Original Article

Effect of intrathecal fentanyl on the incidence, severity, and duration of postdural puncture headache in parturients undergoing caesarean section: A randomised controlled trial

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ABSTRACT

Background and Aims: Postdural puncture headache (PDPH) is a side effect of spinal anaesthesia (SA). This study was conducted to investigate the effect of intrathecal fentanyl on the incidence, severity, and duration of PDPH. **Methods:** This was a prospective randomised controlled study including 220 parturients, who underwent Caesarean section (CS). They were divided into two groups for administration of SA with bupivacaine (bupivacaine group [B0], n = 111) or bupivacaine with fentanyl (bupivacaine fentanyl group [BF], n = 109). Haemodynamics, quality of anaesthesia, maternal side effects, and postoperative analgesia were noted. The neonatal Apgar score was recorded. The patients were followed up for 14 days after CS for the occurrence of PDPH, and its severity and duration. The collected data were statistically analysed, using the Statistical Package for the Social Sciences software version 25. **Results:** Regarding haemodynamics, heart rate increased at 5 min post-induction and blood pressure decreased at 2min post-induction in both groups. Excellent intraoperative anaesthesia was obtained in 91.7% and 79.3% of cases in groups BF and B0, respectively ($P < 0.01$). Longer duration of postoperative analgesia was present in the BF group as compared to the B0 group ($P < 0.001$). The incidence of PDPH decreased in the BF group in a non-significant manner, whereas its severity and duration increased significantly in the B0 group. **Conclusion:** Although the addition of intrathecal fentanyl to bupivacaine for SA in CS patients did not reduce the incidence of PDPH significantly, its severity and duration decreased significantly.

Key words: Caeserean section (CS), intrathecal fentanyl, postdural puncture headache

INTRODUCTION

Spinal anaesthesia (SA) is the preferred anaesthetic technique for Caeserean section (CS) due to its advantages over epidural or general anaesthesia (GA). It is simple to perform, economical, and produces rapid onset of anaesthesia and complete muscle relaxation. However, it can cause unwanted complications. Post dural puncture headache (PDPH) is a common problem following SA in parturients.[1] PDPH is not a life-threatening condition, but it can lead to severe limitation of daily activities. Moreover, it may cause catastrophic sequelae, such as subdural hematoma and seizures, when severe. Persistently low cerebrospinal fluid (CSF) pressure can impose traction and rupture subdural blood vessels, leading to the formation of a subdural hematoma.[2] With this background, emphasis on its prevention by optimising the controllable factors such as the anaesthetic technique, number of dural puncture attempts, needle size, and needle tip design, is important.[1]

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Clinical research has shown that the use of smaller-gauge needles, particularly of the pencil-point design, are associated with a lower risk of PDPH than cutting-point needle tips.[3,4] However, the cost and lack of availability of the pencil-point needles make it difficult to be routinely used in parturients, especially in low-income countries. Neuraxial narcotics were found to reduce the incidence of PDPH after accidental dural puncture (ADP) during epidural anaesthesia.[5-7] In addition, Martlew conducted a 9-year prospective audit and found that spinal opioids might prevent PDPH.[8] With this background, we hypothesised that the addition of intrathecal (IT) fentanyl to local anaesthetics may reduce the incidence, severity, and/or duration of PDPH in patients undergoing CS under SA. Therefore, it can be a cost-effective alternative to the expensive pencil-point needles in case of limited resources. The primary outcome was defined as the incidence of PDPH, while the secondary outcomes were the severity and duration of PDPH in the two groups.

METHODS

This prospective, double-blinded randomised study was performed during August 2018 to September 2019, after obtaining approval from the ethical committee of the Department of Anaesthesia and Intensive care and written informed consent from all parturients. This study enrolled 252 obstetric patients, aged 18-40 years, with American Society of Anesthesiologists (ASA) grade I or II, and undergoing CS under SA. They were randomised equally into two groups according to computer-generated numbers (n = 126, each). Group B0 patients were administered IT hyperbaric bupivacaine 0.5% (2.5 ml) with 0.5 ml normal saline. Group BF patients were administered IT hyperbaric bupivacaine 0.5% (2.5 ml) with 25 μg fentanyl (0.5 ml).

Patients with contraindications to regional anaesthesia, history of migraine, chronic headache, psychiatric illness, neurological dysfunction, or complicated pregnancy, were excluded from the study. Parturients who required more than three attempts for lumbar puncture (LP) were also excluded.

In the operating theater, heart rate (HR), electrocardiogram, arterial oxygen saturation (SpO_2), and non-invasive blood pressure monitoring were performed. The baseline values of these parameters were recorded. A LP was performed in the L3-4 or L4-5 intervertebral space using a 25-G Quincke spinal needle with the bevel directed parallel to the dural fibers, with the parturients in the sitting position. After free flow of CSF, IT administration of drugs was performed according to the study protocol.

Haemodynamics (HR, systolic blood pressure [SBP], and diastolic blood pressure [DBP]) and SpO_2 were monitored throughout the surgery. Their values were recorded at the following time points: baseline, 2 min post-induction, and 5, 10, 15, 20, 30, 40, and 50 min after anaesthesia.

Surgical anaesthesia was graded as "excellent" if there were no complaints from the patients, "good" if there was complaint of pain that was relieved by small doses of IV opioids, and "poor" if more than one dose of opioids or other medications (e.g., propofol, midazolam, etc) and/or rescue general anaesthesia (GA) had to be administered.[9] Maternal side effects, such as hypotension, bradycardia, respiratory depression, nausea and vomiting, shivering, and pruritus were noted and appropriately treated. A fall in SBP ≥30% of the baseline value was considered hypotension and treated with IV fluid boluses and IV ephedrine. HR <60 beats/min was defined as bradycardia and managed with IV atropine 0.01 mg/kg. The neonatal Apgar score was assessed by a paediatrician at 1 and 5 min after delivery. The duration of effective analgesia was measured and recorded from the time of SA until the first request for analgesics by the patient.

The parturients were monitored for PDPH during the postoperative period until discharge from the hospital. On the 7th postoperative day, all patients received phone calls from an anesthetist, who was unaware of the anesthetic medications used, and they were asked about the occurrence of headache. They were then contacted after 1 week to evaluate any signs or symptoms of a delayed-onset headache. A PDPH was defined as a postural headache within 5 days after LP, which is aggravated in the upright position and relieved in the supine position, along with at least one accompanying symptom such as nausea, photophobia, hypoacusis, tinnitus, or neck stiffness.[10] Patients with headache were questioned about onset, duration, and severity. Severity was evaluated using the verbal rating scale (VRS) rated from 0-10, where 0 = no pain and 10 = worst imaginable pain. They were also asked regarding the presence of any associated symptoms such as nausea, vomiting, vertigo, blurred vision, tinnitus, or neck rigidity.

The collected data were coded, tabulated, and statistically analysed using the Statistical Package for the Social Sciences (SPSS) software version 25. Before the study, the number of patients required in each group was determined after a power calculation according to data obtained from a pilot study. A total of 35 patients were enrolled in each group, and the proportion of headache was assessed in each group. In groups B0 and BF, 9 (25.7%) and 4 (11.4%) patients developed headache, respectively. A sample size of 126 patients in each group was determined to provide 80% power for Fisher' s exact test at the level of 0.05 significance using G Power 3.1 9.2 software. Descriptive statistics were performed for parametric quantitative data by mean ± standard deviation. Analyses were performed for parametric quantitative data between the two groups using independent samples t-test, and twice within the same group using paired samples t-test. Analyses were performed for qualitative data using the Chi square test or Fisher's exact test. The level of significance was set at $P < 0.05$.

RESULTS

In this study, 252 pregnant patients were recruited, and data were analysed from 111 and 109 parturients in groups B0 and BF, respectively [Figure 1]. Both groups were comparable with respect to age, weight, height, body mass index (BMI), ASA grade, and approach for SA (midline vs. paramedian). There was no significant difference in the number of attempts before successful LP between the two groups [Table 1].

The baseline values of haemodynamic parameters (HR, SBP, and DBP) were comparable between the groups [Figures 2 and 3]. HR values increased significantly at 5 min after anaesthetic induction as compared to the baseline values in both groups [Figure 2]. SBP and DBP decreased significantly at 2 min post-induction in both groups as compared to the baseline values [Figure 3]. There were no significant differences between the groups or within the same group regarding SpO_2 at any point during the operation. No parturients in either group developed respiratory depression.

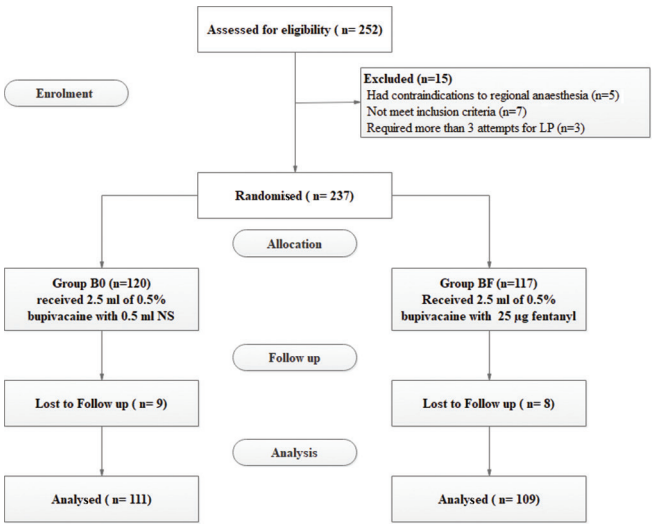

Figure 1: Flow chart of the study groups

There was a significant improvement in surgical anaesthesia in the BF group as compared to the B0 group ($P < 0.01$) [Table 2]. The duration of effective analgesia was longer in the BF group than that of group B0 ($P < 0.001$) [Table 2].

The most common maternal side effect encountered in group B0 was intraoperative nausea and vomiting (19.8%). The most frequent side effect in group BF was pruritus (36.7%). Other adverse events were similar in both groups [Table 2]. The neonatal Apgar score did not differ significantly at 1 min and 5 min post-delivery in both groups [Table 2].

PDPH developed in 19.8% and 12.8% of parturients in groups B0 and BF, respectively. This difference was not

Table 1: Patient characteristics and operative data in the study groups

Variables	Group B0 (*n*=111)	Group BF (*n*=109)	*P*
Age (years)	29±6.4	29.5±6.5	0.586
Weight (Kg)	79.7±12.8	80.3±13.7	0.725
Height (cm)	161.3±4.7	161.6±4.6	0.604
Body Mass Index (BMI) (Kg/m^2)	30.8±5.5	30.9±6.1	0.880
ASA grade: I/II	90/21	85/24	0.569
Number of dural puncture attempts: 1st, 2nd, 3rd attempt.	75/28/8	70/31/8	0.858
Approach: Midline/Paramedian	40/71	46/63	0.349

Data are expressed as mean±SD or numbers.

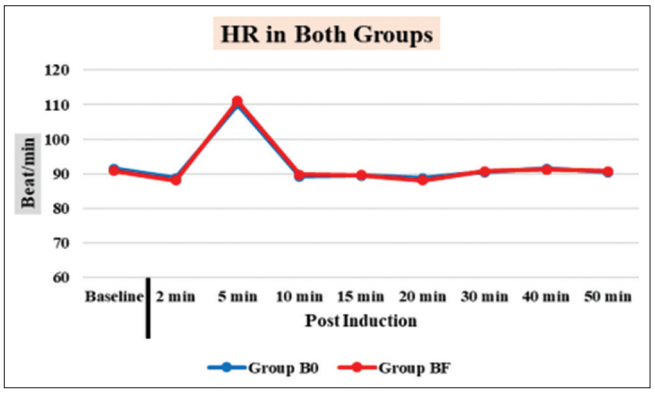

Figure 2: Heart rate changes (bpm) in study groups

Table 2: Clinical characteristics in the study groups

	Group B0 (*n*=111)	Group BF (*n*=109)	*P*
Quality of anaesthesia:	88/15/8#	100/9/0#	0.006
(excellent/good/poor)	(79.3%, 13.5%, 7.2%)	(91.7%, 8.3%, 0%)	
Duration of effective analgesia (min.)	149.5±6.2#	259.2±5.6#	<0.001
Maternal side effects:			
Hypotension	20	18	0.768
Bradycardia	3	2	1
Pruritus	0	40 #	<0.001
Shivering	20	22	0.683
Nausea and Vomiting	22#	4#	<0.001
Neonatal Apgar Score:			
At 1 min.	7-9 (7.9±0.6)	6-8 (7.8±0.9)	0.332
At 5 min.	7-10 (8.6±0.9)	7-10 (8.7±0.8)	0.385

Data are presented as mean±SD, numbers or percentages. #Significant difference between the two groups.

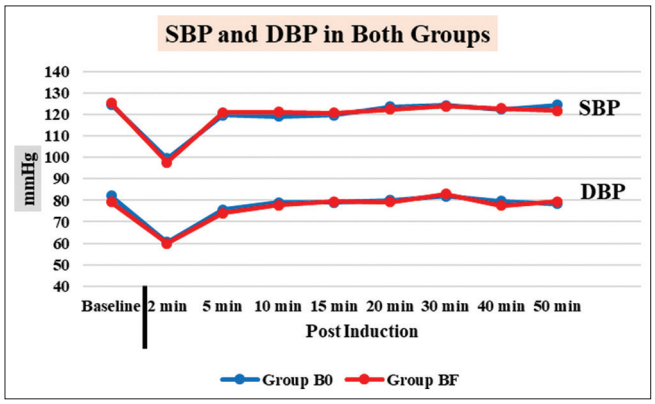

Figure 3: SBP and DBP in study groups. SBP- Systolic blood pressure; DBP-Diastolic blood pressure

statistically significant [Table 3]. The parturients who reported PDPH were managed conservatively with bed rest, hydration, simple analgesics, or pregabalin tablets. The severity and duration of PDPH differed significantly between the 2 groups [Table 3]. In the B0 group, the PDPH was more severe, indicated by higher VRS, and lasted for a longer duration as compared to group BF. Associated symptoms such as nausea and vomiting or neck rigidity were similar in both groups [Table 3].

DISCUSSION

PDPH is one of the most painful complications of neuraxial anaesthesia. Parturients are at a higher risk of developing PDPH due to the widespread use of neuraxial anaesthesia. Moreover, female sex, young age, and pregnancy, are considered unmodifiable risk factors for post-spinal headache.[11,12] Therefore, we chose the obstetric population for our study.

PDPH occurs due to intentional dural puncture or ADP during neuraxial anaesthesia. Neuraxial narcotics were found to reduce the incidence of PDPH after SA and in cases of ADP during epidural anaesthesia.[5-7,12] Therefore, we hypothesised that the addition of IT fentanyl to local anaesthetics during SA and use of the traditional cutting needle could decrease the incidence of PDPH.

Our research demonstrated a low frequency of PDPH with IT fentanyl as compared to the (B0) group, but the difference was insignificant. However, it significantly reduced the severity and duration of headache. Associated symptoms such as vertigo, tinnitus, blurred vision, and photophobia, that are indicators of severe PDPH according to the Corbey severity grading,[13] were not reported in either group. This was due to the use of a fine 25-G spinal needle. The factors that might influence the incidence of PDPH, such as age, BMI, number of dural puncture attempts, or approach for LP[14] were comparable between both groups. The effect of ambulation on the incidence of PDPH was not studied, as bed rest was ineffective in preventing PDPH.[15]

Numerous studies have investigated the effect of neuraxial opioids in reducing the incidence of PDPH after SA or ADP during epidural block with conflicting results. Consistent with our findings, two early studies demonstrated the beneficial effect of adding an IT opioid to prevent PDPH after SA.[8,16] Johnson *et al*.[16] performed a retrospective analysis of parturients who received SA, and demonstrated a 50% reduction in the incidence of post-spinal headache when fentanyl was added to the local anaesthetic. Martlew[8] found that IT diamorphine decreased the incidence of PDPH significantly after SA. Additionally, the incidence of PDPH in patients who received IT fentanyl was 0.88%, which was lesser than that in patients with no IT opioid with SA (1.4%). However, this difference was not significant. Contrary

Table 3: Postdural Puncture Headache (PDPH) in the study groups

Variable	Group B0 (*n*=111)	Group BF (*n*=109)	*P*
Occurrence of PDPH (Yes/No)	22/89	14/95	0.162
Incidence	19.8%	12.8%	
Onset			
3rd day	13	9	NS.
4th day	6	4	
5th day	3	1	
Duration (days)	5.5±1.1#	3±0.8#	<0.001
Severity of PDPH median (IQR)	7 (6-8)#	4 (3-5)#	<0.001
Associated symptoms:			
nausea and vomiting	2	2	NS
vertigo	0	0	
neck stiffness	10	8	

Data are presented as mean±SD, numbers, or percentages. #Significant difference between the two groups. NS: nonsignificant.

to our findings, Devcic *et al*. did not report a reduction in PDPH due to IT fentanyl. This was due to their smaller sample size.[17] In a small prospective study,[18] subarachnoid morphine did not decrease the incidence or severity of PDPH after SA. This was also attributed to the small sample size and short follow-up period.

Neuraxial narcotics have been successfully used after ADP to prevent PDPH.[5-7] Cohen *et al*.[7] found 0% incidence of PDPH with prolonged (>24 h) IT catheterisation and the use of postoperative IT analgesia. Additionally, Al-Metwalli used epidural morphine vs. saline, after ADP and subsequent epidural analgesia in a randomised double-blinded trial; the incidence of PDPH was 48% and 12% in the saline and morphine groups respectively.[5] Cesur *et al*.[6] reported epidural postoperative analgesia with morphine boluses for 36-72 h after ADP in caesarean delivery. A lower incidence of PDPH was found in the study group (7.1%) than that of the control group (58%). There have been two reports of successful use of epidural morphine in the treatment of PDPH after ADP in non-obstetric patients.[19,20]

In contrast, other studies did not prove the protective effect of neuraxial opioids for the prevention of PDPH after ADP with epidural analgesia.[21,22] Brinser *et al*.[22] depended on retrospective medical records. Moreover, their sample size was small, and the mode of delivery was significantly different between both groups i.e., incidence of vaginal delivery was 50% in the morphine group vs. 2% in the group not administered morphine. After dural puncture, pushing in the second stage was an additional risk factor for PDPH as compared to those with CS.[23]

We reported better quality of intraoperative anaesthesia and longer duration of postoperative analgesia with IT fentanyl added to bupivacaine in CS, as reported by others.[9,24-26]

Regarding haemodynamics, HR increased significantly at 5-min post-induction when compared to the baseline values in both groups. This increase coincided with oxytocin administration after delivery. The IV oxytocin, administered as a bolus-continuous infusion, similar to our study, causes haemodynamic changes, such as tachycardia or hypotension.[27] The blood pressure decreased significantly at 2-min post-induction in both groups, which might be due to the use of a high dose of bupivacaine. A high dose of bupivacaine is associated with a significant drop in the blood pressure.[28] We administered bupivacaine >10 mg as most obstetricians in our hospital use the technique of exteriorisation of the uterus during closure, which is more stimulating than closure in situ. However, a number of strategies have been used to prevent spinal-induced hypotension, such as rapid crystalloid co-loading, prophylactic vasopressor administration, left uterine displacement, and slight head-up position.

Among the maternal side effects, pruritus occurred in 36.7% of patients in group BF due to IT fentanyl. This was similar to that reported by Lee *et al*.[9] Other researchers found negligible or lower incidence of pruritus (0-15%), because they used smaller doses of IT fentanyl (12.5 μg).[24,29] The incidence of emetic episodes was significantly higher in group B0 than in group BF. Peritoneal traction and manipulation of the intraabdominal organs during CS result in intraoperative visceral pain, and parturients complain of nausea and/or vomiting. The addition of IT fentanyl to the local anaesthetic abolishes this visceral pain and prevents nausea and vomiting.[24] The IT fentanyl did not affect the neonatal Apgar score in our study, as demonstrated in other studies.[24,30]

We plan to conduct a multi-center study on a larger sample size of parturients, including those with a younger age (20-30 years) and lower BMI. Future studies on non-obstetric patients can be performed to confirm our findings.

CONCLUSION

We concluded that the addition of IT fentanyl to bupivacaine for SA in obstetric patients reduced the severity and duration of headache in the affected

mothers, and they were satisfied with their postpartum recovery.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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