Original Article

Comparative study of hemodynamic effects of intrathecal bupivacaine with butorphanol in cardiac and non-cardiac patients

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Abstract

Background and Aims: The synergism between intrathecal opioids and low dose local anesthetics makes it possible to achieve reliable spinal anesthesia (SA) with minimal hypotension. The study objective was to compare the hemodynamic effects of reduced dose of 0.5% intrathecal bupivacaine (2mL) with 25 μg butorphanol in cardiac vs non-cardiac patients.

Material and Methods: We included sixty patients aged 30-80 years, undergoing infraumbilical surgeries in the study and compared thirty cardiac patients with mild to moderate reduction in left ventricular ejection fraction (LVEF) on 2D echocardiography (Group C) with 30 non-cardiac patients (Group NC) for similar types of surgery. Both the groups received 0.5% bupivacaine 2.0 ml with 25 μg butorphanol.

Results: The spinal block characteristics were similar in both groups ($P > 0.05$). The blood pressure of the patients in the two groups was comparable till 80 min $P > 0.05$ after which Group NC had significant increase in blood pressure compared to Group C upto 95 min ($P < 0.05$). Similarly, heart rate was comparable until 90 min ($P > 0.05$) after which Group NC had significant increase in heart rate versus Group C upto 100 min ($P < 0.05$). Eight patients in group C and five patients in group NC showed hypotension. Bradycardia was seen in 4 patients in group C in comparison to only one patient in group NC.

Conclusion: We can safely consider spinal anesthesia with 10 mg bupivacaine and 25μg butorphanol in cardiac patients with mild to moderately reduced ejection fraction presenting for infraumbilical non-cardiac surgeries with the advantage of intraoperative hemodynamic stability and adequate postoperative analgesia.

Keywords: Bupivacaine, butorphanol, ejection fraction, spinal anesthesia

Introduction

Improved management of chronic diseases like hypertension, diabetes, and coronary artery disease has led to an increase in the number of patients with poor cardiac function, presenting for non-cardiac surgery. General anesthesia or regional anesthesia is often chosen alone or in combination, depending upon the type of surgery and patient requirement. However, stimulation of hemodynamic response to intubation is the significant concern with the use of general anesthesia.[1]

Spinal anesthesia (SA) is a rapid and reliable technique for surgery below the umbilicus. The primary concern of spinal anesthesia is hypotension and bradycardia due to sympathetic blockade. The fall in systemic vascular resistance (SVR) and blood pressure can precipitate myocardial ischemia

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especially in patients with compromised ventricular function.[2] Preserving the cardiac output during spinal anesthesia is necessary for the maintenance of oxygen delivery to the vital organs and various prophylactic measures have been employed to this aspect.[3]

Decreasing the dose of local anesthetic (LA) has the potential to minimize spinal induced hypotension with the limitation of an inadequate level of sensory block. Adjuncts like clonidine, tramadol, nalbuphine, fentanyl and butorphanol have been evaluated extensively in non-cardiac patients to improve the level of anesthesia and prolong the duration of postoperative analgesia. Sanatkar *et al.* have studied low dose bupivacaine (1.5 mL) with sufentanil in ASA Grade III cardiac patients with minimal episodes of hypotension.[4] It causes synergism by enhancing sensory blockade, without measurably increasing sympathetic or motor blockade.[5] Butorphanol, a partial agonist-antagonist, when used spinally, produces hemodynamic stability with longer duration of postoperative analgesia as compared to sufentanil or fentanyl.[6,7] It is five to eight times more potent than morphine.[8]

Keeping these aspects in mind along with the paucity of data regarding the use of SA in cardiac patients, we designed this study to compare the hemodynamic effects of SA using 2 ml of 0.5% bupivacaine and 25µg butorphanol in cardiac versus non-cardiac patients.

Material and Methods

The study was conducted at tertiary care hospital after due ethical committee clearance (vide no. SGRD/1619 dated: 10/5/18) and informed written consent from the patients in their vernacular language. We compared thirty patients with history of cardiac disease and mild to moderate reduction in left ventricular ejection fraction (LVEF) between 30-53% on 2D echocardiography (ECHO), undergoing infraumbilical surgeries (not leading to blood loss or massive fluid shifts) under SA with 30 non-cardiac patients (with normal LVEF) undergoing similar surgeries as controls.

Group C (cardiac) included patients of either sex, aged 30-80 years belonging to ASA physical status II and III with history of cardiac disease; minor or intermediate clinical predictors and moderate or excellent functional capacity (METS > 4) (cardiac). Patients with poor functional capacity (METS < 4) having low cardiac risk on noninvasive testing were also included. Group NC (non-cardiac) included patients with ASA physical status I and II without any history of cardiac disease.

The exclusion criteria were patient's refusal to participate in the study, pregnancy, acute decompensated left/right ventricular failure, presence of unstable coronary syndromes, significant arrhythmias (2ndand 3rddegree atrioventricular block, symptomatic ventricular arrhythmias, supraventricular arrhythmias with uncontrolled ventricular rate), severe valvular diseases like severe aortic/mitral stenosis), high-risk surgical procedures, a severe reduction in LVEF <30%, high cardiac risk on noninvasive testing, deranged coagulation profile- International Normalized Ratio >1.5 and activated partial thromboplastin time >40 seconds, patients with bare-metal stent <4-6 weeks ago and drug-eluting stents <12 months, contraindications to subarachnoid block and history of drug allergy to opioids/local anesthetics.

Minimum of 30 or all the eligible cardiac patients (whichever number was higher) presenting during the study period of one year (May 2018-April 2019) comprised the sample size for the study with thirty non-cardiac patients as controls.

All patients underwent a detailed pre-anesthetic checkup. They were scored according to Goldman Cardiac Risk Index to predict the risk of complications after surgery. Cardiac patients were optimized before surgery by getting a cardiologist consultation. Clopidogrel was omitted seven days before surgery, warfarin discontinued 14 days and unfractionated heparin stopped 12 hours before surgery. Patients on low dose aspirin (75mg) continued taking it perioperatively. Overnight fasting was advised to all the patients.

Cardiologist supervision/backup, with arrangements for trans-cutaneous pacemaker and intra-aortic balloon pump was provided for all the procedures, as a safety measure directed by the ethics committee.

On the day of surgery, all the patients were reassessed in the preoperative holding area for their preoperative status and allocation to the study groups. In the operation theater, baseline vitals were recorded including heart rate, respiratory rate, peripheral arterial oxygen saturation, systolic blood pressure and diastolic blood pressure. Intravenous cannula was inserted and co-loading with 500 ml normal saline started with small aliquot of 50-100 ml I/V solution given as preload. Subarachnoid block was performed in lateral or sitting position, under strict aseptic conditions at the level of L3-L4 intervertebral space using 23G spinal needle and 2mL 0.5% bupivacaine (heavy) along with 25µg butorphanol was injected. After injection, the patients were turned supine with a pillow under the shoulders. Hemodynamic parameters were continuously monitored throughout the procedure with recording at 5 min intervals. Ephedrine 6mg increments or phenylephrine infusion were given to treat hypotension; defined as more than 15% fall of baseline MAP or SBP <90 mm of Hg. Cardiac patients were given

Inj.atropine only in cases of bradycardia (HR <60 bpm) with coexisting hypotension not responding to ephedrine/phenylephrine. In non-cardiac patients injection atropine 0.5 mg IV was given to treat bradycardia (HR <60 bpm).

Maximum sensory block was determined in the midclavicular line bilaterally, by pinprick test using a 20-G sterile hypodermic needle. The onset of sensory block was defined as the time taken to reach the highest level of sensory block. Further sensory testing was performed at 15-min intervals to note the time to 2 segment regression, recorded as the duration of sensory block.

Modified Bromage Scale (MBS) [Grade 0 = no motor block; Grade 1 = inability to raise extended legs, able to move knees and feet; Grade 2 = inability to raise an extended leg and move the knee, able to move feet and Grade 3 = complete motor block of the lower limbs] was used to assess motor block. We defined the onset of motor block as the time taken to achieve the highest motor level and the duration of motor block as the time taken for grade one regression of motor block.

Patients with neuraxial block failure or unexpected prolonged duration of surgery with complaints of intraoperative pain would have received general anesthesia and excluded from the statistical analysis. The occurrence of side effects such as hypotension, bradycardia, nausea/vomiting, sedation, pruritis, shivering, delirium, agitation, irritability, urinary retention and respiratory depression, was recorded and treated.

VAS (0-4 Mild Pain, 5-8 Moderate Pain, 9-10 Severe Pain) was assessed at 15 minute (min), 30 min and after that every 30 min, up to two hours and then every hour, up to four hours then four hourly for 24 hours in the postoperative period. Injection tramadol 2mg/kg i.v.was started for analgesia when VAS ≥4 or as per patient request on priority basis. The duration of analgesia was taken as the time from the spinal injection to the first analgesic. Paracetamol 1g i.v. provided the rescue analgesia if tramadol was ineffective or for breakthrough pain.

All the cardiac patients were monitored postoperatively in the ICU and non-cardiac patients in the ward. ICU follow-up was for three postoperative days, especially for the occurrence of any critical events like LV failure, myocardial ischemia, arrhythmias or cardiac arrest.

Statistical analysis

We used excel spreadsheet to compile the data which was analyzed statistically with the Statistical Package for Social Sciences (SPSS) version 20.0. We presented categorical variables in numbers and percentages while continuous variables were shown as mean ± standard deviation. Chi-square test and students' t-test were used respectively for qualitative and quantitative variables. Odds Ratio was calculated using Medcalc 19.0 software for the chance factor of hypotension or bradycardia for risk factors such as preoperative METS score, ASA grade and Goldman Cardiac Risk Index. Statistically P value of <0.05 was taken as significant, while a $P < 0.001$ was considered highly significant. We show the precision of our estimates as 95% confidence limits.

Results

The participating patients were between 40 and 79 years of age. The demographic profile of patients was comparable for age, weight, height and mean duration of surgery in both the groups [Table 1].

There was a significant difference in the distribution of patients according to ASA Grade, METS scoring, Goldman cardiac risk index and Lee's RCRI between the two groups ($P < 0.05$) [Table 1]. The mean ejection fraction on 2-D echocardiography was 36.53 ± 5.93 in Group C, considered as a moderate reduction (30-40%) whereas 62.73 ± 3.97 (normal EF) in Group NC. There was a highly significant difference in both the groups ($P < 0.001$) [Table 2].

The incidence of hypotension in group C was 26.7% and 16.7% in group NC. Intraoperatively blood pressure was comparable in group C and NC from 0-80 min. It was statistically significant from 80-95 min between the two groups ($P < 0.05$) [Figure 1]. A single patient received four doses of injection ephedrine before starting vasopressor (phenylephrine) support. The difference in the total number of doses of ephedrine was significant between the two groups ($P < 0.05$) but no difference in the number of patients receiving it [Table 3].

The incidence of bradycardia was 13.3% in group C and 3.3% in group NC. Intraoperatively heart rate was

Table 1: Demographic Profile

Variables	Group C (n=30)	Group NC (n=30)	C vs NC P
Age (years)	63.9±9.26	60.97±9.28	0.225
Weight (kg)	75.1±6.49	75.63±5.09	0.724
Height (cm)	167.63±6.13	168.23±5.18	0.684
Duration of surgery (min)	77.5±23.59	75.83±18.9	0.764
*METS <4/>4	13/17	9/21	0.037‡
†ASA Grade I/II/III	0/15/15	4/26/0	0.004‡
Goldman Class I/II/III	15/14/1	25/5/0	0.026‡

**METS=Metabolic Equivalent of Task Score, †ASA=American Society of Anesthesiologist, C=Cardiac, NC=Non-Cardiac, n=Number of patients, P>0.05=Non Significant, ‡P<0.05=Significant, §P<0.001=Highly Significant*

comparable in both groups from 0-90 min ($P > 0.05$). The difference was statistically significant only from 90-100 min ($P < 0.05$) [Figure 2]. On further evaluation, bradycardia occurred in four patients in group C, who received six doses of injection atropine. Only one patient in group NC had bradycardia requiring a single dose of injection atropine. The number of doses of injection atropine between the two groups was statistically significant ($P < 0.05$) but the number of patients receiving it was not significant ($P > 0.05$) [Table 3]. We observed no significant perturbation in other parameters such as SPO_2 and RR intraoperatively.

We could not establish correlation of risk of hypotension and bradycardia with ASA physical status (0.3498 and 0.9675) Goldman Cardiac Risk Index (0.3498 and 0.7420) or METS (OR 0.1419 and 0.4401) ($P > 0.05$) [Table 4].

Spinal block characteristics such as time to onset (min) of sensory (4.70 ± 0.95 vs 4.76 ± 1.04)/motor block (6.17 ± 1.02 vs 5.8 ± 1.1), the highest level of sensory block (T8) as well as the duration (min) of sensory (88.5 ± 13.66 vs 94.5 ± 12.55)/motor block (123 ± 9.88 vs 120 ± 10.75) and duration of analgesia (min) (236.67 ± 36.14 vs 233 ± 31.53) were similar and statistically insignificant ($P > 0.05$).

We did not observe complications like hypertension, tachycardia or arrhythmias in any of the patients. Four patients in group C and only one patient in group NC complained of nausea/vomiting ($P > 0.05$). Three patients in group C and two patients in group NC had urinary retention, but the comparison was statistically insignificant ($P > 0.05$). No patient experienced respiratory depression or pruritis [Table 5].

Table 2: Comparison of Mean Ejection Fraction and number of Patients with Reduced Ejection Fraction in Both Groups

Variables	Group C (*n*=30)	Group NC (*n*=30)	C vs NC *P*
Ejection Fraction (Mean±SD)	36.53±5.93%	62.73±3.97%	0.000§
Normal EF (53-65)%	0	30	
Mildly reduced EF (41-53)%	6	0	
Moderately reduced EF (30-40)%	24	0	

C=Cardiac, NC=Non-Cardiac, EF=Ejection Fraction, n=Number of patients, P>0.05=Non Significant, ‡P<0.05=Significant, §P<0.001=Highly Significant

Table 3: Comparison of Number of Patients Receiving and Number of Administered Doses of Ephedrine, Atropine and Phenylephrine in Study Groups

Variables	Group C	Group NC	C vs NC *P*
Doses of Ephedrine	20	11	0.020‡
Number of patients	8	5	0.347
Doses of Atropine	6	1	0.044‡
Number of patients	4	1	0.161
Phenylephrine	1	0	0.472
Number of patients	1	0	0.472

C=Cardiac, NC=Non-Cardiac, n=Number of patients, P>0.05=Non Significant, ‡P<0.05=Significant, §P<0.001=Highly Significant

Table 4: Relative Risk of Hypotension and Bradycardia

Parameter	Risk Factors	Odds' Ratio	C vs NC *P*
Hypotension	*METS >4 or <4	0.3619	0.1419
Hypotension	†ASA Grade >II or <II	0.9697	0.9675
Hypotension	Goldman Class 1 or >1	0.5294	0.3498
Bradycardia	*METS >4 or <4	0.4792	0.4401
Bradycardia	†ASAGrade >II or <II	4.6712	0.3067
Bradycardia	Goldman Class 1 or >1	0.7297	0.7420

**METS=Metabolic Equivalent of Task Score, †ASA=American Society of Anesthesiologist, C=Cardiac, NC=Non-Cardiac, n=Number of patients, P>0.05=Non Significant, ‡P<0.05=Significant, §P<0.001=Highly Significant*

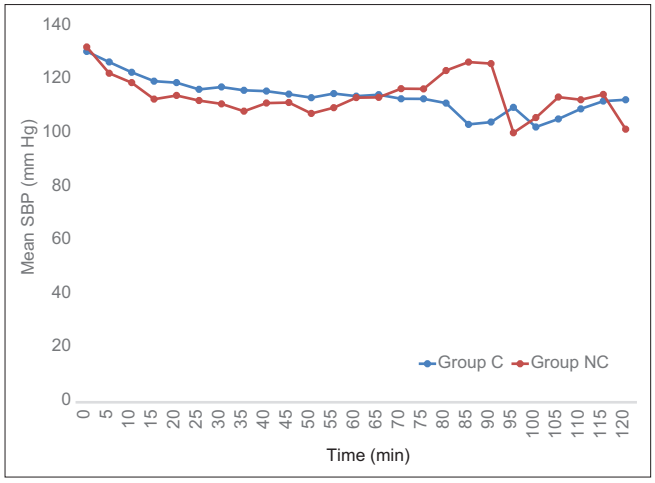

Figure 1: Intraoperative Systolic Blood Pressure (mm of Hg) in Study Groups at Various Time Intervals

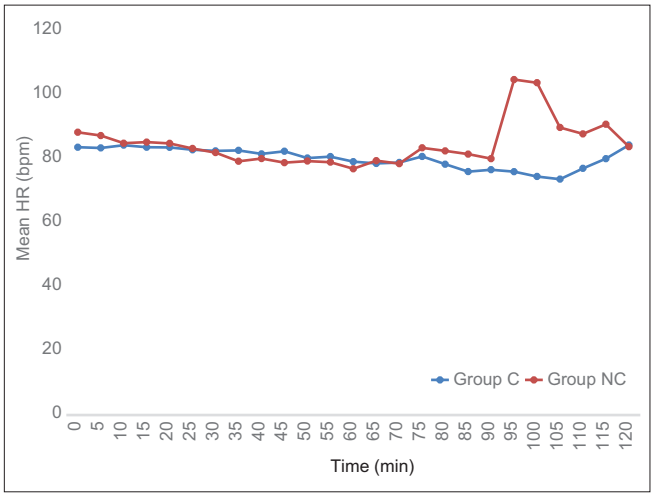

Figure 2: Intraoperative Mean Heart Rate (bpm) in Study Groups at Various Time Intervals

Discussion

Spinal anesthesia produces a combination of sympathetic, sensory and motor blockade depending on the dose, concentration, volume and type of local anesthetic administered, but its hemodynamic effects can have adverse implications in cardiac patients coming for non-cardiac surgeries. A lower dose of local anesthetic (LA) with adjuvants such as opioids, α2-agonist, NMDA receptor antagonist reduces the chances of cardiovascular complications.[9,10]

Intrathecal local anesthetics inhibit voltage-gated sodium channels in the spinal cord and interfere with afferent and efferent sensory and motor impulses.[11] Opioids injected in the intrathecal space activate opioid receptors in the dorsal gray matter of spinal cord, thereby modulating the function of afferent pain fibers.[12] The synergism between intrathecal opioids and local anesthetics is due to a different mechanism of action of the drugs, i.e., blockade of Na^+ channel by local anesthetics and voltage-gated Ca^{++} channels with opioids, thereby leading to considerably less sympathetic blockade.[13,14] This synergism may especially be beneficial in ASA Grade III as well as cardiac patients.[10] It prolongs the duration of action of LA, thereby reducing the requirement of additional analgesics. However, not much data is available for the use of SA along with opioid adjuncts in cardiac patients with low ejection fraction. Due to a problem in the supply chain of licensed opioids, we used butorphanol 25μg as an adjunct with bupivacaine.

Although there was bound to be a difference in risk factors in cardiac versus non-cardiac patients, the anesthetic technique had been kept same.

As expected, a clinically insignificant fall in BP compared to baseline was observed after SA in both the groups. A significant difference was seen among the groups between 80-95 min for blood pressure and 90-100 min for heart rate. Both groups had similar blood pressure and heart rate for the rest of the intraoperative period, i.e., up to 80 min and intraoperative and postoperative mean blood pressure was comparable. The statistically significant difference during 80-100 min was probably an aberration due to only a few patients left at that time in both the groups (four patients in group C and three patients in group NC) and any hemodynamic perturbations in these patients reflected on the group as a whole. If we consider that all surgeries lasted for < 80 min (mean duration), both the groups become comparable hemodynamically.

Table 5: Complications

Complications	Group C	Group NC	Chi square	C vs NC *P*
Hypotension	8	5	0.373	0.542
Bradycardia	4	1	1.964	0.161
Arrhythmias	0	0	0.000	1.000
Myocardial ischemia	0	0	0.000	1.000
HF	0	0	0.000	1.000
Nausea	3	1	1.071	0.301
Vomiting	3	1	1.071	0.301
Urinary retention	3	2	0.218	0.640
Respiratory depression	0	0	0.000	1.000
Cardiac arrest	0	0	0.000	1.000

C=Cardiac, NC=Non-Cardiac, n=Number of patients, P>0.05=Non Significant, $^{s}P<0.05$=Significant, $^{s}P<0.001$=Highly Significant

Different authors have defined hypotension as a decrease of <20% to 30% of baseline MAP in a normal circumstance (ASA grade I and II). In our study MAP >15% of baseline or SBP <90 mmHg was considered hypotension. Taking into account the cardiac condition in Group C, the threshold for giving treatment was more stringent and kept low.[15] Eight patients (26.6%) in group C were administered a total number of 20 doses of injection ephedrine compared to findings by other authors.[10]

In group NC, five patients (16.7%) had hypotension. One patient received three doses, and four patients received two doses each, of injection ephedrine to treat it. The results in group NC are very similar to other studies which used the same volume of bupivacaine (2 ml) with 25μg butorphanol but criteria to define hypotension were kept less stringent, i.e., MAP <70 mmHg or <20% of baseline.[7,16,17]

The mean heart rate in our study was comparable in both the groups intraoperatively as well as postoperatively. Although there were mild variations in HR from baseline, they were clinically insignificant. Mehta S *et al.* observed 6.6% (2/30 patients) incidence of bradycardia in non-cardiac patients, which was quite similar to the results of group C in our study having low EF patients.[15] None of the patients of Sanatkar M *et al.* had HR <60 or >90 bpm. This difference may be due to the lower dose of bupivacaine used in their study.[4]

Gupta M *et al.*[16] and Kumar A *et al.*[18] did not observe bradycardia in any of the patients which could be due to only ASA grade I and II patients in their study and thus the concordance with group NC of our study where only one patient experienced bradycardia.

While studying the effect of preoperative risk factors on hemodynamic changes, we observed no correlation between hypotension and ASA grading, Goldman cardiac risk index. Prause G *et al.* evaluated the ASA grade and Goldman cardiac

risk index (CRI) and found a direct correlation between perioperative mortality, ASA grade and Goldman CRI.[19] This could be because of different endpoints, i.e., mortality (in their study) vs hemodynamic instability (in our study).

Physical capacity has been found inversely proportional to the incidence of perioperative cardiac and long term complications.[20,21] However, we found no increased risk of minor complications like hypotension and bradycardia in patients with METS <4.

Time of onset and duration of sensory or motor block were similar in both the group due to the same drug volume, concentration and use of adjuvant. These results are similar to observed by various authors.[7,16,22-24] Our purpose of studying spinal characteristics was to determine the maximum level of sensory effect achieved and to observe whether cardiac illness makes any difference in drug/adjuvant absorption levels.

Serious complications like new-onset arrhythmias, myocardial infarction and cardiac arrest were not observed in the immediate perioperative period and the incidence of other complications like nausea, vomiting and urinary retention was similar in both the groups. No patient had respiratory depression or pruritis as observed by various other authors.[7,8,18]

Strengths and limitations

Strengths: Spinal anesthesia is traditionally not considered safe in cardiac patients with low EF even if the procedure is infraumbilical and of short duration. The present study can open new avenues for further research.

Limitations: Age matching of controls and cases was not done. We also could not consider a particular disease process responsible for low EF in this sample size.

Scope of the study: A bigger sample size would enable a better evaluation of individual risk factors, thus prove the safety of SA in low EF cardiac patients in more elaborated manner.

Conclusion

Thus, we can conclude that lower dose SA (2 ml) with bupivacaine and 25μg butorphanol exhibits comparable hemodynamic effects in cardiac and non-cardiac patients. Hence, it can be considered a viable option in cardiac patients with mild to moderately reduced ejection fraction on 2-D echocardiography presenting for infraumbilical non-cardiac non-vascular surgeries with minimum alterations in hemodynamic parameters.

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Conflicts of interest

There are no conflicts of interest.

References

1. Hedge J, Balajibabu PR, Sivaraman T. The patient with ischaemic heart disease undergoing non cardiac surgery. Indian J Anaesth 2017;61:705-11.
2. Ben-David B, Frankel R, Arzumonov T, Marchevsky Y, Volpin G. Minidose bupivacaine-fentanyl spinal anesthesia for surgical repair of hip fracture in the aged. Anesthesiology 2000;92:6-10.
3. Liu SS, McDonald SB. Current issues in spinal anesthesia. Anesthesiology 2001;94:888-906.
4. Sanatkar M, Farhanchi A, Manouchehrian N, Najafi A, Haddadi S, Rahmati J, *et al*. Subarachnoid block with low dose of bupivacaine and sufentanil in patients with coronary artery disease. ARYA Atheroscler 2014;10:94-9.
5. Swain A, Nag DS, Sahu S, Samaddar DP. Adjuvants to local anesthetics: Current understanding and future trends. World J Clin Cases 2017;5:307-23.
6. Ranga Chari VR, Goyal AA, Singh V. A study of addition of Inj. butorphanol to hyperbaric Inj.bupivacaine given intrathecally to patients undergoing lower segment caesarean section: A randomized, controlled trial. Med J DY Patil Univ2013;6:156-60.
7. Kaur M, Katyal S, Kathuria S, Singh P. A comparative evaluation of intrathecal bupivacaine alone, sufentanil or butorphanol in combination with bupivacaine for endoscopic urological surgery. Saudi J Anaesth 2011;5:202-7.
8. Commiskey S, Fan LW, Ho IK, Rockhold RW. Butorphanol: Effects of a prototypical agonist-antagonist analgesic on κ-opioid receptors. J Pharmacol Sci2005;98:109-16.
9. Sivevski AG, Karadjova D, Ivanov E, Kartalov A. Neuraxial anesthesia in the geriatric patient. Front Med 2018;5:254.
10. Reddy GN, Manohar S, Supriya P, Himani A. Comparison of efficacy of butorphanol and fentanyl as intrathecal adjuvant to bupivacaine. J Evol Med Dent Sci 2015;4:5675-81.
11. Butterworth JF, Strichartz GR. Molecular mechanisms of local anesthesia: A review. Anesthesiology 1990;72:711-34.
12. Verma D, Naithani U, Jain DC, Singh A. Postoperative analgesic efficacy of intrathecal tramadol versus nalbuphine added to bupivacaine in spinal anesthesia for lower limb orthopaedic surgery. J Evol Med Dent Sci 2013;2:6196-206.
13. Zieglgansberger W. Opioid action on mammalian spinal neurons. Int Rev Neurobiol 1984;25:243-75.
14. Kumar B, Williams A, Liddle D, Verghese M. Comparison of intrathecal bupivacaine-fentanyl and bupivacaine-butorphanol mixtures for lower limb orthopedic procedures. Anesth Essays Res 2011;5:190-5.
15. Mehta S, Dalwadi H, Shah TD. Comparative study of low dose bupivacaine-fentanyl vs conventional dose of bupivacaine in spinal anesthesia for orthopedic procedures in elderly patients. Guj Med J 2015;70:25-8.
16. Gupta M, Arora N. A comparative study of efficacy of intrathecal fentanyl and butorphanol as an adjuvant to bupivacaine 0.5% heavy for lower limb and lower abdominal surgeries. Sch J App Med Sci 2018;6:2066-72.

17. Reddy IR, Aasim SA, Komravelli KK. A comparative study of efficacy of anesthesia and analgesia between intrathecal fentanyl and butorphanol with bupivacaine 0.5% heavy for lower limb orthopedic surgery: A prospective randomized study in a tertiary care teaching hospital. Int J Res Health Sci2018;6:1-8.
18. Kumar A, Kumar R, Verma VK, Prasad C, Kumar R, Kant S, *et al*. A randomized controlled study between fentanyl and butorphanol with low dose intrathecal bupivacaine to facilitate early postoperative ambulation in urological procedures. Anesth Essays Res 2016;10:508-11.
19. Prause G, Ratzenhofer-Comenda B, Pierer G, Smolle-Juttner F, Glanzer H, Smolle J. Can ASA grade or Goldman's cardiac risk index predict peri-operative mortality? A study of 16 227 patients. Anesthesia 1997;52:203-6.
20. Fleisher LA, Fleischmann KE, Auerbach AD, Barnason SA, Beckman JA, Bozkurt B, *et al*. 2014 ACC/AHA guideline on perioperative cardiovascular evaluation and management of patients undergoing non-cardiac surgery: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines. J Am Coll Cardiol 2014;64:e77-137.
21. Reilly DF, McNeely MJ, Doerner D, Greenberg DL, Staiger TO, Geist MJ, *et al*. Self-reported exercise tolerance and the risk of serious perioperative complications. Arch Intern Med 1999;159:2185-92.
22. Purohit S. Intrathecal butorphanol: An effective option for post operative pain relief in caesarean patients.J Med Sci Clin Res 2017;5:32236-42.
23. Singh V, Gupta LK, Singh GP. Comparison among intrathecal fentanyl and butorphanol in combination with bupivacaine for lower limb surgeries. J Anaesth Clin Pharmacol 2006;22:371-5.
24. Biswas C, Basak J, Bhattacharjee DP. Comparison of intrathecal bupivacaine and bupivacaine with butorphanol for postoperative analgesia in patients undergoing lower abdominal surgery. Glob J Res Anal 2019;8:121-5.