

Intrathecal nalbuphine vs. buprenorphine as an adjuvant in lower limb orthopedic surgeries: a prospective randomized controlled study

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Abstract

This study aimed to compare the efficacy of intrathecal nalbuphine and buprenorphine as an adjuvant to heavy bupivacaine (0.5%) for spinal anesthesia in lower limb orthopedic surgeries to improve the quality of spinal anesthesia (onset, duration, and side effects) and prolongation of postoperative analgesia. Sixty patients were recruited into this single-centered, double-blinded, hospital-based, prospective, comparative study conducted in 2017–2018. They were randomly and equally ($n = 30$) allocated into two groups: nalbuphine group which received 0.5 mL (0.8 mg) of nalbuphine with 3 mL of heavy (0.5%) hyperbaric bupivacaine and buprenorphine group which received 0.5 mL (60 mg) of buprenorphine with 3 mL of heavy hyperbaric bupivacaine. Intraoperatively, onset and duration of blockade (motor and sensory), and time for first dose of rescue analgesia were recorded in both groups at regular intervals. Heart rate, blood pressure, Visual Analogue Scale score and side effects were also recorded postoperatively for 12 hours. The demographic parameters, time of onset of sensory block and motor block, and duration of motor block were comparable between nalbuphine and buprenorphine groups. The duration of sensory block in the buprenorphine group was longer than in the nalbuphine group. Time to the first dose of rescue analgesia was delayed in buprenorphine group as compared to nalbuphine group. In both groups maximum patients achieved maximum height of sensory block at 90 minutes. There were significant differences in the mean heart rate and blood pressure between buprenorphine and nalbuphine groups. Nalbuphine group patients achieved a Visual Analogue Scale score > 4 earlier as compared to buprenorphine group. Few side effects were observed in both groups. Intrathecal buprenorphine is a better adjuvant to 0.5% bupivacaine in the spinal anesthesia for lower limb orthopedic surgeries, as it provides longer sensory block and delayed administration of first dose of rescue analgesia with negligible side-effects. The study was approved by Institutional Ethics Committee of Krishna Institute of Medical Sciences (approval number: KIMSUD/IEC/03/2017) on November 23, 2017.

Key words: analgesia; anesthesia; bupivacaine; buprenorphine; double-blinded; intraoperative period; nalbuphine; pain

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INTRODUCTION

Despite advances in pharmacology such as neuraxial drug administration and exponential improvement in the apprehension of pain physiology, postoperative pain management remains a challenge in anesthesia.¹ Furthermore, in lower abdominal surgeries, the regional anesthesia not only provides shorter analgesia duration, but also causes local anesthetic toxicity and increases the incidence of higher regional blockade.²

Hyperbaric bupivacaine, a local anesthetic, has a short half-life of 2 hours.³ Hence, several adjuvants have been tested to enhance its analgesic effect. Consequently, the preemptive combination of analgesics such as intrathecal opioids like fentanyl, nalbuphine, buprenorphine with this local anesthetic for regional anesthesia, provides a better alternative.^{1,4} Opioids not only prolong both anesthesia and analgesia, but also improve the quality of analgesia and provide stability in hemodynamic variables.⁵ By acting at two different sites opioids and local anesthetic together eliminate pain: opioids act on the receptors present on spine while local anesthetics act at axon level.⁶ Fentanyl is a pure opioid agonist which has already established its role as analgesic, but it is costlier and needs narcotic licensing. Its side effects, such as respiratory depression, urinary retention, vomiting, nausea, etc., have

left researchers in search of a better alternative for analgesic employment.⁷ Nalbuphine, a kappa agonist exerts opioid action by binding with a μ -receptor antagonist and produces analgesia devoid of the undesirable side effect of alpha 1 agonist.⁸ Intrathecal addition improves quality of analgesia both intra- and postoperatively with fewer side effects, less respiratory depression and potential of abuse as compared to other centrally acting opioids.⁹ Its side effects include bradycardia, dizziness, vomiting, nausea, urinary retention and pruritis.¹⁰ Buprenorphine, a highly lipid soluble opioid, acts as an antagonist at κ -receptor, with a partial agonist activity at the μ -opioid receptor.¹¹ It is more potent than other opioids. As compared to full agonists, it has higher affinity at μ -receptors. This partial agonist has a low dose-effect ceiling than that of a full agonist. It is cost effective and lacks significant side effects such as respiratory depression.¹²

No study has been conducted to compare the effects of nalbuphine and buprenorphine with intrathecal bupivacaine.¹⁰ The better adjuvant among the two still needs to be explored. Therefore, the study focused on the efficacy of intrathecal nalbuphine versus buprenorphine as adjuvants to heavy (0.5%) bupivacaine in spinal anesthesia in lower limb orthopedic surgeries, to improve the quality of spinal anesthesia (onset, duration, and side effects) and prolongation of postoperative analgesia.

SUBJECTS AND METHODS

Study design

With the approval of Institutional Ethics Committee of Krishna Institute of Medical Sciences (approval number: KIMSDU/IEC/03/2017 on November 23, 2017), the single-centered, double-blinded, hospital-based, prospective, comparative study was conducted at a private medical college over a period of 18 months between 2017–2018. Informed consent was obtained from all the patients. To show a small difference statistically significant we need to choose a small effect size (Cohen's d). With a small effect size ($d = 0.8$), power = 80%, confidence level 95%, about 26 patients are required in each group for two-independent sample t -test. Therefore, the sample size used in this study was 30 per group.

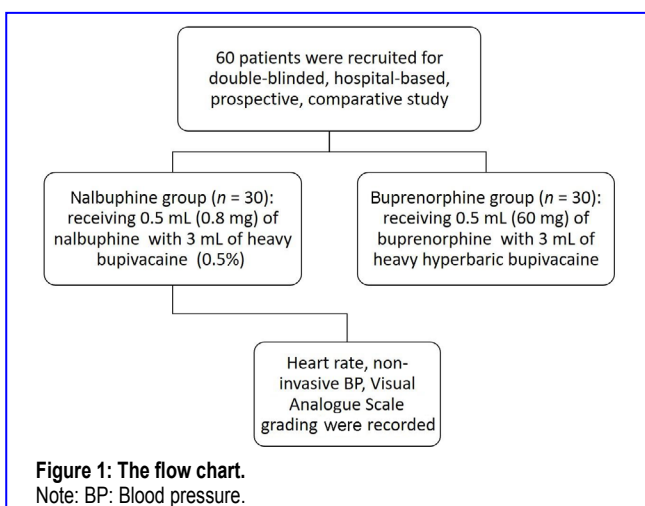
Subjects

Sixty patients of either sex and aged between 18–60 years, admitted to the Krishna Institute of Medical Sciences hospital during the study period and met the inclusion criteria were recruited. As per American Society of Anesthesiologist physical status I and II, patients scheduled to undergo lower limb orthopedic surgery under intrathecal anesthesia were considered for the study.¹⁰ The patients with American Society of Anesthesiologist physical status III and IV status, with gross spinal deformity, local infection, neurological diseases, bleeding disorder, cardio-respiratory diseases, liver diseases, chronic users of narcotics, sedatives, and drug abusers or alcoholics and those allergic to any of the medications used in the study, were excluded.

All the patients were randomly allocated into two groups by the Randomizer software. Allocated groups were nalbuphine group ($n = 30$): receiving 0.5 mL (0.8 mg) of nalbuphine with 3 mL of heavy bupivacaine (0.5%) (Abott, Abbott Park, IL, USA) and buprenorphine group ($n = 30$): receiving 0.5 mL (60 mg) of buprenorphine with 3 mL of heavy hyperbaric bupivacaine (0.5%; Paksons Pharma Pvt. Ltd., Delhi, India). The flow chart is shown in **Figure 1**.

Preoperative assessment

The baseline preoperative parameters such as blood pressure (BP), pulse oximetry, and electrocardiogram (Waveline EZ, DRE Veterinary, Louisville, KY, USA) were recorded before



anesthesia induction.

Study procedure

A day before the surgery, alprazolam (0.25 mg; Alprax MT, Torrent Pharmaceuticals Ltd., Ahmedabad, India) was taken orally the night before surgery and on the day of surgery 2 hours prior to scheduled time of surgery for anxiolysis. The anesthesiologist performed subarachnoid block under aseptic conditions using 25-gauge Quincke needle (0.5 mm) by a midline lumbar puncture at L3–4 interspace in lateral recumbent position. After assuring free flow of clear cerebrospinal fluid, anesthetic drug (heavy bupivacaine, 0.5%) with respective adjuvants (0.8 mg nalbuphine and 60 µg buprenorphine) was injected slowly to respective group members in supine position. The time of intrathecal injection was considered as 0 and parameters such as sensory block (onset, level and duration of recovery), motor block (onset, block regression, and duration of recovery), heart rate (HR), BP and side effects (hypotension, bradycardia, and respiratory depression) were recorded.

Hypotension was defined as decrease of systolic BP by more than 20% from baseline. It was treated with IV fluids and incremental doses of vasopressors when it was required. Bradycardia was defined as HR < 60 beat/min and was treated with injection atropine.¹⁰

Sensory block was assessed by loss of sensation to pinprick using 23-G sterile needle. Onset or induction of sensory block was the time from intrathecal injection administration to loss of pinprick sensation at L2 segment. Assessment was initiated just after the administration of agents and continued after every 15 seconds, till loss of pinprick sensation at L2 level. After 30 minutes of subarachnoid blockage and at the end of surgery, the dermatome (area of skin with single spinal nerve) level of sensory block was noted (maximum level of sensory block). This was followed by assessment at 15 minutes interval, till return of pinprick sensation to L2 dermatome was reported.

Motor block assessment was initiated immediately after intrathecal injection by using modified Bromage Scale.¹³ Onset of motor block was taken as time to achieve modified Bromage score 3 from the time of subarachnoid blockage injection. Thereafter, motor block regression was noted and duration for complete motor block recovery was taken as the time from subarachnoid injection to return of Bromage score to zero.

Vital signs were recorded every 5 minutes throughout intraoperative period and at the completion of surgery. Hypotension was managed with intravenous fluids and incremental doses of vasopressors; bradycardia was managed with injection. Atropine 0.01 mg/kg was injected intravenously. After complete resolution of motor blockade, the patients were shifted to postoperative ward or recovery ward.

Postoperative assessment

In the current double blind study, postoperatively, the HR, non-invasive BP, Visual Analogue Scale (VAS) grading was recorded every 15 minutes for the first 2 hours and then hourly for 12 hours. VAS scale was used for scoring.¹⁴

Rescue analgesic (intravenous injection tramadol 100 mg,



Tramzac, Zybus, Ahmedabad, India) was administered when the VAS score was > 3 and the time to rescue analgesia was recorded time to return of motor senses, and time from intrathecal injection to the first request of analgesics (i.e., duration of analgesia) were also recorded. Total analgesic dose in first 12 hours and adverse effects (nausea, vomiting, shivering, respiratory depression and hypotension) were recorded.

Statistical analysis

Statistical analysis was performed by using R software (Version. 3.6.0; <https://www.r-project.org/>). Data were recorded in Microsoft excel (Microsoft office 2019, Redmond, WA, USA) and expressed as mean and standard deviation along with frequency and percentage. Qualitative variables were analyzed using chi-square test for dependence of sex and paired t-test for continuous variables like duration of surgery, onset. Mann Whitney *U* test and Friedman's test were employed for the variables like BP, HR without a normal distribution. General linear mixed effect model was used when data had more than one source of random variability. A value of $P < 0.05$ was considered statistically significant.

RESULTS

A total of 60 patients were recruited into this prospective study. The demographic parameters were comparable between groups ($P > 0.05$; **Table 1**), indicating that most of the patients undergoing lower limb surgery were in their middle age and were healthy in other aspects.

No significant difference was observed between the average time taken for onset of sensory block and motor block between the groups ($P > 0.05$). Duration of sensory block in buprenorphine group was significantly longer as compared to nalbuphine group ($P < 0.05$). However, no significant difference was observed between the two groups in terms of duration of motor block ($P > 0.05$). Time for first dose of rescue analgesia was delayed in buprenorphine group compared to nalbuphine group ($P < 0.05$; **Table 2**).

The patients achieving maximum height of sensory block at level T10 was 36.6% in the buprenorphine group and 33.3% in the nalbuphine group. There were significant differences in the mean HR ($P < 2.2e^{-16}$) and mean BP ($P < 2.2e^{-16}$) between

buprenorphine and nalbuphine groups (**Figure 2**). However, there was no significant fall in the BP and HR in both groups during the entire intraoperative and postoperative period.

The mean VAS score monitoring in the extended postoperative period in the respective groups indicated that in nalbuphine group patients achieved a VAS > 4 at an earlier time as compared to buprenorphine group (**Figure 3**).

Both groups had minimal side effects. No pruritus, respiratory depression, euphoria dysphoria, desaturation was observed in both groups. Postoperative nausea was found in one patient in nalbuphine group (3.2%) and three patients in buprenorphine group (10%). Postoperative vomiting was found in one patient (3.2%) in buprenorphine group. No clinically significant bradycardia or hypotension was observed in either group.

DISCUSSION

Intrathecal opioids such as nalbuphine and buprenorphine are utilized as an adjunct in regional anesthesia to local anesthetics with multiple advantages. Intrathecally, these opioids decrease nociceptive inputs from A delta and C fibers without affecting somatosensory evoked potentials or dorsal root axons.¹³ The study focused on comparison of these intrathecal nalbuphine and buprenorphine as adjuvant to 0.5% (heavy) bupivacaine in spinal anesthesia in lower limb orthopedic surgeries. The primary objective was to compare the total duration of effective analgesia, i.e., the request for first dose for analgesia. Further, comparison of onset and duration of sensory and motor block along with occurrence of adverse effects were evaluated as the secondary objective.

In terms of demographic data, no significant differences were observed between nalbuphine and buprenorphine groups in the age, sex, weight, height and duration of surgery and were comparable with Naaz et al.¹⁵ The time taken for onset of sensory and motor block by the two groups (nalbuphine and buprenorphine) was same with both groups taking almost equal time. This is in accordance with the study conducted by Manjula et al.¹⁰ in which the onset of sensory and motor block was almost equal in the nalbuphine and buprenorphine groups.

Duration of sensory block was different between nalbuphine and buprenorphine groups, with buprenorphine group provid-

Table 1: Demographic profile of patients with lower limb orthopedic surgeries using different adjuvants for spinal anesthesia

Variables	Buprenorphine	Nalbuphine	P-value
Age (yr)	39.8±13.38	44±13.60	0.2395 ^a
Sex			–
Male	22 (73)	22 (73)	
Female	8 (27)	8 (27)	
Weight (kg)	66.3±10.55	63.83±9.25	0.3177 ^a
Height (cm)	162.76±10.27	164.06±8.71	0.5992 ^b
Duration of surgery (min)	130.9±42.60	140.83±38.82	0.2572 ^a

Note: Data are expressed as the mean \pm SD ($n = 30$), except for sex [number(percentage)]. a indicates data analyzed by Mann Whitney *U* test; superscript b indicates data analyzed by *t*-test.

Table 2: Comparison of onset and duration of sensory and motor block, total duration of patients with lower limb orthopedic surgeries using different adjuvants for spinal anesthesia

	Buprenorphine	Nalbuphine	P-value
Sensory blockade			
Onset (min)	2.74±0.83	2.80±0.81	0.7740
Duration (min)	265.63±26.63	187.9±16.99	0.000
Motor blockade			
Onset (min)	2.84±0.84	2.92±0.80	0.6927
Duration (min)	183.97±22.56	181.36±8.56	0.5587
Total duration of analgesia			
Duration (min)	471.20±76.29	371.56±33.70	0.0000

Note: Data are expressed as the mean \pm SD ($n = 30$), and were analyzed by *t*-test.

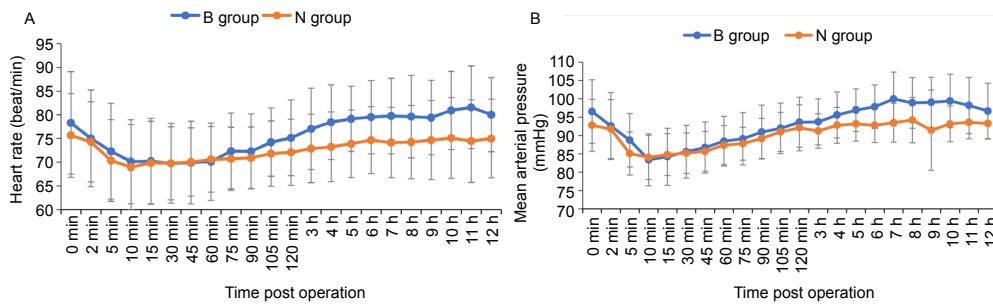


Figure 2: Change in heart rate (A) and blood pressure (B) in patients with lower limb orthopedic surgeries using different adjuvants for spinal anesthesia.

Note: Data are expressed as the mean \pm SD ($n = 30$), and were analyzed by *t*-test. B: Buprenorphine; N: nalbuphine.

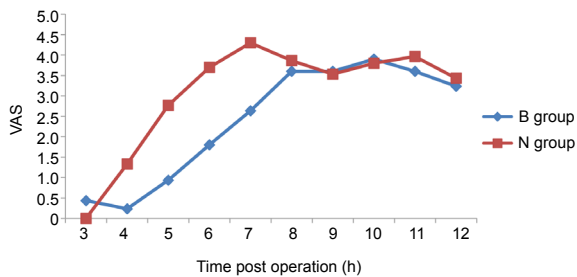


Figure 3: Change in VAS Score with lower limb orthopedic surgeries using different adjuvants for spinal anesthesia.

Note: Data are expressed as the mean \pm SD ($n = 30$), and were analyzed by *t*-test. B: Buprenorphine; N: nalbuphine; VAS: Visual Analogue Scale.

ing comparatively higher duration of sensory block. Further, the duration of motor block by buprenorphine was also slightly more although not significant. Similar results were obtained by Sheth et al.¹⁶ The faster and prolonged effect of buprenorphine could be a result of its high lipid solubility resulting in faster penetration into lipid membrane, causing fast and prolonged binding to receptors and thus hastening the block.

The duration of postoperative analgesia was significantly prolonged with addition of buprenorphine in comparison to nalbuphine. Thus, in the buprenorphine group the duration of rescue analgesia was also prolonged as compared to the nalbuphine group. These results were comparable with Manjula et al.,¹⁰ in which the postoperative analgesia duration was significantly prolonged with addition of buprenorphine compared to nalbuphine to bupivacaine. The prolonged duration of analgesia by buprenorphine group could be due to the high binding capacity and affinity of buprenorphine for μ receptors. It shows slow dissociation from its receptors. Due to its highly lipophilic nature it results in low plasma concentration and further prolongs duration.

In terms of hemodynamic parameters, a significant difference was observed between buprenorphine and nalbuphine groups in terms of mean HR and BP. As in buprenorphine group, patients had slightly higher HR and BP. Similar results were obtained by Sheth et al where no hemodynamic variabilities or instability was noted with nalbuphine compared to buprenorphine.¹⁶ This attributes to high affinity of nalbuphine for κ -opioid receptors, it causing cardiovascular stability along with analgesia, sedation and minimal respiratory depression.

The monitoring of VAS indicated that patients in nalbuphine group achieved a VAS score below 4 (moderate pain) at an earlier time as compared to buprenorphine group. This is in line with the study conducted by Sapkal Pravin et al.¹⁷ which showed that quality of spinal analgesia was acceptable to pa-

tients in buprenorphine group as VAS assessment was better in this group with VAS score below 4. This could be due to prolonged duration of analgesia provided by buprenorphine.

In terms of side effects, both groups had minimal side effects. No pruritus, respiratory depression, euphoria dysphoria, desaturation was observed in both groups. However, post-operative nausea and vomiting was more in buprenorphine group patients. Similar observations were made by other investigations.^{18,19}

Although no major side effects were noticed in our study, further studies are obligatory to rule out any long-term or short-term adverse effects of the drugs.²⁰ Besides, the study involved only patients undergoing lower abdominal surgeries. Further, futures studies need to be conducted on other surgeries using both the intrathecal agents to assess whether similar results can be achieved with lesser doses.

Intrathecal buprenorphine can be used as a better adjuvant to 0.5% (heavy) bupivacaine in spinal anesthesia for lower limb orthopedic surgeries.

Author contributions

All authors participated in the trial design, implementation and evaluation.

Conflicts of interest

Nil.

Financial support

None.

Institutional review board statement

The study was approved by Institutional Ethics Committee of Krishna Institute of Medical Sciences (approval number: KIMSUDU/IEC/03/2017) on November 23, 2017.

Declaration of patient consent

The authors certify that they have obtained patients' consent forms. In the form, patients have given their consent for their images and other clinical information to be reported in the journal. The patients understand that their names and initials not be published and due efforts will be made to conceal their identity.

Reporting statement

The writing and editing of the study report was performed in accordance with the CONSolidated Standards Of Reporting Trials (CONSORT) statement.

Biostatistics statement

The statistical methods of this study were conducted and reviewed by the biostatistician of Krishna Institute of Medical Sciences, India.

Copyright transfer agreement

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Data sharing statement

Individual participant data that underlie the results reported in this article, after deidentification (text, tables, figures, and appendices) have been available. Study protocol, informed consent, and clinical study report have been available within 6 months after completing the trial.

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REFERENCES

- Chakraborty S, Chakrabarti J, Bhattacharya D. Intrathecal tramadol added to bupivacaine as spinal anesthetic increases analgesic effect of the spinal blockade after major gynecological surgeries. *Indian J Pharmacol.* 2008;40:180-182.
- Ramsay MA. Acute postoperative pain management. *Proc (Bayl Univ Med Cent).* 2000;13:244-247.
- Brown D. Spinal, Epidural and caudal anesthesia. In: Miller RD, ed. *Miller's Anesthesia.* 7th ed. Philadelphia: Churchill living stone; 2010:1611-1638.
- Murali Krishna T, Panda NB, Batra YK, Rajeev S. Combination of low doses of intrathecal ketamine and midazolam with bupivacaine improves postoperative analgesia in orthopaedic surgery. *Eur J Anaesthesiol.* 2008;25:299-306.
- Yu SC, Ngan Kee WD, Kwan AS. Addition of meperidine to bupivacaine for spinal anaesthesia for Caesarean section. *Br J Anaesth.* 2002;88:379-383.
- Alhashemi JA, Kaki AM. Effect of intrathecal tramadol administration on postoperative pain after transurethral resection of prostate. *Br J Anaesth.* 2003;91:536-540.
- Yang T, Breen TW, Archer D, Fick G. Comparison of 0.25 mg and 0.1 mg intrathecal morphine for analgesia after Cesarean section. *Can J Anaesth.* 1999;46:856-860.
- Fournier R, Van Gessel E, Macksay M, Gamulin Z. Onset and offset of intrathecal morphine versus nalbuphine for postoperative pain relief after total hip replacement. *Acta Anaesthesiol Scand.* 2000;44:940-945.
- Culebras X, Gaggero G, Zatloukal J, Kern C, Marti RA. Advantages of intrathecal nalbuphine, compared with intrathecal morphine, after cesarean delivery: an evaluation of postoperative analgesia and adverse effects. *Anesth Analg.* 2000;91:601-605.
- Manjula R, Karthik K, Damodar Reddy Y, Ranjitha C. Comparative study of bupivacaine with nalbuphine and buprenorphine intrathecally for postoperative analgesia in lower limb surgeries. *MedPulse Int J Anesthesiol.* 2019;11:189-193.
- Huang A, Katznelson R, de Perrot M, Clarke H. Perioperative management of a patient undergoing Clagett window closure stabilized on Suboxone® for chronic pain: a case report. *Can J Anaesth.* 2014;61:826-831.
- Barash P, Cullen B, Stoelting R, Cahalan M, Stock M. *Clinical anaesthesia.* 6th ed. Philadelphia: Lippincott, Williams, and Wilkins. 2009.
- Hindle A. Intrathecal opioids in the management of acute postoperative pain. *Contin Educ Anaesth Crit Care Pain.* 2008;8:81-85.
- Hawker GA, Mian S, Kendzerska T, French M. Measures of adult pain: Visual Analog Scale for Pain (VAS Pain), Numeric Rating Scale for Pain (NRS Pain), McGill Pain Questionnaire (MPQ), Short-Form McGill Pain Questionnaire (SF-MPQ), Chronic Pain Grade Scale (CPGS), Short Form-36 Bodily Pain Scale (SF-36 BPS), and Measure of Intermittent and Constant Osteoarthritis Pain (ICOAP). *Arthritis Care Res (Hoboken).* 2011;63 Suppl 11:S240-252.
- Naaz S, Shukla U, Srivastava S, Ozair E, Asghar A. A comparative study of analgesic effect of intrathecal nalbuphine and fentanyl as adjuvant in lower limb orthopaedic surgery. *J Clin Diagn Res.* 2017;11:UC25-28.
- Sheth RA, Joshi SA, Pandya M. Comparative study of nalbuphine and buprenorphine as an adjuvant to local anesthetics in supraclavicular brachial plexus block. *J Anesth Surg.* 2019;6:31-37.
- Sapkal Pravin S, Kulkarni Kalyani D, Rajurkar Sampda S, Nandedkar Prerna D. Comparative study of intrathecal clonidine and intrathecal buprenorphine for postoperative analgesia after lower limb orthopedic surgery. *Int J Cur Res Rev.* 2013;5:87-91.
- Chahar P, Cummings KC 3rd. Liposomal bupivacaine: a review of a new bupivacaine formulation. *J Pain Res.* 2012;5:257-264.
- Arora R, Pandey V, Sodhi GS, Mohindra BK. A comparative study of intrathecal bupivacaine and bupivacaine with different doses of clonidine in lower limb surgeries. *Anesth Essays Res.* 2018;12:412-416.
- Najafianaraki A, Mirzaei K, Akbari Z, Macaire P. The effects of warm and cold intrathecal bupivacaine on shivering during delivery under spinal anesthesia. *Saudi J Anaesth.* 2012;6:336-340.

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