

POST OPERATIVE ANALGESIC EFFECT ON ADDITION OF FENTANYL VS NALBUPHINE WITH INTRATHECAL BUPIVACAINE IN LSCS –A PROSPECTIVE RANDOMIZED DOUBLE BLINDED INTERVENTIONAL STUDY

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Abstract

Background: Subarachnoid block or spinal anaesthesia is the most common anaesthetic technique employed worldwide for LSCS. In this study we compare the post operative analgesic effect on addition of Fentanyl Versus Nalbuphine as adjuvants to intrathecal Bupivacaine in patients who are undergoing elective LSCS. **Materials and Methods:** Sixty-four patients aged 20 to 45 yrs, of ASA I or II who are undergoing elective LSCS were included in this study. The patients were randomized into two groups of 32 each (Group N n=32) or (Group F n=32). The parameters monitored were onset of sensory and motor block, duration of sensory and motor block, post operatively pain score, sedation score, heart rate, blood pressure and respiratory rate, newborn Apgar score, time to first rescue analgesia noted. Adverse events also compared. These parameters were tabulated and analysed statistically. **Result:** There was no statistically significant difference in the onset of sensory block. There was statistically significant increase in duration of sensory block and motor block in Group N in our study. Also, there was statistically significant difference in mean duration of post operative analgesia in Group N. The mean VAS Score for postoperative pain was lower in Group N as compared to Group F. Also, there was no statistically significant difference in haemodynamic parameters in between the study groups. **Conclusion:** We found that the duration of postoperative analgesia following the addition of intrathecal nalbuphine to the local anaesthetic mixture was significantly longer than intrathecal fentanyl with fewer adverse events in patients who underwent elective lower segmental caesarean section.

INTRODUCTION

Subarachnoid block commonly known as spinal anaesthesia is a type of regional anaesthesia. It is the preferred anaesthesia for lower segment caesarean section, as the procedure is simple to perform, economical and has a rapid onset and recovery. Addition of certain drugs as adjuvant to intrathecal local anaesthetic mixture in spinal anaesthesia improves quality and duration of sensory block and prolongs postoperative analgesia.

Opioid agents given intrathecally have synergistic action with local anaesthetic agents. They intensify the sensory block without an increase in sympathetic block. Fentanyl is a lipophilic mu (μ) opioid receptor agonist and has a rapid onset following intrathecal injection. Various studies have shown that it improves duration of sensory anaesthesia and

postoperative analgesia when used along with hyperbaric bupivacaine without producing significant side effects.

Nalbuphine an agonist-antagonist opioid when used as adjuvant to hyperbaric bupivacaine has also improved the quality of perioperative analgesia with fewer side effects. It is a mixed synthetic agonist antagonist which attenuates the μ -opioid effects and enhances the κ -opioid effects. A study to compare the efficacy of the above drugs with respect to postoperative analgesia was done in patients who underwent elective LSCS.

Aim of the Study

To compare the post operative analgesic effect on addition of fentanyl versus nalbuphine as an adjuvant to intrathecal bupivacaine in patients who are undergoing elective lower segment caesarean section (LSCS).

MATERIALS AND METHODS

The study was conducted in the Department of Anaesthesiology involving the Department of Obstetrics and Gynaecology in Kanyakumari Government Medical college and Hospital after obtaining institutional ethical committee approval, approval from Department of Obstetrics and Gynaecology, and written informed consent from the patients.

Aim of Study

This study is designed to compare the post-operative analgesic effect on addition of fentanyl vs nalbuphine as an adjuvant to intrathecal bupivacaine in patients undergoing elective lower segment caesarean section (LSCS).

Study design: A prospective randomized double blinded interventional study.

Randomization: The samples were randomized with opaque closed/ sealed envelope method. 64 plain opaque envelope covers were taken with a single sheet of paper.

32 sheets were written N for nalbuphine and other 32 sheets were written F for fentanyl.

The envelopes are sealed and kept in operation theatre waiting room.

The envelope covers were mixed thoroughly.

Before the start of LSCS, the patient was asked to pick an envelope of choice and was randomized accordingly.

Sample size calculation: Sample size for mean difference between two groups

$$n_1 = (\sigma^2 + \sigma^2 / K) (z + z)^2 / \Delta^2 \quad n_2 = (K * \sigma^2 + \sigma^2) (z + z)^2 / \Delta^2$$

n1	=	sample size of group 1
n2	=	sample size of group 2

Onset of complete motor block Fentanyl = 5.57 +/- 0.23 minute

Nalbuphine = 5.72 +/- 0.17 minutes Mean difference = - 0.15

Confidence interval (2 sided) = 95%

Power (1-β error) = 80%

Ratio of sample size (group 2 /group 1) = 1 Sample size in each group = $(0.23^2 + 0.17^2) (1.96 + 0.84)^2 / (-0.15)^2$
= 28.50

~ 29 in each group

Sampling: Sample size was calculated based on the standard deviation from parent study with alpha error of 0.05 and power 80% with effect size as duration of post-operative analgesia of 0.8%, sample size was estimated to be 29 in each group. After accounting to dropout, sample size was approximated as 32 in each group.

Blinding

1. Observer
2. Patient

Group Allocation: 64 patients scheduled for elective LSCS were randomized into two groups with 32 patients each.

Group N - patients in this group received 1.6 ml of 0.5% hyperbaric bupivacaine with addition of 0.4 ml solution of nalbuphine (0.8 milligram),

Group F - patients in this group received 1.6 ml of 0.5% hyperbaric bupivacaine with addition of 0.4 ml solution of fentanyl (20 micrograms). Patients aged between 20-45 yrs with ASA I, II with no comorbidities posted for elective LSCS were included in this study. And those patients ASAIII, IV patients with contraindication for Spinal anaesthesia, patient refusal, Drug allergy, localised sepsis, those with raised ICP, Coagulation disorders were excluded from this study.

Outcome

Primary outcome

Time to First Rescue Analgesia

Secondary outcome

1. Intra operative hemodynamic changes
2. Sedation
3. Respiratory depression
4. Pruritus
5. Nausea / vomiting
6. New born APGAR score Methods

Pre-operative preparation

Patient's age, body weight, height, BMI and baseline vital parameters were recorded. A comprehensive preanesthetic evaluation of all systems, recording of vital parameters and basic laboratory investigations were done for all the patients involved in this study.

Patients were given a brief introduction to the visual analogue scale (VAS) (0 – No pain, 10 – Worst pain) a day before surgery to get the patients oriented for the post-operative periods.

Intervention

Before the Procedure, a vein was cannulated for intravenous access with a 18G cannula, and all patients were preloaded with 10 ml/kg of Ringer lactate solution.

Standard monitors were connected in all patients. No sedative or hypnotics were given before the procedure.

Intra-operatively, baseline blood pressure (systolic, diastolic, and mean), heart rate, respiratory rate, and peripheral blood oxygen saturation (SpO₂) were recorded.

The study medication (2 ml of the drug solution) was prepared by the anaesthesiologist who did not take part in the study depending on the group specified in the sealed envelope. Group N - patients in the group received 1.6 ml of 0.5% hyperbaric bupivacaine with addition of 0.4 ml solution of nalbuphine (0.8 milligram) via intrathecal injection,

Group F - patients in the group received 1.6 ml of 0.5% hyperbaric bupivacaine with addition of 0.4 ml solution of fentanyl (20 microgram) via intrathecal injection.

Oxygen was provided to the patient at the rate of 4 litres/minute using a Venturi mask.

Blood Pressure (systolic, diastolic, and mean), heart rate, respiratory rate, and oxygen saturation of the blood were monitored continuously and recorded at every 2 minutes till the delivery of foetus, at every 5

minutes till the end of surgery and every 15 minutes till time to first rescue analgesia.

Hypotension was treated with intravenous fluid and intravenous injection of 5 milligram ephedrine.

Bradycardia (defined as heart rate of <60) was treated with 0.6 milligrams of intravenous atropine sulphate. Sensory block was assessed by pinprick method and motor block by Modified Bromage Scale. The onset of sensory blockade (defined as the time from the injection of intrathecal drug to the absence of pain at the T6 dermatome) and onset of complete motor blockade (time taken from the injection to development of Bromage's Grade 3 motor block) were recorded.

The duration of sensory blockade (two segment regression from highest level of sensory blockade) was also recorded in each patient. Duration of motor blockade (time required for motor blockade to return to Bromage's Grade 1 from the time of onset of motor blockade) was also noted. Grades of sedation during surgery were assessed by the Modified Ramsay's sedation scale.

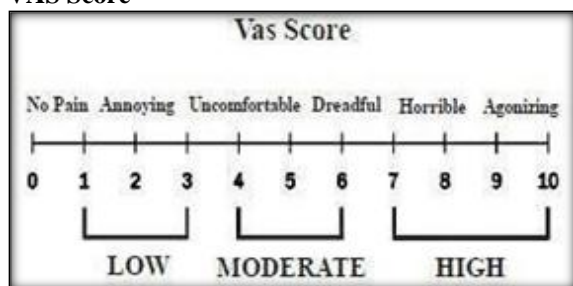
The level of motor blockade is assessed by modified Bromage scale.

The level of sedation was assessed by the Ramsay sedation score.

Postoperatively, pain score (VISUAL ANALOGUE SCALE), sedation score (RSS), heart rate, blood pressure and respiratory rate were assessed every 15 minutes till the first request for rescue analgesia. The total duration of effective analgesia from the time of intrathecal injection of local anaesthetic mixture to the first rescue analgesic requirement i.e., VISUAL ANALOGUE SCALE score >3) was noted. Injection of 20 milligram Tramadol was administered Intramuscularly as rescue analgesia.

Patients were also observed for potential drug related adverse events such as nausea, vomiting, respiratory depression, hypotension, pruritis, and bradycardia along with the assessment of the new born with APGAR score.

VAS Score



Visual analogue scale

Apgar Score

Apgar is a quick test performed on a baby at 1 and 5 minutes after the birth. 1 minute score determines how well the baby tolerated the birthing process. The 5 minute score tells the health care provider how well the baby is doing outside the mother's womb. Maximum score is 10 and the minimum score is 0.

Statistical Analysis and Interpretation:

- The continuous variables of the study subjects were described in form of mean and standard deviation.
- The Mean and standard deviation were derived by independent sample t test.
- Pearson's chi square test was used to test statistical significance between the two groups.
- P-value < 0.05 will be considered as statistically significant.

The above statistical tests were performed with the help of statistical package namely IBM SPSS service version 22.

RESULTS

The study subjects of fentanyl versus nalbuphine groups were compared for their homogeneity with respect to Age, Weight, Height, BMI. Preoperative parameters like Respiratory rate and SPO₂ also compared. Intra operative parameters like time to onset of sensory block and motor block, effective duration of sensory block and motor block, Heart Rate and mean arterial pressure also compared. Post-operative parameters like new-Born Apgar, Time to First Rescue Analgesia, Adverse events also compared.

Comparison of Ages Between Two Groups

The mean age of group N was 27.78 ± 4.24 years and the mean age of group F was 27.09 ± 3.80 years. The difference between the age of group N and group F was not statistically significant (p value > 0.05).

Comparison of Weights Between the Two Groups

The mean weight of group N was 72.47 ± 5.35 kg and the mean weight of group F was 73.44 ± 5.20 kg. The difference between the two groups with respect to weight was not statistically significant (p value > 0.05).

Comparison of Heights Between the Two Groups

The mean height of the group N was 154.22 ± 4.09 cm and the mean height of group F was 153.94 ± 2.99 cm.

The difference of heights between group N and group F was not statistically significant (p value > 0.05).

Comparison of BMI Between the two Groups

The mean BMI of the group N was 31.56 ± 2.38 kg/m² and the mean BMI of group F was 31.85 ± 2.24 kg/m². The difference of BMI between group N and group F was not statistically significant (p value > 0.05).

Comparison of Pre-Op Respiratory Rate Between the Two Groups

The mean pre-op respiratory rate of the group N was 19.53 ± 0.84 / minute and the mean pre-op respiratory rate of group F was 19.19 ± 0.97 / minute. The difference of pre-op respiratory rate between group N and group F was not statistically significant (p value > 0.05).

Comparison of Pre- Operative Spo2 Between the Two Groups

The mean pre-op SpO₂ of the group N was 98.78 ± 0.42% and the mean pre-op SpO₂ of group F was 98.72 ± 0.46%. the difference of pre-op SpO₂ between group N and group F was not statistically significant (p value > 0.05).

Comparison of Onset of Sensory Block Between Two Groups

The time to onset of sensory block in the patients of group N was 1.91 ± 0.458 minutes and the total duration of sensory block in the patients of group F was 1.93 ± 0.496 minutes. There was no significant difference between the onset of sensory blockade in group N and group F (p value > 0.05).

Comparison of Onset of Motor Block Between Two Groups

The average duration of onset of motor blockade in the patients of group N was 3.91 ± 0.521 minutes and the average duration of motor blockade in the patients of group F was 3.96 ± 0.529 minutes. There was no significant difference between the onset of motor blockade in group N and group F (p value > 0.05).

Comparison of Sensory Block Duration Between Two Groups

The total duration of sensory block in the patients of group N was 88.88 ± 11.65 minutes and the total duration of sensory block in the patients of group F was 77.66 ± 8.64 minutes. There was a statistically significant difference between the duration of sensory blockade in group N and group F (p value < 0.05).

Comparison of Motor Block Duration Between Two Groups

The average duration of motor blockade in the patients of group N was 102.88 ± 14.10 minutes and the average duration of motor blockade in the patients of group F was 89.13 ± 11.61 minutes. There was a statistically significant difference between the duration of motor blockade in group N and group F (p value < 0.05).

Heart Rate Comparison Between Two Groups

There were lower heart rates observed in group N compared to group F which were mostly statistically insignificant. However, significant difference was observed in heart rate (HR) between the two groups

at 6th (p-value = 0.045) and 8th (p-value = 0.024) minutes with lower heart rate in group N.

Comparison Of Map Between Two Groups

Statistically significant decrease in mean arterial pressure of group F compared to group N was recorded at 2nd (p- value = 0.012), 4th (p-value = 0.023 and 6th (p- value = 0.048) minutes in the early block period which was corrected with intravenous fluids and bolus dose of sympathomimetic agents. Statistically significant increase in mean arterial pressure of group F compared to group N was recorded at 90th (p- value = 0.018), 105th (p-value = 0.042) and 120th (p- value = 0.027) minutes which can be attributed to increased visual analogue score

Comparison of Newborn Apgar Between Two Groups

Comparison of the APGAR of new-born between group N and group F at 1 minute and 5 minutes post-partum. The mean APGAR at 1 minute for group N was 7.13 ± 0.55 and for group F was 7.16 ± 0.57. The mean APGAR at 5 minutes for group N was 9.91 ± 0.09 and for group F was 9.86 ± 0.14. The difference between group N and group F with respect to APGAR of new born at 1 minute and 5 minutes was not statistically significant.

Comparison of Time to Rescue Analgesia Between Two Groups

The time to rescue analgesia between group N and group F was compared in the above table. The mean time to rescue analgesia for group N was 134.06 ± 11.88 and the mean time to rescue analgesia for group F was 122.03 ± 11.56. Group N had a statistically significant increase in time to rescue analgesia compared to group F.

Comparison of Adverse Events Between Two Groups

The adverse events during the intraoperative and postoperative period were compared between group N and group F in [Table]. Group N had statistically significant decrease in the incidence of nausea and vomiting (p-value = 0.039), pruritus (p-value = 0.02) and hypotension (p-value = 0.016) compared to group F. There was no statistically significant difference between group N and group F in the incidence of bradycardia.

Table 1

	Group	N	Mean	Std. Deviation	P value
Sensory Duration	Group N	32	88.88	11.65	<0.000
	Group F	32	77.66	8.64	1

Table 2

	Group	N	Mean	Std. Deviation	P value
Motor Duration	Group N	32	102.88	14.10	<0.0001
	Group F	32	89.13	11.61	

Table 3

	GROUP	Mean	Std. Deviation	P value
Rescue analgesia	Group N	134.06	11.88	<0.0000
	Group F	122.03	11.56	1

Table 4

Complications	Group N		Group F	
	Number	Percent	Number	Percent
Nausea / Vomiting	4	12.5%	11	34.4%
Pruritis	0	0.0%	5	15.6%
Hypotension	3	9.4%	11	34.4%
Bradycardia	1	3.1%	1	3.1%

DISCUSSION

A randomized double-blind interventional study was conducted to compare the post operative analgesic effect on addition of intrathecal nalbuphine and intrathecal fentanyl as adjuvants to local anaesthetic mixture of 0.5 percentage hyperbaric solution of bupivacaine hydrochloride in patients undergoing lower segment caesarean section under spinal anaesthesia/ subarachnoid block. Nalbuphine an agonist – antagonist opioid agent, exhibits a ceiling effect to analgesic action. There was no further increase of analgesic action of nalbuphine even after increasing the dosage of nalbuphine after a certain point called ceiling point. In this study we compare 0.8 milligrams of nalbuphine with 20 micrograms of fentanyl similar to the studies conducted by Amutharani et al, and Bindra et al, Jyothi et al, had observed that increasing the dosage of nalbuphine from 0.8 milligrams to 1.6 milligrams and 2.4 milligrams had not resulted in its increased analgesic efficacy. We found that the onset of sensory block was comparable in the two groups which was 2 to 3 minutes. Gomaa et al,^[1] compared intrathecal nalbuphine 0.8 milligrams and intrathecal fentanyl 25 micrograms and found that there was rapid onset of sensory block with fentanyl group (1.64 minutes) than nalbuphine group (1.60 minutes) without any statistical significance.

However, significantly faster onset of sensory block with intrathecal fentanyl as adjuvant to local anaesthetic mixture was observed by Venkata et al and Gaurav Singh et al.^[2,3] There was a statistically significant increase in the total duration of sensory block in Group N compared to Group F in my study. Studies by Bindra et al, Choi et al,^[2] Ahmed et al,^[3] Naaz et al, and Kumaresan et al, showed similar results. However, Umesh et al and Vashishth et al had an increased duration of sensory block in the fentanyl group.

We found that there was no statistically significant difference in the onset of motor block between the two groups which was 3 to 5 minutes. Similar results were obtained by Hunt et al and Tiwari et al. Gomaa et al found significantly rapid onset of motor block in patients given fentanyl (5.57 min) than in patients given nalbuphine (5.72 min) in cesarean section. This can be explained that the study population was different.

I found that there was a statistically significant increase in the duration of motor block in patients who received nalbuphine and fentanyl. Our results were comparable with results of Gomaa et al,^[1] and Bisht et al.^[4] However, Tilkar et al observed no

significant difference in duration of motor block between fentanyl and control group in orthopedic procedure.

There was no statistical difference between the group N and group F in the Modified Ramsay sedation score and all the patients were arousable, and there was no incidence of respiratory depression. Results of Gupta et al were comparable to our study and showed comparable sedation scores with intrathecal fentanyl (25 micrograms) and nalbuphine (2 milligrams).

The difference in mean duration of post operative analgesia was statistically significant in the two groups with group N having longer duration of analgesia than group F. Our results were comparable to Jyothi et al and Gupta et al.^[5,6] However, Bindra et al showed an increased post operative analgesia with fentanyl than nalbuphine.

The mean VAS (VISUAL ANALOGUE SCALE) score for postoperative pain was lower in Group N as compared to Group F. Patients who received intrathecal nalbuphine required significantly low duration to first rescue analgesia than Group F. Similar results were obtained by Naaz et al,^[7] and Mostafa et al.^[8] The two groups were statistically comparable with regard to heart rate, respiratory rate, and SpO₂. Also, there was no statistically significant difference in hemodynamic parameters in between the study groups.

The various side effects following administration of spinal anesthesia such as pruritus, nausea, vomiting, urinary retention, bradycardia, and hypotension were seen more in group F than group N. Similar results were seen in Gaurav Singh et al.^[9] However, Various studies like Gupta et al, Ahamed et al and Gomaa et al,^[1] have shown that incidence of adverse effects was not increased with nalbuphine or fentanyl. The two groups had no statistically significant difference in the new born APGAR and there was no incidence of respiratory depression in our study. This was comparable to the study conducted by Gomaa et al.^[1]

CONCLUSION

The duration of post operative analgesia following the addition of intrathecal nalbuphine to the local anaesthetic mixture was significantly longer than intrathecal fentanyl with fewer adverse events in patients who underwent elective lower segmental caesarean section.

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