

ORIGINAL RESEARCH ARTICLE

**INTRATHECAL DEXMEDETOMIDINE WITH
BUPIVACAINE DELAYS THE NEED OF RESCUE
ANALGESIA POSTOPERATIVELY**

¹Dr. Rohini Arora, ²Dr. Syed Azizur Rahman, ³Dr. Pratibha Lavania, ⁴Dr. Yogendra Bhati

¹Assistant Professor, Department of Anaesthesiology, Noida International Institute of Medical Sciences(NIIMS), Noida International University, NIU Campus Yamuna Expressway Sector 17A, Greater Noida, Uttar Pradesh, India

²Assistant Professor, Department of Medicine, Noida International Institute of Medical Sciences(NIIMS), Noida International University, NIU Campus Yamuna Expressway Sector 17A, Greater Noida, Uttar Pradesh, India

³Associate Professor, Department of Pharmacology, Noida International Institute of Medical Sciences(NIIMS), Noida International University, NIU Campus Yamuna Expressway Sector 17A, Greater Noida, Uttar Pradesh, India

⁴Associate Professor, Department of Pharmacology, Noida International Institute of Medical Sciences(NIIMS), Noida International University, NIU Campus Yamuna Expressway Sector 17A, Greater Noida, Uttar Pradesh, India

Corresponding Author:

Dr. Yogendra Bhati(drbhati23@gmail.com)

Abstract

Background: Spinal anesthesia is widely used for infraumbilical surgeries. Commonly bupivacaine, Ropivacaine, lidocaine and tetracaine are agents used for spinal anesthesia. Adjuvants like butorphanol and Dexmedetomidine are frequently used to increase duration as well as quality of spinal anesthesia. Butorphanol and Dexmedetomidine are frequently used as adjuvant for spinal anesthesia along with bupivacaine.

Aims and Objectives: To evaluate the efficacy of the Bupivacaine with Dexmedetomidine significantly delays the need of postoperative rescue analgesia for infraumbilical surgeries.

Materials and Methods: This study retrieved retrospective records of spinal anesthesia for infraumbilical surgeries. Records were analyzed if bupivacaine dose was 2.5 ml of 0.5% heavy bupivacaine and adjuvant used was either Dexmedetomidine 5µg or Butorphanol 25 µg. Records were divided into two groups-Bupivacaine + butorphanol and Bupivacaine + Dexmedetomidine. Data of time to rescue analgesia and events of hypotension, bradycardia and shivering were collected and compared.

Results and Observations: We retrieved 196 medical records of infraumbilical surgeries under spinal anesthesia for inclusion in the study excluding lower segment

caesarian section. Of these records 32 cases were excluded due to use of different anesthetic agent or dose used was different. Applying age exclusion criteria removed 9 records. We are left with 164 records that satisfied all inclusion and exclusion criterias (FIG1). Bupivacaine and butorphanol (Group B) was used in 68 cases while Bupivacaine and Dexmedetomidine (Group D) was used in 96 patients. Time for rescue analgesia was found to be 345.46 ± 38.21 minutes for group B (Bupivacaine + Butorphanol) and 436.8 ± 48.23 for Group D (Bupivacaine+ Dexmedetomidine). The difference was found to be statistically significant. The study found 11 records of hypotension, 14 of Bradycardia and one record of shivering in Group D (Bupivacaine + Dexmedetomidine). In Group B (Bupivacaine + Butorphanol) we found two cases of hypotension and one record of Bradycardia. 7 events of shivering were recorded in group B. All differences in safety parameters were statistically significant.

Conclusion: In our study we have concluded, that Bupivacaine with Dexmedetomidine significantly delays the need of postoperative rescue analgesia for infraumbilical surgeries. Adverse effects of hypotension and bradycardia was more frequent with Dexmedetomidine while shivering was found to be more frequent with butorphanol.

Keywords: Dexmedetomidine, spinal anaesthesia, butorphanol, infraumbilical surgeries, hypotension, bradycardia, bupivacaine

Introduction

Spinal anesthesia is widely used for infraumbilical surgeries^[1]. An efficient management of perioperative and postoperative pain after lower extremity orthopedic surgery represents an important component of early postoperative recovery as it serves to blunt autonomic, somatic and endocrine reflexes with a resultant potential of decreasing perioperative morbidity^[2]. Thus, adequate pain management is essential to facilitate rehabilitation and accelerate functional recovery, enabling patients to return to their normal activity more quickly. Polypharmacological approach is the most common practice to treat perioperative pain, as no single agent has yet been identified to specifically inhibit nociception without associated side effects^[3]. Different techniques and drugs had been studied in order to prolong the duration of regional anesthesia and achieve postoperative pain relief^[4]. Opioids are commonly added to local anaesthetics to produce spinal and epidural anesthesia. However, significant adverse effects such as, urinary retention, respiratory depression, hemodynamic instability, pruritus and occasionally severe nausea and vomiting, may limit their use^[5, 6, 7]. Spinal anesthesia is widely used for infraumbilical surgeries^[7, 8]. Commonly bupivacaine, Ropivacaine^[9, 10] lidocaine^[11] and tetracaine are agents used for spinal anesthesia^[12]. Adjuvants like butorphanol^[13] and Dexmedetomidine^[14], are frequently used to increase duration as well as quality of spinal anesthesia. Butorphanol is a synthetic opioid agonist-antagonist and produces analgesic effect^[15]. Its duration of analgesia is dependent on its route of administration^[16]. Dexmedetomidine is an alpha agonist and blocks central sympathetic outflow by decreasing release of norepinephrine^[17]. It has sedative, hypnotic, anxiolytic, analgesic and sympatholytic activity. Spinal anesthesia is associated with a few adverse events like hypotension^[18,19,20,21,22], bradycardia^[23,24] and shivering^[25,26], Postoperative pain^[27,28], is a major issue and different strategies are used for its management^[29,30,31]. However there is paucity of data to objectively prefer one over another. Present study was an attempt to generate data and advocacy regarding their

use.

Primary objective of the study was to compare Bupivacaine (2.5ml of 0.5% hyperbaric Bupivacaine) and butorphanol (25µg) with bupivacaine (2.5ml of 0.5% hyperbaric Bupivacaine) and Dexmedetomidine (5µg) time needed for rescue analgesia postoperatively. Primary outcome measure was time duration from start of surgery to first use of analgesic (rescue analgesia) postoperatively. Secondary objective was to compare adverse events associated with their use-hypotension, bradycardia and shivering.

Materials and Methods

We have collected the data from the Department of Anaesthesiology, Noida International Institute of Medical Sciences(NIIMS), Noida International University, Greater Noida, Noida, UP, India. Ethical clearance was taken from institutional ethics, committee before start of the study (NIIMS/IEC/April-2022/D-1). Site of study was a tertiary care hospital in National Capital region, India. Convenience sampling was done by using hospital records of spinal anesthesia for infraumbilical surgeries in the study. All records of elective infraumbilical surgeries under spinal anesthesia of adult patients (18-60 years) in these months were retrieved. Lower segment cesarean sections were excluded. Records were assessed to find out those records of patients who were given bupivacaine 10 mg and adjuvants used were either butorphanol 5µg or Dexmedetomidine 10µg. Records with other agents or with different doses were excluded. Use of any analgesics preoperatively (within 6 hours) or intra-operatively were kept as exclusion criteria. Conversions to general anesthesia due to any cause were to be excluded.

Time to rescue analgesia was measured from start of surgery to first dose of analgesic given on complaint of the patient postoperatively irrespective of the analgesic used.

Safety parameters of hypotension, bradycardia and shivering were to be noted. Pruritus and nausea were not included in the study due to our concern that these events might not be accurately registered in records. Absence of the terms hypotension, bradycardia and shivering from operative/postoperative notes were taken to mean absence of any of these events. Absence of time of rescue analgesia would be regarded as missing data and that record would be excluded from analysis.

Potential confounders like duration of surgery, type of surgery and underlying cause of operation were recorded. In case of significant differences between the two groups, sub group analysis was planned.

To standardize data extraction, a data extraction form was developed which was simple, specific and unambiguous. It included demographic details (Age, gender, weight) dose of anesthetic used, duration of surgery, safety parameters (Hypotension, Bradycardia and Shivering) and time of rescue analgesia.

Statistical analysis

Statistical analysis was done using SPSS software (version 24). Time for rescue analgesia was treated as continuous data and safety parameters as dichotomous variable. Significance testing was done and data tabulated using Microsoft excel. Continuous data has been presented as mean \pm standard deviation and significance test was done with unpaired T-test. Two tailed Z score test was used for safety parameters

of hypotension, bradycardia and shivering.

Results and Observations: We retrieved 196 medical records of infraumbilical surgeries under spinal anesthesia for inclusion in the study excluding lower segment caesarian section. Of these records 32 cases were excluded due to use of different anesthetic agent or dose used was different. Applying age exclusion criteria removed 9 records. We are left with 164 records that satisfied all inclusion and exclusion criterias (FIG1). Bupivacaine and Butorphanol (Group B) was used in 68 cases, 44 cases were males and 24 cases were females while Bupivacaine and Dexmedetomidine (Group D) was used in 96 patients, 62 cases were males and 34cases were females. Table 1and Figure 1. Baseline characteristics and final outcomes are presented in Table 2 and Figure 2 There was no significant difference between the two groups with regards to baseline characteristics.

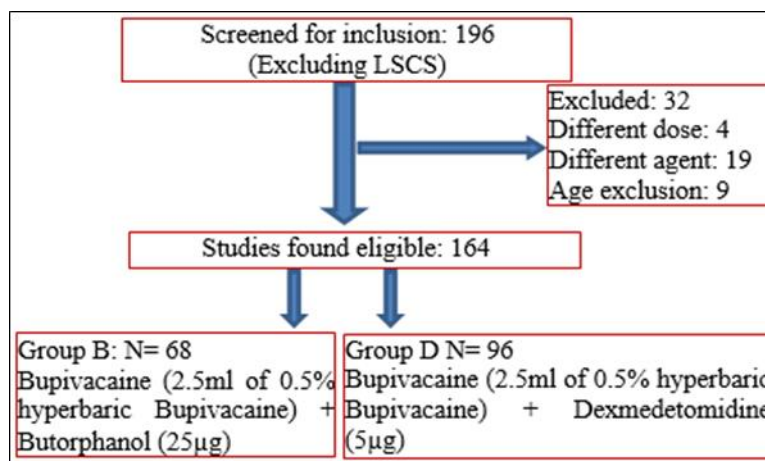


Fig1: Patient cohort for retrospective review of medical records of infraumbilical surgeries under spinal anesthesia

Time for rescue analgesia was found to be 345.46±38.21 minutes for group B (Bupivacaine + Butorphanol) and 436.8± 48.23 for Group D (Bupivacaine+ Dexmedetomidine). The difference was found to be statistically significant as in Table 3.

The study found 11 records of hypotension, 14 of Bradycardia and one record of shivering in Group D (Bupivacaine + Dexmedetomidine).In Group B (Bupivacaine + Butorphanol)we found two cases of hypotension and one record of Bradycardia.7 events of shivering were recorded in group B. All differences in safety parameters were statistically significant. As in Table 3 and Figure 3.

Table 1:Gender Distribution

Subjects	Group B	Group D
	Bupivacaine+Butorphanol	Bupivacaine+Dexmedetomidine
Male	44	62
Female	24	34
Total	68	96

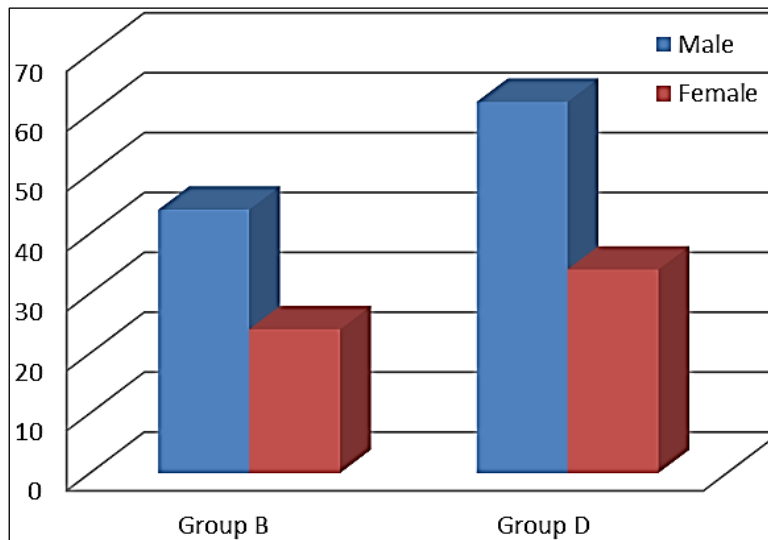


Fig 2: Gender distribution in both the groups

Table 2: Baseline characteristics

Baseline Characteristics	Group B (68) Bupivacaine + Butorphanol	Group D (96) Bupivacaine + Dexmedetomidine	P value
Mean Age(years)	43.31±8.3	45.31±5.78	0.0706
Mean Weight(kg)	65.11± 10.82	68.31±13.12	0.1005
Mean Duration of Surgery(min)	56.65±16.09	58.09±14.03	0.5433

Table 3: Outcome measures

Parameters	Group B Bupivacaine + Butorphanol n= 68	Group D Bupivacaine + Dexmedetomidine n= 96	P value
Rescue analgesia(min)	345.46±38.21	436.8±48.23	< 0.0001
Hypotension	2 (2.9%)	11 (11.5%)	.0466
Bradycardia	1 (1.2%)	14(14.6%)	.0041
Shivering	7 (1.0%)	1 (1.0%)	.00672

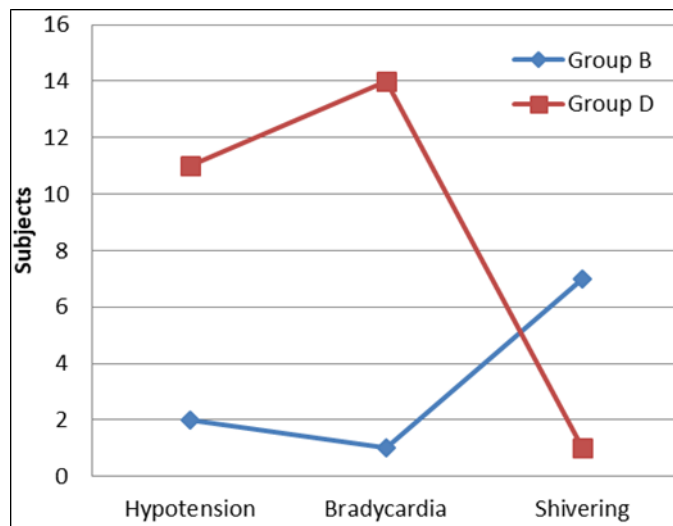


Fig 3: Symptoms noticed in the subjects

Discussion

The study found that time for rescue analgesia was significantly delayed in patients receiving Bupivacaine and Dexmedetomidine 10 µg in comparison to bupivacaine + butorphanol 5 µg. In Dexmedetomidine group mean time to rescue analgesia was 436.8±48.23 minutes. It was similar to results reported in other clinical trials. Study by Gautam B *et al.*^[32] reported 326 ±91 min and Rahimzadeh P *et al.*^[33] reported 496.63 ±70.19 min. However, it was much less than time reported by Yektas A *et al.*^[34], who found it to be 1042.50±366.78 minutes. It could be due to difference in type of surgery as the reported time was for patient undergoing transurethral resection of prostate only. This study found that time for rescue analgesia in butorphanol group was 345.46±38.21. This was higher than those reported by Kumari *et al.*^[35] 156.17±43.918. We expect that review is likely to show greater time duration as data from drug chart consisted of time when rescue analgesia was administered and not the time when patient first complained of pain which would more accurately reflect the duration of analgesia. On comparison of safety parameters, hypotension and bradycardia was significantly more frequent in Dexmedetomidine group in comparison to butorphanol group. Shivering was more frequent in butorphanol group. Shivering is expected to be low in dexmedetomidine group as it has been used to decrease shivering during anaesthesia^[36]. However, none of the events were serious in nature and were adequately managed.

Limitations

1. As it was a retrospective medical records review, there is a possibility that time lines mentioned in the records might not be strictly accurate.
2. Time for rescue analgesia was calculated from the time of administration while more accurate measure would have been the time when the patient complained of pain.
3. Many parameters for quality and duration of spinal anaesthesia could not be assessed as time to reach highest sensory level, duration of sensory and motor block are not routinely recorded in medical notes.

4. Further safety parameters were not defined in a strict manner and may be prone to random errors due to subjective judgments of attending physician.
5. Quality of anesthesia was also not assessed.

These limitations could be overcome in randomized control trial which we plan to do in the future.

Conclusion

Our study suggests that the Dexmedetomidine could be a better choice for spinal anesthesia especially in those patients and conditions where postoperative pain is a major issue. Further studies are warranted to conclusively advocate its use.

Source of funding: None.

Conflict of interest: None.

References

1. Kataria AP, Jarewal V, Kumar R, Kashyap A. Comparison of Levobupivacaine and Levobupivacaine with Dexmedetomidine in Infraumbilical Surgeries Under Spinal Anesthesia. *Anesth Essays Res.* 2018 Jan-Mar;12(1):251-255. Doi: 10.4103/aer.AER_227_17. PMID: 29628591; PMCID: PMC5872874
2. Perlas A, Kirkham KR, Billing R, Tse C, Brull R, Gandhi R, *et al.* The impact of analgesic modality on early ambulation following total knee arthroplasty. *Reg Anesth Pain Med.* 2013;38:334-39.
3. Hyllested M, Jones S, Pedersen JL, Kehlet H. Comparative effect of paracetamol, NSAIDs or their combination in postoperative pain management: a qualitative review. *Br J Anaesth.* 2002;88:199-214.
4. Smith OHW, Nielsen LA, Gaumann D, Tassonyi E, Rifat KR. Sensory changes and pain after abdominal hysterectomy: a comparison of anesthetic supplementation with fentanyl versus magnesium or ketamine. *Anesth Analg.* 1986;1:95-101.
5. Durant PA, Yaksh TL. Drug effects on urinary bladder tone during spinal morphine-induced inhibition of the micturition reflex in unanesthetized rats. *Anesthesiology.* 1988;68:325-34.
6. Chinachoti T, Nilrat P, Samarnpiboonphol P. Nausea, vomiting and pruritus induced by intrathecal morphine. *J Med Assoc Thai.* 2013;96:589-94.
7. Sultan P, Gutierrez MC, Carvalho B. Neuraxial morphine and respiratory depression: finding the right balance. *Drugs.* 2011;71:1807-19.
8. Sen J, Sen B. Anaesthetic management protocol in a medical college hospital in Orange zone Maharashtra, India during the 2019-nCoV lockdown period. *Research J Pharm. and Tech.* 2020;13(9):4399-4402. Doi: 10.5958/0974-360X.2020.00778.7
9. Taksande K, Reddy GS. A Randomized Comparative Trial to Study the effect of Preoperative single shot Epidural with Ropivacaine in Lumbar Laminectomy. *Research Journal of Pharmacy and Technology.* 2021;14(6):2945-9.
10. Katke P, Baig MS, Ismail TSES, Gade P. Comparison of Efficacy and Safety of Bupivacaine 0.5% and Ropivacaine 0.5% in Patients Undergoing Upper arm Surgeries by Supraclavicular Block Technique using Nerve Locator. *Research Journal of Pharmacology and Pharmacodynamics.* 2015;7(4):187-190.

11. Madhavan S, Gajnedran PL. A Preliminary Study to compare The Pain Perception of Topical gel Versus Injected Local Infiltration/Block Anaesthesia during Non-Surgical Periodontal Therapy. *Research J Pharm. and Tech.* 2018;11(10):4257-4262.
12. Olawin AM, M Das J. Spinal Anesthesia. [Updated 2021 Jul 2]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing, 2022 Jan.
13. Kumar B, Williams A, Liddle D, Verghese M. Comparison of intrathecal bupivacaine-fentanyl and bupivacaine-butorphanol mixtures for lower limb orthopedic procedures. *Anesthesia, essays and researches.* 2011;5(2):190-195. <https://doi.org/10.4103/0259-1162.94775>
14. Gupta R, Verma R, Bogra J, Kohli M, Raman R, Kushwaha JK. A Comparative study of intrathecal dexmedetomidine and fentanyl as adjuvants to Bupivacaine. *J Anaesthesiol Clin Pharmacol.* 2011 Jul;27(3):339-43. Doi: 10.4103/0970-9185.83678. PMID: 21897504; PMCID: PMC3161458.
15. Sasaki K, Ishikawa T, Ikeda K, Kasai S. Antinociceptive effects of the combined use of butorphanol and buprenorphine in mice. *Neuropsychopharmacol Rep.* 2021 Dec;41(4):522-525. Doi: 10.1002/npr2.12202. Epub 2021 Sep 10. PMID: 34505754; PMCID: PMC8698687.
16. https://www.accessdata.fda.gov/drugsatfda_docs/label/2002/19890s171bl.pdf Accessed on 3/06/22
17. Afonso J, Reis F. Dexmedetomidine: current role in anesthesia and intensive care. *Rev Bras Anesthesiol.* 2012 Jan-Feb;62(1):118-33. Doi: 10.1016/S0034-7094(12)70110-1. PMID: 22248773.
18. Ferré F, Martin C, Bosch L, Kurrek M, Lairez O, Minville V. Control of Spinal Anesthesia-Induced Hypotension in Adults. *Local and regional anesthesia.* 2020;13:39-46.
19. Yu C, Gu J, Liao Z, Feng S. Prediction of spinal anesthesia-induced hypotension during elective cesarean section: a systematic review of prospective observational studies. *International journal of obstetric anesthesia.* 2021;47:103-175.
20. Lee JE, George RB, Habib AS. Spinal-induced hypotension: Incidence, mechanisms, prophylaxis, and management: Summarizing 20 years of research. *Best practice & research. Clinical anaesthesiology.* 2017;31(1):57-68.
21. Chandak AV, Bhuyan D, Singam AP, Patil B. Comparison of bolus phenylephrine, Ephedrine and Mephentermine for maintenance of Arterial pressure during Spinal anaesthesia in Caesarean section. *Research J Pharm. and Tech.* 2021;14(3):1349-1352.
22. Kayukov L, Agarkova L, Agarkova T, Shipakov V, Zakharova I, Bukharina I. Disorders of the Functional State of the Haemostatic System during Intraoperative and Postoperative Anesthesia and their Prevention. *Research J Pharm. and Tech.* 2018;11(7):3043-3048.
23. Lesser JB, Kevin V, Valskys SR, Kuroda M. Severe Bradycardia during Spinal and Epidural Anesthesia Recorded by an Anesthesia Information Management System. *Anesthesiology.* 2003;99:859-866.
24. Dyamanna DN, Bs SK, Zacharia BT. Unexpected bradycardia and cardiac arrest under spinal anesthesia: case reports and review of literature. *Middle East journal of anaesthesiology.* 2013;22(1):121-125.

25. Crowley LJ, Buggy DJ. Shivering and neuraxial anesthesia. *Regional anesthesia and pain medicine*. 2008;33(3):241-252.
26. Esmat IM, Mohamed MM, Abdelaal WA, *et al*. Postspinal anesthesia shivering in lower abdominal and lower limb surgeries: a randomized controlled comparison between paracetamol and dexamethasone. *BMC Anesthesiol*. 2021;21:262.
27. Rallabhandi S, Chakole V, Singam A. Comparison of Transdermal Fentanyl Patch and Intravenous Fentanyl for Postoperative pain relief in patients undergoing major abdominal surgeries under general Anaesthesia. *Research Journal of Pharmacy and Technology*. 2021;14(4):1915-8.
28. BhavikkumarGD, Raiyani PD. Postoperative pain after spine surgery: Comparative efficacy of diclofenac and etoricoxib in combination with tramadol and paracetamol at lower doses. *Research J Pharmacology and Pharmacodynamics*. 2013;5(1):62-69.
29. Ramamoorthy L. Post-operative Pain Management Strategies: Nursing Perspectives. *Asian J Nursing Education and Research*. 2021;11(2):189-192.
30. Jejani AS, Chaudhari A, Singam A. Study of Intrathecal Buprenorphine for Postoperative Analgesia after Cesarean section. *Research J Pharm. and Tech*. 2019;12(12):6062-6066.
31. VijayaM. Effectiveness of Play Therapy in Reducing Postoperative Pain among Children (2-5 yrs) in Selected Pediatric Hospitals Madurai. *Asian J Nur. Edu. & Research*. 2014 July-Sept;4(3):288-289.
32. Gautam B, Niroula S, Sharma M, Lama SM. Effects of Intrathecal Dexmedetomidine as an Adjuvant to Hyperbaric Bupivacaine for Spinal Anaesthesia in Adults Undergoing Elective Infra-umbilical Surgery. *JNMA; journal of the Nepal Medical Association*. 2017;56(208):379-387.
33. Rahimzadeh P, Faiz S, Imani F, Derakhshan P, Amniati S. Comparative addition of dexmedetomidine and fentanyl to intrathecal bupivacaine in orthopedic procedure in lower limbs. *BMC anesthesiology*. 2018;18(1):62.
34. Yektaş A, Belli E. The effects of 2 µg and 4 µg doses of dexmedetomidine in combination with intrathecal hyperbaric bupivacaine on spinal anesthesia and its postoperative analgesic characteristics. *Pain research & management*. 2014;19(2):75-81.
35. Kumari A, Kullar KK, Gupta R. Duration of postoperative analgesia with Nalbuphinevs Butorphanol as an adjunct to spinal anesthesia for lower limb orthopedic surgeries: A randomized double-blind active control trial. *Journal of anaesthesiology, clinical pharmacology*. 2021;37(4):592-597.
36. Lamontagne C, Lesage S, Villeneuve E. *et al*. Intravenous dexmedetomidine for the treatment of shivering during Cesarean delivery under neuraxial anesthesia: a randomized-controlled trial. *Can J Anesth/J Can Anesth*. 2019;66:762-771.