Original Article

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Comparison of Analgesic Efficacy of Levobupivacaine and Levobupivacaine with Nalbuphine in Inguinal Hernia Surgeries Under Subarachnoid Block

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Abstract

Background: Recently there has been an interest to explore the efficacy of nalbuphine as' an adjuvant to local anaesthetic agents. This study was designed to compare its analgesic efficacy when added to levobupivacaine in patients undergoing inguinal hernia surgeries under subarachnoid block.

Methods: Fifty patients belonging to ASA I/II, between 18-65 years of age undergoing inguinal hernia repair were randomly allocated to receive subarachnoid block with either 12.5 mg of 0.5% isobaric levobupivacaine (2.5 ml)+ normal saline (0.5 ml) (Group-LS) or 12.5 mg of 0.5% isobaric levobupivacaine (2.5 ml)+ 1 mg nalbuphine (0.1 ml) + normal saline (0.4 ml) (Group-LN). Onset of sensory block, two segment regression time, time of regression to T12, duration of effective analgesia and intensity of motor block were assessed.

Results: Onset of sensory block was comparable in the two groups (P=0.774). Time of regression of sensory block to T12 dermatome was 161.09 ± 40.50 min in group LS and 167.50 ± 50.17 min in group LN (P=0.633).The duration of effective analgesia was 177.39 ± 43.53 min in group LS and 183.75 ± 56.69 min in group LN (P=0.669).Motor block parameters were also comparable.More number of patients in group LN had a sedation score of one as compared to group LS.No major side effects were seen.

Conclusion: 12.5 mg levobupivacaine with or without nalbuphine is sufficient for conducting inguinal hernia surgeries. Intrathecal nalbuphine 1 mg did not affect the sensory and motor block characteristics of levobupivacaine.

Keywords*:* Nalbuphine; Inguinal hernia; Levobupivacaine; Subarachnoid block.

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Introduction

Inguinal hernia surgeries are commonly performed under subarachnoid block because of safety, reliability, good postoperative analgesia and cost effectiveness.[1,2] Since bupivacaine is implicated with high cardiovascular and neurological toxicity[3-5] newer local anesthetics are being explored. Levobupivacaine is the S-isomer of bupivacaine [6]which supposedly has less cardiac and neurological toxicity than racemic bupivacaine.[3,7]

Various 'adjuvants may be added to intrathecal local anaestheticsto improve the quality and intensity of block and to provide post-operative analgesia. Nalbuphine is a mixed opioid i.e. kappa agonist and μ antagonist. So, it provides analgesia without significant sedation, respiratory depression and pruritus.[8,9]

The block characteristics of hyperbaric drugs such as bupivacaine along with nalbuphine have been studied extensively. However, there is limited literature available on the effect of addition of nalbuphine on the block characteristics of isobaric drug such as levobupivacaine when given via the intrathecal route. Hence, this study was planned to compare the analgesic efficacy of nalbuphine as an adjuvant to levobupivacaine in patients undergoing inguinal hernia surgery under subarachnoid block. The primary objective was assessment of analgesic efficacy and secondary objective were assessment of sensory and motor block parameters and side effects.

Materials and Method

This randomized, double blind, prospective study was undertaken after getting clearance from the Institutional Ethical Committee- Human Research (IEC-HR). The trial was registered with Clinical Trials Registry-India (ctri.nic.in) before enrolling the patients.All the procedures followed were in accordance with the Helsinki Declaration of 1975, as revised in 2000. Patients belonging to American Society of Anesthesiologists(ASA) physical status I/II between 18-65 years of age, height between 150 and 180 cm, scheduled for inguinal hernia surgery under subarachnoid block were included. Patients who did not give consent for subarachnoid block, who had infection at injection site, coagulopathy, any space occupying lesion, increased intracranial tension, seizure disorder, spine deformity, hepatic or renal disease, arrhythmias,drug addicts and chronic alcoholics were excluded.

Written informed consent was taken before recruiting the patients. Patients were transferred to operation theatre where non-invasive blood pressure, ECG and pulse oximetry were monitored. An intravenous access was established and preloading was done with ringer lactate 15 ml/kg over 15-30 minutes. Patients were randomly allocated to one of the two groups using a computer generated table of random numbers.

Group-LS: 12.5 mg of 0.5% isobaric levobupivacaine (2.5 ml) [Levo-anawin, Neon pharmaceuticals Ltd]+ normal saline (0.5 ml)

Group-LN: 12.5 mg of 0.5% isobaric levobupivacaine (2.5 ml) [Levo-anawin, Neon pharmaceuticals Ltd] + 1 mg nalbuphine(0.1 ml) (Nacphin, Neon pharmaceuticals Ltd) + normal saline (0.4 ml)

The total volume of intrathecal drug injected was 3 ml in both the groups.

Study drug was prepared by an anesthesiologist who was not involved in the further conduct of the study. Both, the patient and the anesthesiologist who assessed the block characteristics and other parameters were kept blinded to group allocation.

Subarachnoid block was performed under all aseptic precautions in sitting position with midline approach. A 25 G Quincke's spinal needle was introduced at L2-L3/L3-L4 intervertebral space with bevel facing cephalad and 3 ml of the study drug was injected at the rate of 0.5 ml/sec after confirming free flow of cerebrospinal fluid. After removing spinal needle, patient was made supine. Oxygen was given by facemask at the rate of 4 L/min. Heart rate, blood pressure, arterial oxygen saturation, respiratory rate, VAS score, motor block as per Modified Bromage scale (MBS) and sedation score were recorded every 5 min for first 30 min and then every 15 min till the end of surgery. The level of sensory block was assessed by pin prick method in mid clavicular line using a 26G hypodermic needle every 2 min until the level had stabilized for 3 consecutive tests and this sensory level was recorded as the highest level of sensory block following which it was assessed at intervals mentioned above for other parameters.

Any episode of hypotension, determined by fall in systolic blood pressure (SBP) >20% from pre-operative baseline value or SBP<90 mm Hg was managed by rapid infusion of additional intravenous fluids and mephentermine 6 mg I.V.Bradycardia (heart rate less than 50/minute) was treated with atropine 0.6 mg I.V. Intraoperative nausea, vomiting, headache, dizziness, pruritus and any other side effects were noted and treated accordingly. Quality of sensory block was assessed

as the time of onset of block at T10 dermatome, maximum block height, time of two segment regression of sensory block (from the maximum height of block), time of regression of sensory block to T12 dermatome and duration of effective analgesia. Motor block was assessed as per the Modified Bromage Scale[10] as follows:

Grade	Criteria
0	No motor loss
1	Inability to flex the hip
2	Inability to flex the knee
3	Inability to flex the ankle

In case the sensory block level of T10 was not achieved by 20 min after intrathecal injection, patient was given general anaesthesia and was counted as failure.

After completion of surgery, patients were shifted to postoperative ward and all the parameters mentioned above were recorded at every 15 min till the time when the patient first complained of pain (VAS ≥ 3). Pain was evaluated by using a 0-10 cm Visual Analogue Scale (VAS) where '0' represents no pain and '10' represents worst imaginable pain.[11]

Pain was noted at intervals mentioned previously. Duration of effective analgesia was defined as time from giving subarachnoid block to patient's first complaint of pain (VAS ≥ 3). At the time of patient's first complaint of pain, paracetamol 1g I.V.was given as rescue analgesia.

Sedation was assessed as per University of Michigan Sedation Scale as mentioned below.[12]

0	Awake and alert
1	Minimally sedated: tired/sleepy, appropriate response to verbal conversation and/or sound
2	Moderately sedated: somnolent/ sleeping, easily aroused with light tactile stimulation or a simple verbal command
3	Deeply sedated: deep sleep, arousable only with significant physical stimulation
4	Unarousable

Considering a standard deviation of 46.9 min from a previous study7 to estimate a difference of 40 min in time of regression of sensory block to T12 dermatome, at 5% level of significance and 80% power, 22 cases were required in each group. To account for failures, a total of 50 patients were randomized to one of the two groups (25 patients per group).

Statistical analysis was carried out using SPSS, software version 20.0. The quantitative parameters like age, height, weight, time of onset of block, time to two segment regression of sensory block, time of regression of sensory block to the level of T12 dermatome and duration of effective analgesia which were measured at one-time point were compared using unpaired t-test. Level of block and Modified Bromage Scale were represented as median [inter-quartile range] and were compared by Mann-Whitney U-test. Sedation score was analysed using Chi-square test. Repeated measure ANOVA was used to compare the haemodynamic variables. A p-value <0.05 was considered as significant.

Results

A total of 78 patients were enrolled. Twenty eight were excluded for various reasons. A total of 50 patients were randomized into two groups of 25 each to receive allocated intervention (Figure 1). Two patients from group LS and one patient from group LN were excluded due to failure of subarachnoid block. So, a total of 47 patients were analysed.

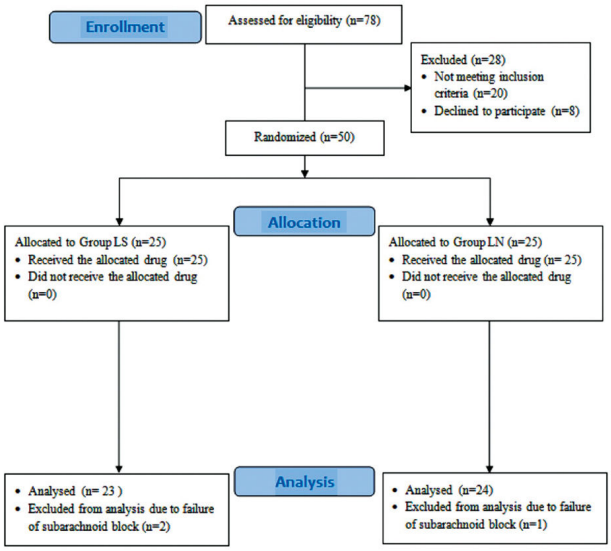

Fig. 1: Consort flow diagram.

Table 1: Demographic Profile.

Parameter	Group LS (n=23)	Group LN (n=24)	P
Age (yr)	36.2 ± 13.0	42.0 ± 13.8	0.146
Weight (kg)	61.8 ± 7.2	56.6 ± 6.9	0.015
Height (cm)	163.6 ± 5.5	160.2 ± 4.1	0.021
Duration of surgery (Min)	80.87 ± 11.74	70.00 ± 13.75	0.006

Yr=year, kg=kilogram, cm=centimetre, Min=

minutes. P< 0.05 is considered statistically significant, Values are expressed as Mean ± SD.

Table 2: Characteristics of Sensory Block.

Parameter	Group LS (n = 23)	Group LN (n = 24)	P
Maximum Block height*	T6 [T6-T8]	T6 [T6-T8]	0.798
Time of onset of block (min)†	5.30 ± 2.34	5.41 ± 2.07	0.774
Time of two segment regression(min)†	61.09 ± 28.88	54.58 ± 19.33	0.372
Time of regression to T12 (min)†	161.09 ± 40.50	167.50 ± 50.17	0.633
Duration of effective analgesia (min)†	177.39 ± 43.53	183.75 ± 56.69	0.669

* values are expressed as Median [IQR], †values are expressed as Mean ± SD

P < 0.05 is considered statistically significant, min = minutes

Table 3: Motor Block (Modified Bromage Scale (MBS).

Time	Group LS (n = 23)	Group LN (n = 24)	*P*
5 min	2.00 [1.00-2.00]	2.00 [2.00-2.00]	0.342
10 min	2.00 [2.00-3.00]	2.00 [2.00-3.00]	0.924
15 min	3.00 [3.00-3.00]	3.00 [2.00-3.00]	0.220
20 min	3.00 [3.00-3.00]	3.00 [3.00-3.00]	0.912
25 min	3.00 [3.00-3.00]	3.00 [3.00-3.00]	0.956
30 min	3.00 [3.00-3.00]	3.00 [3.00-3.00]	0.176
45 min	3.00 [3.00-3.00]	3.00 [3.00-3.00]	0.322
60 min	3.00 [3.00-3.00]	3.00 [3.00-3.00]	0.322
75 min	3.00 [3.00-3.00]	3.00 [3.00-3.00]	0.322
90 min	3.00 [3.00-3.00]	3.00 [3.00-3.00]	0.322

min = minutes, P< 0.05 is considered statistically significant. values are expressed as Median [Inter-quartile range. Demographic profile and duration of surgery is shown in table 1. There was a statistically significant difference in the mean weight and height of patients between the two groups but these were clinically comparable. The mean duration of surgery also showed a statistically significant difference between the two groups. However, the absolute time difference was approximately 10 min.

The sensory block characteristics are shown in table 2. There was no significant difference between the two groups.

Motor block intensity was also comparable in both groups at all the time points. (Table 3)

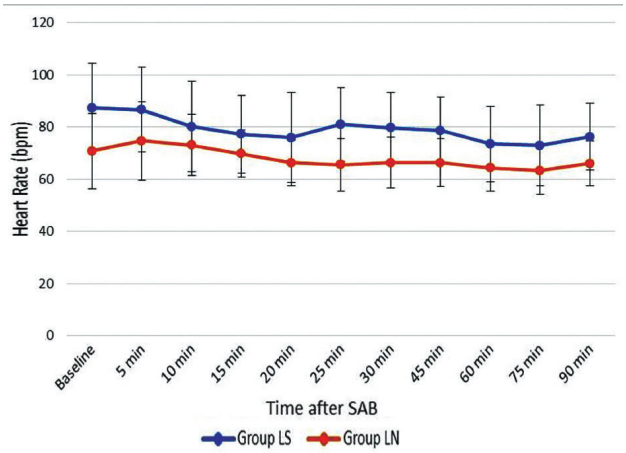

Fig. 2: Heart rate trends in both groups.

Numerical data on which figures are based for figure 2-Heart rate trends in both groups.

Time	Group LS (n = 23)	Group LN (n = 24)	P
Baseline	87.4 ± 17.0	70.8 ± 14.5	
5 min	86.7 ± 16.3	74.7 ± 15.0	
10 min	80.2 ± 17.2	73.1 ± 11.7	
15 min	77.3 ± 14.9	69.8 ± 9.0	
20 min	76.0 ± 17.4	66.3 ± 8.7	
25 min	81.0 ± 14.1	65.5 ± 10.1	= 0.001
30 min	79.7 ± 13.5	66.3 ± 9.8	
45 min	78.6 ± 13.0	66.3 ± 9.2	
60 min	73.5 ± 14.4	64.4 ± 8.9	
75 min	73.0 ± 15.6	63.3 ± 9.2	
90 min	76.3 ± 12.7	66.0 ± 8.6	

min = minutes, p<0.05 is considered statistically significant, values are expressed as Mean ± SD.

Heart rate was significantly less in group LN patients starting from baseline value and at all the time points as compared to group LS and same trend was observed till the last measured time point (Figure 2). There was no statistically significant difference in SBP and DBP (Figure 3).

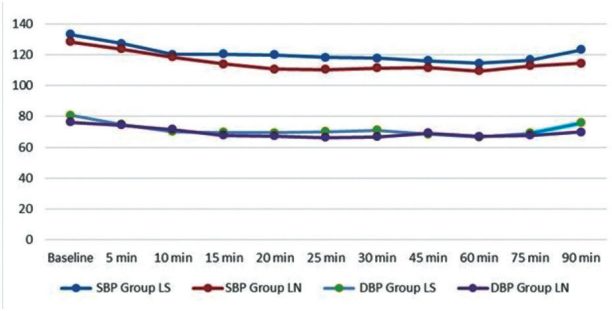

Fig. 3: Blood pressure trends in both groups.

For Figure 3 Blood pressure trends in both groups Systolic Blood Pressure (SBP in mmHg).

Time	Group LS (n = 23)	Group LN (n = 24)	P
Baseline	133.1 ± 10.8	128.3 ± 14.5	
5 min	127.3 ± 13.1	123.7 ± 13.7	
10 min	120.0 ± 14.0	118.5 ± 14.5	
15 min	120.3 ± 12.0	114.0 ± 13.4	
20 min	119.8 ± 11.3	110.7 ± 14.0	
25 min	118.2 ± 14.0	110.4 ± 12.4	0.061
30 min	117.7 ± 12.7	111.3 ± 11.8	
45 min	116.2 ± 12.7	111.7 ± 10.2	
60 min	114.5 ± 12.0	109.4 ± 10.2	
75 min	116.5 ± 10.0	112.7 ± 8.8	
90 min	123.2 ± 14.7	114.4 ± 9.2	

min = minutes p< 0.05 is considered statistically significant, values are expressed as Mean ± SD

Diastolic Blood Pressure (DBP in mmHg)

Time	Group LS (n = 23)	Group LN (n = 24)	P
Baseline	80.9 ± 8.7	76.4 ± 8.7	
5 min	74.9 ± 10.7	74.4 ± 10.3	
10 min	70.1 ± 13.8	71.5 ± 10.8	
15 min	69.7 ± 11.7	67.8 ± 9.1	
20 min	69.3 ± 9.7	67.2 ± 9.4	
25 min	70.1 ± 12.0	66.3 ± 9.8	0.433
30 min	71.1 ± 12.4	66.8 ± 11.1	
45 min	68.4 ± 10.0	69.2 ± 9.4	
60 min	66.6 ± 10.3	67.0 ± 8.4	
75 min	69.2 ± 7.6	67.7 ± 9.2	
90 min	75.9 ± 15.5	69.8 ± 8.3	

min = minutes

p< 0.05 is considered statistically significant,values are expressed as Mean ± SD

Respiratory rate was within normal range and comparable in both groups. (Figure 4) (P=0.318)

All the patients in group LS and LN had a sedation score of 0 or 1. None of the patients had sedation score ≥ 2. The degree of sedation was comparable in both the groups at 5, 10 and 90 min.

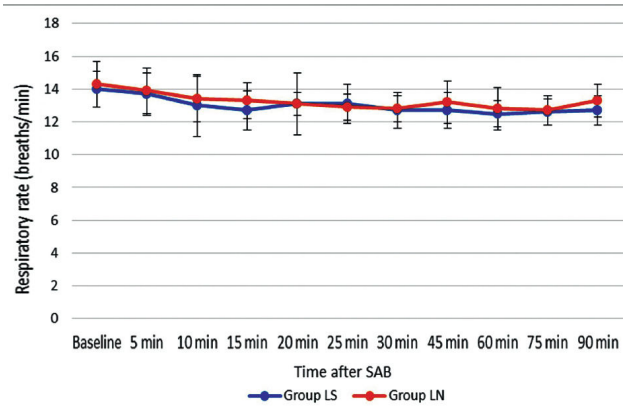

Fig. 4: Respiratory rate trends in both groups.

For figure 4 Respiratory rate trends in both groups.

Time	Group LS (n = 23)	Group LN (n = 24)	P
Baseline	14.0 ± 1.1	14.3 ± 1.4	
5 min	13.7 ± 1.3	13.9 ± 1.4	
10 min	13.0 ± 1.9	13.4 ± 1.4	
15 min	12.7 ± 1.2	13.3 ± 1.1	
20 min	13.1 ± 1.9	13.1 ± 0.7	0.318
25 min	13.1 ± 1.2	12.9 ± 0.8	
30 min	12.7 ± 1.1	12.8 ± 0.8	
45 min	12.7 ± 1.1	13.2 ± 1.3	
60 min	12.5 ± 0.8	12.8 ± 1.3	
75 min	12.6 ± 0.8	12.7 ± 0.9	
90 min	12.7 ± 0.9	13.3 ± 1.0	

min = minutes

p< 0.05 is considered statistically significant, values are expressed as Mean ± SD.

However at all-time points from 15 min to 75 min, more number of patients in group LN had a sedation score of 1 compared to group LS and a statistically significant difference was seen. (Table 4)

Hypotension was seen in two patients in group LS and one patient in group LN. Bradycardia was seen in six patients in group LS compared to none in group LN. There was no incidence of pruritus, headache, dizziness, nausea, vomiting or any other side effects. (Table 5)

Discussion

'Intrathecal nalbuphine' has been used in many studies as an adjuvant to hyperbaric bupivacaine in dose ranging from 0.2 to 2.4 mg. Also, many studies have been conducted in past by using levobupivacaine through subarachnoid route in dose ranging from 8-15 mg. But there are only

limited number of studies which have analysed the effect of addition of nalbuphine to levobupivacaine via subarachnoid route. Hence this study was planned to find out the effect of addition of 1 mg nalbuphine to 12.5 mg isobaric levobupivacaine for the conduct of inguinal hernia surgeries under subarachnoid block.

The major findings of our study were that the duration of effective analgesia and the time of regression of sensory block to T12 dermatome were not prolonged with the addition of nalbuphine to levobupivacaine. Patients in the nalbuphine group had minimal sedation and were easily arousable on verbal commands (score 1). The quality of sensory and motor block and frequency of side-effects were also not affected by the addition of nalbuphine.

There were three cases of failed subarachnoid block (two in group LS and one in group LN), where the sensory block remained below T10 level. However, in all the other patients, the duration of sensory block provided by 12.5 mg levobupivacaine was sufficient to conduct the surgery in both the groups. Previous studies have also found a similar dose of levobupivacaine to be sufficient for the conduct of TURP procedures under subarachnoid block.[7]

In our study the time of onset of block to T10 was 5.30 ± 2.34 min in control group and 5.41 ± 2.07 min in nalbuphine group (P= 0.774). Previous study[13] has reported the median time of onset of levobupivacaine alone to be 3 min, which is early as compared to our study. This difference may be attributed to the different definition adopted by them for the onset.They defined the onset of block to be at the level of T12, which is a lower dermatome than T10, defined in our study. In the study by Vanna et al[7], the onset of block was 10.4 ± 4.3 min which is delayed as compared to our finding. This difference may be due to the lower volume of the intrathecal drug used in their study (2.5 ml) compared to 3 ml in our study. In our study, addition of nalbuphine to levobupivacaine had no effect on the time of onset of SAB.In most of the previous studies, 'intrathecal nalbuphine had' no effect on the time of onset of hyperbaric bupivacaine.[14,15]

The median maximum block height of T6 [T6-T8] was attained in both the groups. Other studies have also reported similar block height with levobupivacaine.[13,16] However, in the study by 'Vanna et al'[7], the median maximum block height was T9, with a very large variation ranging from T4-T10. This may be due to isobaric nature of drug. In our study, the interquartile range of block height was between T6-T8. However, in three patients sensory block height was lower than T10 and hence these patients were excluded from the analysis as defined in the protocol.

Studies have shown that use of isobaric local anaesthetic by subarachnoid route has been associated with a greater variability in spread of block and a less predictable spread, so the block height achieved may be low, being inadequate for surgery or high leading to side effects.[17,18] Mukherjee et al[19] studied nalbuphine in dose of 0.2 mg, 0.4 mg and 0.8 mg as adjuvant to 12.5 mg of 0.5% bupivacaine versus 0.5 ml normal saline plus 12.5 mg of 0.5% bupivacaine and found the maximum block height as T6 in all the groups.This finding was similar to our study as the addition of nalbuphine did not affect the maximum block height attained by using local anaesthetic alone.

In the studies by Mantouvalou et al[20] and Jindal et al[21] the time to two segment regression was found to be 65 ± 11 min and 69.8 ± 6.61 min respectively. These observations are very close to our findings where the time to two segment regression was 61.09 ± 28.88 min in control group. Longer time to two segment regression with levobupivacaine have however been reported in the study by Hoda et al[2], Vanna et al[7] and Sinha et al[22] (129.68 ± 15.54, 101.0 ± 54.3, 111.77 ± 6.03 respectively).We did not find any prolongation in time to two segment regression with addition of nalbuphine (54.58 ± 19.33 min). Our findings are in contrast to those of Sinha et al[22] who reported an increase in the time to two segment regression with 0.4 mg nalbuphine (111.77 ± 6.03 min with plain levobupivacaine versus 175.03 ± 7.93 min with levobupivacaine plus nalbuphine).

In our study, the time of regression of block to T12 was 161.09 ± 40.50 min in group LS while it was 167.50 ± 50.17 min in group LN and was comparable. None of the studies with levobupivacaine-nalbuphine combination have reported regression time to T12 level. However, the study by Shraddha et al[23] found that addition of nalbuphine to intrathecal bupivacaine prolonged the time of regression of block to S1.

In our study, duration of effective analgesia was 177.39 ± 43.53 min in group LS and 183.75 ± 56.69 min in group LN and there was no significant prolongation with addition of nalbuphine. The finding of Sinha et al[22] is contradictory to our result as in their study,the duration of effective analgesia was 168.47 ± 6.49 min with plain levobupivacaine and 316.13 ± 15.62 min with levobupivacaine-nalbuphine combination.

A median motor block grade 3 Modified Bromage Scale i.e. complete motor block was obtained in both the groups by 15 min and was present till the end of surgery. So the operating conditions were reported as good by most of the surgeons.

Though in our study, there was a statistically significant difference seen in the heart rate between the two groups, this was because the mean baseline heart rate was less in nalbuphine group. The same trend was continued till the last measured time point. The difference in baseline cannot be attributed to our study drug and therefore it was purely by chance. All other haemodynamic parameters like systolic blood pressure, diastolic blood pressure and mean arterial blood pressure were comparable in both groups at all the time points. So, the addition of nalbuphine to levobupivacaine did not alter the haemodynamic parameters. Similar to our study, Sinha et al[22] reported comparable hemodynamics with levobupivacaine with or without addition of nalbuphine.

In our study, there was no evidence of respiratory depression with the addition of nalbuphine. Similar findings were also reported by Rehab et al[24] and Sinha et al[22] Nalbuphine exhibits ceiling effect on respiratory depression. This is because respiratory depression is μ receptor mediated and nalbuphine is μ antagonist.[25]

In our study, all the patients had a sedation score of 0 or 1. None of the patients had sedation score ≥ 2. At all the time points from 15 min to 75 min, more number of patients in nalbuphine group had a sedation score of 1 compared to control group. Sedation was minimal as per University of Michigan Sedation Scale and these patients were easily arousable with verbal commands. Similar to our study, Jyothi et al[25] and Shakooh et al[26] also reported occurrence of sedation with addition of nalbuphine. The patients undergoing surgery under subarachnoid block are aware of their surroundings, and it becomes necessary to sedate them. Intrathecal nalbuphine provides light sedation, thus reducing the need for any additional sedative drug. However, none of the patients had deeper levels of sedation as seen with the μ-agonists. The incidence of hypotension, bradycardia, pruritus, dizziness, headache, nausea, vomiting or any other side effect was not increased due to the addition of nalbuphine to levobupivacaine.

This was one of the few studies which compared the block characteristics of intrathecal levobupivacaine with or without nalbuphine in a uniform group of patients undergoing similar type of surgery, i.e. inguinal hernia surgeries. So the degree of pain, the extent of tissue handling during the surgery was similar among the patients, thus removing the element of bias due to these factors. However, the study has a few limitations. The detailed motor block parameters like onset, time to peak motor blockade and duration of motor blockade and time to home readiness were not studied.

From the above observations, we conclude that 12.5 mg levobupivacaine with or without nalbuphine is sufficient to conduct inguinal hernia surgery. Intrathecal nalbuphine in a dose of 1 mg when added to 12.5 mg levobupivacaine provided similar sensory and motor block characteristics as 12.5 mg levobupivacaine alone with minimal sedation and without any increase in the incidence of side effects.We recommend that further studies using higher dose of nalbuphine as adjuvant to levobupivacaine via subarachnoid route should be conducted to assess its analgesic efficacy for providing postoperative analgesia.

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