Journal of Population Therapeutics & Clinical Pharmacology

RESEARCH ARTICLE
DOI: 10.53555/qdg6we74

A COMPARATIVE STUDY OF INTRATHECAL HYPERBARIC BUPIVACAINE 0.5% WITH FENTANYL VERSUS HYPERBARIC BUPIVACAINE 0.5% WITH NALBUPHINE AS ADJUVANTS IN PARTURIENTS UNDERGOING ELECTIVE LSCS - A RANDOMIZED DOUBLE-BLINDED STUDY

Dr. Reetika Gupta[1], Dr. Atul Kumar Singh[2*], Dr. Braj Nandan Singh[3], Dr. Neelesh Anand[4], Dr. Sanjeev Kumar[5]

[1]Assistant Professor, Department of Anaesthesiology, Heritage Institute of Medical Sciences, Bhadwar, Varanasi, Uttar Pradesh, India. ORCID id: 0000-0002-3829-7749
[2*]Associate Professor, Department of Anaesthesiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India. ORCID id: 0000-0002-7034-8577
[3]Senior Resident, Department of Anaesthesiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India. ORCID id: 0000-0001-5232-6932
[4]Senior Resident, Department of Anaesthesiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India. ORCID id: 0000-0003-1477-3517
[5]Assistant Professor, Department of Anaesthesiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India. ORCID id: 0009-0007-0712-8794

***Corresponding Author:** Dr. Atul Kumar Singh
*Associate Professor, Department of Anaesthesiology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India. ORCID id: 0000-0002-7034-8577

ABSTRACT

BACKGROUND AND AIM: Bupivacaine is the most common among the local anesthetic drugs used for spinal anaesthesia. Fentanyl is a lipophilic opioid, with a rapid onset, improving the density of subarachnoid block without producing significant side effects and improves postoperative analgesia. Nalbuphine, a mixed agonist-antagonist opioid, has the potential to attenuate μ-opioid effects and to enhance the kappa-opioid effects. It produces analgesia without the undesirable side effects of a μ agonist. The aim of this study was to compare the intraoperative and postoperative analgesic effect of intrathecal fentanyl versus intrathecal nalbuphine as an adjuvant to bupivacaine during elective lower segment caesarean section (LSCS).

MATERIAL AND METHODS: Sixty parturients of American Society of Anesthesiologists (ASA) physical status I and II, aged between 20 to 35 years, scheduled for elective LSCS, were randomly allocated into two groups of 30 each. The study medication (2.5 ml of the drug solution) was prepared by the anesthesiologist who did not take part in the study. Group BF (n=30) parturient received 2.25 ml of 0.5% hyperbaric bupivacaine plus 0.25 ml fentanyl (12.5 mcg), Group BN (n=30) parturient received 2.25 ml of 0.5% hyperbaric bupivacaine with 0.25 ml nalbuphine (250 mcg). Onset time of sensory and motor block, Visual Analogue Scale (VAS) score, duration of analgesia, hemodynamic changes, and adverse effects were documented. Systolic Blood Pressure (SBP), Diastolic Blood

Pressure (DBP), Mean arterial pressure (MAP) and Heart rate (HR) were recorded at varied intervals during intraoperative and postoperative period.

RESULTS: There was no pain in both groups at 1st and 2nd hours. At 5th hours after surgery VAS score were significant as p- value <0.05 but at 12 hours and 24 hours, it was statistically non-significant as p- value > 0.05. The time to first analgesic requirement was significantly prolonged in Group BN as compared to Group BF ($p < 0.001$). No difference in sensory onset and motor blockage in both groups. The time to attain peak sensory level were comparable in both groups. Rescue analgesia requirement was more in group BF compared to group BN in first 24 hours. No significant changes in hemodynamics were observed.

CONCLUSION: When comparing between the two given opioids, addition of nalbuphine 250mcg to hyperbaric bupivacaine 0.5%(10mg) provide efficient and prolonged postoperative analgesia with minimum or no side effects (Pruritus, nausea, respiratory depression) than addition of fentanyl 12.5mcg to same baricity and dose of bupivacaine.

KEYWORDS: Bupivacaine, Fentanyl, Lower segment caesarean section (LSCS), Nalbuphine, Spinal anaesthesia.

INTRODUCTION

The number of caesarean sections has increased over the last two decades,especially in developed countries. It is a unique situation for anaesthesia provider as they have to care for both mothers as well as the baby. Our modern clinical practice has been changed with the development of newer medication, devices and techniques. While caesarean deliveries were historically performed using general anaesthesia, nowadays regional anaesthesia is the technique of choice. Spinal anaesthesia being a simple with rapid onset and adequate muscle relaxation is commonly performed technique.[1] Intrathecal opioids are synergistic with local anaesthetics and intensify the sensory block without increasing the sympathetic block. They are commonly administered with local anaesthetics for potentiating their effects, reducing the doses of either drug and therefore decrease the associated side effects. They also prolong the duration of postoperative analgesia. Fentanyl is a lipophilic opioid with a rapid onset following intrathecal injection. It improves the quality of anaesthesiawithout producing significant side effects and improves postoperative analgesia and hemodynamic stability.[2]

Nalbuphine, a mixed agonist-antagonist opioid, has the potential to attenuate μ-opioid effects and to enhance the kappa-opioid effects. It was the synthesized in an attempt to produce analgesia without the undesirable side effects of a μ agonist. Also, its combination with μ agonist opioids was tried by many researchers to decrease the incidence and severity of the common μ- agonist side effects (respiratory depression, undesirable sedation, pruritus, nausea, vomiting and urinary retention).[3] Meanwhile, the benefits of both κ and μ receptors mediated analgesia can be obtained. Very few studies had compared intrathecal nalbuphine with other opioids.[4] The study was a prospective, randomized, single-center, double blinded study to compare the efficacy of intrathecal fentanyl versus nalbuphine added as an adjuvant to bupivacaine in parturients undergoing elective LSCS.

MATERIAL AND METHODS

Study Design and Participants

The study was a randomized, double-blinded, comparative study where the patients and observer were blinded about the group. After obtaining the Institute Ethics Committee's (IEC 2018/EC/459) approval written informed consent was taken from the parturients of American Society of Anaesthesiologists (ASA) physical status class II, aged 20-35 years, who were scheduled for elective lower segment caesarean section under spinal anaesthesia. Sixty parturients were included in the study from March 2018 to August 2018.

Inclusion Criteria

Parturients aged between 20-35 years with term pregnancy, those who gave written informed consent, categorized as American Society of Anaesthesiologists (ASA) physical status class II, undergoing elective LSCS were included in the study.

Exclusion Criteria

All high-risk pregnancies, refusal to participate, parturients allergic to the drugs used in intervention, contraindications to perform regional anaesthesia, hemodynamic instability, history of cardiac, renal, neural and liver disease, obesity were excluded from the study.

Intervention

The parturients were randomized into two groups (30 each); group BF and group BN, using sealed opaque envelopes technique concealing the randomization number. To achieve blinding the drugs were loaded in similar syringes with equal volumes by staff nurse who was not involved in the study. The primary outcome was the comparison of block characteristics and duration of postoperative analgesia. The secondary outcome is the comparison of hemodynamic parameters and adverse events. Sixty patients were randomly allocated into two groups.

1. **Group BF (n=30)** – Bupivacaine heavy (0.5%) 2.25ml with fentanyl 0.25ml (12.5mcg).
2. **Group BN (n=30)** – Bupivacaine heavy (0.5%) 2.25ml with Nalbuphine 0.25ml (250mcg).

Preanesthetic evaluation by history, physical examination and basic laboratory investigations were done in all the parturients and they were explained in detail about the procedure of the spinal anaesthesia during the preanesthetic visit. All parturients were premedicated with ranitidine 50 mg and metoclopramide 10 mg intravenously forty-five minutes prior to the start of the procedure as per hospital protocol. After receiving the parturients into the operation theatre, intravenous access was done, ASA standard monitors including electrocardiogram, pulse oximetry and non-invasive blood pressure were attached. Parturients were instructed on how to evaluate their own pain by using 10-point Visual analogue scale (VAS) pain score, which ranges from '0' (meaning no pain) to '10' (meaning worst pain). The parturients were coloaded with approximately 10-15 ml/kg lactated Ringer's solution. Baseline blood pressure, heart rate, oxygen saturation and respiratory rate were noted. In the lateral decubitus position under standard aseptic precautions, using a midline approach, a lumbar puncture was performed at either L2-L3 or L3-L4 intervertebral space (the better felt space with palpation) with 26-gauge Quincke spinal needle. After confirming the free flow of cerebrospinal fluid through the spinal needle, the studied drug was injected intrathecally over a period of about 10 seconds and parturients were turned to the supine position with 15-degree Trendelenburg position along with wedge under right buttock placed to avoid aorto-caval compression.

Sensory block was assessed by pinprick method with a blunt needle and motor block by Modified Bromage Scale.[5] The onset of sensory blockade (defined as the time from the injection of intrathecal drug to the absence of pain at the T6 dermatome) and onset of complete motor blockade (time taken from the injection to development of Bromage's Grade 3 motor block) were recorded. The duration of sensory blockade (two segment regression from highest level of sensory blockade) was also recorded in each patient. Duration of motor blockade (time required for motor blockade to return to Bromage's Grade 1 from the time of onset of motor blockade) was also noted.

Duration of sensory analgesia was noted and recorded from the time when the spinal drug was given to postoperative follow up until the parturients first complained of pain. Time at which parturients complained of pain with the Visual analogue scale more than 3 was given rescue analgesia. That point was taken as the end of fair analgesia. Electrocardiogram, non-invasive blood pressure and oxygen saturation at 0, 3, 5, 10, 15, 30, 45, 60, and 90 minutes after administration of spinal anaesthesia. Any episode of hypotension (systolic blood pressure <90 mmHg or >20% below baseline) was managed by ephedrine (5 mg) and an additional fluid bolus of Ringer's lactate solution. Bradycardia (<50 beats/min) was managed by injection atropine 0.6mg IV bolus. Parturients were shifted to post-anesthesia care unit (PACU) and post-operative analgesia was assessed by Visual analogue scale

(VAS) pain score and hemodynamic parameters were recorded at 1 h, 2 h, 3 h, 4 h, 8 h, 12 h, 18 h, and 24 hours post-operatively. The time to first rescue analgesia (aqueous diclofenac sodium 75 mg slow intravenous injection), the number of doses of rescue analgesic were recorded. Complications such as nausea, vomiting, hypotension, pruritus, and bradycardia were managed accordingly.

Statistical Analysis

The sample size was calculated using data from the study of Bindra et al which used similar interventions as in the present study. The sample size was chosen so as to maintain the overall alpha error <0.05 and power (1-β) >0.9. We enrolled 30 parturients in each group. The statistical analysis of data was performed using SPSS, version 23 IBM Corp. The categorical data of the demographic profile were analyzed by Chi-square test and non-categorical data using an unpaired T-test. Analysis of all-time comparisons (onset and duration of sensory and motor blockade, number of doses of resque analgesic, and resque analgesia time) were performed using an unpaired T-test.

RESULTS

As per the CONSORT flow diagram, 60 parturients were assessed for eligibility and enrolled in the study (Figure 1). All parturients were randomized and received the allocated treatment as per the groups (Group BF and Group BN, having equal number of parturients in each group).

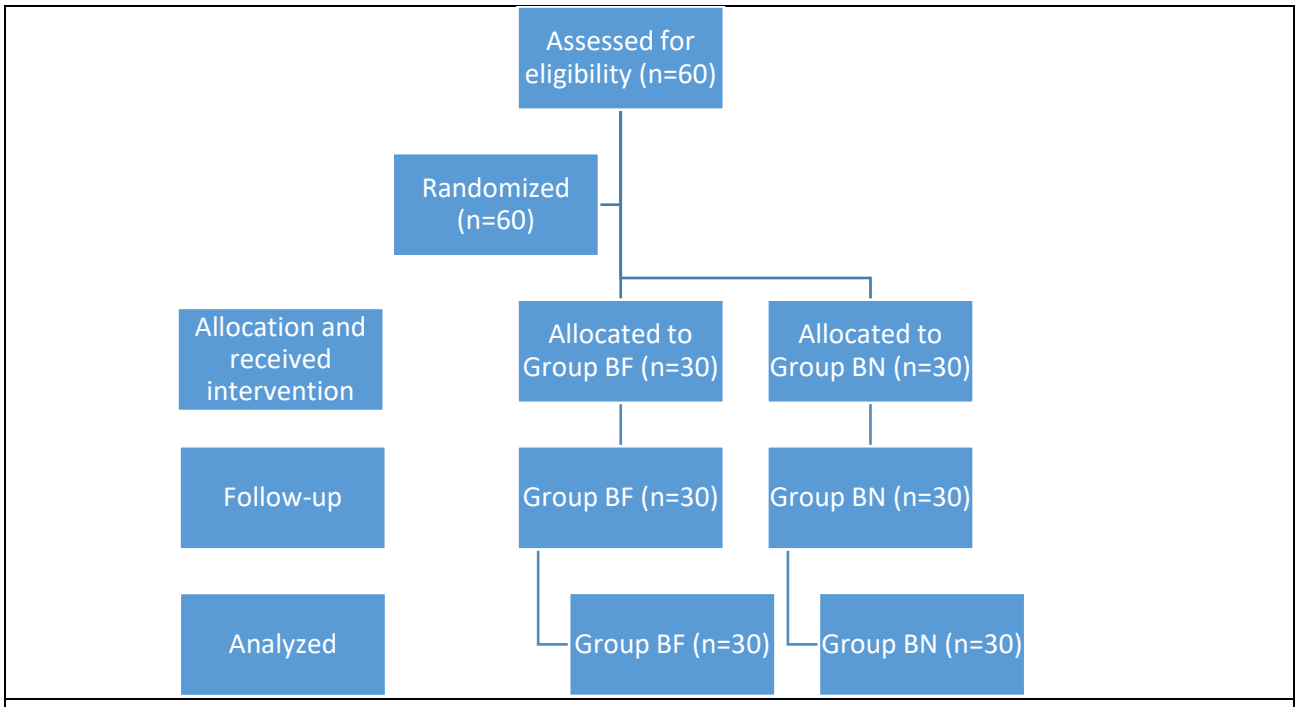

Figure 1: CONSORT flow diagram

Both groups were comparable with respect to mean age, weight, height and duration of surgery (p>0.05) [Table 1]. The mean time of onset of sensory block was 98.77 ± 9.24 sec and 99.67 ± 10.94 sec in Group BF and Group BN, respectively. The difference was statistically nonsignificant (p>0.05). The mean duration of sensory block was 270.8 ± 18.99 min in Group BF and 271.6 ± 11.22 min in Group BN which was statistically nonsignificant between the two groups. The mean time of onset of motor block was 398 ± 26.66 sec and 392 ± 25.45 sec in Group BF and Group BN, respectively. The difference was statistically nonsignificant (p>0.05). The mean duration of motor block was 180.6 ± 15.50 min and 186.9 ± 16.6 min in Group BN which was statistically nonsignificant between the two groups (Table 2). The resque analgesia time in Group BN (219.93 ± 6.37 min) was significantly more in comparison to Group BF (193.63 ± 8.92 min) which was statistically significant between the two groups (P<0.001) [Table 3].

The mean VAS score was lower in Group BN as compared to Group BF at various time intervals during the postoperative period (Table 3). The number of doses of resque analgesic was less in Group BN as compared to Group BF which was statistically significant between the two groups (P<0.001) [Table 3].

Parameters	**Group BF (n=30)**	**Group BN (n=30)**	**P value**
Age (years)	26.3 ± 2.98	26.16 ± 2.32	0.848
Weight (Kg)	63.43 ± 5.17	62.63 ± 4.26	0.539
Height (cm)	155.97 ± 2.59	156.43 ± 23.10	0.465
Duration of surgery (min)	66.16 ± 29.14	56.33 ± 9.99	0.09
Table 1: Demographic profile and operative characteristics			
Data are presented as the mean ± standard deviation (SD). P-value <0.05: significant			

Spinal characteristics	**Group BF (n=30)**	**Group BN (n=30)**	**p value**
Onset of sensory (T 6 dermatome) block (sec)	98.77 ± 9.24	99.67 ± 10.94	0.73
Duration of sensory block (min)	270.8 ± 18.99	271.6 ± 11.22	0.84
Onset of motor (modified Bromage's scale 3) block onset (sec)	398 ± 26.66	392 ± 25.45	0.37
Duration of motor (modified Bromage's scale 1) block (min)	180.6 ± 15.50	186.9 ± 16.6	0.42
Table 2: Sensory and motor block characteristics			
Data are presented as the mean ± standard deviation (SD). P-value <0.05: significant			

Variable	**Group BF (n=30)**	**Group BN (n=30)**	**P value**
VAS score postoperatively			
VAS 1 hour	0 ± 0	0 ± 0	
VAS 2 hours	0 ± 0	0 ± 0	
VAS 3 hours	1.77 ± 0.57	0.2 ± 0.40	**<0.005**
VAS 4 hours	0.9 ± 0.76	0.86 ± 0.77	0.87
VAS 8 hours	1.03 ± 0.81	0.86 ±0.77	0.41
VAS 12 hours	0.9 ± 0.76	0.86 ± 0.77	0.87
VAS 18 hours	0.88 ± 0.74	0.9 ± 0.80	0.76
VAS 24 hours	1.03 ± 0.81	0.86 ± 0.77	0.41
Rescue analgesia time (min)	193.63 ± 8.92	219.93 ± 6.37	**<0.001**
Number of doses of rescue analgesic	2.07 ± 0.69	1.43 ± 0.50	**<0.001**
Table 3: VAS score between two groups postoperatively, rescue analgesia time (hours)			
Data are presented as the mean ± standard deviati on (SD). P-value <0.05: significant			

Variable		**Group BF**	**Group BN**	**P value**
Bradycardia	1. No	30	30	0.906
	2. Yes	0	0	
PONV	1. No	30	30	N/A
	2. Yes	0	0	
Hypotension	1. No	26	27	0.663
	2. Yes	4	3	
Pruritus	1. No	30	30	N/A
	2. Yes	0	0	
Respiratory depression	1. No	30	30	N/A
	2. Yes	0	0	
Table 4: Adverse events				
PONV: postoperative nausea and vomiting. P-value <0.05: significant				

DISCUSSION

Spinal anaesthesia is the most commonly used technique in parturients undergoing caesarean section due to its efficacy in providing surgical anesthesia and postoperative pain relief. The addition of opioids to local anesthetics reduces the dose requirement of both drugs with subsequent decrease in the incidence of the associated side effects. The analgesic property of the intrathecal opioids is attributed to spinal selectivity; the lipophilic property of fentanyl and nalbuphine leads to rapid vascular uptake and redistribution causing a higher concentration in brain as well.[6] Their combination with intrathecal local anesthetics limits the regression of the sensory block seen with local anesthetics alone.[7,8]

It also allows early ambulation of patients because of their sympathetic and motor nerve-sparing activities[9,10] with disadvantages of respiratory depression, sedation, postoperative nausea and vomiting (PONV), pruritus and urinary retention.[11]

In the study of Culebras et al[12] and Ahmed et al,[13] they had observed the potentiating effect of intrathecal nalbuphine with bupivacaine for postoperative analgesia in three different doses (0.8, 1.6, and 2.4 mg), according to them 0.8 mg was the best dose to improve the intraoperative analgesia and prolong early postoperative analgesia, without increasing the frequency of side effects. Tiwari et al[14] had compared intrathecal nalbuphine 0.2 and 0.4 mg added to hyperbaric bupivacaine with bupivacaine alone. They concluded that prolonged duration of analgesia was seen in nalbuphine 0.4 mg without adverse effects. The mean duration of analgesia was significantly prolonged in Group BN as compared to Group BF in our study. Our result coincides with the studies done by Culebras et al[12] and Ahmed et al.[13]

In the present study the onset of sensory and motor block was similar in both the groups and was nonsignificant. Bindra et al,[15] Gupta et al.[16] and Garg et al.[17] had also observed non-significant difference in the onset of motor block. The duration of sensory and motor block was comparable in both the study groups and was nonsignificant. Gomma et al,[18] Bindra et al,[15] and Ahmed et al,[13] had also observed nonsignificant difference in terms of duration of sensory and motor block. This observation is due to lower doses of both bupivacaine and opioids used in our study.

In our study a statistically significant difference was noted in mean VAS score at 3h postoperatively ($p<0.05$). However, at 1h and 2h the VAS was 0 in both groups and it was statistically nonsignificant from 4th hour till 24 hours postoperatively. The mean VAS score was lower in Group BN as compared to Group BF in postoperative hours. The parturients in Group BN required lesser amount of resque analgesics than in Group BF ($p<0.05$), the finding of our study was comparable with Bindra et al.[15] Both groups in our study were comparable with regard to various hemodynamic parameters. This was in accordance with Gomma et al,[18] and Bindra et al.[15] who found no statistically significant difference in hemodynamic parameters between the groups. There was no significant difference in regard to adverse events between the two studied groups.

CONCLUSION

Fentanyl and nalbuphine both can be used as additive to hyperbaric bupivacaine in subarachnoid block in parturients undergoing lower segment caesarean section to make the block denser and provide adequate post-operative analgesia. Nalbuphine being not included under the narcotic act, so widely available and is cost-effective also.

In spite of calculating the sample size, the number of parturients included in the study was too small to generate the study outcomes. Any effect of both fentanyl and nalbuphine in newborn was not taken into consideration. The patients were followed for a shorter period of time, i.e only 24 hours.

Financial Support: Nil.

Conflicts of Interest: None Declared.

REFERENCES

[1] Bogra J, Arora N, Srivastava P. Synergistic effect of intrathecal fentanyl and bupivacaine in spinal anesthesia for cesarean section. BMC Anesthesiol 2005;5(1):5.

[2] Chu CC, Shu SS, Lin SM, et al. The effect of intrathecal bupivacaine with combined fentanyl in cesarean section. Acta Anaesthesiol Sin 1995;33(3):149-54.

[3] Schmauss C, Doherty C, Yaksh TL. The analgetic effects of an intrathecally administered partial opiate agonist, nalbuphine hydrochloride. Eur J Pharmacol 1982;86(1):1-7.

[4] Raghuraman M. Intrathecal nalbuphine – Will it gain wider acceptance? - A narrative review. Egyptian Journal of Anaesthesia 2017;33(3):289-93.

[5] Bromage PR. Epidural Analgesia. Philadelphia: WB Saunders 1978: p. 144.

[6] Zeng Z, Lu J, Shu C, et al. A comparision of nalbuphine with morphine for analgesic effects and safety: meta-analysis of randomized controlled trials. Scientific Report 2015;5:109-27.

[7] Verstraete S, Van de Velde M. Post caesarean section analgesia. Acta Anaesthesiol Belg 2012;63:147-67.

[8] Gehling M, Tryba M. Risks and side -effects of intrathecal morphine combined with spinal anaesthesia: A meta-analysis. Anaesthesia 2009;64:643-51.

[9] Bujedo BM, Santos SG, Azpiazu AV. A review of epidural and intrathecal opioids used in treatment of postoperative pain. J Opioid Manag 2012;8(3)177-92.

[10] Tawfik MO. Mode of action of intraspinal opioids. Pain Rev 1994;1:275-94.

[11] Terajima K, Onodera H, Kobayashi M, et al. Efficacy of intrathecal morphine for analgesia following elective cesarean section: comparison with previous delivery. Journal of Nippon Medical School 2003;70(4):327–33.

[12] Culebras X, Gaggero G, Zatloukal J, et al. Advantages of intrathecal nalbuphine, compared with intrathecal morphine, after cesarean delivery: an evaluation of postoperative analgesia and adverse effects. Anesth Analg 2000;91:601-5.

[13] Ahmed FI. Intrathecal nalbuphine versus fentanyl as an adjuvant to bupivacaine in spinal anesthesia for elective caesarean section: a randomized double-blinded study. Res Opin Anesth Intensive Care 2019;6:112-8.

[14] Tiwari AK, Tomar GS, Agrawal J. Intrathecal bupivacaine in comparison with a combination of nalbuphine and bupivacaine for subarachnoid block. American Journal of Therapeutics. 2013;20(6):592–5.

[15] Bindra TK, Kumar P, Jindal G. Postoperative analgesia with intrathecal nalbuphine versus intrathecal fentanyl in caesarean section: a double blind randomized comparative study. Anesth Essays Res 2018;12:561-5.

[16] Gupta K, Rastogi B, Gupta P, et al. 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 Journal of Pain 2016;30(2):90.

[17] Garg K, Garg P, Katyal S. Comparative analysis of intrathecal nalbuphine vs fentanyl as an adjuvant to bupivacaine for urological procedures. MGM J Med Sci 2020;7:203.

[18] Gomaa HM, Mohamed NN, Zoheir HA, et al. A comparison between post-operative analgesia after intrathecal nalbuphine with bupivacaine and intrathecal fentanyl with bupivacaine after caesarean section. Egypt J Anaesth 2014;30:405-10.