >3 out of 10 was determined as the border of pain and treatment. The following measures were taken to treat the pain: 1) bed rest, 2) using liquids more than the daily need, 3) using caffeinated drinks, 4) use of first-line analgesics in this study, including oral acetaminophen, 5) use of non-steroidal anti-inflammatory analgesics, and 6) use of theophylline in the case of lack of response to the above-mentioned measures. The obtained data were statistically analyzed by SPSS-16 software using U-Mann-Whitney test for comparison of pain severity in the two groups, t-test or U-Mann-Whitney for comparison of pain duration, and chi-square for comparison of the side effects.

Results

The results showed no significant difference between groups in terms of demographic variables such as height, weight, age, surgery duration, duration of anesthetic block following spinal anesthesia, and education (Table 1).

Table 1. Comparison of mean and percentage of the patients' characteristics in both groups

Mean	Propofol group	Control group	P-value
Age	30.5±6.6	31.68±7.7	0.360
BMI	25.6	26	0.3
Height	166.3	164/6	0.4
Gravidity	2.1±1.1	2.2±1.1	0.739
Surgery duration	65±10	62±10	0.580
Duration of block after anesthesia	2H±20min	2H±20min	0.1
≤Diploma	80%	83.4%	0.664

From among 60 patients receiving propofol, only 2 cases were found to have headache; whereas from 60 patients in control group, 18 cases were reported to have headache. The incidence of headache in propofol group was 3.3% compared with 30% in control group, indicating a statistically significant difference (p=0.001) (Table 2).

Table 2. Comparison of headache incidence in both groups

Headache	Group		Total
	Control	Propofol	
Yes	18 30%	2 3.3%	20 16.7%
No	42 70%	58 96.7%	100 83.3%
Total	60 100%	60 100%	120 100%

The severity of headache in propofol group in the first and sixth hours after surgery was reduced significantly compared with control group in terms of both frequency and severity. With regard to headache severity, the comparison of two patients in propofol group showed that VAS in one of them was 0.4 and in the other was 0.3, while VAS in control group was observed to range from 0.3-0.8.

The incidence of nausea, diplopia, and tinnitus was the secondary finding of the study. The incidence rates of nausea in propofol and control groups were 3.3% and 38.3%, respectively, which showed a significant difference (p=0.001). The incidence of diplopia in propofol group was found to be 1.7% compared with 10% in control group, showing no significant difference between groups (p=0.051). The incidence of tinnitus in control group was 1.7%, while no tinnitus was observed in propofol group, indicating no significant difference (p=0.315). Regarding education, 2 out of 42 samples under diploma in propofol group suffered from headache. From 46 samples under diploma in control group, however, 18 samples suffered from headache and from 32 patients over diploma, none had headache.

Discussion

The findings of this study showed that 30 µg/kg/min propofol could reduce the incidence of headache after spinal anesthesia in the pregnant women candidate for elective cesarean. Numerous studies have been done to analyze the effect of needle type, needle penetration technic, hydration, bed rest, and various drugs on decreasing the incidence of headache. For example, with development of needles with lower diameter as well as manufacturing of Sprotte needle, the severity and incidence of PDPH have reduced (2, 7).

A study carried out on 518 pregnant women showed that the incidence of PDPH was declined with an increase in BMI (11). Another interesting finding indicated a significant reduction in the incidence of PDPH in the smokers in comparison with non-smokers (2). Prophylactic intrathecal administration of saline (5 cc) before administration of hypertonic bupivacaine has been used as a simple strategy to reduce PDPH in the patients undergoing cesarean section (12). Catheterization after accidental dural puncture (ADP) prevents PDPH (13). Prophylactic epidural morphine (3 mg) after anesthesia and daily administration of epidural morphine (3 mg) afterwards were reported to reduce PDPH from 48% to 12% (13). Also, daily consumption of 2.5 mg frovatriptan for five days decreased the incidence of PDPH (14).

In a study, 200 mg intravenous hydrocortisone as loading dose and 100 mg every eight hours were used for two days after surgery for treatment of the headache following spinal anesthesia, which was found to be effective (3). Dexamethasone is often used for the treatment of the headache with various origins (3, 15). A study compared aminophylline and dexamethasone in the treatment of PDPH and showed that aminophylline (1.5mg/kg) in combination with dexamethasone (0.1 mg/kg) significantly reduced PDPH compared to the groups receiving only one medication or a placebo, with least requirement for analgesics (19).

Another study examined the effect of theophylline on PDPH treatment and revealed that headache was reduced more in 6 patients taking oral theophylline than in 5 patients receiving no theophylline from among 11 patients with PDPH (17). The use of ACTH or its

analogues (cosyntropin) for treatment of PDPH has been studied in several cases. Cosyntropin (1 mg) was administered during 5 minutes and PDPH was reduced about 70% (VAS was reduced from 10 to 3 during 6 hours) (8). When drug therapy is failed and PDPH symptoms are remained or intensified, the management of PDPH is directed toward aggressive actions like epidural blood patch (EBP), which is still the treatment of choice for PDPH and has a high success and low side effects. Studies have shown that 1-1.5 Lit sterile saline over the first 24 hours after puncture, 35 cc/h for 24-48 h or after the incidence of headache, single bolus dose of saline (30 cc) in epidural space after the occurrence of headache or 10-12- cc saline as bolus through caudal epidural space can reduce headache (1). Fibrin glue, a biologic glue with known fibrinogen and thrombin, is used in tissues binding them together (2). Surgery is the last choice of treatment for PDPH; however, the puncture is sutured preferably under microscopic surgery. The leakage site of CSF should be determined before suture by techniques such as magnetic resonance, delayed CT myelography, and dynamic CT myelography (2, 16).

Many studies have assessed the effect of various drugs like cosyntropin (ACTH), morphine, aminophylline, theophylline, serotonins, dexamethasone, fentanyl, indomethacin, acetaminophen, sumatriptan, gabapentin, methergine, and antidepressants such as mirtazapine on PDPH treatment, all with side effects. Propofol is an excellent drug for the induction of anesthesia in pregnant women owing to its short activity, rapid metabolism, lack of active metabolism, and anti-nausea effect. Propofol directly affects the cerebrovascular muscles by reducing CMR and causes cerebrovascular vasoconstriction (6). Propofol (20-30 mg per 3-4 minutes and maximum 400 mg) can be used for chronic recurrent headaches (20).

Migraine is caused by cerebrovascular vasodilation, and there is ample information to show propofol is involved in the treatment of migraine (3, 21). In a study, propofol was reported to decrease the migraine-oriented pain faster than dexamethasone. The harmful side effects were not observed in any of these two drugs. Propofol is currently used as a safe and effective medication for the treatment of migraine in emergency departments (3).

In a similar study carried out on the patients with migraine, propofol was administered intravenously. Headache was dramatically eliminated in all patients. The associated problems such as nausea, vomiting, photophobia and phonophobia were eliminated in all patients. Also, tachycardia and bradycardia were not observed in any of the patients (18). Hypotension and apnea are major side effects of propofol, which are rarely seen with its sub-anesthetic doses. The less common complications of propofol are rash, arrhythmia, and bradycardia (6). The secretion level of propofol in human breast milk is not equal to that of the infant's exposure to it (10). In a study conducted on 21 cesarean patients, 2.5 mg/kg propofol was used for induction of anesthesia. The researchers measured the concentration of propofol in milk and concluded that propofol level was trivial after 2 h, so propofol could be administered with certainty owing to its bioavailability, low oral consumption, and rapid metabolism in infants (10). In general, there is little evidence supporting the treatment of PDPH with propofol, and the existing vague issues need a more comprehensive examination to find the potential effects of propofol.

The treatment-resistant or untreated PDPH may dwindle the performance of a person's life and lead to repeated hospitalization (4). Considering the occurrence of mental problems and lack of a definitive prevention method for this kind of headache as well as the results of previous studies about the effect of propofol on the treatment of benign and migraine headaches, the present study was carried out to evaluate the impact of intravenous propofol on the incidence of post-dural puncture headache following spinal anesthesia in cesarean section (7).

In this study from the 60 patients taking propofol, only two patients suffered from headache for two hours, which was lower than that of control group. From 60 patients in control group, however, 18 patients had headache. The incidence of headache in control and propofol groups were reported to be 30% and 3.3%, respectively. The number of patients and severity of headache in propofol group were reduced significantly in propofol group 6 hours after surgery compared to control group. Headache was observed in the second and third days in control group. The findings of this study indicated that propofol reduced both the severity and duration of headache and duration of headache relief from 18 to 2 hours. Moreover, the occurrence of nausea and vomiting was significantly declined in propofol group; i.e. from 38.3% in control group to 3.3% in propofol group. The incidence of diplopia in propofol and control groups were found to be 1.7% and 10%, respectively. Tinnitus in control group was reported to be 1.7%; whereas, no tinnitus was seen in propofol group. Furthermore, the side effects of propofol were taken into consideration in this study and no complications were observed.

Conclusion

The results of the present study, in addition to determining the efficacy of propofol in reducing headache following spinal anesthesia, can be a basis for comparison of the effects of this drug and other drugs on this headache. Future studies are suggested to employ a larger sample size to more accurately evaluate the side effects of this medication. Based on the findings of this study propofol can be used for the treatment of PDHP.

Few studies have assessed the effect of propofol **(**2**,** 6-Diisopropylphenol) on PDPH. This study showed that propofol, in addition to reducing headache significantly, decreased the severity of headache and duration of headache relief. The incidence of nausea in propofol group was significantly declined. However, diplopia and tinnitus were not significantly reduced. Regarding the effect of propofol, no definite conclusion can be drawn, so a larger population is needed to analyze this issue given the low incidence of the side effects.

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