EVALUATION OF EFFICACY OF VARYING DOSES OF 0.5% BUPIVACAINE HEAVY WITH FENTANYL IN SPINAL ANESTHESIA IN PATIENTS UNDERGOING LOWER EXTREMITY SURGERIES: A COMPARATIVE, RANDOMIZED PROSPECTIVE STUDY

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Abstract

Background: Hypotension is a side effect often associated with spinal anesthesia which can be detrimental in certain clinical situations.Lesser doses of bupivacaine have been associated with lower incidence of hypotension and associated complications. Fentanyl when used intra-thecally enhances the sensory block of local anesthetics. We have evaluated the effect of three different doses of 0.5% heavy bupivacaine along with intrathecal fentanyl on intraoperative hypotension and recovery profiles.

Methods: 45 patients were randomly divided in three groups. Group A received 7.5 mg (1.5 ml) 0.5% heavy bupivacaine, 25 µg fentanyl and 0.5 ml of normal saline; Group B received 9 mg (1.8 ml) 0.5% heavy bupivacaine, 25 µg fentanyl and 0.2 ml of normal saline; and Group C received 10 mg (2 ml) 0.5% heavy bupivacaine and 25 µg fentanyl. All the groups were assessed for non-invasive blood pressure, two segment sensory regression, motor regression and the level of sensory block.

Results: Group C had a significant fall of blood pressure compared to Group A and B. The time to two segment sensory regression and time to motor regression was significantly longer in group C compared to the other two groups. Highest level of sensory block was up to T10 in group A, T7 in group B and T4 in group C.

Conclusion: Lower bupivacaine doses (9 mg and 7.5 mg)along with fentanyl 25 µg provide reliable spinal anesthesia with better hemodynamic stability and early recovery in lower limb orthopedic surgeries of duration two hours or less.

Key words: Spinal anesthesia; Bupivacaine; Low-dose; Intrathecal; Fentanyl

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Introduction

Spinal Anesthesia (SA) is a commonly used technique to anesthetize patients for lower extremity surgeries; however, it is associated with some unwanted side effects like hypotension, bradycardia intra-operatively, urinary retention, and prolonged immobility in the postoperative period.[1] In elderly and in patients with cardiovascular and respiratory diseases, hypotension can be particularly hazardous. White *et al.*[2] have demonstrated a significant correlation between hypotension, mortality and dose of intrathecal local anesthetic.

Hypotension during SA can be treated or prevented with the use of vasopressors and intravenous fluids which are associated with their own set of ill effects.[3,4] Lower doses of bupivacaine have been found to be associated with reduced incidence of hypotension and other complications during SA.[5]

The synergism of intrathecal fentanyl and local anesthetics is well established. Intrathecal fentanyl provides a rapid onset of sensory block and decreases the rebound pain without increasing the intensity of motor block contributing to early recovery.[6-8]

The present study was designed to compare three doses of heavy bupivacaine 0.5% with fentanyl 25 µg in SA with respect to incidence and degree of hypotension (systolic and mean) and time to recession of sensory and motor block. Comparison of level of sensory block and Bromage score was also done as a secondary outcome.

Methods

This was a prospective randomized controlled study conducted in a tertiary care health center. The study was approved by institutional ethics committee (KPCMCH/IEC/870) and was prospectively registered with clinical trial registry, India (Registration No-CTRI/2018/01/011593).

Forty-five patients of age more than 18 years and ASA physical status I and II scheduled for lower limb orthopedic surgery were included in the study. A written informed consent was obtained from all the study subjects prior to enrollment. Patients with a history of spine surgery, spine deformities, skin infection and abnormal coagulation profile were excluded from the study. Patients were randomized into three groups using a sealed envelope technique to receive one of the three subarachnoid doses of 0.5% hyperbaric bupivacaine. Group A received 7.5 mg (1.5 ml) 0.5% heavy bupivacaine, 25 µg fentanyl and 0.5 ml normal saline; Group B received 9 mg (1.8 ml) 0.5% heavy bupivacaine, 25 µg fentanyl and 0.2 ml normal saline; and group C received 10 mg (2 ml) 0.5% heavy bupivacaine and 25 µg fentanyl.

After a thorough preoperative assessment and appropriate aspiration prophylaxis, patients were taken to the operation room. An intravenous infusion was started and monitoring of non-invasive blood pressure, oxygen saturation and electrocardiogram were established. Before the block, all patients were given a rapid infusion of 5- 8 ml/kg of ringer lactate as most patients posted for elective surgeries are on 7-8 hours of fasting. Subarachnoid block was given in sitting or lateral position as appropriate with the use of 25 or 26 G spinal needle at L3-L4 or L2-L3 interspace, and the patients received the drug as per randomization and were immediately placed in a supine position. The patients and physicians were blinded regarding the dosage of 0.5% heavy bupivacaine administered. The drug was prepared by one anesthesiologist who was not part of the study, and the commencement of anesthesia, assessment of patient and recording of study data were done by another anesthesiologist. Patients received intravenous midazolam 2 mg for sedation and amnesia. Patient's complaint of pain was treated with a bolus of intravenous fentanyl 1 µg/kg.

The following parameters were measured in all patients: Non-invasive blood pressure – Pre-procedure baseline blood pressure (mean of three readings taken at five minutes interval on the operation table) and then at five minutes interval for 30 minutes and throughout surgery. and throughout surgery. Hypotension was considered as a drop of more than 20% of the preoperative systolic blood pressure or a systolic pressure less than 90 mm Hg.

Sensory assessment–Height of sensory block achieved after the block and time to two dermatomal sensory regression was recorded.

Motor assessment– Final Bromage scale score

achieved after the block and time to motor recovery (one grade improvement in Bromage scale) was recorded.

Statistical analysis

Based on previous studies, the probability of occurrence of hypotension with the use of normal dose bupivacaine in spinal anesthesia is 90%. Taking the confidence level of 95% and a power of 80% and assuming a clinical significance of 4%, the minimum number of sample required is 13.We recruited 15 patients in each group.

Data obtained was tabulated and analyzed by using Statistical Package for Social Sciences (SPSS) version 17 (New York). Statistics applied for the interpretation of results was mean and standard deviation, two way ANOVA with post hoc Bonferroni test for continuous variables and Chi square test for non-parametric and grouped variables. P value <0.05 was considered statistically significant.

Results

A total of 57 patients were enrolled for the study and final analysis was done for 45 patients with 15 patients in each group (Figure 1). The three groups were comparable with respect to the demographic variables of the patients, and type and duration of surgeries (Table-1). One case of spinal failure in group B (9 mg of bupivacaine with fentanyl) and two cases of group A (7.5 mg of bupivacaine with fentanyl) which required conversion to general anesthesia in the later part of surgery were excluded from the study.

The baseline systolic and mean blood pressures of the three groups were comparable. After giving SA there were drops of systolic and mean blood pressures in group B and group C. The mean and systolic blood pressure in group C was significantly lower compared to group A at all time points (P<0.05; Figures 2, 3). In group B the mean blood pressure was significantly lower compared to Group A at 20, 25 and 30 minutes (Figure 2). However, the consumption of vasopressors was lesser in group B compared to group C. Patients in group A did not have a significant fall of blood pressure

Fig. 1
Consort diagram of the study

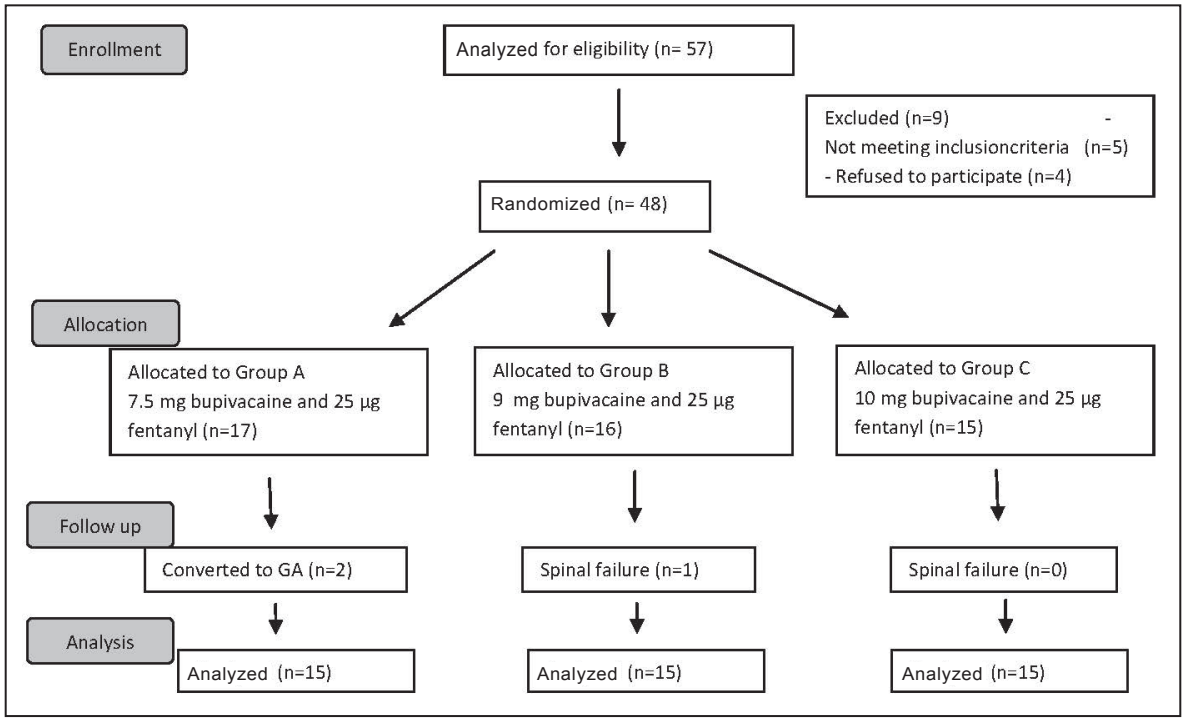


Table 1

Demographics of the patients recruited for the study.

Parameters	Group A (n=15)	Group B (n=15)	Group C (n=15)	p Value
Age (yrs)	56.6±15	52.5±13	47.1±16	0.233
Weight (Kg)	68±10	65±11	69±9	0.82
Height (cm)	163.2±8.9	163.4 ± 8.7	164.2 ± 7.8	0.244
Sex(male/female)	6/9	7/8	7/8	0.914
Duration of surgery (mins)	90±25	93±20	85±30	0.69

Data are mean ± SD or number of patients.

at any time points throughout the study period.

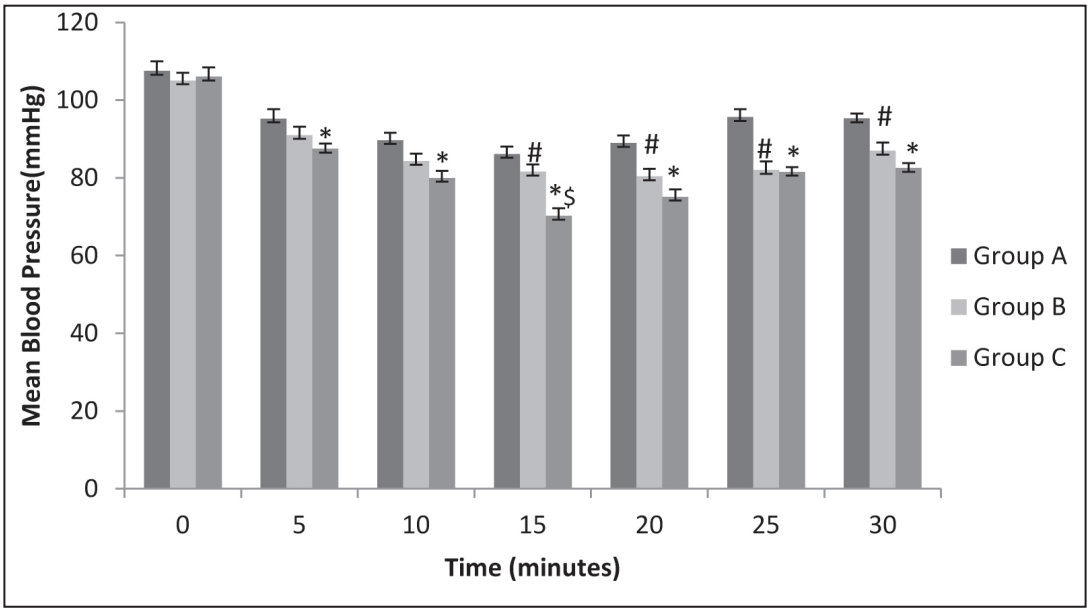
The two segment sensory regression time in group C was significantly longer than group A and group B ($p<0.05$), whereas it was comparable for group A and group B ($p> 0.05$). Similarly the time for one grade improvement in Bromage scale (motor recovery) was significantly longer in group C as compared to group A and group B ($p< 0.05$; Table-2), whereas it was comparable in group A and group B ($p>0.05$).

The highest level of sensory blocks achieved in group A, group B and group C were T9-T11, T7-T9 and T4-T6 respectively (Table-2). Bromage scale scoring achieved in Group A was only 1 and 2; none of the patients had a score of 3. In group B and Group C the scores were mainly 2 and 3 (Table-2).

Regarding side effects, postoperative vomiting was observed in only two patients in group C and one patient in group B and none in group A. Hypotension was observed in six patients in group C and two patients in group B. Two patients in group A required general anesthesia at a later phase of the surgery and one patient in group B had a failed spinal. Pruritis was

Fig. 2

Comparison of mean blood pressure of the three groups.



* Significant - Group C to Group A, # Significant - Group B to Group A, $ - Significant Group C to Group B.

Table 2

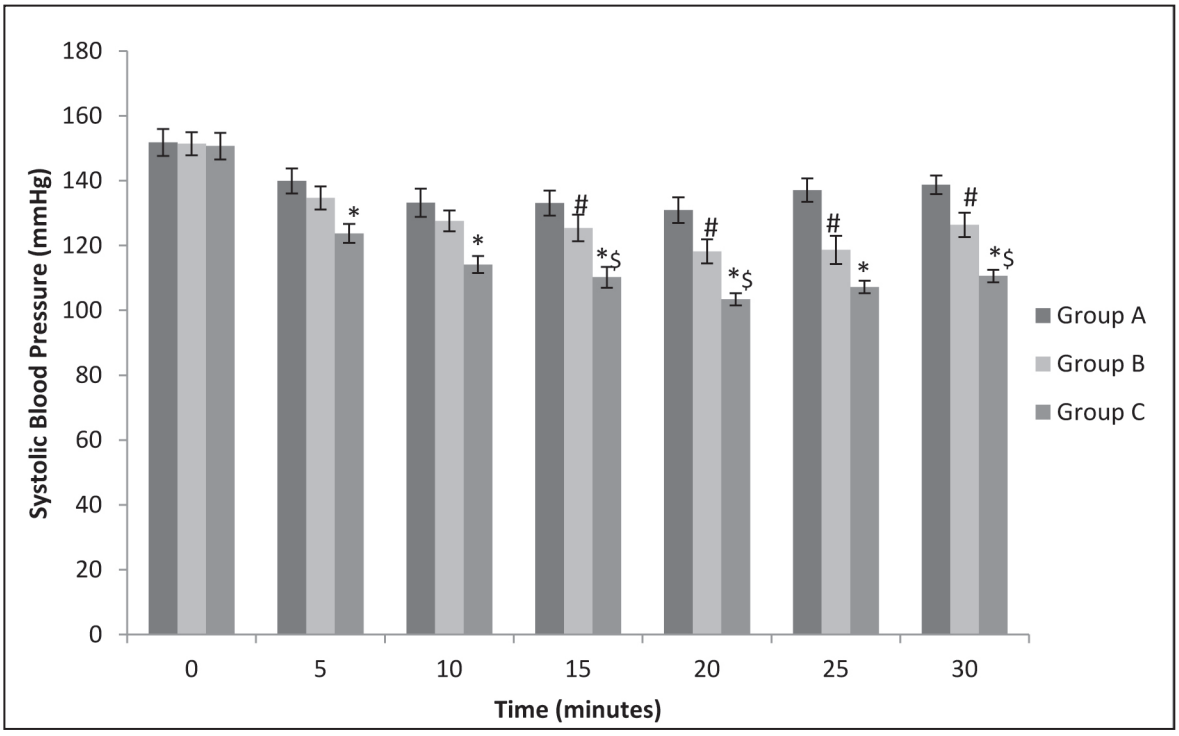
Sensory and motor blockade characteristics.

parameters	Group A (n=15)	Group B (n=15)	Group C (n=15)	p Value
Highest level of sensory block	T9-T11	T7-T9	T4-T6	NA
Bromage Score (0/1/2/3)	0/8/7/0	0/0/10/5	0/2/8/5	0.003
Time to two dermatomal sensory regression (minutes)	122.6±10.79	119.7±10.27	132.3±7.32	0.002
Time to motor recovery (minutes)	93.2±12.53	99.2±9.80	119.0±3.60	0.0001

Data is expressed as numbers or mean±standard deviation. NA: Not applicable.

Fig. 3

Comparison of systolic blood pressure of the three groups.



* Significant - Group C to Group A, # Significant - Group B to Group A, $ Significant - Group C to Group B.

Table 3

Side effects and complications among the three groups.

Side effect	Group A (n=15)	Group B -(n=15)	Group C (n=15)
Vomiting	0	1	2
Hypotension	0	2	6
Failure	2	1	0
Pruritis	7	6	7

Data is expressed as numbers.

observed in 47% of patients in group A, 40% of patients in group, and 47% of patients in group C (Table-3).

Discussion

This dose finding study was designed to find the lowest effective dose of bupivacaine which can be given along with 25 µg fentanyl to provide satisfactory anesthesia without the cardiovascular side effects in lower limb orthopedic surgeries. The optimum dose of intrathecal fentanyl as an adjuvant of local anesthetic is not clearly defined and have been used in the range of 10 µg to 25 µg.[8-12] Though, some authors have claimed the lesser doses to be effective with no incidence of respiratory depression and pruritis, the most commonly used dose of intrathecal fentanyl with minimal side effects is 25 µg.

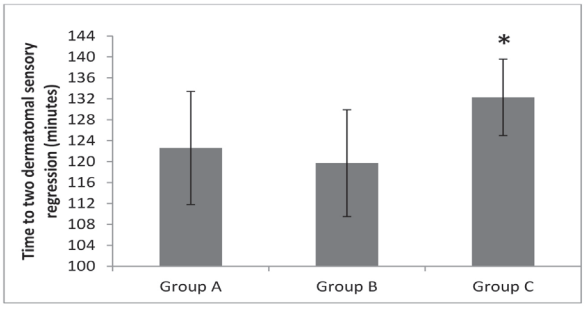
In the present study, the groups A and B showed better hemodynamic stability compared to group C. This is evident by the findings of marked reduction in blood pressure values in group C, despite the calculated use of vasopressors. The blood pressure was recorded every 5 minutes for 30 minutes after administering the spinal block. The drug gets fixed to the spinal cord in 20-30 minutes after administration, so maximum sensory level and sympathetic block will be achieved during that time. There was a significant fall in the mean blood pressure and systolic blood pressure in group C compared to group A at all time points. Similarly in group B significantly lower blood pressures (mean and systolic) were observed at 15 and 20 minutes compared to group A. However the requirement of rescue vasopressors was much lesser in group B compared to group C. Patients in group A didn't have a significant fall in blood pressure at any time point.

Ben-David compared 4 mg of bupivacaine along with 20 µg fentanyl with 10 mg of bupivacaine and found a significant difference in the incidence and severity of hypotension with no failures in patients undergoing hip fracture repair.[10] Similar findings were experienced by Hoda *et al*.[11] in patients undergoing surgical repair of hip fracture with 6 mg of bupivacaine and 20 µg fentanyl. In both the studies, the study population included elderly patients and there was no failure or conversion to general anesthesia. In elderly patients there is a delayed pharmacokinetics of drug which may be the reason for zero failure rates with the mini-doses of bupivacaine.

In the current study, the study population included both young adults and elderly patients so the dose lesser than 7.5 mg was not used. Intrathecal bupivacaine in a dose of 7.5 mg along with 10 µg fentanyl have been demonstrated to provide a reliable neuraxial block for patients subjected to percutaneous nephrolithotomy, with stable hemodynamics, good post-operative analgesia and acceptable patient and endoscopist satisfaction by Atallah *et al* .[12]

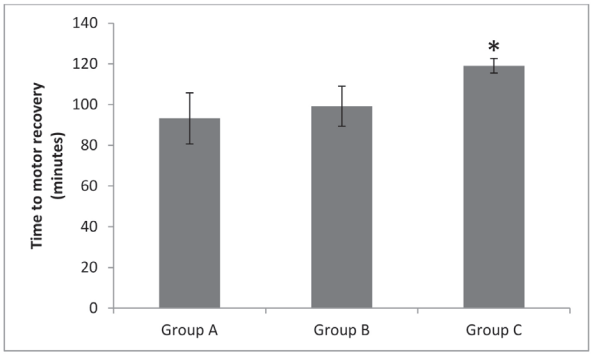
Hypotension due to pharmacological sympathectomy is the most common and serious side effect of SA with the use of conventional doses of local anesthetics. Large surveillance studies have observed

Fig. 4
Comparison of the two dermatomal sensory regression of the three Groups.



* Significant compared to Group A and B.

Fig. 5
*Comparison of the motor recovery of the three Groups. * Significant compared to Group A and B.*



incidences of hypotension around 33% in non-obstetric populations.[1]

Elderly, pregnant patients and patients with cardiovascular disease are susceptible to the negative impact of the hypotension. Besides, the usual dose of bupivacaine might delay the recovery of motor functions and can cause urinary retention, leading to delayed ambulation and discharge of the patient.[1,2]

Several techniques are adopted to prevent or treat the spinal anesthesia induced hypotension with varying results. The most common is preloading or co-loading with the crystalloid or colloid. This technique is much debated with not much convincing literary evidence.[3] Fluid loading, whether with crystalloids or colloids, alone is not effective to prevent sympathectomy induced hypotension and needs to be coupled with vasopressors. Excessive fluid loading can lead to other complications like pulmonary edema and full bladder requiring urinary catheterization. Nonetheless, 8 ml/kg of Ringer's lactate was used to preload all the study patients as they remained nil per oral for more than six hours before surgery.

Vasopressors which are commonly used in our institution to prevent and manage spinal anesthesia induced hypotension are the directly acting selective α1 receptor agonist phenylephrine and both direct and indirectly acting mephentermine. The best vasopressor for the treatment of spinal anesthesia induced hypotension is still unclear. Each vasopressor is associated with its own set of side effects and mandates a judicious use.[4]

Though, the use of low doses of local anesthetics may reduce the incidence and severity of hypotension, but may not provide adequate and reliable anesthesia. Opioids and local anesthetics administered together intrathecally have a potent synergistic analgesic effect. Intrathecal opioids, lipophilic as well as hydrophilic enhance analgesia from sub therapeutic doses of local anesthetic without prolonging motor block and recovery while making it possible to achieve successful SA using otherwise inadequate doses of local anesthetic. As intrathecal fentanyl does not cause depression of efferent sympathetic activity either alone or in combination with local anesthetic, it is possible to enhance the sensory blockade without altering the degree of sympathetic blockade.[6,7]

Chambers *et al*.[13] have demonstrated that an increase in the volume of 0.5% bupivacaine not only increases the cephalad spread of the drug but also the duration of action significantly. Many authors have demonstrated that addition of fentanyl to spinal anesthesia with diluted small-dose bupivacaine intensifies and increases the duration of sensory blockade without increasing the intensity of motor blockade or prolonging recovery to micturition or street fitness.[6,9,11,12] In the present study the dose of fentanyl was the same in all the groups. The maximium upper level of block was much higher in the group where 10 mg of bupivacaine was used compared to the other two groups and the time for sensory and motor recovery was also significantly more in the same group.

Many factors have been shown to be involved in the cephalic spread of the intrathecal drug. The concentration, dose and volume of the local anesthetic, and their interplay with the lumbosacral volume of cerebrospinal fluid are some of the aspects which determine the level of spread and the duration of the block. In a well-controlled study designed to understand the effects of volume, dosage and concentration on the intrathecal distribution of plain bupivacaine, Sheskey *et al*.[14] observed that dosage rather than volume or concentration was the important determinant. Patient posture and baricity of the drug are among the other factors which can affect the spread of the drug. It has been demonstrated that glucose concentration in excess of 0.8% in local anesthetic behaves as hyperbaric solution for all practical purposes. Though normal saline was added to the drugs used in group A and B to make the volumes identical in all the three groups, the bupivacaine had remained hyperbaric.[15] With lower concentration of glucose, the time of spread of the local anesthetic increases, which can be due to drug gliding off the slope of the lordotic lumbar curve towards the thoracic spine more 'lazily' compared to its more hyperbaric counterparts. As the lower limb is innervated by lumbar and sacral plexuses, levels up to T4 may not be required for the surgery.

There was a significant delay in two dermatomal sensory regression in group C compared to the other two groups. Similarly time of motor regression (recovery of one grade on Bromage scale) was significantly delayed in group C. Since the amount of

fentanyl used was constant, so the dose of bupivacaine is responsible for the delayed regression.

Nausea and vomiting associated with hypotension can be an unpleasant sensation for the patient. Venkata *et al.*[16] reported a significantly reduced incidence of nausea and vomiting with the use of lower dose of bupivacaine and 25 µg fentanyl compared to the conventional dose of bupivacaine due to the lesser hypotension associated with the lower dose of bupivacaine which concurs with the present study.

None of our patients in any group had cardiovascular instability requiring resuscitation. Intrathecal opioids are associated with late respiratory depression. Fentanyl is said to have lesser incidence of such events compared to morphine due to its shorter half life. There was no incidence of late respiratory depression in the present study which is consistent with the findings of other studies.[8,9]

All our patients were admitted at least one day before surgery and were not to be discharged on the same day so the assessment for street fitness was not taken into consideration. Urinary retention in the postoperative period is a common occurrence following SA. But time to urination though an important aspect of recovery from SA was not taken into consideration as many patients especially elderly males were catheterized preoperatively. This can be a limitation of our study.

Failed spinal was observed in one patient of the group where medium dose (9 mg) of bupivacaine was used. The etiology of a failed spinal is multi-factorial and is dependent on technical, drug and patient-related factors.[17]

Two patients in the group where low dose bupivacaine was used needed conversion to general anesthesia in the later parts of the surgery as the surgery got prolonged than the anticipated time. The speed and experience of the surgeon plays an important role in the outcome when lower doses are used. *Niar et al.* in a systematic review have established that the low dose spinal anesthesia has a high efficacy in ambulatory surgery. They found the lowest effective doses of bupivacaine for knee arthroscopy surgery was 4 mg and a reasonable discharge times were achieved using bupivacaine in doses 7.5 mg. They stressed that the type of surgery and the duration of surgery are very important factors influencing the efficacy of low dose SA.[18]

Pruritis is the most common side effect of intrathecal fentanyl but seldom requires treatment.[1] In the present study also mild pruritis was observed in 44% of patients but none needed treatment.

Conclusion

Lower limb orthopedic surgeries of duration of 2 hours or less can be done with lower doses of bupivacaine (7.5 mg and 9 mg) with fentanyl as adjuvant. The incidence of hypotension is nearly absent with 1.5 ml (7.5 mg) and minimal with 1.8 ml (9mg) of 0.5% bupivacaine with 25 µg of fentanyl and can be beneficial in circumstances where intraoperative hypotension can be detrimental for the patient outcome. However, a dose of 7.5 mg may be associated with lower Bromage scale scores, higher rates of conversion to general anesthesia and lesser patient satisfaction, and therefore needs an extra consideration for the type and duration of surgery.

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Conflicts of interest: None.

References

1. Liu SS, McDonald SB. Current Issues in Spinal Anesthesia. *Anesthesiology* 2001; 94: 888-906.
2. White SM, Moppett IK, Griffiths R, et al. Secondary analysis of outcomes after 11,085 hip fracture operations from the prospective UK Anesthesia Sprint Audit of Practice (ASAP-2). *Anesthesia* 2016; 71: 506-14.
3. Bajwa SJS, Kulshrestha A, Jindal R. Co-loading or preloading for prevention of hypotension after spinal anesthesia! A therapeutic dilemma. *Anesth Essays Res.* 2013; 7: 155-59.
4. Veeser M, Hofmann T, Roth R, Klöhr S, Rossaint R, Heesen M. Vasopressors for the management of hypotension after spinal anesthesia for elective caesarean section. Systematic review and cumulative meta-analysis. *Acta Anaesthesiol Scand.* 2012; 56: 810-6.
5. Arzola C, Wieczorek PM. Efficacy of low-dose bupivacaine in spinal anaesthesia for Caesarean delivery: systematic review and meta-analysis. *Br J Anaesth.* 2011; 107: 308-18.
6. Wang C, Chakrabarti MK, Whitwam JG. Specific enhancement by fentanyl of the effects of intrathecal bupivacaine on nociceptive afferent but not on sympathetic efferent pathways in dogs. *Anesthesiology* 1993; 79: 766-73.
7. Ben-David B, Solomen E, Levin H, Admoni H, Goldik Z. Intrathecal fentanyl with small-dose dilute bupivacaine: better anesthesia without prolonging recovery. *Anesth Analg* 1997; 85: 560-5.
8. Wong CA, Scavone BM, Slavenas JP, Vidovich MI, Paeceman AM, Ganchiff JN et al. Efficacy and side effect profile of varying doses of intrathecal fentanyl added to bupivacaine for labor analgesia. *Int J Obstet Anesth.* 2004; 13:19-24.
9. Ali MA, Ismail S, Sohaib M, Aman A. A double blind randomized control trial to compare the effect of varying doses of intrathecal fentanyl on clinical efficacy and side effects in parturients undergoing caesarean section. *J Anaesthesiol Clin Pharmacol*. 2018; 34: 221-226.
10. Ben-David B, Frankel R, Arzumanov T, Marchevsky Y, Volpin G. Minidose bupivacaine-fentanyl spinal anesthesia for surgical repair of hip fracture in the aged. *Anesthesiology* 2000; 92: 6-10.
11. Hoda MQ, Saeed S, Afshan G, Sabir S. Haemodynamic effects of intrathecal bupivacaine for surgical repair of hip fracture. *J Pak Med Assoc.* 2007; 57: 245-8.
12. Atallah MM, Shorrab AA, Abdel Mageed YM, Demian AD. Low-dose bupivacaine spinal anesthesia for percutaneous nephrolithotomy: the suitability and impact of adding intrathecal fentanyl. *Acta Anaesthesiol Scand.* 2006; 50: 798-803.
13. Chambers WA, Littlewood DG, Edstorm HH, Scott DB. Spinal anesthesia with hyperbaric bupivacaine: Effects of concentration and volume administered. *Br. J. Anaesth.* 1982; 54: 75-89.
14. Sheskey MC, Rocco AG, Bizzarri-Schmid M, Francis DM, Edstrom HH, Covino BG. A dose-response study of bupivacaine for spinal anesthesia. *Anesth Analg* 1983; 62: 931-5.
15. Hocking G, Wildsmith JAW. Intrathecal drug spread. *Br J Anaesth.* 2004; 93: 568-78.
16. Venkata HG, Pasupuleti S, Pabba UG, Porika S, Talari G. A randomized controlled prospective study comparing a low dose bupivacaine and fentanyl mixture to a conventional dose of hyperbaric bupivacaine for caesarean section. *Saudi J Anaesth.* 2015; 9: 122-7.
17. Fettes PDW, Jansson JR, Wildsmith JAW. Failed spinal anaesthesia: mechanisms, management and prevention. *Br J Anaesth.* 2009; 6: 739-48.
18. Niar GS, Abrishami A, Lermitte F, Chung F. Systematic review of spinal anesthesia using bupivacaine for ambulatory knee arthroscopy. *Br J Anaesth.* 2009; 102 (3): 307-15.