

Effect of low dose Bupivacaine with Fentanyl on hemodynamic response: A Prospective cohort study

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Abstract

Background: A conventional dose of local anesthetics is used during spinal anesthesia. However an unwanted hemodynamic effect by administration of adjuvants with low dose of local anesthetics has been observed. The purpose of the study was to compare the effect of low dose Bupivacaine with Fentanyl versus normal dose Bupivacaine alone on hemodynamic response in elderly patients.

Methods: A Prospective cohort study was employed on a total of 64 elderly patients undergoing lower extremity orthopedics surgery. An exposed group (group BF) received 10mg of 0.5% isobaric bupivacaine with 25mcg of fentanyl and a non-exposed group (Group B) received 15 mg of 0.5% isobaric bupivacaine alone. Systematic random sampling technique was used to select study participants. Parametric data was analyzed by using independent t-test, nonparametric data by using Mann-Whitney U-test and homogenous categorical data by using chi-square test and fisher exact test. The level of statistical significance for all tests was found to be $P < 0.05$.

Results: The incidence of hypotension was higher in group B than group BF (37.5% vs. 9.4%, respectively) and statistically significant differences was observed ($p=0.008$). The onset of sensory block and regression of motor block to zero were faster in group BF than in group B ($p < 0.05$). TAR was also prolonged in group BF ($P < 0.05$).

Conclusion: Low dose Bupivacaine with Fentanyl has lower incidence of hypotension, fast onset of sensory block and prolonged first analgesia request time than bupivacaine alone Therefore, we recommends the use of low dose bupivacaine with fentanyl to have a better hemodynamic stability than conventional dose of bupivacaine for elderly patients who undergoes lower extremity surgery.

Introduction

Spinal anesthesia (SA) is a type of regional anesthetic technique which is commonly used for surgery in the elderly patients. It is often preferred for its simplicity, efficacy, rapidity, high success rate, minimal effect on mental status, reduction of blood loss, and protection against thromboembolic complications compared with general anesthesia[1, 2]. Spinal anesthesia may be indicated as the primary anesthetic used for major or minor surgeries involving the abdomen, perineum, or lower extremities[2].

Advanced diagnostic and therapeutic facilities have enhanced the life expectancy of humans, as a result of which elderly population is expected to rise 25% by 2020; 506 million as of 2008 and by 2040 will increase to 1.3 billion across the world[3]. As humans age increases, there is a general decline in organ function, although there is wide inter individual variability (e.g., some organs might be affected more than others). Most importantly, the cardiovascular and pulmonary systems have reduced function that might impact patients' physiologic responses during surgery and anesthesia[4].

Age and concurrent diseases make these patients at high risk for perioperative complications. Despite regional anesthesia has a better postoperative outcome, hypotension and bradycardia is common and

increases the risk of myocardial ischemia. The main effect of spinal anesthesia was the reduction of systemic vascular resistances (SVR) which were reduced by $18\% \pm 17.2\%$. The average cardiac index (CI) was initially reduced by 5.2- 6.6%, and it was persistently reduced during the surgical period[5, 6].

The elderly population is especially challenging when one has to consider all of the pharmacodynamics changes that occur with normal aging. Blood vessel distensibility is drastically decreased in elderly patients and, combined with increased intimal thickness and endothelial dysfunction, will increase systolic blood pressure, as well as left ventricular workload. Myocardial hypertrophy, along with increased collagen content, creates a stiff left ventricle that depends on adequate preload to maintain cardiac output. This makes elderly patients much more susceptible to fluid overload and this is due failure of autonomic reflexes responsible for of cardiovascular homeostasis in aged population[7, 8].

Orthopedic injuries, especially to the long bones such as the femoral neck, osteoarthritis and rheumatoid arthritis increase with age, were the most common injury which needs surgery in elderly patients[9, 10].

Spinal anesthesia in the elderly is associated with exaggerated responses to conventional doses of local anesthetics, thereby increasing the incidence of hemodynamic complications. Some studies suggested that Spinal anesthesia for elderly patients undergoing lower limb surgeries with 2cc bupivacaine 0.5% and 25µg fentanyl is a safer and better option, both in terms of maintaining hemodynamic stability and lower incidence of complications without compromising the surgical conditions[11].

Bupivacaine is an amide-type, long-acting local anesthetic widely used for spinal anesthesia[12]. Hypotension after conventional dose of bupivacaine accounts about 50%[11]. Whereas low dose of bupivacaine with fentanyl caused dramatically less incidence of hypotension during spinal anesthesia in elderly patients which also eliminates the need for vasopressor and intravenous fluids[13].

As far as the investigators knowledge, there is no published data found in Ethiopia that shows the effects of low-dose bupivacaine with fentanyl versus conventional dose of bupivacaine on hemodynamic response in elderly patients. Therefore, the aim of this study was to compare hemodynamic response of low dose bupivacaine with fentanyl versus conventional dose of bupivacaine in elderly patients who undergo lower extremity orthopedics surgery under spinal anesthesia at black lion Specialized hospital (BLSH), Addis Ababa, Ethiopia.

Methods And Materials

Institutional based prospective cohort study was used from November, 2018 - April, 2019 at black lion Specialized hospital. Source population were all elderly patients who undergone orthopedics lower extremity surgery under spinal anesthesia during study period. Selected elderly patients who undergone elective orthopedics lower extremity surgery under spinal anesthesia on the study period. Preoperative hyper or hypotensive patients, failed spinal anesthesia, Allergic to medication and emergency procedures were excluded from the study.

Hemodynamics response (hypotension) was one of our primary outcome indicators and preliminary data was taken from India showed the incidence of intraoperative hypotension with conventional dose of bupivacaine alone and low dose of bupivacaine with fentanyl group were 40% and 10% respectively[14].

Systematic random sampling technique was used to select study participants. From BLSH Orthopedics operation registration book, we got 88 elective orthopedics lower extremity procedures were performed in elderly patients for four consecutive months before study period. To recruit 64 study participants 1.5 skipping interval was used. Two patients from every 3 patients were recruited from the elective surgical schedule during the study period.

2 BSC anesthetists collected the data and 1 MSc anesthetist supervised by using pretested structured check list. Assessing onset of sensory block and onset and regression of motor block was documented during and after surgery after providing brief explanation for the patients preoperatively, and an informed consent was taken. We named bupivacaine 15mg alone group as Group B and the 10mg bupivacaine with fentanyl regime as Group BF. Hemodynamic response (SBP, DAP, MBP, PR, RR and SpO₂) at baseline then after administration of spinal anesthesia at 5 min, 10min, 15 min, 30 min, 60 min, 90 min and 120 min for both the groups were Monitored.

The mean BP, HR, SaO₂ and intraoperative patient complaints were recorded. Hypotension was defined as systolic blood pressure decrease of more than 25% from baseline. PR <60/min was graded as bradycardia. Respiratory rate was monitored and respiratory depression was estimated as a decrease in SaO₂ less than 90%. Patients were followed for 24 hours postoperatively to assess postoperative pain.

The onset of sensory block was assessed by using cold sensation every minute following spinal anesthesia administration. Motor block was assessed at the same time intervals up to onset of motor block using modified Bromage scale and we decide the motor block, at Bromage score of 3. Duration of analgesia was calculated in both groups from the time of spinal block to the time of first analgesic requirement. Complication of spinal anesthesia such as shivering, pruritus, seizures, nausea and vomiting and severity were graded and recorded intra and postoperatively. Pretesting with 10% of respondents (3 patients in each group) was done at Zewditu memorial referral hospital to assure quality of data. Investigators cross checked data completeness and consistency and accuracy on daily basis. Finally data was sorted, categorized and summarized.

Data Processing and Analysis

Data were checked and cleaned manually for completeness and then coded and entered in to SPSS version 25 computer program for analysis. Descriptive statistics were summarized with tables and figures reported as means \pm SD for continuous variables, and numbers or percentages for quantitative variables. Normality of distribution for continuous variable was tested by Shapiro-Wilk test and parametric variables were analyzed by independent t-test and Mann-Whitney for nonparametric test as needed, while chi-

square test was used for hypotension. Association was measured by 95% confidence interval and $p < 0.05$ was considered as statistically significant.

Operational Definitions

Bromage scale: is a tool used to assess motor block after administration of spinal anesthesia as scored below in this study

Activity	Score
Able to lift legs against gravity	0
Able to flex knee but unable to flex legs	1
Able to move feet but unable to flex knee	2
Unable to move any joints	3

Conventional dose of bupivacaine: is a dose of intrathecal 0.5% of 15mg bupivacaine alone

Elderly patients: refers to patients that are 60 years old and above.

Elective surgery: is surgery done before on set (appearance) of any complication that may constitute urgent surgical indication.

Emergency surgery: is surgery done at onset or near appearance of any complication that may constitute urgent indication.

Failed Spinal anesthesia: implies that spinal anesthesia was attempted, but without resulting in a sensory block or a block that resulted is inadequate for that surgery

Grading status of shivering: "0" = no shivering, 1 = One or more of: piloerection, 2 = visible muscular activity confined to one muscular group, 3 = visible muscular activity more than one muscular group and 4 = gross muscular activity involving the whole body.

Grading of pruritus: 1 = no itching, 2 = mild itching, 3 = moderate itching 4 = severe itching

Low dose of Bupivacaine: is considered as a dose of intrathecal 0.5% 10mg bupivacaine.

Numeric Rating scale (NRS): NRS pain assessment tool was used for grading severity of pain. Patients were informed about this pre-operatively. It has 0–10 (11point scale) numeral and viewing or listening to the numbers the rating by number on how the pain feels whereby 0 is no pain, (1–3) mild pain, (4–6) moderate pain, (7–10) severe pain [24].

Pruritus: is an unpleasant sensation leading to scratching.

Time for first analgesic request (TAR): is the time from spinal anesthesia injection to first complaint of pain by the patient [25].

Ethics approval and consent to participate

Ethical clearance letter was taken from Institutional Review Board of Addis Ababa University, department of anesthesia research ethical committee. Additionally, permission was obtained from BLSH administration. Finally, verbal consent was requested from each study participants during data collection process after giving brief explanation about the objectives of the study. Furthermore, confidentiality was maintained through not asking personal identifiers like name and address.

Results

Sociodemographic and Perioperative characteristics

A total of 64 patients were included in the study and 32 in each group. Group B given 15mg of 0.5% bupivacaine alone and group BF took 10mg of 0.5% bupivacaine with 25mcg fentanyl. Age, gender, height, weight was compared in our study and they were comparable ($p>0.05$). There were also no statistically significant difference between the groups in ASA physical status, BMI, duration of surgery preload fluid administered and preoperative hemodynamic parameters. Significant difference was obtained while comparing mean of total fluid intake between the two study groups. Which was statistically significant having ($p<0.001$) (*Table 1*).

Table 1: Demographic data, peri-operative variables among groups at Black lion Specialized Hospital, Addis Ababa, Ethiopia, 2019.

Time (minuets)		Bupivacaine alone	Bupivacaine with fentanyl	P-value
Gender	Male	19(30%)	15(23%)	.316
	Female	13(20%)	17(27%)	
Age(range and mean \pm SD) in Yrs.		60 – 80	60 -79	.429
		68.78 \pm 6.1	67.63 \pm 5.5	
Weight (range and mean \pm SD) in kg		55 – 80	55 – 81	.478
		67 \pm 7.6	65.66 \pm 7.45	
Height (cm)		170.2 \pm 3.3	170.2 \pm 3.1	.969
BMI (Kg/m ²)	<18.5	0%	1(1.6%)	.422
	18.5-24.9	24(37.5%)	25(39.1%)	
	25-29.5	8(12.5%)	6((9.5%)	
ASA	ASA I	13(20.3%)	11(17.2%)	.606
	ASA II	19(29.7%)	21(32.8%)	
Fluid preload(ml)		398.44 \pm 92.007	387.5 \pm 87.067	.625
Total fluid used(ml)		1420 \pm 97	1215 \pm 94	.000
Amount of blood loss(ml)		273 \pm 85	282 \pm 99	.684
Duration of surgery		106.41 \pm 31.45	100.88 \pm 33.54	.406
Baseline SBP		132.94 \pm 10.94	131.34 \pm 10.01	.546
Baseline MAP		96.75 \pm 9.82	96.76 \pm 8.11	.989
Baseline HR		72.91 \pm 4.55	72.63 \pm 5.09	.817
Baseline SaO ₂		95.81% \pm 1.87	95.72% \pm 1.46	.779

NB: ASA= American Society Anesthesiologist (surgical risk stratifications) SBP= systolic blood pressure
MAP = mean arterial blood pressure HR = heart rate SaO₂ = arterial oxygen saturation.

Change in systolic blood pressure

In group B maximum fall of 11.5% in mean systolic BP was observed at 30 min following spinal block. In Group BF, maximum fall of 6.5% in mean SBP at 30min. But no statistically significant difference was observed between groups (*Figure 1*).

Incidence of hypotension and Mean arterial pressure

Relatively higher incidences hypotension were observed in group B (12(37.5%) than group BF 3(9.4%) (Figure 2). In addition, higher normal values of MAP was found in BF group (Figure 3)

Change in Heart rate

HR was compared between groups; a decreased mean heart rate was noticed in Group B at 15 minutes after spinal block but no statistically significant differences were seen between the groups at all study timings (*Table 2*).

Table 2: Comparison of heart rate change in at different time interval among the groups at Black lion Specialized Hospital, Addis Ababa, Ethiopia, 2019.

Time (minuets)	Bupivacaine alone	Bupivacaine with fentanyl	P-value
05	73.25 ±5.13	73.88±5.08	.500
10	73.19±5	73.66±5.5	.722
15	70.84±5.05	72.53±4.41	.159
30	74.53±5.92	73.22±5.22	.419
60	73.28±4.71	72.91±4.92	.757
90	73.22±4.8	73.25±5.15	.989
120	73.63±4.77	74.47±5.41	.511

Independent t-test for Mean and standard deviation at 10, 15, 60 and 120minutes, Mann-Whitney U-test for median at 05, 30 and 90minutes.

When we compared SaO₂ between groups: there was no statistically significance different at all-time interval but at 30min after spinal anesthesia block lower mean SaO₂ observed in group BF in respect to Group B (*Table 3*).

Table 3: Comparison of SaO₂ change in different time interval among the groups at Black lion Specialized Hospital, Addis Ababa, Ethiopia, 2019.

Time in minuets	Bupivacaine alone	Bupivacaine with fentanyl	P-value
Baseline	95.81±81	95.72±1.46	.779
05	96.3±1.76	95.75±1.59	.412
10	96.34±2.16	96.13±1.64	.347
15	96.5±2.06	95.69±1.69	.361
30	97.09±2	95.94±1.78	.185
60	96.19±1.75	96.14±1.74	.285
90	96.13±1.96	95.81±1.23	.888
120	96.41±1.58	96.15±1.49	.408

SaO_2 =arterial oxygen saturation

Spinal anesthesia block characteristics

The onset of sensory block and regression of motor block to zero was faster in group BF than in group B ($p < 0.05$). TAR was also prolonged in group BF ($P < 0.05$). The mean level of sensory block at surgery, onset of motor block and motor bromage score at start of surgery were compared and found that values were not significant in both the groups (Table 4). According to numeric rating scale (NRS) pain severity score in our study, statistically significant difference was observed at 4hrs after spinal block ($p = 0.014$). Otherwise in all-time interval comparable result was seen (Table 5).

Table 4: Characteristics of the spinal block among the groups at Black lion Specialized Hospital, Addis Ababa, Ethiopia, 2019.

Characteristics of the spinal block	Bupivacaine alone	Bupivacaine with fentanyl	P-value
Onset(Sensory)	5.09 ± 1.57	4.31±1.26	0.032*
Level (at surgery)	T8	T9	0.690
TAR (in minutes)	213.19±51.46	233.41±46.46	0.033*
Motor			
Onset(Motor)	6.72±1.782	6.91±1.573	0.821
Bromage (at surgery)	3	3	.786
Bromage zero (after surgery)	158.88 ±14.661	145.69±15.53	0.01*

TAR= time of analgesia request, Independent t-test for Mean and SD, Mann-Whitney U- test for median (for sensory level and motor bromage)

Table 5: Comparison of numeric rating score for pain severity at different time intervals from 2.5hrs, 3, 4, 6, 8 and 12hrs among the groups at Black lion Specialized Hospital, Addis Ababa, Ethiopia, 2019.

Time (hours)	No pain		Mild pain		Moderate pain		P-value
	B	BF	B	BF	B	BF	
3	24	26	6	5	2	1	.777
4	7	18	11	8	14	6	0.014*
6	3	5	11	11	18	16	.734
8	4	1	21	25	7	6	.329
12	2	4	17	18	11	9	.749

Chi-square test

Discussion

This study aimed to compare hemodynamic response of conventional dose of bupivacaine versus low dose bupivacaine with fentanyl elderly patients who undergo lower extremity orthopedics surgery under spinal anesthesia at Black lion specialized hospital, Addis Ababa, Ethiopia, 2019. The result of this study showed that, the overall incidence of hypotension was 37.5% in non-exposed (group B), ((0.5% of 15mg isobaric bupivacaine) and 9.4% in study groups (0.5% of 10mg isobaric bupivacaine with 25mcg fentanyl) (group BF). Higher incidence of hypotension was observed in non-exposed than study groups and it is statistically significant between groups. This result is incomparable with study done in India[14] and Pakistan[15], which showed higher incidence of hypotension in non-exposed group (73%) than study groups (10%).

On this study, maximum fall in MAP in group B was greater than in group BF after administration of spinal anesthesia. Similarly another comparative study in India[11], showed more decreased in systolic BP in non-exposed group than study group. In contrast to the present study, comparative study conducted in Australia[16], showed there were no differences on incidence and severity of hypotension between the groups.

The result of this study showed statistically insignificant differences on HR value between the groups after administration of spinal anesthesia and none of the patients were treated for bradycardia. This is in agreement with comparative study conducted in India [11], revealed HR was better maintained in group BF than group B but it was not statistically significant.

The onset of sensory block and regression of motor block to zero was faster in group BF ($p < 0.05$). TAR was also prolonged in BF group (233.41 ± 46.46 min) than in group B (213.19 ± 51.46 min), and it is statistically significant ($p < 0.05$). This result is in accordant with prospective comparative study done in India [14], showed earlier onset of sensory analgesia, time to achieve peak sensory level, and recovery from motor blockade in group BF than in group B. This is also in line with another study conducted in Iran [17][22], showed the mean duration of sensory block was much longer in group BF than in group B but time to achieve maximum level of block and Mean time of two-segment regression was much shorter in group BF than in group B.

When we compare pain severity between groups according to numeric rating scale (NRS) pain severity score in this research, statistically significant difference was observed at 4hrs after spinal block ($p = 0.014$). This result is in line with prospective comparative study done in India [21], revealed that the time of first analgesia request (FAR) was lower in BF group than in group B, ($p < 0.01$).

Strength of the study: Both the exposed and unexposed groups were selected from the same source population. No lost to follow up of patients which results in missing data.

Limitations of the study: Inaccessibility of invasive arterial blood pressure to measure parturient beat to beat systolic blood pressure. Duration of hypotension couldn't measure with every hypotensive episodes.

Conclusion

Low dose bupivacaine with fentanyl has less incidence of hypotension, fast onset of sensory block, and regression of motor block to zero and has prolonged first analgesia request time than normal dose bupivacaine for spinal anesthesia in elderly patients undergoing lower extremity orthopedics surgeries.

Declarations

Competing interest

The authors declared that they have no competing interests

Author contributions

BA have contributed to the conception, design of the study, data acquisition, data entry, analyzing and interpretation of the data, and drafted and revised the manuscript. AA, SJ, SE and MS have contributed to the conception and assisted in the initial design of the study, analyzed and interpreted the data and critically revised the manuscript. Both authors read and approved the final manuscript.

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Availability of data and materials

Data will be available with reasonable request of corresponding author

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Figures

Figures 1-3 were not provided with this version.