A double-blind randomized control trial to compare the effect of varying doses of intrathecal fentanyl on clinical efficacy and side effects in parturients undergoing cesarean section

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Abstract

Background and Aims: It is a common practice to add intrathecal lipophilic opioids to local anesthetics to improve the quality of subarachnoid block. This study was designed to find a dose of intrathecal fentanyl, which can improve the quality of surgical anesthesia with minimal side effects in parturients undergoing cesarean section under spinal anesthesia with intrathecal bupivacaine.

Material and Methods: In a prospective randomized double-blind study, 243 parturients undergoing cesarean section under spinal anesthesia were randomly allocated to receive 10, 15, or 25 µg of intrathecal fentanyl with 10 mg of 0.5% hyperbaric bupivacaine. Patients were assessed for clinical efficacy by measuring pain score, need for rescue analgesia, conversion to general anesthesia, and complaints of inadequacy of surgical anesthesia by the surgeon. The side effects assessed were pruritus, nausea, vomiting, dizziness, and decrease in saturation and respiratory rate. In addition, neonatal APGAR score, patients' hemodynamics, need for vasopressors, onset and duration of sensory, and motor block were measured.

Results: Patients receiving 25 µg of fentanyl had a significantly higher incidence of pruritus, nausea, and dizziness in addition to a significantly prolonged sensory and motor block (P < 0.001). All patients in three groups had adequate surgical anesthesia with no statistically significant difference in the onset of block, quality of surgical anesthesia, pain scores, neonatal APGAR score, hemodynamic variables, and need for vasopressor.

Conclusion: For patients undergoing cesarean section, 10 or 15 µg of intrathecal fentanyl with 10 mg of bupivacaine provided adequate surgical anesthesia and analgesia with minimal side effects.

Keywords: Analgesia, cesarean section, fentanyl dose, pruritus, side effects, spinal anesthesia, surgical anesthesia

Introduction

Bupivacaine is commonly used for subarachnoid block in parturients undergoing cesarean section; however, intrathecal bupivacaine alone may be insufficient to provide complete anesthesia. To improve the quality of subarachnoid block, it is a common practice to add intrathecal opioids. Highly lipophilic short-acting opioids such as fentanyl, when added to local anesthetics improve the quality and duration of anesthesia and analgesia in obstetric population.

Intrathecal fentanyl is, however, associated with side effects such as pruritus, nausea/vomiting, and respiratory depression. The evidence regarding appropriate dose of intrathecal fentanyl is still under investigation. Studies assessing varying doses of intrathecal fentanyl for clinical efficacy did not have sufficient power to detect the differences in secondary outcome variables such as pruritus, respiratory depression, nausea, and vomiting. In the investigators' department, 25 µg of fentanyl is used with bupivacaine for spinal anesthesia during cesarean section. It was observed in one of the quality assurance audit that the incidence of pruritus was 34% among these patients.

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The objectives of this study were to compare 25 µg of intrathecal fentanyl with 10 and 15 µg in parturients undergoing cesarean section under spinal anesthesia with intrathecal bupivacaine to assess: (1) clinical efficacy measured in terms of quality of surgical anesthesia, onset, and duration of block; (2) occurrence of side effects such as pruritus, respiratory depression, nausea, and vomiting in parturients and low APGAR score in the newborns; (3) hemodynamic stability; and (4) requirement of vasopressors.

**Material and Methods**

After approval from the hospital clinical trial unit and ethics review committee, a prospective randomized double-blind study was conducted in 243 full-term pregnant patients with age ranging from 20 to 40 years, having singleton pregnancy, belonging to American Society of Anesthesiologist physical status class I and II, scheduled for elective cesarean section under subarachnoid block. The excluded patients were those with preexisting or pregnancy-induced hypertension, cardiovascular or cerebrovascular disease, neuropathies, body mass index (BMI) >30, contraindication or refusal for subarachnoid block, allergy to any of the drugs used in the study, and neuropathies. Patients fulfilling the inclusion criteria were approached the night before the surgery and a written informed consent was taken. All enrolled patients were instructed on the methods used for sensory and motor assessments. In addition, patients were instructed to score their pain using a numerical rating score from 0 to 10 and mention the occurrence of pruritus and nausea anytime during the stay in the operating room (OR) and recovery room (RR).

All patients fasted for at least 6 h prior to surgery and were premedicated with ranitidine (50 mg) and metoclopramide (10 mg) intravenously, and oral sodium citrate (30 cc) half an hour before surgery. On arrival to the OR, 15 ml/kg of intravenous fluids (lactated Ringer’s solution or normal saline) were infused over 15 min while inducing spinal anesthesia till the surgery was started. Surgery was allowed to proceed if the upper dermatome level of sensory block was at or above T5 and Bromage scale of 1 or above. Time to reach T5 sensory level and onset time of motor block (Bromage scale 1) was noted.

Sensory level was assessed bilaterally along the mid-clavicular line using ice packs. Motor block was assessed based on a modified Bromage scale. Sensory and motor tests were performed every minute after the institution of spinal anesthesia till the surgery was started. Surgery was allowed to proceed if the upper dermatome level of sensory block was at or above T5 and Bromage scale of 1 or above. Time to reach T5 sensory level and onset time of motor block (Bromage scale 1) was noted.

Obstetricians were asked to report if they encountered inadequate relaxation during surgery. Surgical anesthesia was considered “adequate,” when there was no complaint of inadequate relaxation from the obstetricians, no complaint of pain from the patient, and/or need for additional analgesia. Before anesthesia,
parturients were instructed that fetal extraction might be associated with some degree of discomfort. Pain scores were measured at the time of incision and every 15 min thereafter in the OR and RR. However, patients were instructed to report pain score of 4 or more at any point of time. Pain score $\geq 4$ was considered inadequate analgesia/anesthesia and treated with 50 $\mu$g of fentanyl and if the pain was unbearable after three doses of fentanyl, general anesthesia was administered. The need to convert to general anesthesia was noted. Patient’s level of consciousness was measured using scores from 1 to 4 (1: awake and nervous, 2: awake and calm, 3: sleepy and easily arousable, and 4: sleepy and difficult to arouse), every 15 min both in OR and RR.

Occurrence of side effects, such as nausea, vomiting, dizziness, pruritus, decrease in saturation to $<90$, and respiratory rate of $<8$ per minute, was recorded both in the OR and RR. Patients were instructed to report nausea, vomiting, and dizziness. We considered occurrence of one episode of any of these side effects as a positive event irrespective of its multiple occurrence and severity. Any patient who complained of nausea, vomiting, pruritus, and dizziness was assessed every 15 min in the OR and RR and treated according to the hospital protocols. APGAR score of neonates was evaluated at 1 and 5 min, and the number of babies with APGAR score $<7$ was recorded.

Patients were observed in the RR for 2 h. Duration of analgesia was measured from the time of achieving the T5 block to the first request of analgesia. At this time, intravenous opioid infusion was started after a bolus dose of opioid. Recovery of the motor block was considered when the patient was able to bend her knee (Bromage scale 1). The duration of motor block was the time difference between achieving Bromage 1 to regaining Bromage 1.

**Statistical analysis**

Statistical Package for the Social Sciences (SPSS, version 19) was used to analyze the data. Frequencies and percentages were estimated for qualitative characteristics and compared with Chi-square test among groups, while mean and standard deviation (SD) with 95% confidence interval were computed for qualitative observation and compared using one-way analysis of variance (ANOVA) and Bonferroni’s multiple comparison test. $P \leq 0.05$ was considered significant. Sample size was based on the study by Belzarena in which pruritus was observed in $>30\%$ women with higher doses of fentanyl. A sample size of 69 in each group was needed to achieve 80% power ($\alpha = 5\%$) to detect a 20% difference among the groups. We assumed the incidence of pruritus in lower dose (10 $\mu$g) to be 10%. Therefore, a sample size of 207 patients was calculated. It was assumed that the dropout rate would be 15%; therefore, 243 patients (81 in each group) were recruited.

**Results**

This study was conducted from June 1, 2013 to May 31, 2015. A total of 269 patients fulfilling the inclusion criteria were approached; 243 patients agreed to participate. Results for the 243 patients, 81 in each group were analyzed. There was no difference in the demographics variables between the groups [Table 1]. There was no statistically significant difference in the quality of surgical anesthesia between the three groups [Table 2]. However, 3 patients in each of Group 10 and Group 25 complained of pain and were given rescue analgesia, and in 1 patient the surgeon complained of inadequate relaxation. None of the patients in Group 15 complained of pain, but in 3 patients there was complaint of inadequate relaxation by the surgeon [Table 2]. None of the patients in any of the group required conversion to general anesthesia. There was no difference in the level of consciousness of parturients and APGAR score of the neonate at 1 and 5 min among the three groups [Table 2].

There was no significant difference in the mean time of onset of sensory and motor block between the three groups [Table 3]. However, the duration of sensory and motor block was

**Table 1: Comparison of demographic characteristics of patients among groups**

| Variables                  | Group 10 (n=81) | Group 15 (n=81) | Group 25 (n=81) | P   |
|----------------------------|-----------------|-----------------|-----------------|-----|
| Age (years)                | 30.4±4.3        | 28.8±4.4        | 29.7±4.9        | 0.148|
| Height (cm)                | 156.4±6.2       | 158.2±6.0       | 155.9±5.2       | 0.030|
| Weight (kg)                | 74.1±13.7       | 76.9±13.5       | 75.1±14.5       | 0.045|
| BMI (kg/m$^2$)             | 30.2±5.5        | 30.7±5.2        | 30.8±5.1        | 0.802|

Data are expressed as mean±standard deviation and analyzed using ANOVA.

BMI=Body Mass Index

**Table 2: Comparison of surgical anesthesia, level of maternal consciousness, and neonatal APGAR scores among three groups**

| Variables                   | Group 10 (n=81) | Group 15 (n=81) | Group 25 (n=81) | P   |
|-----------------------------|-----------------|-----------------|-----------------|-----|
| Surgical anesthesia         |                 |                 |                 |     |
| Adequate relaxation         | 77 (95.1)       | 78 (96.3)       | 77 (95.1)       | 0.909|
| Intraoperative rescue analgesia | 3 (3.7) | 0 | 3 (3.7) | 0.215|
| Level of consciousness      |                 |                 |                 |     |
| Awake and nervous           | 29 (35.8)       | 25 (30.9)       | 35 (43.2)       | 0.260|
| Awake and clam              | 52 (64.2)       | 56 (69.1)       | 46 (56.8)       | 0.333|
| APGAR score                 |                 |                 |                 |     |
| 1 min                       | 7.9±0.3         | 7.9±0.2         | 7.9±0.4         | 0.681|
| 5 min                       | 8.9±0.2         | 8.9±0.1         | 8.9±0.1         | 0.774|

Data are expressed as n (%) and analyzed using Chi-square test or as mean±standard deviation and analyzed using ANOVA.
significantly longer in Group 25 and Group 15 compared to Group 10 [Table 3].

A significant difference was observed in the occurrence of side effects between the three groups, both in the OR and RR [Table 4]. Nausea, dizziness, and pruritus occurred in significantly more patients in Group 25 in OR. Similarly, more patients in Group 25 complained of nausea and pruritus in RR. However, in the RR significantly higher number of patients in Group 10 had pain scores of >3 as compared to Group 15 and Group 25 [Table 4]. There was no statistically significant difference in the greatest decrease in mean HR and mean SBP in the three groups and in the MAP. Similarly, there was no statistically significant difference in the use of vasopressors between the three groups at different times with overall requirement of vasopressors in 44 (54.3%) patients in Group 10, 34 (42%) in Group 15, and 40 (49.4%) in Group 25.

Discussion

In this study, there was no significant difference in the quality of surgical anesthesia among the three groups. Majority of the patients (95–96%) had excellent surgical anesthesia with all three doses of fentanyl, with only 6 (2.46%) requiring rescue intravenous analgesia and none requiring conversion to general anesthesia. Previous studies have shown significantly higher number of failed blocks in patients receiving intrathecal fentanyl in the doses of 7.5 µg. [5,11] Chu et al. found that all patients receiving 12.5 and 15 µg of intrathecal fentanyl with 0.5% hyperbaric bupivacaine experienced excellent intraoperative and postoperative analgesia contrary to patients receiving 7.5 µg of fentanyl. [5] Furthermore, Goel et al. found that the patients receiving 7.5 µg of fentanyl in combination with low-dose bupivacaine had a significantly higher number of failed blocks (almost 27%) than those receiving 10 or 12.5 µg of fentanyl. [11] Therefore, most of the authors prefer to use doses of intrathecal fentanyl higher than 10 µg. In the present study, the lowest dose of intrathecal fentanyl was 10 µg and there was no difference in the quality of surgical analgesia and anesthesia provided by this dose and the higher doses of fentanyl (15 and 25 µg), which is in accordance with the findings of previous studies. [3,5,9] Therefore, it seems that increasing the dose of intrathecal fentanyl to more than 10 µg does not add to the quality of surgical anesthesia.

The dose of intrathecal opioid added to the local anesthetic is important not only for the quality of surgical anesthesia but also for the onset and duration of the block. [5,11,12] Opioids interrupts pain transmission in the dorsal horn, while local anesthetics block conduction in the motor and sensory nerves. [13-16] Therefore, adding an opioid to the local anesthetic may offer local anesthetic sparing effects and lead to shorter onset time and prolonged duration for sensory block. Parpaglioli et al. found shorter onset time and longer regression time in patients in whom opioid was added to local anesthetics. [13] In our study, the time of achieving sensory block of T5 and motor block was similar in all three groups, indicating that it is the presence of opioid and not the dose of opioid that affects the onset of block. However, the duration of motor and sensory block increased with the increase in dose of fentanyl. This has also been observed in other studies, indicating possible synergistic effect of increasing dose of opioid with local anesthetic, prolonging the duration of the block. [11,13]

The side effects observed in the study were pruritus, nausea, and vomiting. The incidence of pruritus was highest in the patients from Group 25 among the three groups. Previous studies have shown similar findings. [6,9,12] Hunt et al. observed a significant increase in the overall incidence of itching in patients who received 25 and 50 µg of intrathecal fentanyl. [12] Similarly, Belzarena et al. also found that the group of patients who received 20 µg of intrathecal fentanyl showed a significantly higher incidence of pruritus. [6] Seewal et al. found high incidence of pruritus with increasing the dose of fentanyl above 10 µg in lower abdominal surgery. [9] On the contrary, some studies have shown nonsignificant pruritus in patients receiving 25 µg and less of intrathecal fentanyl. [17-20] One of the possible reasons might be that as none of these studies have measured pruritus as the main outcome, these studies were not

![Table 3: Comparison of mean time of onset and duration of sensory and motor blocks](image)

| Variables                                | Group 10 (n=81) | Group 15 (n=81) | Group 25 (n=81) | Group 10 vs. Group 15 | Group 10 vs. Group 25 | Group 15 vs. Group 25 |
|------------------------------------------|----------------|----------------|----------------|----------------------|----------------------|----------------------|
| Time of onset of sensory level (min)     | 4.8±2.9        | 4.8±1.9        | 5.3±2.4        | 0.998                | 0.819                | 0.861                |
| Time of onset of motor block (min)       | 7.2±2.4        | 7.4±3.3        | 7.7±2.7        | 0.993                | 0.767                | 0.999                |
| Duration of motor block (min)            | 113.8±22.4     | 133.9±30.5     | 136.3±25.2     | <0.001               | <0.001               | 0.998                |
| Duration of sensory block (min)          | 113.9±29.9     | 138.0±33.9     | 145.7±28.4     | <0.001               | <0.001               | 0.351                |

Data are expressed as mean±standard deviation and analyzed using ANOVA. Multiple post hoc test: Bonferroni. T0 is the time of institution of spinal anesthesia. *Time of onset of sensory level: Time taken from T0 to loss of cold sensation at T5 dermatome level. *Time of onset of motor block: Time taken from T0 till the patient develops Bromage score 1. *Duration of motor block: Time taken from T0 till the patient attains Bromage score 1. *Duration of sensory block: Time taken from T0 till the time of first request for analgesia.
Table 4: Comparison of side effects among groups in the OR and RR

| Side effects                              | Group 10 (n=81) | Group 15 (n=81) | Group 25 (n=81) | Group 10 vs. Group 15 | Group 10 vs. Group 25 | Group 15 vs. Group 25 |
|-------------------------------------------|-----------------|-----------------|-----------------|----------------------|----------------------|----------------------|
| Overall - In OR                            | 26 (32.1)       | 15 (18.5)       | 40 (49.4)       | 0.047                | 0.025                | <0.001               |
| Vomiting                                  | 12 (14.8)       | 9 (11.1)        | 8 (9.9)         | 0.483                | 0.339                | 0.789                |
| Nausea                                    | 16 (19.8)       | 9 (11.1)        | 25 (30.9)       | 0.128                | 0.104                | 0.002                |
| Desaturation <92%                         | 1 (1.2)         | 0               | 1 (1.2)         | 0.998                | 0.999                | 0.999                |
| Respiratory depression rate <8 per min    | 0               | 0               | 0               | NA                   | NA                   | NA                   |
| Pruritus                                  | 0               | 3 (3.7)         | 22 (27.2)       | 0.245                | <0.001               | <0.001               |
| Dizziness                                 | 3 (3.7)         | 2 (2.5)         | 10 (12.3)       | 0.998                | 0.043                | 0.016                |
| Pain score >4                             | 3 (3.7)         | 0 (0)           | 3 (3.7)         | 0.245                | 0.999                | 0.245                |
| Overall in recovery                       | 24 (29.6)       | 16 (19.8)       | 37 (45.7)       | 0.145                | 0.035                | <0.001               |
| Vomiting                                  | 2 (2.5)         | 2 (2.5)         | 7 (8.6)         | 1.000                | 0.167                | 0.167                |
| Nausea                                    | 4 (4.9)         | 5 (6.2)         | 16 (19.8)       | 0.732                | 0.004                | 0.018                |
| Desaturation <92%                         | 1 (1.2)         | 0               | 0               | 0.998                | 0.999                | NA                   |
| Respiratory depression rate <8 per min    | 0               | 0               | 0               | NA                   | NA                   | NA                   |
| Pruritus                                  | 6 (7.4)         | 8 (9.9)         | 31 (38.3)       | 0.576                | <0.001               | <0.001               |
| Dizziness                                 | 1 (1.2)         | 5 (6.2)         | 5 (6.2)         | 0.210                | 0.210                | 0.999                |
| Pain score >3                             | 16 (19.8)       | 2 (2.5)         | 3 (3.7)         | <0.001               | 0.003                | 0.650                |

Data are expressed as n (%) and analyzed using Chi-square test and Fisher exact test. NA, Not applicable

powered to detect differences in the incidence of pruritus. Our study was designed with a sample size large enough to detect the differences in pruritus, respiratory depression, nausea, and vomiting. This is one of the main strengths of this study.

Nausea and vomiting are other frequent complications of intrathecal fentanyl administration. In this study, the incidence of nausea was highest in the patients from Group 25, while no difference was noted in the incidence of vomiting among the three groups. The high incidence of nausea in this study is not comparable to other studies which showed either less or no differences.[1,2,9,13,14] The possible reasons for higher incidence of nausea in the study could be variation in surgical technique, including uterine exteriorization in some patients, as well as variations in the level of anxiety among patients.

Respiratory depression is a deleterious side effect, which may have serious consequences such as respiratory arrest and even death. Belzarena et al. reported decrease in the respiratory rate in patients receiving 0.5 and 0.75 µg/kg of intrathecal fentanyl, as early as 4 min after the drug administration, but the respiratory rate did not fall below 10 breaths/min.[6] Most authors used doses below 25 µg in later studies and did not find respiratory depression in any patient.[18,24] The study findings are consistent with the previous studies as none of the patients were reported to have respiratory depression.

In this study, APGAR score of the babies remained same in all groups and it was consistent with other studies.[12,23] González Cárdenas studied patients undergoing cesarean section who received intrathecal fentanyl for regional anesthesia and found no association between fentanyl and neonatal respiratory depression.[23]

One of the limitations of the study is that we did not consider height and used the same dose of bupivacaine (10 mg) in all patients, which might be associated with high incidence of hypotension in patients with short stature. The other limitation is that we did not assess anxiety level of the target population and whether the obstetrician exteriorize the uterus as these two factors can affect the incidence of nausea among the three groups. Another limitation could be the absence of control group in this study as baseline level of side effects can be observed without fentanyl. However, in our institution, fentanyl is added to intrathecal local anesthetics for all patients undergoing cesarean section under spinal anesthesia as a policy, unless the use of fentanyl is contraindicated. Lastly, there was a need to add a 20 µg dose in addition to 10, 15, and 25 µg. However, our main aim was to compare the commonly practiced dose of 25 µg in the investigators’ department with the commonly recommended dose of 10 and 15 µg.

Conclusion

In conclusion, intrathecal fentanyl in a dose of 25 µg did not improve anesthesia or analgesia compared to the two lower doses (10 and 15 µg), but increased the incidence of pruritus and nausea, while 10 µg was associated with earlier occurrence of pain in the RR. Therefore, we recommend 15 µg of fentanyl as the optimal dose of intrathecal fentanyl to supplement intrathecal hyperbaric bupivacaine (10 mg) for cesarean section under spinal anesthesia.
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Conflicts of interest
There are no conflicts of interest.

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