e-ISSN: 0975-1556, p-ISSN:2820-2643

Available online on www.ijpcr.com

International Journal of Pharmaceutical and Clinical Research 2024; 16(6); 390-395

Original Research Article

Efficacy of Intrathecal Nalbuphine Hydrochloride as an Adjuvant to Hyperbaric Bupivacaine 0.5% in Abdominal Hysterectomy

Dipika M. Parmar[1], Vikram C. Gohil[2]

[1]Associate Professor, Department of Anaesthesiology, Nootan Medical College and Research Centre, Visnagar, Gujarat

[2]Senior Resident, Department of Anaesthesiology, GMERS Medical College, Vadnagar, Gujarat

Received: 25-03-2024 / Revised: 23-04-2024 / Accepted: 26-05-2024

Corresponding Author: Dr. Vikram C. Gohil

Conflict of interest: Nil

Abstract:

Introduction: Intrathecal nalbuphine hydrochloride has been explored as an adjuvant to bupivacaine for improved anesthesia and analgesia. This study aimed to evaluate its effectiveness in enhancing sensory and motor blocks and reducing postoperative analgesic requirements in patients undergoing abdominal hysterectomy.

Material and Methods: This double-blinded, randomized study at a tertiary care center in Gujarat included 60 ASA I and II patients aged 30-60 undergoing elective abdominal hysterectomy. After obtaining informed consent, patients were randomly assigned to receive either intrathecal bupivacaine 0.5% alone (control group) or with 1.6 mg nalbuphine hydrochloride (study group). Baseline vitals were recorded, and spinal anesthesia was administered. Sensory and motor block onset times, duration of surgery, and block regression times were monitored. Postoperative pain was assessed using VAS, and rescue analgesia was provided as needed. Adverse effects were recorded and managed appropriately. Data analysis was performed using SPSS 21.1 with one-way ANOVA and post hoc Tukey tests.

Results: The study group had a faster onset of sensory block (4.1±0.7 minutes vs. 6.3±1.0 minutes, P=0.03) and motor block (4.1±0.8 minutes vs. 6.8±1.3 minutes, P=0.00). The time for two-segment regression was longer in the study group (120.0±20.0 minutes vs. 92.0±4.0 minutes, P=0.03), and the duration of motor block was extended (132.0±21.0 minutes vs. 115.0±15.0 minutes, P=0.02). The study group required the first rescue analgesic later (215.0±30.0 minutes vs. 135.0±18.0 minutes, P=0.01) and a lower total dose of diclofenac (160.0±28.0 mg vs. 225.0±20.0 mg, P=0.02) within the first 24 hours. Adverse effects such as hypotension, bradycardia, respiratory depression, nausea, vomiting, and pruritus were observed but were not statistically significant between the groups (P>0.05).

Conclusion: In conclusion, our study demonstrates that intrathecal nalbuphine hydrochloride, when used in combination with bupivacaine 0.5%, significantly improves the onset and duration of both sensory and motor blocks compared to bupivacaine alone.

Keywords: Intrathecal Nalbuphine, Bupivacaine, Sensory Block, Motor Block, Postoperative Analgesia.

Introduction

Intrathecal administration of anesthetics has become a cornerstone in the management of perioperative pain for various surgical procedures, including abdominal hysterectomy. [1] Abdominal hysterectomy, a common surgical procedure for treating various gynecological conditions, often requires effective pain management strategies to ensure patient comfort and optimal recovery. [2]

The combination of local anesthetics with adjunct medications in intrathecal administration aims to enhance analgesic efficacy, reduce side effects, and improve patient outcomes. [3] This study focuses on comparing intrathecal nalbuphine hydrochloride combined with hyperbaric bupivacaine 0.5% versus hyperbaric bupivacaine 0.5% alone in patients undergoing abdominal hysterectomy, evaluating their analgesic effectiveness and safety profiles. Nalbuphine hydrochloride, a mixed agonist-antagonist opioid, is known for its potential to provide effective analgesia with a reduced risk of respiratory depression and other opioid-related side effects. [4]

When combined with bupivacaine, a widely used local anesthetic, it may offer superior pain control compared to bupivacaine alone. [5] Hyperbaric bupivacaine, characterized by its higher specific gravity, ensures a more predictable spread in the cerebrospinal fluid, leading to reliable and

consistent anesthesia during surgery. [6] This study aims to investigate whether the addition of nalbuphine to hyperbaric bupivacaine enhances the analgesic effects without compromising patient safety, thus potentially providing a more effective and safer anesthesia regimen for patients undergoing abdominal hysterectomy.

Material and Methods

This prospective, double-blinded, randomized interventional study was conducted at a tertiary care center in Gujarat, following approval from the Institutional Ethical Committee. The study included 60 patients classified under the American Society of Anesthesiologists (ASA) physical status Classes I and II, aged between 30 and 60 years, scheduled for elective total abdominal hysterectomy under subarachnoid block.

Patients underwent comprehensive pre-anesthetic evaluations. Exclusion criteria encompassed individuals with ASA physical status Class III or above, coagulation disorders, severe hypovolemia, increased intracranial pressure, local infections at the spinal injection site, known allergies to study medications, and those with pre-existing neurological, cardiovascular, metabolic, hepatic, respiratory, or renal diseases.

Informed consent was obtained from all participants. They were then randomly assigned to one of two groups (n = 30 per group) using a computerized randomization method. The Control group received intrathecal bupivacaine 0.5% (3 ml, 15 mg) with 0.5 ml normal saline (placebo). The Study group received intrathecal bupivacaine 0.5% (3 ml, 15 mg) with 1.6 mg nalbuphine hydrochloride. The total volume of the intrathecal injection was standardized to 3.5 ml for all groups, using sterile isotonic saline.

Patients fasted for 6 hours preoperatively. Baseline noninvasive blood pressure (NIBP), pulse rate (PR), and oxygen saturation (SpO2) were recorded. An 18-gauge intravenous (IV) cannula was inserted, and patients were preloaded with 15 ml/kg Ringer's lactate solution over 10 minutes. Spinal anesthesia was administered in the left lateral position at the L3–L4 interspace using a 25G Quincke spinal needle. The 3.5 ml of the respective drug solution was injected over 30 seconds without barbotage. Patients were immediately placed in a supine position with a 15° Trendelenburg tilt to achieve a sensory block level of T5–T6. The anesthetist performing the spinal block was different from the investigator monitoring the outcomes.

Sensory block levels were assessed every minute until the maximum level was reached and subsequently every 30 minutes for one hour, using a cold stimulation method bilaterally at the mid-clavicular line. Onset of sensory block was defined as the time to reach T6 dermatome. Motor block onset was defined as the time to achieve modified Bromage Grade II from injection.

Vital signs, including blood pressure, PR, SpO2, and sedation scores, were monitored at 2, 5, 10, 15, 30, 60, 90, and 120 minutes intervals and postoperatively at 30-minute intervals until rescue analgesia was administered. Postoperative monitoring continued at 30-minute intervals for the first 4 hours, every 2 hours for the next 8 hours, and every 4 hours for the following 12 hours.

The duration of surgery, two-segment regression time (time to regress by two sensory levels), and motor block regression to modified Bromage Grade I were recorded. Analgesia duration was defined as the time from intrathecal drug administration until the visual analog scale (VAS) score exceeded 3. Patients were instructed on using the VAS, a 10-cm horizontal strip labeled from “No pain” to “Worst pain ever,” to quantify pain intensity. Rescue analgesia was provided with intramuscular diclofenac 75 mg when VAS exceeded 3.

Patients were monitored for adverse effects such as nausea, vomiting, pruritus, sedation, and respiratory depression (respiratory rate and SpO2). Nausea and vomiting were treated with intravenous ondansetron 4 mg, and pruritus was managed with intramuscular promethazine 25 mg, repeatable after one hour if necessary. Oxygen was administered via a Hudson mask if SpO2 fell below 94%. Naloxone (0.1–0.2 mg IV bolus, repeatable every 3–4 minutes) was reserved for respiratory rates below 8 per minute. The study concluded 24 hours after intrathecal drug administration.

Data analysis was conducted using SPSS version 21.1. Continuous variables were presented as means and standard deviations and analyzed with one-way ANOVA and post hoc Tukey tests. Categorical variables were expressed as frequencies and percentages and analyzed using the Chi-square test. The Mann-Whitney U test was used for non-normally distributed variables. Statistical significance was set at $p < 0.05$.

Results

The study included 60 patients, evenly divided into two groups. There were no significant differences in age, height, weight, ASA physical status, or duration of surgery between the control and study groups, indicating comparable baseline characteristics.

Table 1: Demographic Characteristics

Characteristics	Control group	Study group I	P
Age (years)	40.3±6.1	41.8±5.8	0.115
Height (cm)	164.0±7.5	166.2±9.0	0.499
Weight (kg)	60.2±5.3	62.0±6.0	0.361
ASA physical status-I	56 out of 60	55 out of 60	0.430
ASA physical status-II	4 out of 60	5 out of 60	0.430
Duration of surgery (min)	62.0±10.5	59.5±8.7	0.287

In our study, comparing the control group receiving intrathecal bupivacaine 0.5% alone and the study group receiving intrathecal bupivacaine 0.5% with nalbuphine hydrochloride, significant differences were observed in several parameters. The onset of sensory block was faster in the study group, occurring at 4.1±0.7 minutes, compared to 6.3±1.0 minutes in the control group (P=0.03). The onset of motor block also occurred more quickly in the study group, at 4.1±0.8 minutes, versus 6.8±1.3 minutes in the control group (P=0.00). Additionally, the time for two-segment regression was longer in the study group, averaging 120.0±20.0 minutes, compared to 92.0±4.0 minutes in the control group (P=0.03). Finally, the duration of motor block was extended in the study group, lasting 132.0±21.0 minutes, in contrast to 115.0±15.0 minutes in the control group (P=0.02).

Table 2: Characteristics of spinal block

Parameters	Control group	Study Group	P
Onset of sensory block (min) (time to reach T5-T6)	6.3±1.0	4.1±0.7	0.03
Onset of motor block (min)	6.8±1.3	4.1±0.8	0.00
Time for two-segment regression (min)	92.0±4.0	120.0±20.0	0.03
Duration of motor block (min)	115.0±15.0	132.0±21.0	0.02

The comparison between the control group and the study group showed significant differences in the onset of sensory block (P=0.03), onset of motor block (P=0.02), time for two-segment regression (P=0.03), and duration of motor block (P=0.05).

Table 3: Post Hoc Comparison of Anesthetic Parameters Between Control and Study Groups

Parameters	Control group versus Study Group
Onset of sensory block (time to reach T5-T6)	0.03
Onset of motor block	0.02
Time for two-segment regression	0.03
Duration of motor block	0.05

In our study, the control group (receiving intrathecal bupivacaine 0.5% alone) and the study group (receiving intrathecal bupivacaine 0.5% with nalbuphine hydrochloride) showed significant differences in both the time to first rescue analgesic and the total dose of diclofenac in the first 24 hours. The study group required the first rescue analgesic later (215.0±30.0 minutes) compared to the control group (135.0±18.0 minutes) with a P-value of 0.01.

Additionally, the study group required a lower total dose of diclofenac (160.0±28.0 mg) compared to the control group (225.0±20.0 mg) within the first 24 hours, with a P-value of 0.02.

Table 4: Post Hoc Comparison of Rescue Analgesic Parameters

Parameters	Control group	Study Group	P
Time for first rescue analgesic (min)	135.0±18.0	215.0±30.0	0.01
Total dose of diclofenac in 1st 24 h (mg)	225.0±20.0	160.0±28.0	0.02

Intraoperatively, heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial pressure (MAP) were comparable between the control and study groups. Postoperatively, the study group receiving nalbuphine hydrochloride with bupivacaine had significantly lower HR, SBP, DBP, and MAP compared to the control group up to 4 hours. After 4 hours, these values were similar between both groups.

Adverse effects such as hypotension, bradycardia, respiratory depression, nausea, vomiting, and pruritus were observed, but the incidence was not statistically significant between the two groups ($p>0.05$).

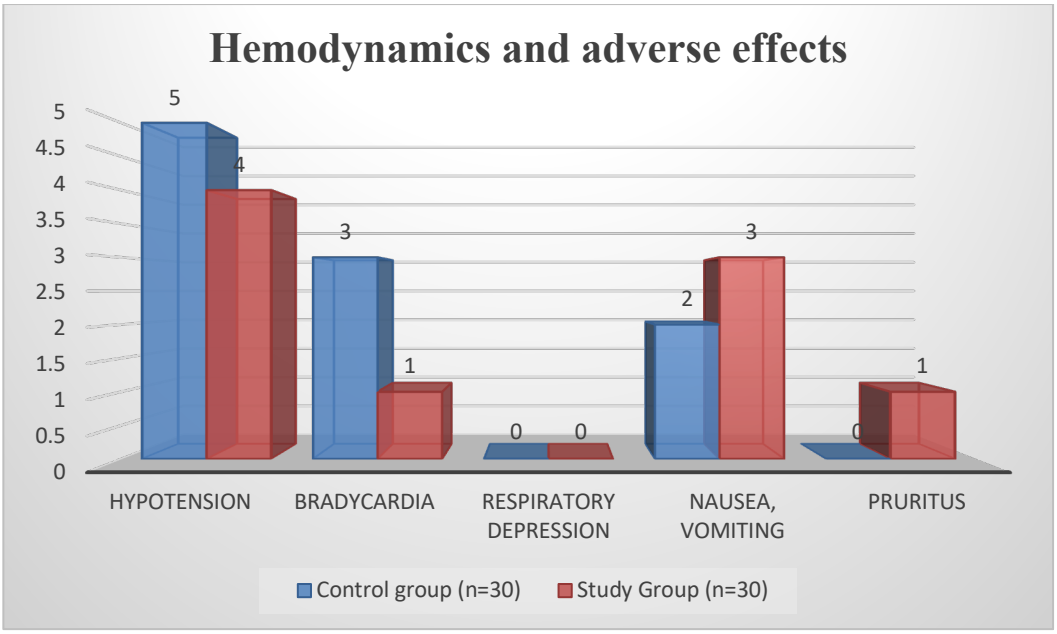

Figure 1: Hemodynamics and adverse effects

Discussion

Bupivacaine, a local anesthetic, blocks sodium channels to inhibit nerve conduction, providing effective regional anesthesia. [7] Nalbuphine hydrochloride, a partial agonist–antagonist opioid, enhances analgesia by activating κ-receptors and antagonizing μ-receptors, reducing side effects like respiratory depression. [8,9] This combination leverages bupivacaine's anesthetic properties with nalbuphine's extended analgesia, aiming for more effective and safer pain management in patients undergoing abdominal hysterectomy.

In our study, the onset of sensory block (time to reach T5-T6) was significantly faster in the study group receiving intrathecal bupivacaine 0.5% with nalbuphine hydrochloride (4.1±0.7 min) compared to the control group receiving bupivacaine 0.5% alone (6.3±1.0 min), with a P-value of 0.03. This quicker onset can be attributed to the synergistic effects of nalbuphine, which enhances the efficacy of bupivacaine. Bansal et al. [10] also demonstrated a faster onset of sensory block due to nalbuphine. The analgesic effect of nalbuphine is mediated by its agonism at κ-receptors, providing effective pain relief without the undesirable side effects associated with μ-receptor agonists. [11] This mechanism likely contributes to the rapid onset observed in our study.

The onset of motor block was also significantly faster in the study group (4.1±0.8 min) than in the control group (6.8±1.3 min), with a P-value of 0.00. The presence of nalbuphine likely enhances the anesthetic effect of bupivacaine, resulting in a quicker motor block onset. Chetty et al. [12] observed similar findings, where the addition of nalbuphine to bupivacaine resulted in a faster onset of motor block. Nalbuphine's partial agonist–antagonist properties, with agonism at κ-receptors, contribute to its efficacy in enhancing motor block onset. [13]

The time for two-segment regression of the sensory block was significantly prolonged in the study group (120.0±20.0 min) compared to the control group (92.0±4.0 min), with a P-value of 0.03. Nalbuphine's prolonged duration of action contributes to this extended regression time, offering sustained analgesia. Chetty et al. [12] also noted a significantly longer two-segment regression time in groups receiving nalbuphine compared to the control group.

This prolongation is supported by Tiwari et al. [14], who found that nalbuphine as an adjuvant prolonged the two-segment regression time. Similarly, Dobrydnjov et al. [15] demonstrated that clonidine also extends the duration of sensory block. The extended regression time is beneficial for postoperative pain management, reducing the need for early rescue analgesia. The extended regression time is beneficial for postoperative pain management, reducing the need for early rescue analgesia. This is consistent with findings from studies on clonidine, where doses from 15 to 450 μg have shown to increase both sensory and motor block durations.

The duration of motor block was significantly longer in the study group (132.0±21.0 min) compared to the control group (115.0±15.0 min), with a P-value of 0.02. This extended duration is likely due to the combined effects of nalbuphine and bupivacaine, which enhance the overall anesthetic effect. Our findings are supported by Chetty et al.[12], who observed a significantly

longer duration of motor block in the nalbuphine group. Additionally, Tiwari et al. [14] reported that higher doses of nalbuphine significantly prolonged the duration of both sensory and motor blocks. The enhanced duration of motor block improves postoperative pain control, reducing the need for additional analgesics. Makram et al. [16] found that nalbuphine improved onset times and prolonged analgesia when used with bupivacaine.

Furthermore, studies on clonidine, such as those by Chopra and Talwar [17], and Khandelwal et al. [18], show that intrathecal clonidine enhances sensory and motor block durations, similar to nalbuphine. Clonidine's mechanism involves α2-adrenoceptor agonism, contributing to its analgesic effects. [19] The use of nalbuphine as an adjuvant to bupivacaine provides significant benefits in terms of faster onset and prolonged duration of anesthesia, as demonstrated in our study and supported by the literature. [20]

The time for the first rescue analgesic was significantly longer in the study group (215.0±30.0 min) compared to the control group (135.0±18.0 min), with a P-value of 0.01. This indicates that nalbuphine extends the duration of effective analgesia, delaying the need for additional pain relief. Gupta et al. [21] found that nalbuphine significantly enhanced the duration of both motor and sensory blocks, resulting in prolonged postoperative analgesia. Similarly, Mostafa et al. [22] reported that nalbuphine combined with bupivacaine significantly reduced pain scores compared to bupivacaine alone. The total dose of diclofenac required in the first 24 hours was significantly lower in the study group (160.0±28.0 mg) compared to the control group (225.0±20.0 mg), with a P-value of 0.02. This reduction in analgesic requirement reflects the superior pain control provided by the nalbuphine-bupivacaine combination. Studies by Tiwari et al. [14] and Mostafa et al. [22] also indicated that nalbuphine reduces the need for postoperative analgesics, further supporting our findings.

In our study, side effects such as hypotension, bradycardia, respiratory depression, nausea, vomiting, and pruritus were observed, but the incidence was not statistically significant between the control group (intrathecal bupivacaine 0.5% alone) and the study group (bupivacaine 0.5% with nalbuphine hydrochloride). This is consistent with findings from Tiwari et al. [14] and Mostafa et al. [22], who reported minimal side effects with nalbuphine as an adjuvant. Similarly, Gupta et al. [21] found that nalbuphine had fewer side effects compared to other opioids like fentanyl, highlighting its safety profile. Our results suggest that nalbuphine is a safe and effective adjuvant to bupivacaine for enhancing analgesia without increasing adverse effects.

Despite the positive findings, our study has several limitations. The sample size was relatively small, which may affect the generalizability of the results. Additionally, the study was conducted at a single tertiary care center, potentially limiting the applicability of the findings to other settings or populations. The study also did not evaluate the long-term outcomes and side effects of nalbuphine and bupivacaine beyond the immediate postoperative period. Furthermore, the subjective assessment of pain and block levels could introduce observer bias, despite efforts to standardize these measurements.

Conclusion

Our study demonstrates that the combination of intrathecal bupivacaine 0.5% with nalbuphine hydrochloride significantly enhances the onset and duration of both sensory and motor blocks compared to bupivacaine alone in patients undergoing abdominal hysterectomy. This combination also extends the time to first rescue analgesic and reduces the total dose of diclofenac required in the first 24 hours postoperatively. These findings suggest that nalbuphine is an effective adjuvant to bupivacaine, providing superior postoperative analgesia with a favorable side effect profile, thus offering a valuable option for enhancing pain management in surgical patients.

Bibliography

1. 1. Wong M, Morris S, Wang K, Simpson K. Managing postoperative pain after minimally invasive gynecologic surgery in the era of the opioid epidemic. J Minim Invasive Gynecol. 2018; 25(7):1165–78.
2. Carey ET, Moulder JK. Perioperative management and implementation of enhanced recovery programs in gynecologic surgery for benign indications. Obstet Gynecol. 2018; 132(1): 137–46.
3. Swain A, Nag DS, Sahu S, Samaddar DP. Adjuvants to local anesthetics: Current understanding and future trends. World J Clin Cases. 2017; 5(8):307.
4. Yaksh TL, Wallace MS. Opioids, analgesia, and pain management. Goodman Gilman's Pharmacol Basis Ther. 2011; 481–526.
5. in Z, Ding O, Islam A, Li R, Lin J. Comparison of liposomal bupivacaine and conventional local anesthetic agents in regional anesthesia: a systematic review. Anesth Analg. 2021; 132(6):1626–34.
6. Whiteside J, Wildsmith J. Developments in local anaesthetic drugs. Br J Anaesth. 2001; 87(1):27–35.
7. Paganelli MA, Popescu GK. Actions of bupivacaine, a widely used local anesthetic, on NMDA receptor responses. J Neurosci. 2015; 35(2):831–42.

8. Raghav R, Jain R, Dhawan A, Roy T, Kumar P. Chronic co-administration of nalbuphine attenuates the development of opioid dependence. Pharmacol Biochem Behav. 2018; 175:130–8.
9. Gutstein HB, Akil H. Opioid analgesics. Goodman Gilman's Pharmacol Basis Ther. 2006; 11:547–90.
10. Bansal M, Agarwal S, Gupta K, Gupta PK, Agarwal S, Pandey MN. Clinical efficacy of clonidine versus nalbuphine as intrathecal adjuvants to 0.5% hyperbaric bupivacaine for subarachnoid block during gynaecological procedures: a double blind study. Int J Res Med Sci. 2017; 5:2540–5.
11. Gress K, Charipova K, Jung JW, Kaye AD, Paladini A, Varrassi G, et al. A comprehensive review of partial opioid agonists for the treatment of chronic pain. Best Pract Res Clin Anaesthesiol. 2020; 34(3):449–61.
12. Chetty DK, Ahmed F, Chatterjee R, Rathore M. Comparison of intrathecal nalbuphine hydrochloride and clonidine hydrochloride as an adjuvant to hyperbaric bupivacaine in abdominal hysterectomy. Anesth Essays Res. 2018; 12(2):402–6.
13. Hammond R, Macdonald C, Nicholson A. Opioid analgesics. Small Anim Clin Pharmacol. 2008; 309–29.
14. Tiwari AK, Tomar GS, Agrawal J. Intrathecal bupivacaine in comparison with a combination of nalbuphine and bupivacaine for subarachnoid block: A randomized prospective double-blind clinical study. Am J Ther. 2013; 20(6):592–5.
15. Dobrydnjov I, Axelsson K, Thörn SE, Matthiesen P, Klockhoff H, Holmström B, et al. Clonidine combined with small-dose bupivacaine during spinal anesthesia for inguinal herniorrhaphy: a randomized double-blinded study. Anesth Analg. 2003; 96(5):1496–503.
16. Makram E, Abd-Elazeem I, Khashba M, Youssef L. A Comparative Study between Hyperbaric Bupivacaine Alone Versus Fentanyl versus Nalbuphine in Three Different Doses Intrathecally Adjuvant to Hyperbaric Bupivacaine for Lower Abdominal Surgeries. Benha J Appl Sci. 2020; 5(8 part (1)-(2)):87–94.
17. Chopra P, Talwar V. Low dose intrathecal clonidine and fentanyl added to hyperbaric bupivacaine prolongs analgesia in gynecological surgery. J Anaesthesiol Clin Pharmacol. 2014; 30(2):233–7.
18. Khandelwal M, Rao H, Kumar P, Bafna U, Beniwal S. Comparative study of morphine or dexmedetomidine as intrathecal adjuvants to 0.5% hyperbaric bupivacaine in infraumbilical surgeries. Indian J Pain. 2019; 33(3):156–60.
19. Giovannoni MP, Ghelardini C, Vergelli C, Dal Piaz V. α2-Agonists as analgesic agents. Med Res Rev. 2009; 29(2):339–68.
20. Nirmal A, Singh Y, Mathur SK, Patel S. Comparison between intrathecal nalbuphine and butorphanol as adjuvants to isobaric ropivacaine in elective lower limb orthopedic surgeries: A prospective, randomized, double blind study. Anaesth Pain Intensive Care. 2019; 382–6.
21. Gupta K, Rastogi B, Gupta PK, Singh I, Bansal M, Tyagi V. Intrathecal nalbuphine versus intrathecal fentanyl as adjuvant to 0.5% hyperbaric bupivacaine for orthopedic surgery of lower limbs under subarachnoid block: A comparative evaluation. Indian J Pain. 2016; 30(2):90–5.
22. Mostafa MG, Mohamad MF, Farrag W. This has greater analgesic effect: intrathecal nalbuphine or intrathecal tramadol. J Am Sci. 2011; 7(7):480.