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Research Article

COMPARISON OF TWO DOSES OF INTRATHECAL NALBUPHINE AS AN ADJUVANT TO BUPIVACAINE IN LOWER ABDOMEN AND LOWER LIMB SURGERIES

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A B S T R A C T

Background and aim: Our aim was to compare and evaluate the effect of addition of two doses of Nalbuphine 0.2 mg and 0.4 mg to Hyperbaric 0.5% Bupivacaine intrathecally in patients undergoing lower abdominal and lower limb surgeries.
Methods: The study was conducted on 50 patients randomly divided into two groups of 25 each belonging to ASA grade I and II, aged between 18 to 60 years of either gender, scheduled for elective lower abdomen or lower limb surgeries under spinal anaesthesia. In Group A, 0.2 mg nalbuphine diluted to 0.5 ml was added to 3 ml 0.5% hyperbaric bupivacaine to make a total volume of 3.5 ml whereas in Group B, 0.4 mg nalbuphine diluted to 0.5 ml was added to 3 ml 0.5% hyperbaric bupivacaine to make a total volume 3.5 ml. The onset of sensory and motor block, time taken for peak sensory block, two segment regression of sensory block, duration of motor and sensory block and time taken for rescue analgesia were noted. Side effects and haemodynamic changes were also noted.
Results: The demographic profile of the study subjects was comparable. Parameters observed revealed that the onset of sensory blockade was comparable in both the groups and onset of complete motor block was faster in the Nalbuphine 0.4 mg group as compared to the Nalbuphine 0.2 mg group. The total duration of sensory and motor block were significantly prolonged in the Nalbuphine 0.4 mg group. The duration of analgesia was longer in the patients who received Nalbuphine 0.4 mg. The VAS scores in the postoperative period were lower in the patients who received Nalbuphine 0.4 mg as compared with Nalbuphine 0.2 mg. Hemodynamic and respiratory parameters were stable and comparable among both groups throughout the surgery. Side effects were also comparable in the two groups.
Conclusion: We compared two doses of Nalbuphine, 0.2 mg and 0.4 mg when added intrathecally to hyperbaric 0.5% Bupivacaine for surgeries of lower abdomen and lower limb surgeries and recommend 0.4 mg nalbuphine as the preferred dose when compared to 0.2 mg as an adjuvant to 0.5 % hyperbaric bupivacaine given intrathecally with prolonged duration of sensory and motor blockade and prolonged duration of postoperative analgesia with minimal side effects.

INTRODUCTION

Sub arachnoid block also known as intrathecal block[1] is a form of neuraxial regional anesthesia which was first introduced in 1885 by Corning and further experimented by Bier in 1898 which is marked as a revolution in history of anesthesia. It is a relatively simple and a quick technique with a rapid onset of action used as an alternative to general anesthesia allowing surgical incision to be made sooner hence reducing the total time of the surgical procedure significantly with reduced risk of airway complications, better margin of safety, early ambulation with good quality of post-operative analgesia[2]

It is prudent to ensure adequate alleviation of pain and an anxiety post operatively. For surgeries performed on lower abdomen and lower limb, subarachnoid block with local anesthetic agents provides dense blockade suitable for the procedure. Preservative free 0.5 % hyperbaric bupivacaine is a commonly used and aneconomical local anaesthesia drug which provides a definitive motor and sensory blockade[3,4,5]

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Spinal anesthesia with 0.5 % bupivacaine provided postoperative analgesia for a short time, hence various adjuvants have been used to accelerate the onset of the neuraxial block, augment the quality and prolong the total period of neuraxial blockade. Commonly used pharmacological agents as adjuvants include opioids, sodium bicarbonate, vasoconstrictors (epinephrine), alpha-2-adrenoceptor agonists (clonidine and dexmedetomidine) etc. Nearly all opioids have been attempted through spinal anesthesia with varied degree of success.

Morphine and fentanyl are one of the most often used opioids. Fentanyl is an opioid agonist with significant action on mu opioid receptors[6]. Nalbuphine is a novel introduction in pharmacology as an adjuvant to local anesthesia drugs. It is a mixed agonist-antagonist synthetic opioid which has agonist action on kappa receptors and a partial antagonist action on mu receptors[7,8]. This distinct mixed agonist-antagonist action of nalbuphine on opioid receptors helps provide reasonably potent analgesia with less nausea and respiratory depression when compared with morphine[9]. As far as morphine, fentanyl

and nalbuphine are concerned, nalbuphine is easily available in India and is devoid of side effects.

The aim of our study was to compare two doses of intrathecal nalbuphine 0.2 mg and 0.4 mg as an adjuvant to 0.5% Bupivacaine and determine the optimum dose with quicker onset and longer duration of sensory and motor block, longer analgesic effect and minimal side effects for lower abdomen and lower limb surgeries under sub arachnoid block.

METHODS

The study was conducted at our institute and Institute Ethics Committee Clearance was obtained before start of the study. The study was conducted on 50 patients randomly divided into two groups of 25 each belonging to ASA grade I and II, aged between 18 to 60 years of either gender, scheduled for elective lower abdomen or lower limb surgeries under spinal anaesthesia. In Group A, 0.2 mg nalbuphine diluted to 0.5 ml was added to 3 ml 0.5% hyperbaric bupivacaine to make a total volume of 3.5 ml whereas in Group B, 0.4 mg nalbuphine diluted to 0.5 ml was added to 3 ml 0.5% hyperbaric bupivacaine to make a total volume 3.5 ml.

Patients who were not willing to get enrolled in this study, with systemic disorders like Diabetes Mellitus, Hypertension, heart disease, renal and hepaticdisease, patients with bleeding or coagulation disorders, any neurological or psychiatricdisorders, any contraindication for neuraxialblockade, patients posted for emergencysurgery were excluded from our study.

After thoroughly evaluating pre-operatively, one day prior to surgery, all the patients were kept nil per oral (NPO) for a period of at least 6 hours prior to the surgery. A good and secure intravenous line was obtained using a 20 G IV cannula. In the operation theatre, all the monitors such as NIBP, pulse oximeter and ECG were connected to the patients and baseline parameters were recorded. All the subjects were preloaded with Ringer Lactate at the rate of 10 ml/kg and maintained on IV fluids throughout the procedure. Under all aseptic precautions lumbar puncture was performed using 26G Quincke spinal needle. The drug to be given was prepared by one of the authors who did not take part in the further study and both the anaesthesiologist and the patient were kept blinded to the study drug. All hemodynamic parameters were monitored at 3/5/10/15/20/25 and 30 minutes and thereafter every 15 minutes till the end of surgery and postoperatively for half and hour. Intraoperative hypotension and bradycardia was managed by colloids and inj atropine 0.6 mg, respectively. Supplemental oxygen was administered to the needful patients at the rate of 3 L/min with Hudsons' mask. Sensory block was tested by pinprick method in the left mid-clavicular line till the block reached the highest sensory level and then surgical incision was allowed. Time of onset of sensory block was measured as time taken from the end of intrathecal injection to loss of the pinprick sensation at T12 level.

Motor blockade was assessed using BROMAGE SCALE [10] and time of onset of complete motor blockade was measured as time taken from intrathecal injection to development of Grade IV on Bromage Scale ie inability to move legs or feet.

The quality of postoperative analgesia was assessed with the help of Visual Analogue Scale (VAS) [11] which involves use of a 10 cm line on a piece of white paper and it represents patient's opinion for degree of pain. It was explained to all patients preoperatively that one end of the line i.e., "0" marks "no pain" at all, while other end i.e., "10" represents "Worst pain" he/she has ever felt. Patients rated the degree of pain by making a mark on the scale. Thus the pain score was obtained by measuring the distance from the "0" end to the indicated mark. Subsequent rescue analgesics with inj. Tramadol 50mg IV were given if the patient had a pain score of 4 or more than 4. Duration of analgesia was measured from time of subarachnoid block till the patient demanded the first rescue analgesic.

Side effects such as nausea, vomiting, pruritus, hypotension, bradycardia, respiratory depression, etc. were noted.

Statistical analysis: The data obtained was collected, compiled and tabulated. The graphs and tables were prepared using Microsoft Word and Excel. For quantitative data, "Unpaired t test" was used to determine whether there were any statistically significant differences between the means of two independent groups. P value was considered significant if lesser than 0.05 at 95 % confidence interval. For categorical data, Chi square test was applied. All statistical calculations were done using computer programs Microsoft Excel 2007 and SPSS version 21.

RESULTS

Table 1 Demographic profile

	Nalbuphine 0.2mg	Nalbuphine 0.4 mg	T value	P value
Age	36.64±9.94	37.2±8.77	0.211	0.833
Height	155.84±5.24	154.56±5.50	0.842	0.403
Weight	59.04±3.95	58±4.35	0.884	0.380

Both the groups were similar in terms of their age, height and weight as seen in Table 1.Unpaired t test was used to compare mean and standard deviation , p value of <0.05 was considered as statistically significant.

Table 2 Block Characteristics

	Nalbuphine 0.2mg	Nalbuphine 0.4 mg	T test	P value
Time of onset of Senory Block (in Mins)	1.62±0.20	1.57±0.18	0.929	0.357
Time of Onset of Motor Block (in Mins)	5.81±0.26	5.62±0.25	2.63	0.001*
Time of Peak Sensory Block (in Mins)	8.18±0.43	7.12±0.80	5.83	<0.0001*
Two Segment Regression (In Mins)	128.88±2.99	142.28±6.91	8.89	<0.0001*
Duration of Motor Block (In Mins)	170.4±9.56	184.8±8.22	5.71	<0.0001*
Duration of sensory block (in mins)	186.2±7.53	210.2±5.29	11.85	<0.0001*

Unpaired t test was used to compare mean and standard deviation, p value of <0.05 was considered as statistically significant

In Nalbuphine 0.2 mg group, mean time for sensory block onset was (1.62 ± 0.20 mins) and in Nalbuphine 0.4 mg group, it was (1.57 ± 0.18 mins). As the "p value" was >0.05; there was a statistically insignificant variation in the two groups as seen in Table 2 In Nalbuphine 0.2 mg group, mean time taken for onset of complete motor block was (5.81 ± 0.26 mins) and in Nalbuphine 0.4 mg group it was (5.62 ± 0.25 mins). As the "p value" was 0.001, there was a highly significant difference with faster onset of complete motor block in the Nalbuphine 0.4 mggroup as seen in Table 2

In Nalbuphine 0.2 mg group, the mean time to peak sensory level block was (8.18 ± 0.43 mins) whereas in Nalbuphine 0.4 mg group, it was (7.12 ± 0.8 mins). As the "p value" was 0.001, there was a highly significant difference with faster peak sensory block in the Nalbuphine 0.4 mggroup as seen in Table 2

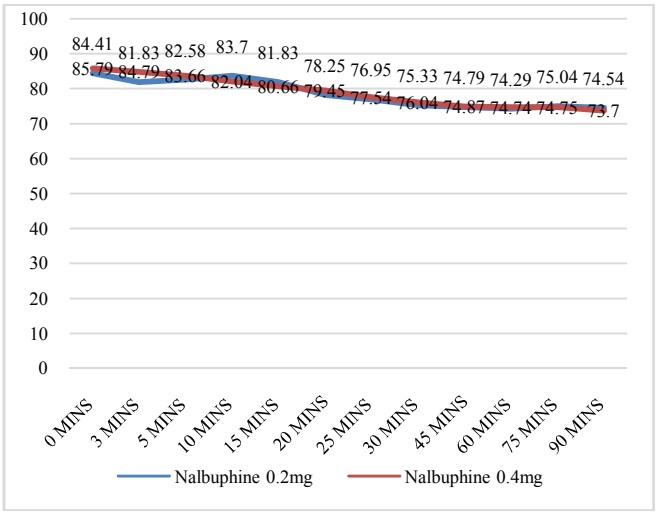
In Nalbuphine 0.2 mg group, the mean value of two segment regression was (128.88 ±2.99 mins) whereas in Nalbuphine 0.4 mg group, it was (142.28 ± 6.91 mins). Statistical analysis revealed a highly relevant variation with "p value < 0.0001", with prolonged two segment regression in patients who received Nalbuphine 0.4 mgas seen in Table 2

In Nalbuphine 0.2 mg group, the mean value of total duration of motor block was (170.40 ± 9.56 mins) whereas in Nalbuphine 0.4 mg group, it was (184.80 ± 8.22 mins). Statistical analysis revealed a highly relevant variation with "p value < 0.0001" with prolonged duration of motor blockade in patients who received Nalbuphine 0.4 mg as seen in Table 2

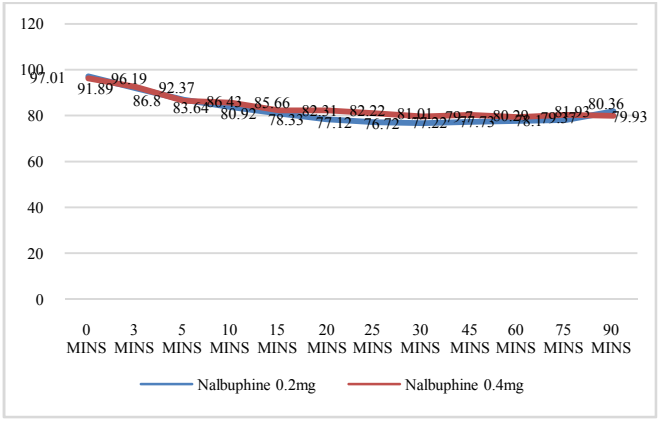
In Nalbuphine 0.2 mg group, the mean duration of sensory block was (186.2 ± 7.53 mins) whereas in Nalbuphine 0.4 mg group, it was (210.2 ± 5.29 mins). Statistical analysis revealed a highly relevant variation with "p value < 0.001". The time to rescue analgesia was significantly prolonged in the patients who received Nalbuphine 0.4 mg as seen in Table 2

Haemodynamic parameters

There was no statistically significant variation in Heart rate and Mean Arterial Pressure in both the study groups



Graph 1 Comparison of HEART RATE in both the study patients groups



Graph 2 Comparison of Mean Arterial Pressure in mm of Hg in both the study patients groups

There was no statistically significant variation in Respiratory Rate and Oxygen Saturation as well between the two groups at all time intervals since p value was > 0.05.

Duration of Analgesia

Table 3 Comparison of time taken for rescue analgesia in both the groups

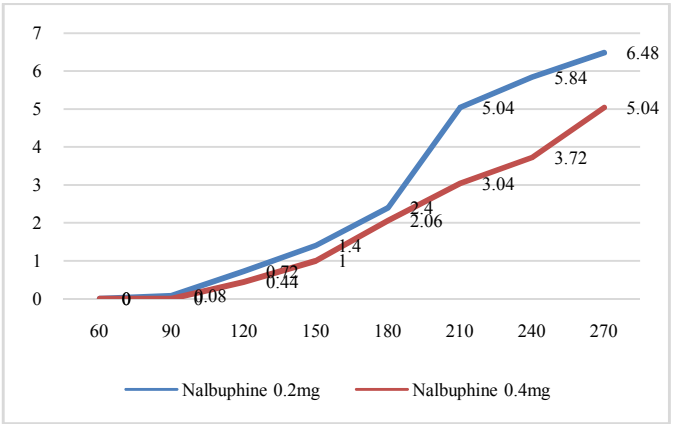
	Nalbuphine 0.2mg	Nalbuphine 0.4 mg	T test	P value
Time to rescue analgesia	208.92±9.68	250.6±8.81	15.92	**<0.0001***

Unpaired t test was used to compare mean and standard deviation, p value of <0.05 was considered as statistically significant.

In Nalbuphine 0.2 mg group, the **mean duration of analgesia** was (208.92 ± 9.68 mins) whereas in Nalbuphine 0.4 mg group, it was (250.6 ± 8.81 mins). Statistical analysis revealed a highly relevant variation with "p value < 0.001". The time to rescue analgesia was significantly prolonged in the patients who received Nalbuphine 0.4 mg.

Table 4 Showing the comparison of visual Analogue Scale in both the study patients groups

TIME (in minutes) from Induction	Nalbuphine 0.2mg	Nalbuphine 0.4mg	P VALUE
60	0	0	-
90	0.08±0.27	0	0.110
120	0.72±0.79	0.44±0.53	0.112
150	1.4±0.50	1±0.86	0.031*
180	2.4±0.50	2.06±0.68	0.033*
210	5.04±0.61	3.04±0.67	<0.001*
240	5.84±0.55	3.72±0.4	<0.001*
270	6.48±0.51	5.04±0.73	<0.001*



Graph 3 Showing the comparison of VISUAL ANALOGUE SCALE in both the study patients groups

Unpaired T test was used to compare 2 means with 95% confidence interval (2 sided) and p value < 0.05 was considered statistically significant. The VAS scores were lower in the Nalbuphine 0.4 mg group at all time intervals showing better postoperative analgesia.. VAS score more than 4 was noted at 210 minutes in Nalbuphine 0.2 mg group whereas it was noted at 270 minutes in 0.4 mg group showing better intraoperative and postoperative analgesia with Nalbuphine 0.4 mg. Statistical analysis revealed a highly relevant variation with "p value < 0.05 at all time intervals starting from 150 minutes from induction.

Table 5 Comparison of SIDE Effects in both the study patients groups

Side Effects	Nalbuphine 0.2mg	Nalbuphine 0.4mg	P VALUE
Bradycardia	2 (8%)	2(8%)	
Nausea	1 (4%)	1(4%)	
Hypotension	0	2(8%)	
Vomiting	0	0	
Pruritis	0	0	
Respiratory depression	0	0	
Total	3(12%)	5(20%)	0.449

Chi square test, p value <0.05 was considered statistically significant. Out of 25 patients in Nalbuphine 0.2 mg group, 2 patients had bradycardia and 1 had nausea. Whereas in Nalbuphine 0.4 mg group, 2 patients had hypotension, 2 had bradycardia and 1 patient had nausea. Using the Chi square test, our findings were statistically insignificant since p value was >0.05

DISCUSSION

Subarachnoid block is a common, relatively simple and a cost effective technique of regional anesthesia for lower abdomen and lower limb surgeries

Bupivacaine, a highly lipid soluble amino amide is the most common local anaesthetic agent used for subarachnoid block because it is easily available, inexpensive and highly potent. But administration of Bupivacaine alone is not effective in extending the analgesic effects in postoperative period for long because of short duration of action.

Hence various adjuvants have been added to Bupivacaine to accelerate the onset of neuraxial blockade and prolong the duration of blockade.

Nalbuphine is a synthetic opioid structurally similar to oxy-morphone, and is highly lipid soluble. It has a mixed agonist-antagonist action which has agonist action at κ receptors and antagonist action at μ receptors.[12]Thus intrathecal administration of Nalbuphine can result in potent analgesia due to κ receptor activity without any μ receptor associated adverse effects. This antagonistic action at μ receptors also confersa property of minimal respiratory depression [13]. It has a short duration of action consistent with it's lipid solubility and rapid clearance when compared to other opioids, therefore allowing early ambulation and discharge of the patient. Various studies have been done using intrathecal nalbuphine as an adjuvant to 0.5 % hyperbaric bupivacaine.

Culebras *et al*[14] were the first to conduct a study which used intrathecal nalbuphine to compare the analgesic efficacy and adverse effects with intrathecal morphine. The study was conducted on 90 parturients posted for elective cesarean delivery under spinal anaesthesia who were divided into 4 equal groups. They comparedthree doses of Nalbuphine 0.2 mg, 0.8 mg and 1.6 mg and morphine 0.2 mg added to 10 mg of 0.5% Hyperbaric Bupivacaine. They found that postoperative analgesia was significantly longer in the morphine category than Nalbuphine but the incidence of adverse effects like pruritus, nausea and vomiting were also significantly higher with Morphine. Among the Nalbuphine categories, 0.8 mg Nalbuphine provided significantly prolonged duration of action with minimal side effects and the best postoperative analgesia. 1.6 mg Nalbuphine did not increase efficacy but had increased incidence of adverse effects.

Fournier *et al*.[15] conducted a study to compare the postoperative analgesic effects of intrathecal morphine 160mcg and nalbuphine 0.4mg in geriatric patients undergoing Total Hip Replacement. They concluded that nalbuphine produces faster onset of pain relief with shorter duration of analgesia when compared with morphine Mukherjee *et al*.[16] performed a study on 100 patients undergoing orthopedic lower limb surgeries under spinal anesthesia to compare different doses of nalbuphine 0.2, 0.4, and 0.8 mg added to 0.5% bupivacaine and they concluded that time of onset of sensory blockade was similar in all groups whereas two segment regression and duration of effective analgesia was prolonged with 0.4 and 0.8 mg but incidence of adverse effects was significantly higher with 0.8 mg dose compared with the other groups Our findings of onset of sensory block and motor block and duration of analgesia as seen in Table 2 were consistent with the study done by Mukherjee *et al*[16]

Tiwari *et al*.[17] did a study to evaluate the effects of addition of 2 different doses of intrathecal Nalbuphine0.2 mg and 0.4 mg to hyperbaric 0.5% Bupivacaine in 75 patients posted for lower abdominal, urologic and lower limb surgeries. The visual analog scale scores were highest when Bupivacaine was given alone. He concluded that Nalbuphine hydrochloride (0.4 mg) significantly prolonged the duration of sensory blockade and postoperative analgesia with fewer side effects and complications when introduced intrathecally along with hyperbaricBupivacaine

Kumaresan *et al*.[18] conducted a study on 120 patients undergoing lower limb orthopaedic surgery under spinal anesthesia to compare three doses of nalbuphine 0.4, 0.6 and 0.8 mg added to 0.5% bupivacaine. They noted there was no difference in the onset of sensory and motor blockade among the four groups. Duration of two-segment regression time of sensory block, duration of motor blockade, and duration of analgesia time were prolonged in Groups B (0.6 mg) and C (0.8 mg) and found to be significant. The incidence of adverse effects was frequently higher in Group C ($P < 0.005$) compared to other groups and they concluded nalbuphine is an effective adjuvant, in a dose of 0.6 mg to prolong the duration of analgesia without increased side effects.

Dr. Avinash Bapurao Pawar *et al*.[19] compared the efficacy of intrathecalNalbuphine 0.8 mgand Fentanyl 25 mcg added to 15 mg 0.5% HyperbaricBupivacaine for duration of analgesia in 60 women posted for elective gynaecological procedures. The onset of sensory block was more significantly more rapid with Fentanyl (2.15 ± 0.7 mins) than Nalbuphine (2.92 ± 0.85 mins) but the duration of post-operative analgesia was more prolonged in Nalbuphine group (280.62± 13.95 mins) as compared to Fentanyl group (208.84 ± 10.7 mins) making it the better adjuvant for postoperative analgesia. There were no significant differences found in various hemodynamic, vital parameters intra operatively or any side effects between the twogroups

Divya Singhal *et al*.[20] compared Nalbuphine 0.4 and 0.8 mg as an adjuvant to 0.5% Bupivacaine intrathecally in lower abdominal and lower limb surgeries and noted that 0.8 mg Nalbuphine intrathecally has a significantly prolonged analgesic effect compared to the 0.4 mg dose of intrathecal Nalbuphine with comparable hemodyanamic variables, onset

of sensory and motor block, and duration of motor block in the three groups. They concluded that Intrathecal Nalbuphine prolongs the duration of postoperative analgesia when used as an adjunct, and 0.4 mg is the most effective dose that prolongs early postoperative analgesia without increasing the risk of side-effects.

We formulated our study to compare and evaluate two doses of nalbuphine 0.2 mg and 0.4 mg to determine the optimal dose as an adjuvant, which will provide prolonged postoperative analgesia without increased side effects. We found there was no statistically significant difference in onset of sensory block between the two groups which was consistent with the study done by Mukherjee *et al*. And Tiwari *et al*. Whereas time of onset of motor block, time for peak sensory blockade, two segment regression and duration of motor and sensory block was significantly prolonged in Nalbuphine 0.4 mg group ($p<0.05$) as seen in Table 2. Haemodynamic parameters were similar in both the groups which was consistent with the study done by Mukherjee *et al*.[16]

The time for rescue analgesia was significantly prolonged in Nalbuphine 0.4 mg group ($p<0.05$) with VAS scores lower at all time intervals when compared with nalbuphine 0.2 mg group as seen in Table 3 and Table 4 respectively. Statistical analysis with chi square test showed comparable adverse effects in two groups. With total 3 patients having adverse effects in nalbuphine 0.2 mg group and 5 patients in nalbuphine 0.4 mg group as seen in Table No 5

CONCLUSION

We recommend 0.4 mg nalbuphine as the preferred dose when compared to 0.2 mg as an adjuvant to 0.5 % bupivacaine given intrathecally with prolonged duration of sensory and motor blockade and prolonged duration of postoperative analgesia with minimal side effects.

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