Original Article

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Analgesic Effect of Intrathecal Nalbuphine in Comparison with Fentanyl as an Adjuvant with Hyperbaric Bupivacaine (0.5%) during Spinal Anaesthesia in Lower Abdominal Surgery: A Double-blinded Randomised Clinical Study

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ABSTRACT

Introduction: Local anaesthetics are sometimes added with intrathecal adjuvants. Nalbuphine is a synthetic agonist-antagonist of opioid μ receptor. Fentanyl is a highly potent lipophilic synthetic opioid with rapid onset of action and it acts like morphine. It can be used during spinal anaesthesia for the purpose of decreasing the postoperative pain.

Aim: To compare the safety and efficacy of preservative free intrathecal nalbuphine and fentanyl as additives to intrathecal hyperbaric bupivacaine (0.5%) for spinal anaesthesia.

Materials and Methods: A randomised double-blinded clinical study was undertaken at Calcutta National Medical College and Hospital, Kolkata, West Bengal, India during March 2020 to August 2021 in which a total of 100 patients, belonging to American Society of Anaesthesiology (ASA) physical status I and II and undergoing elective lower abdominal surgery, were randomised into two equal group of 50 each. Group N received intrathecally 0.5 mg of nalbuphine with 3 mL (15 mg) of 0.5% hyperbaric bupivacaine, and group F received 25 μg of Fentanyl with 3 mL (15 mg) of 0.5% hyperbaric. Visual Analogue Scale (VAS) score, Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Mean Arterial Pressure (MAP) and Heart Rate (HR) were recorded at varied intervals during intraoperative and postoperative period.

Results: Significantly lower (p-value <0.001) mean VAS scores was observed beyond six hour of postoperative period in the group F. No significant changes (p-value >0.05) in SBP, DBP, MAP and HR were there between the groups. Few adverse effects like (hypotension, nausea, vomiting) were observed more in the fentanyl group which was statistically insignificant (p-value >0.05).

Conclusion: Intrathecal fentanyl as compared to nalbuphine produces a significant postoperative analgesia when administered as an adjuvant with hyperbaric bupivacaine in cases of lower abdominal surgery.

Keywords: Intrathecal route, Laparotomy, Supplement

INTRODUCTION

Subarachnoid technique of anaesthetic blockade is regularly practiced for lower abdominal and lower limb surgeries. It is simple to carry out by injecting an anaesthetic drug into the subarachnoid space and with fast initiation of anaesthesia, which provides analgesia both intraoperatively and postoperatively. Spinal anaesthesia with lignocaine was highly popular earlier for short surgical procedures as it had a predictable onset and provided dense sensory and motor blockade of moderate duration [1]. Unfortunately, issue of neurotoxicity had cast doubts on the intrathecal use of lignocaine. The phenomenon of "transient neurological symptoms" may be associated with all local anaesthetics; but it is 7-9 times more common with lignocaine than with bupivacaine [2]. In view of debate and uncertainty surrounding the use of spinal lignocaine, in recent time hyperbaric bupivacaine (0.5%) has put back lignocaine as the gold standard drug for the safe conduct of spinal anaesthesia [3]. Although sensory and motor blockade of bupivacaine is satisfactory and its duration of action is longer than that of lignocaine but its slower onset of action sometimes makes it less popular.

Opioid added to local anaesthetic for spinal anaesthesia was first introduced into clinical practice in 1979 with intrathecal morphine as the forerunner. In order to improve the intraoperative and postoperative analgesia, opioids along with local anaesthetics are administered together [4]. Fentanyl, a synthetic opioid, has fast onset of action following intrathecal administration due to its high lipid soluble nature. It does not tend to migrate to the fourth ventricle in sufficient concentration to cause delayed respiratory depression when administered intrathecally [2]. Its side-effects are much less as compared to morphine. It has become very popular additive to hyperbaric bupivacaine in recent times although, side-effects like pruritus, nausea and vomiting and unexpectedly possible occurance of serotonin syndrome related to intrathecal fentanyl has been reported. Intrathecal fentanyl shows a dose dependant duration of its effect [5].

Nalbuphine, an agonist-antagonist opioid, bind to μ receptors, where they produce limited responses (partial agonists) or no effect (competitive antagonists). In addition, nalbuphine often exert partial agonist actions at other receptors, including kappa and delta receptors [2]. It was synthesised to produce analgesia without any unwanted μ agonist side-effects like respiratory depression, undesirable sedation, nausea, vomiting and urinary retention. There are relatively limited published data on the comparison between the effects of addition of nalbuphine and fentanyl as an adjuvant to bupivacaine in spinal block during lower abdominal surgery [6-9].

Hence, the present study was undertaken with the aim to compare the safety and efficacy of preservative free intrathecal nalbuphine and fentanyl as add-on to intrathecal hyperbaric bupivacaine for spinal anaesthesia. The primary objective was to compare the efficacy of preservative free intrathecal nalbuphine and fentanyl as an additive to intrathecal hyperbaric bupivacaine for spinal anaesthesia. The secondary objective was to observe and compare haemodynamic change, and any adverse effect like hypotension, bradycardia, nausea, vomiting in both the groups.

MATERIALS AND METHODS

A randomised double-blinded study was undertaken at Calcutta National Medical College and Hospital, Kolkata, West Bengal (a tertiary care facility) in eastern India between March 2020 to August 2021. Institutional Ethics Committee (IEC) approval (RKC/459 Dated 17.01.2020) was obtained for initiating the study on patients of either sex undergoing elective lower abdominal surgery under spinal anaesthesia.

Inclusion criteria: Patients aged between 18 to 60 years, willing to give written consent for participation, belonging to ASA physical status I and II were included.

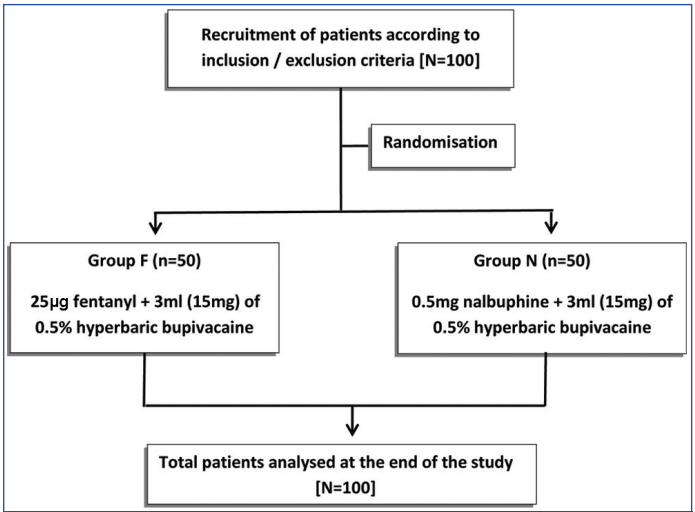
Exclusion criteria: Patients with any contraindication to central neuraxial block, and with known hypersensitivity to any of the study drugs were excluded.

Sample size calculation: The required sample size after calculation turned upto n=41 in each study group which was converted to a round figure of n=50 each, thus recruiting a total on n=100. Sample size was calculated based on formula taking differences in mean and considering alpha and beta errors. Taking Z value of α error (Z_α) as 1.96, Z value of β error (Z_β) as 1.28, success rate (p) as 90% (From pilot study conducted at this institution by this researcher) and difference between mean (d) 18 [10]. During the screening a preanaesthetic evaluation of patients were done a day prior to the surgery and if found eligible for the study, counselling for the spinal anaesthesia procedure was done and informed consent was obtained from the patients. The patients were selected randomly with the help of online random numbers generator.

Procedure

On arrival to the operating theatre, the identification of patient was done and consent was checked. Then multichannel monitors were attached and baseline parameters were noted. Electrocardiogram (ECG), SpO_2 and Non Invasive Blood Pressure (NIBP) was monitored before, during and after the surgery. Then intravenous (i.v.) cannulation was done with 18G i.v. cannula and ringer lactate solution was infused at 15 mL/kg as preloading over 30 minutes and then was continued at maintenance rate. The subarachnoid block was performed with the study drugs with the patient in standard sitting position with a 25G Quincke needle at L3-L4 intervertebral space using midline approach maintaining strict aseptic condition.

Patients of group F received 25 µg of fentanyl with 3 mL (15 mg) of 0.5% hyperbaric bupivacaine, and group N patients were administered 0.5 mg of nalbuphine with 3 mL (15 mg) of 0.5% hyperbaric bupivacaine, diluted upto 4 mL in both the group. All drugs were taken accurately using a 10 mL syringe. The study drug was prepared by an individual who was not involved in the study [Table/Fig-1].



[Table/Fig-1]: Study flow chart.

During operation, all patients received supplemental oxygen with nasal prongs using a flow rate 2 L/min. SBP, DBP, MAP and HR were recorded at the interval of 0, 2, 4, 6, 8, 10, 20, 30, 40, 50, 60 and 90 minutes.

Parameters assessed

Onset of sensory block: The sensory nerve block was assessed bilaterally by using loss of pin prick sensation technique with a 25G hypodermic needle in the mid clavicular line. The time to onset of the sensory block upto T8 dermatome was noted.

Taking into consideration the time of spinal injection as zero, all other durations were calculated accordingly. Patients were observed for intraoperative complications like hypotension, bradycardia, nausea vomiting. Hypotension was defined as >20% fall in baseline MAP or a MAP <65 mmHg. It was treated by fluid bolus for 5 minutes followed by i.v. inj. mephentermine of 3 mg if needed. Bradycardia was defined as heart rate <50 per minute and was treated with inj. atropine 0.6 mg intravenously. A data collection chart was used to record all physiological variables and drugs used during this research activity. During the course of the study, patients who suffered from any surgical complications like severe bleeding or needed re-exploration or needed to be converted into general anaesthesia, such patients were excluded from the study.

In the postoperative period, patients were observed in recovery room for haemodynamic stability and any side-effects or need for additional medications were recorded. Patients were later moved to the ward after normalisation of vital parameters. In the recovery room and in the ward the haemodynamic parameters like MAP, HR starting immediately after operation then till 90 minutes were recorded.

Duration of sensory block: Sensory level of the block was assessed by loss of pin prick sensation using a blunt 25G hypodermic needle along the mid clavicular line bilaterally. The duration of sensory blockade was taken as time from the spinal injection to time of regression to T12 dermatome.

Assessment of analgesia pain was assessed by VAS (where 0 was considered no pain, and 10 as excruciating pain). Rescue analgesia in the form of intramuscular inj. diclofenac 75 mg was given if pain score was more than 4 or on patient's demand which was repeated if needed.

No analgesic was given in the immediate postoperative period until the patient requested for analgesia and time for first analgesia was recorded. Duration of postoperative analgesia was defined as the time between spinal injection and rescue analgesic.

STATISTICAL ANALYSIS

The categorical variables were indicated as the number and percentage of patients and they were compared across the groups using Pearson's Chi-square test for Independence of Attributes/ Fisher's-exact test as seemed appropriate. The continuous variables were shown as mean, median and Standard Deviation and compared over the groups using unpaired t-test. The statistical software Statistical Package for the Social Sciences (SPSS) version 20.0 has been used for the entire analysis of this study. An alpha level of 5% was regarded as significant.

RESULTS

A total of 100 patients were recruited, divided into two equal groups, and administered the two study drugs. The demographic profile like age, gender, and baseline parameters were comparable between two groups as depicted in [Table/Fig-2].

There was a statistically significant change noted in the VAS among the study participants when compared between the groups. Fetanyl appeared to have a better pain control over nalbuphine beyond six hours in the postoperative period till 24 hours of assessment of pain sensation [Table/Fig-3]. The mean time for rescue analgesia was significantly longer in the fentanyl group as compared to the nalbuphine group (p-value <0.0001).

Parameters	Group F (n=50)	Group N (n=50)	p-value
Age years (Mean±SD)	40.07±3.40	39.97±3.10	0.906
Gender			
Male	25	25	1.00
Female	25	25	
American Society of Anaesthesiology (ASA)			
I	25	25	0.782
II	25	25	
Time from injection to T8 level sensory block (minutes)	11.47±1.23	11.72±1.23	0.314
Regression of sensory level upto T12 dermatome (minutes)	153±8.13	152±7.99	0.536

[Table/Fig-2]: Demographic characteristics of the study participants.

Time interval (hours)	Group F (n=50)	Group N (n=50)	p-value
VAS at 6	3.52±0.50	3.50±0.51	0.843
VAS at 12	3.50±0.51	5.90±0.97	<0.001
VAS at 18	5.52±0.51	7.28±0.95	<0.001
VAS at 24	3.80±0.63	5.52±0.95	<0.001
Time from spinal injection to 1st rescue analgesia (minutes)	286.8±14.06	225.49±32.45	<0.0001

[Table/Fig-3]: Comparison of Visual Analogue Scale (VAS) among the two groups in the postoperative period.
A p-value <0.05 is considered to be statistically significant; Values mentioned in Mean±SD

The changes in SBP at different time intervals is depicted in [Table/Fig-4] which was found to be statistically insignificant (p>0.05) when compared among the two study groups. The changes in DBP as shown in [Table/Fig-5] was also found to be statistically insignificant (p>0.05) among the two group at different time intervals. When the MAP was assessed among both the study groups it was also found to be insignificant (p>0.05) across all the time intervals [Table/Fig-6]. An insignificant change (p>0.05) in HR was found while comparing it between the two study groups during assessment at prefixed time intervals [Table/Fig-7].

	SBP (mm Hg) Mean±SD		
Time interval (minutes)	Group F (n=50)	Group N (n=50)	p-value
Preoperative	128.60±11.70	126.20±9.54	0.264
2	125.12±12.11	128.60±11.70	0.147
4	119.10±11.34	114.84±10.85	0.058
6	115.24±9.77	112.76±10.84	0.223
8	112.42±9.04	110.92±10.86	0.445
10	110.22±9.87	110.50±10.50	0.891
20	109.46±9.70	109.38±10.77	0.969
30	107.66±9.49	108.34±10.57	0.736
40	106.64±9.98	107.32±10.20	0.737
50	106.82±10.86	107.12±9.75	0.881
60	108.98±9.74	107.82±8.88	0.156
90	109.38±10.77	110.56±8.55	0.545

[Table/Fig-4]: Comparison of Systolic Blood Pressure (SBP) at various time intervals among the two study groups.

	DBP (mm Hg) Mean±SD		
Time interval (minutes)	Group F (n=50)	Group N (n=50)	p-value
Preoperative	80.10±8.85	80.87±7.81	0.679
2	77.38±9.68	74.18±9.22	0.094
4	72.46±8.56	71.06±9.48	0.440
6	69.04±8.65	69.44±9.56	0.827
8	65.76±7.87	67.74±10.31	0.283
10	64.82±5.86	66.68±10.31	0.270
20	60.92±9.23	61.36±7.40	0.793
30	64.24±5.98	64.80±9.66	0.728
40	64.24±5.98	64.94±9.62	0.663
50	61.28±8.50	64.94±9.62	0.053
60	62.98±8.79	65.16±8.90	0.221
90	69.00±7.54	67.18±8.42	0.258

[Table/Fig-5]: Comparison of Diastolic Blood Pressure (DBP) at various time intervals among the two study groups.

	MAP (mm Hg) Mean±SD		
Time interval (minutes)	Group F (n=50)	Group N (n=50)	p-value
Preoperative	97.02±9.99	94.98±7.02	0.238
2	93.29±10.02	89.25±8.97	0.036
4	88.00±8.86	85.65±9.27	0.198
6	84.44±8.48	83.88±9.50	0.757
8	81.31±7.67	82.13±10.08	0.648
10	78.27±8.37	81.28±9.98	0.105
20	77.10±8.63	79.87±9.84	0.138
30	76.79±7.38	79.31±9.50	0.142
40	76.14±8.15	79.06±9.35	0.099
50	76.46±8.49	78.88±8.95	0.169
60	78.31±8.62	79.38±8.41	0.533
90	84.19±7.14	81.64±8.02	0.096

[Table/Fig-6]: Comparison of Mean Arterial Blood Pressure (MAP) at various time intervals among the two study groups.

	HR (per minute) Mean±SD		
Time interval (minutes)	Group F (n=50)	Group N (n=50)	p-value
Preoperative	82.68±12.42	84.36±13.71	0.522
2	82.04±12.16	83.36±13.94	0.615
4	81.02±11.16	83.82±14.32	0.278
6	79.78±10.72	83.02±14.03	0.198
8	78.58±9.67	80.34±12.51	0.433
10	77.60±8.79	77.75±10.80	0.938
20	76.42±8.14	76.26±11.38	0.936
30	75.46±7.70	75.48±11.20	0.992
40	74.68±7.67	74.92±10.87	0.899
50	74.48±7.70	74.92±9.70	0.802
60	74.18±7.57	74.98±8.64	0.624
90	72.78±7.11	73.84±8.22	0.492

[Table/Fig-7]: Comparison of Heart Rate at various time intervals among the two study groups.

The episodes of hypotension occurred in 14 (28%) in the fentanyl group and 10 (20%) in the nalbuphine group and nausea /vomiting occurred in 4 (8%) in the fentanyl group as compared to 1(2%) in the other group which was statistically insignificant (p>0.05).

DISCUSSION

In the current study, a comparison between a μ agonist- fentanyl with an opioid agonist-antagonist-nalbuphine on postoperative analgesia when used intrathecally with 0.5% hyperbaric bupivacaine were carried out. Wilson J suggested the intrathecal dose of fentanyl as 5-25 mcg as local anesthetic adjuvant [11]. Palmar CM employed fentanyl as a sole agent for labour analgesia and showed that duration of analgesia did not increase by increasing its dose beyond 25 μg [12]. Thus, intrathecal fentanyl at 25 μg dose was chosen for this study.

In the present study, the mean duration of analgesia of fentanyl group was significantly higher than nalbuphine group as indirectly reflected by observing the low VAS score at different time interval [Table/Fig-3]. In contrast, according to Culebras X, postoperative analgesia following nalbuphine 0.5 mg as an intrathecal adjuvant

lasted longer than 0.2 mg or 0.16 mg of the drug [13]. This was also supported by Borah TJ [14], and Mukherjee A [15]. This may have been caused by employment of different doses of adjuvants, local anaesthetics and also probably different postures of the patient. According to Palmar CM, the duration of analgesia of intrathecal fentanyl could not be increased above a dose of 25 µg [12]. On the other hand Culebras X [13], Borah TJ [14], and Mukherjee A [15] stated that the duration of analgesia of intrathecal nalbuphine as adjuvant could be increased by increasing the dose. The significantly longer duration of analgesia was obtained with fentanyl group in this study, over nalbuphine group; which was supported by Prabhakaraiah UN et al., who reported a longer duration of analgesia with fentanyl group [16]. This could be due to a difference in the type of study subjects selected for the conduct of those individual studies. With such findings the VAS score found in the fentanyl group was very significantly low beyond six hours postoperative period as compared to nalbuphine group (p-value <0.001) in the current study.

There was no significant change in onset of sensory block, regression of sensory block to T12 dermatome, MAP and mean HR from baseline values within either group of the present study. The finding was similar to those by Gupta K, who did not find any change in mean HR and SBP between fentanyl 25 µg and nalbuphine even with a very large dose of 2 mg [17]. Adverse effects in between the study groups did not show any significant difference at any point during the study, which was same as in the study by Prabhakaraiah UN et al., [16].

Limitation(s)

The present study was conducted on patients of ASA grade I and II category. Including ASA III or ASA IV could have given different results. Moreover, patients with BMI>35kg/m^2 were not included in this study where drug dose requirement could have been more which might have shown different results. Finally, onset of sensory block may be affected by many other factors like position of the patient which was not taken into account in the present study.

CONCLUSION(S)

Considering more prolonged duration of analgesia, intrathecal fentanyl in postoperative period was found to be significantly better than nalbuphine when used as an adjuvant therapy with 0.5% hyperbaric bupivacaine in elective lower abdominal surgeries with insignificant adverse effects like hypotension, nausea and vomiting.

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