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Original Article

Comparative Study of Analgesic Efficacy of Intravenous versus Intrathecal Fentanyl as an Adjuvant in Subarachnoid Block for Cesarean Section

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Abstract

Introduction: Cesarean section under spinal anesthesia with local anesthetics leads to intraoperative visceral pain, which may require analgesic supplementation.

Objectives/Purpose: To compare analgesic efficacy in perioperative period between intravenous fentanyl and intrathecal fentanyl as an adjuvant in the subarachnoid block for cesarean section.

Materials and Methods: The study was carried out on 100 parturients, aged 18-45 years, ASA status I and II, scheduled for elective cesarean section, randomly allocated in two groups of 50 patients each: Group A (intravenous group): Intrathecal 0.5% hyperbaric bupivacaine 2.0 ml + normal saline 0.25 ml, and intravenous fentanyl 12.5 mcg immediately after administration of spinal bupivacaine. Group B (intrathecal group): Intrathecal 0.5% hyperbaric bupivacaine 2.0 ml (10 mg) + fentanyl 12.5 mcg (0.25 ml), and intravenous normal saline 0.25 ml (placebo). We compared the requirement for intravenous fentanyl supplementation during surgery, the intraoperative pain scores by visual analog scale, and the time to post-operative rescue analgesia.

Results: The intravenous group (Group A) has higher intraoperative pain scores than Group B ($P < 0.05$). Higher amount of intraoperative intravenous fentanyl supplementation was required in the intravenous fentanyl group as compared to the intrathecal group (mean intravenous fentanyl requirement = 19.5 ± 3.56 versus 4.5 ± 1.87 mcg, respectively; $P = 0.002$). The time to first request for post-operative analgesia was significantly longer in the intrathecal fentanyl group than in intravenous fentanyl group (133.9 ± 20.68 vs. 115.4 ± 16.28 min, respectively; $P = 0.003$).

Conclusion: Intrathecal fentanyl supplementation of spinal anesthesia with bupivacaine during cesarean delivery resulted in a better quality of spinal analgesia than the same dose of intravenous fentanyl supplementation.

Key words: Analgesia, Bupivacaine, Cesarean section, Fentanyl, Subarachnoid block

INTRODUCTION

Subarachnoid block for cesarean delivery is a preferred and widely used technique[1] because it is safer and results in less maternal and neonatal morbidity than general anesthesia.[2,3]

The local anesthetics have a relatively short duration of action, thereby limiting the technique for comparatively long duration surgery and increasing the requirement of analgesics in the early post-operative period.[4,5] Furthermore, even the conventional recommended doses of the local anesthetic are unable to completely abolish visceral pain produced by the manipulation of the uterus and peritoneum, leading to intraoperative pain and nausea-vomiting,[4,6] necessitating an increase in doses of the local

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anesthetic, which is associated with a higher incidence of maternal and neonatal morbidity, (such as maternal hypotension).[7,8] Hence, analgesic supplementation is also needed for anesthetic management of visceral pain intraoperatively.[9] Thus, combination of local anesthetics with various adjuvants for spinal anesthesia has been studied.[9-13] Lipophilic opioids, especially fentanyl, is increasingly being administered intrathecally as an adjuvant to spinal anesthesia because they act synergistically with local anesthetics and intensify sensory block without increasing sympathetic blockade and prolonging motor block.[7,14]

In the form of intrathecal fentanyl, spinal opioids induce better analgesia. A significant amount of intrathecally administered fentanyl may diffuse into the epidural space[9,15] and subsequently into plasma, which suggests that the analgesic effect of intrathecal fentanyl may be induced by a systemic rather than a spinal action. If intrathecal fentanyl induces analgesia predominantly through absorption into blood stream, then the same dose injected intravenously should produce the best effect.[16]

In this study, the intrathecal fentanyl was compared with the same dose of fentanyl administered intravenously as an adjuvant regarding the analgesic efficacy in the perioperative period, by studying the need for intraoperative analgesic supplementation, intraoperative pain scores, and the time to request for first post-operative rescue analgesia.

MATERIALS AND METHODS

The prospective, randomized, double-blinded study was carried out on 100 patients, aged 18-45 years, ASA grade I and II physical status, scheduled for elective cesarean section, after obtaining ethical committee approval and written informed consent from the patient.

A detailed pre-anesthetic checkup, gestational age and parity, height, weight, and routine investigations were undertaken.

Exclusion Criteria

- Contraindications to spinal anesthesia
- Pregnancy with obstetric complications
- Uncontrolled diabetes mellitus or hypertension
- Fetal distress
- Women at risk for respiratory complications
- Allergy to study drugs or history of drug abuse
- Failed spinal block.

The patients were randomly allocated into two groups of 50 patients each.

Group A (intravenous fentanyl group) received intrathecal 0.5% hyperbaric bupivacaine 2.0 ml (10 mg) + normal saline 0.25 ml (to achieve the same volume), and IV fentanyl 12.5 mcg (0.25 ml) immediately after administration of spinal bupivacaine.

Group B (intrathecal fentanyl group) received intrathecal 0.5% hyperbaric bupivacaine 2.0 ml (10 mg) + fentanyl 12.5 mcg (0.25 ml) followed by immediate injection of IV normal saline 0.25 ml (placebo).

All patients were pre-medicated with ranitidine 50 mg IV, and metoclopramide 10 mg IV 45 min before surgery. On arriving in the operating room, all monitors were attached and were preloaded with 10 ml/kg ringer lactate solution. Under all aseptic precautions, lumbar puncture was performed in sitting position by midline approach at L3-L4 intervertebral space using a 25G Quincke's spinal needle and after free flow of clear cerebrospinal fluid (CSF) was seen, the study drug was given, immediately followed by the IV injection. Immediately after the block, each parturient was placed supine with 15° to 20° left uterine displacement. Oxygen 5 L/min was given via a face mask during the surgery.

Patients were monitored with a continuous pulse oximeter, heart rate, respiratory rate, and electrocardiogram monitoring. Non-invasive blood pressure measurement was recorded every 3 minutes for 20 minutes, and then every 5 min until the end of surgery. Fall in systolic blood pressure <100 mmHg or fall of ≥20% below the pre-induction level was treated with 5 mg boluses of IV ephedrine.

Level of sensory block was measured by pinprick every minute until the block reached T6 dermatome. Thereafter, the level was checked every 2 min until the maximum sensory block level was confirmed. Level of motor blockade was assessed using modified Bromage scale.[17] Time of onset of motor block to Bromage 3 was noted. Time to regression of sensory block to T12 dermatome and time for motor recovery to Bromage score 0 was assessed.

Pain was evaluated using visual analog scale (VAS), which was introduced to the patients before surgery.[18] Patients were asked to rate the VAS before delivery, when the uterus was exteriorized, after replacement of the uterus into the abdominal cavity, and whenever the patient complained of discomfort or pain during surgery. Each time VAS was >3; 25 μg increments of fentanyl IV was administered every 5 min until VAS became <3. A maximum dose of 2 μg/kg fentanyl IV was given after which rescue analgesia was given with IV ketamine.

Any adverse effects, such as intraoperative nausea, vomiting, pruritus, shivering, and respiratory depression were recorded and treated. After delivery, the Apgar scores of the neonates were assessed at 1 and 5 min. Time to the first request for rescue post-operative analgesia for the patient was recorded. Rescue analgesia was available in the form of IV 75 mg diclofenac sodium aqueous.

The data were analyzed using SPSS software version 20 by inserting the data into MS Excel. Unpaired/independent *t*-test was used on the data to compare the significant difference between the two groups for different parameters under study, and qualitative data were analyzed using non-parametric tests of statistics, that is, Chi-square test and Fisher's exact test, at 0.05 level of significance (that is, a $P < 0.05$ was considered significant). Data are presented as mean value ± standard deviation, median, mode, and incidence *n* (%).

RESULTS

The groups were comparable with respect to age, height, weight, gestational age, and parity (Tables 1 and 2). The sensory and motor block characteristics are summarized in Table 3. The time of onset to T6 sensory block, maximum sensory level achieved, and time required to achieve maximum sensory level is similar between the groups. In most patients, the maximum sensory level in both groups reached a level of T5. The difference between the groups in motor block onset, time for motor block recovery, and time to the recession of sensory block to T12 did not reach statistical significance. There was no significant difference between groups with respect to intrathecal injection to delivery time and duration of surgery (Table 1).

Table 1: Demographic data, time to delivery, and duration of surgery

Parameters	Group A (mean±SD)	Group B (mean±SD)	*P* value
Age (years)	27.26±5.13	25.76±3.11	0.215 (*P*>0.05)
Height (cm)	154.28±2.08	153.86±2.11	0.314 (*P*>0.05)
Weight (kg)	55.38±4.81	55.62±3.47	0.349 (*P*>0.05)
Gestational age in weeks	38.92±1.43	38.6±1.76	0.398 (*P*>0.05)
Time to delivery (min)	13.18±2.28	12.86±2.72	0.074 (*P*>0.05)
Duration of surgery (min)	53.3±5.68	52.7±7.09	0.231 (*P*>0.05)

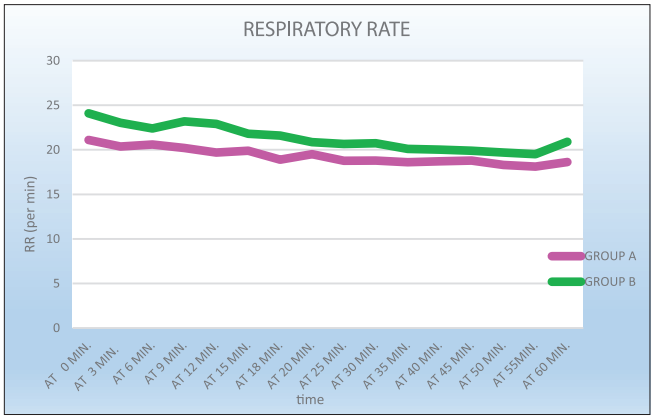
SD: Standard deviation

Table 2: Parity

Parity	Number of patients		*P* value
	Group A	Group B	
0	2	3	0.116 NS
1	28	29	0.123 NS
2	16	12	0.089 NS
3	3	4	0.096 NS
4	1	1	0.333 NS
5	0	1	0.211 NS
Total	50	50	

NS: Non-significant

Intraoperative pain scores are depicted in Table 4. Group A had a higher incidence ($n = 10\%$) of moderate to severe pain (i.e., VAS > 3) than Group B ($n = 2\%$) before delivery, which was of statistical significance ($P = 0.004$). There was also a statistically significant difference between the groups in the incidence of significant pain when uterus was exteriorized and when it was replaced in the abdomen. During exteriorization of the uterus, Group A had a significantly higher incidence of pain ($n = 42\%$) than Group B ($n = 10\%$) ($P < 0.001$); whereas when uterus was replaced in abdomen, 24% of Group A patients complained of moderate to severe pain as compared to only 4% of patients in Group B ($P = 0.002$). Group A patients required IV fentanyl intraoperatively for analgesic supplementation more frequently ($n = 56\%$) than Group B ($n = 14\%$), which was of statistical significance ($P = 0.001$) (Table 5). 22% patients needed IV fentanyl to be repeated intraoperatively in Group A as compared with only 4% patients in Group B ($P < 0.05$). A statistically significant higher amount of mean IV fentanyl supplementation was required intraoperatively in Group A (19.5 ± 3.56 μg) as compared with Group B (4.5 ± 1.87 μg) ($P = 0.001$) (Table 5). The time to first post-operative rescue analgesia showed a statistically significant difference between the two groups, with time being longer in Group B (133.9 ± 20.68 min) than Group A (115.4 ± 16.28 min) ($P = 0.001$) (Table 5). There was no statistically significant difference in the incidence of nausea, vomiting, pruritus, shivering, and respiratory depression between the two groups (Table 6 and Graph 1). The Apgar score of all neonates in both the groups was ≥8 at 1 min and ≥9 at 5 min (Table 6). The patients in both groups remained hemodynamically stable intraoperatively (Graphs 2 and 3).



Graph 1: Intraoperative respiratory rate (mean ± standard deviation)

Table 3: Sensory and motor block characteristics

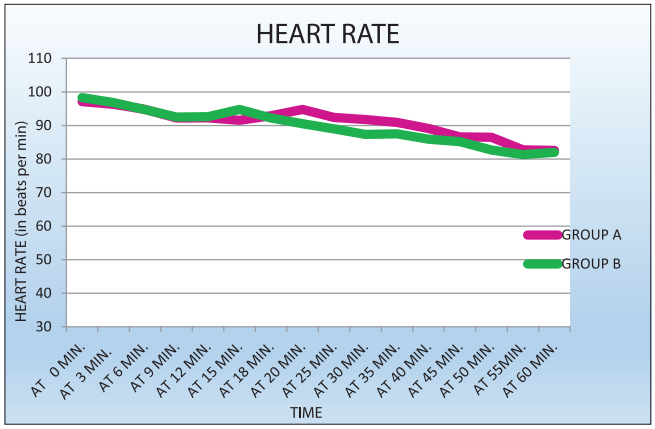
Block characteristics	Group A (mean±SD)	Group B (mean±SD)	*P* value
Time taken for T6 sensory block onset (in min)	2.6±0.728	2.8±0.808	0.136 (*P*>0.05) NS
Maximum sensory level achieved S_{max} (T-)	5.38±0.602	4.9±0.647	0.103 (*P*>0.05) NS
Time for S_{max} (in min)	4.12±1.35	5.0±1.36	0.098 (*P*>0.05) NS
Duration of sensory block recovery (regression to T12 dermatome)	127.9±16.29	137.5±16.23	0.053 (*P*>0.05) NS
Time to motor block onset to Bromage 3 (in min)	1.98±0.68	2.3±0.74	0.098 (*P*>0.05) NS
Motor block recovery time for Bromage 0 (in min)	115.1±15.89	123±17.14	0.090 (*P*>0.05) NS

NS: Non-significant, SD: Standard deviation

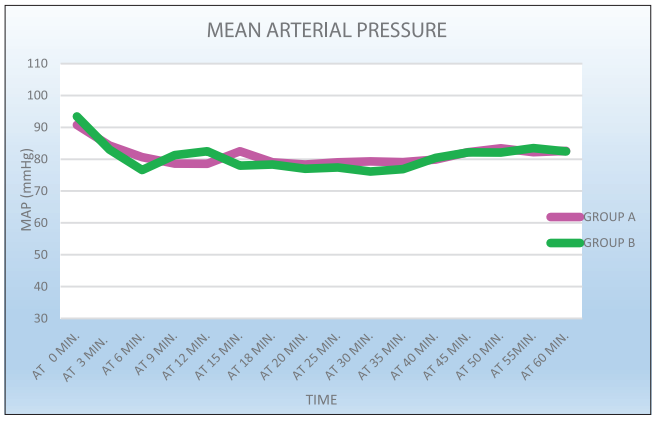
Table 4: Incidence of moderate to severe pain intraoperatively

Incidence of significant pain (VAS >3)	Group A *n* (%)	Group B *n* (%)	*P* value
Prior to delivery	10	2	0.004 (*P*<0.05)*
Uterus exteriorized	42	10	0.0001 (*P*<0.05)*
Uterus replaced	24	4	0.002 (*P*<0.05)*

*Implies statistically significant difference. VAS: Visual analog scale



Graph 2: Intraoperative heart rate (mean ± standard deviation)



Graph 3: Intraoperative mean arterial blood pressure (mean ± standard deviation)

DISCUSSION

Spinal anesthesia is often used for elective cesarean delivery.[19,20] However, even at recommended doses of intrathecal bupivacaine, it alone may be insufficient to provide complete analgesia intraoperatively as the surgery requires manipulation of the uterus and traction of peritoneum, which produces intraoperative visceral pain and nausea-vomiting.[4,6,21,22] Higher doses of intrathecal bupivacaine are associated with severe maternal arterial hypotension and delayed recovery of motor block.[6,11,21,23] Therefore, smaller doses of bupivacaine supplemented by intrathecal opioids have been recommended for spinal anesthesia in patients undergoing cesarean delivery. Their synergistic and potentiating effects on local anesthetics in subarachnoid block result in better perioperative analgesia and fewer adverse effects.[4,8,19,23]

In cesarean section, it is imperative to use the smallest effective dose of opioid to minimize the potential adverse effects on the mother and neonate.[4,24] Dose ranging studies have demonstrated that use of low dose of intrathecal fentanyl, 6.25-12.5 mcg is effective in cesarean delivery with minimal side effects.[19,24]

A significant amount of intrathecally administered lipophilic opioid, such as fentanyl, is lost by diffusion into the epidural space[15] and subsequently into the plasma, suggesting that intrathecally administered fentanyl may induce analgesia by a systemic rather than by a spinal action. It will produce at best the same effects as the same dose injected intravenously.[16]

This study was conducted to compare the analgesic efficacy of intrathecal fentanyl versus the same dose of IV fentanyl as an adjuvant to spinal bupivacaine, in terms of the intraoperative pain scores, amount of intraoperative analgesic supplementation, and duration of post-operative analgesia in women undergoing elective cesarean section.

Siddik-Sayyid *et al.*[16] conducted a similar study on 48 ASA physical status I and II parturients, scheduled for elective cesarean section who were randomly allocated into two groups. 23 patients received 12 mg of hyperbaric bupivacaine (0.75%) plus 12.5 μg of fentanyl intrathecally (followed by injection of IV saline 0.25 ml as placebo), and 25 patients received 12 mg of hyperbaric bupivacaine (0.75%) alone (mixed with CSF to achieve the same final volume) followed by immediate injection of 12.5 mcg IV fentanyl. In a similar study conducted by Sheikh *et al.*,[25] it

Table 5: Intraoperative fentanyl requirement and post-operative analgesia

Number of patients *n* (%)	Group A (%)	Group B (%)	*P* value
Patients requiring fentanyl			
Once	28 (56)	7 (14)	<0.001 (*P*<0.05)*
Twice	11 (22)	2 (4)	0.0001 (*P*<0.05)*
Mean fentanyl requirement intraoperatively (micrograms)	19.5±3.56	4.5±1.87	0.001 (*P*<0.05)*
Time to first rescue post-operative analgesia (in min)	115.4±16.28	133.9±20.68	0.003 (*P*<0.05)*

*Implies statistically significant difference

Table 6: Side effects and neonatal Apgar scores

Number of patients *n* (%)	Group A (%)	Group B (%)	*P* value
Nausea	5 (10)	1 (2)	0.892 (*P*>0.05)
Vomiting	2 (4)	0 (0)	0.112 (*P*>0.05)
Pruritus	1 (2)	0 (0)	0.120 (*P*>0.05)
Shivering	1 (2)	0 (0)	0.211 (*P*>0.05)
Apgar score AT (median value)			
1 min	8 (8-9)	8 (8-9)	0.125 (*P*>0.05)
5 min	9 (9-10)	9 (9-10)	0.163 (*P*>0.05)

included patients with pregnancy-induced hypertension without proteinuria.

There were no significant differences between the intrathecal group and the IV fentanyl group with respect to age, height, weight, parity or gestational age, intrathecal injection to delivery time, and duration of surgery; which is in line with observations of Siddik-Sayyid *et al.*,[16] Sheikh *et al.*,[25] Biswas *et al.*,[26] and others.[4,19] Furthermore, the sensory and motor block characteristics showed no statistically significant difference between the groups. These findings are consistent with the findings of Siddik-Sayyid *et al.*,[16] Biswas *et al.*,[26] and others.[4,19,25,27] It has been documented that intrathecal opioids potentiate the effects of local anesthetic without intensifying motor and sympathetic blockade.[14]

Similar to observations of Siddik-Sayyid *et al.*,[16] the incidence of VAS > 3 (i.e. moderate-severe pain) before delivery was significantly lower in the IT fentanyl group as compared with IV fentanyl group. Furthermore, the incidence of significant pain (VAS > 3) during exteriorization of uterus and replacement of uterus into abdomen was found to be higher in the IV fentanyl group as compared with the intrathecal group in both the studies (Siddik-Sayyid *et al*);[16] the difference was of statistical significance in our study ($P < 0.05$) but was not so in the study by Siddik-Sayyid *et al.*[16] This may be explained by the fact that we used a lower dose and concentration (10 mg, 0.5%) of bupivacaine and a larger sample size as compared with Siddik-Sayyid *et al.*[16] (12 mg, 0.75%) ($n = 48$). Our results corroborate with those of Hunt *et al.*[20] and others,[8,26-29] where administration of more than 10 mcg of intrathecal fentanyl with 0.5% hyperbaric bupivacaine led to a marked decrease in the incidence of intraoperative pain or discomfort, indicating that intrathecal fentanyl effectively abolishes visceral pain. This high incidence of visceral pain in cesarean deliveries during manipulation of uterus and peritoneum under regional anesthesia has been demonstrated earlier.[6,21] This can be attributed to the fact that similar to the tourniquet pain, visceral pain is believed to be conducted by unmyelinated C-fibers. Hence, once the dose of local anesthetic is reduced these fibers become unblocked, while the Aδ-fibers transmitting incisional pain are still blocked.[6,30]

There was a statistically significant difference in the need for intraoperative analgesic supplementation with IV fentanyl and also the mean fentanyl requirements between the groups in our study, in consonance with Siddik-Sayyid *et al.*,[16] with greater requirement for supplementation in the IV group as compared with IT group. The decrease in the intraoperative analgesic requirement has been well documented in other studies as well.[19,20,24,29] However, this is not in agreement with findings of Dahlgren *et al.*,[4] as none of the patients in either group required intraoperative supplementary analgesics in their study. The varying local anesthetic concentrations, baricity, and doses may account for these differences in the requirement for intraoperative analgesic supplementation.

The duration of post-operative analgesia, i.e., the time to first request of post-operative analgesia was prolonged in the intrathecal fentanyl group as compared with the IV fentanyl group, and this difference was statistically significant, which is in agreement with Siddik-Sayyid *et al.*,[16] and most of the studies using an intrathecal fentanyl dose of >10 mcg such as Biswas *et al.*[26] and others.[4,19,25,27,29] Even a moderate increase in the duration of post-operative analgesia must be considered beneficial, as it allows early mobilization of the mother and a sooner mother-baby interaction.

The hemodynamic parameters and the incidence of maternal side effects (such as nausea, vomiting, shivering, pruritus, and respiratory depression) showed no statistically significant difference between the groups, which in conformity with the observations of other workers.[19,25-27]

However, a statistically significant lower incidence of intraoperative nausea and vomiting in the IT fentanyl group was seen by Siddik-Sayyid *et al*.,[16] which was probably due to hypotension and was cured after administration of ephedrine (which corrected the hypotension). The Apgar scores of all neonates were ≥8 at 1 min and ≥9 at 5 min in both the studies.[16] Studies by Frolich *et al*.[31] and Eisele *et al*.[32] found similar results for IV administration of fentanyl in doses up to 1 mcg/kg before delivery in cesarean section.

These results suggest that intraoperative analgesic supplementation of bupivacaine spinal anesthesia with intrathecal fentanyl results in a better quality of spinal anesthesia than IV fentanyl, as evidenced by the lower intraoperative VAS scores, as well as lesser need for additional intraoperative analgesics. In addition, the time to the first post-operative analgesic requirement was longer in the intrathecal fentanyl group as compared with the IV fentanyl group.

CONCLUSION

From our study, it can be concluded that:

- Intrathecal fentanyl analgesic supplementation was more efficacious than intravenous fentanyl supplementation of subarachnoid block in cesarean delivery, as intrathecal fentanyl supplementation was associated with lower intraoperative VAS scores, lower intraoperative analgesic requirements, and a longer time to first post-operative rescue analgesia than with intravenous fentanyl supplementation with comparable maternal adverse effects and fetal outcomes
- In view of better analgesia and lesser side effects, it can be concluded that intrathecal fentanyl supplementation of spinal anesthesia with bupivacaine during cesarean delivery resulted in a better quality of spinal analgesia than the same dose of intravenous fentanyl supplementation.

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