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Accessing the efficacy and peri-operative adverse effects of three different hyperbaric bupivacaine 0.5% dosages for spinal anesthesia induction in lower limb orthopedic surgeries: a randomized clinical trial

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Abstract

Background Spinal anesthesia (SA) is a conventional method for proper nerve block in abdominopelvic and lower extremity surgeries. Compared to general anesthesia, SA has reduced perioperative complications significantly. The hyperbaric type of bupivacaine hydrochloride (HB) induces spinal anesthesia more efficiently with a lower incidence of life-threatening adverse reactions like Perioperative hemodynamic changes and respiratory depression. More investigations are needed to define the best dosage that provides adequate anesthesia while reducing adverse effects for each surgical procedure.

Methods This double-blinded randomized clinical trial compared the consequences of the (12.5mg,15mg,20mg) dosages of HB-bupivacaine in elective lower limb orthopedic surgery. Using block randomization, we allocated 60 participants to three ($n=20$) study groups. Utilizing the same protocol of anesthesia induction, outcome variables assumed and measured as the incidence of the adverse effects (Hypotension, Anxiety, Bradycardia, Nausea and Vomiting(N/V), Hypoventilation, and Decreased o2 saturation), and the requirement for intervention to control the unwanted reaction. Addressing that, outcome variables were measured 10 times perioperatively. One-way ANOVA test, the chi^2 test, or repeated measures ANOVA test with the Bonferroni adjustment were utilized as appropriate.

Results We found that the incidence of hypotension (*P*-value:0.02) and the N/V (*P*-value < 0.001) are associated with the HB-bupivacaine dosage. Contrary, our findings indicate that the incidence of apnea, bradycardia, and hypoventilation did not exhibit a significant dose-dependent pattern between the groups. Repeated measures analysis revealed significant intergroup differences for Herat rate, systolic, diastolic, and mean arterial pressure (group*time *P*value < 0.001). The observed differences were more prominent 10–30 min after injection of HB-bupivacaine. The regression model claimed that gender (*P*-value:0.002) and drug dosage (*P*-value:0.03) significantly predict the incidence of adverse effects.

Conclusion Our results, suggest that the administration of the 12.5mg HB-bupivacaine provides adequate anesthesia while minimizing the risk of adverse events for lower limb orthopedic surgeries lasting up to 180 min.

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Trial registration The study was registered at the Clinical Trial Registry Center (IRCT20160202026328N7), Registered on 2022.01.10.

Keywords Anesthesia, Spinal, Bupivacaine, Orthopedic surgery, Perioperative complications

Background

Spinal anesthesia (SA) is a conventional method to achieve proper nerve block in surgery. The main applications of this method are lower thoracic, abdominopelvic, and lower extremities surgeries. The procedure aims to deliver desirable amounts of an anesthetic substance into the subarachnoid space [1]. SA approximately used in over 5% of surgical interventions worldwide [2]. The process not only provides effective sensory-motor neuron blocks, but also blocks regional sympathetic nerves [3]. In comparison, SA has reduced perioperative complications significantly. As opposed to general anesthesia (GA), SA shrank pulmonary complications, surgical site infections, the need for blood transfusion, thrombotic events, ICU admission, and inpatient care period [4]. The essential contraindications for SA are raised intracranial pressure(RICP), infection at the lumbar puncture site, hypovolemia, and coagulation problems [5].

Bupivacaine hydrochloride is relatively safe and widely used as an anesthetic drug for SA induction. Currently, two types of isobaric (IB) and hyperbaric (HB) bupivacaine are available on the market. Pharmacodynamics attitudes of the HB types bring some advantages for the diffusion, number of blocked dermatomes, the efficacy of the blockage, rapid onset anesthesia, and a lower incidence of side effects [6, 7].

The main side effects of bupivacaine-induced SA can be categorized into procedure-related (like post-lumbar puncture headache) and drug-related adverse effects. The main adverse effects of the drug manifest as perioperative hemodynamic instability and respiratory depression. [2]. Despite the interpersonal and genetical variations in reactions to bupivacaine, it was demonstrated that a higher dose of drug injection was accompanied by more adverse reactions [8, 9]. Furthermore, surgery type, demographic features, patient medical history, American Society of Anesthesiologists (ASA) physical score, spinal cord level of SA induction, and β-blocker consumption are associated with the incidence of adverse effects [10, 11]. Besides, a lower drug dose may cause inadequate sedation and necessitate general anesthesia induction. Previous studies were inconclusive in determining the proper dose of HB-bupivacaine for SA induction in lower limbs orthopedic surgeries, We aimed to compare the efficacy and consequences of the three doses of HB-bupivacaine(12.5,15, and 20mg) in elective lower limb orthopedic surgery in Iranian population. Considering the genetic variation and surgery types, we hypothesized that the 12.5mg HB-bupivacaine dosage could provide proper anesthesia for lower limb orthopedic surgery with a lower incidence of perioperative adverse effects in our study population.

Methods

Study characteristics

In this double-blinded randomized clinical trial, we investigated the efficacy and adverse effects of three dosages of 0.5% HB-bupivacaine (12.5mg/15mg/20mg) among the study groups. The study was performed between August 2022 and January 2023 at Tabriz's Shohada Hospital and registered at the Clinical trial Registry Center (IRCT20160202026328N7). The protocol of the study was approved on 2021.11.29 by the local ethics committee (IR.TBZMED.REC.1400.820) and all participants had informed consent for participation.

Sample characteristics

Participants were adults 18 to 60 years old with class 1 or 2 ASA classification, who were candidates for elective lower limb orthopedic surgery with SA. Surgery types include DHS insertion, PFNA insertion, total knee arthroplasty, patella fracture, tibial shaft fracture, and calcaneal fracture. We considered patients' disagreement with SA, uncontrolled hypertension or Diabetes mellitus, previous neurologic disorders, known coagulopathy, allergy to the HB-bupivacaine, and septicemia or infection at the site of injection of the anesthesia as exclusion criteria.

Considering the previous study of Shahverdi et. al With a power of 80% and a confidence interval of 95%, the sample size was calculated to be approximately 60 patients [12]. The PASS software version 20.0.5 was utilized for sample size calculation. Using convenience sampling and block randomization methods, participants were equally distributed into three dosage groups. Patients were assigned to Groups A (12.5mg), B (15mg), or C (20mg) on a computer-generated random number generator using Random Allocation Software (RAS; Informer Technologies, Inc., Madrid, Spain) (Fig. 1).

Anesthesia induction method

We used 0.5% hyperbaric bupivacaine (AstraZeneca Company, France), intrathecal Injections performed by 23G Quincke spinal needles (Dr.Japan Co. Ltd), and

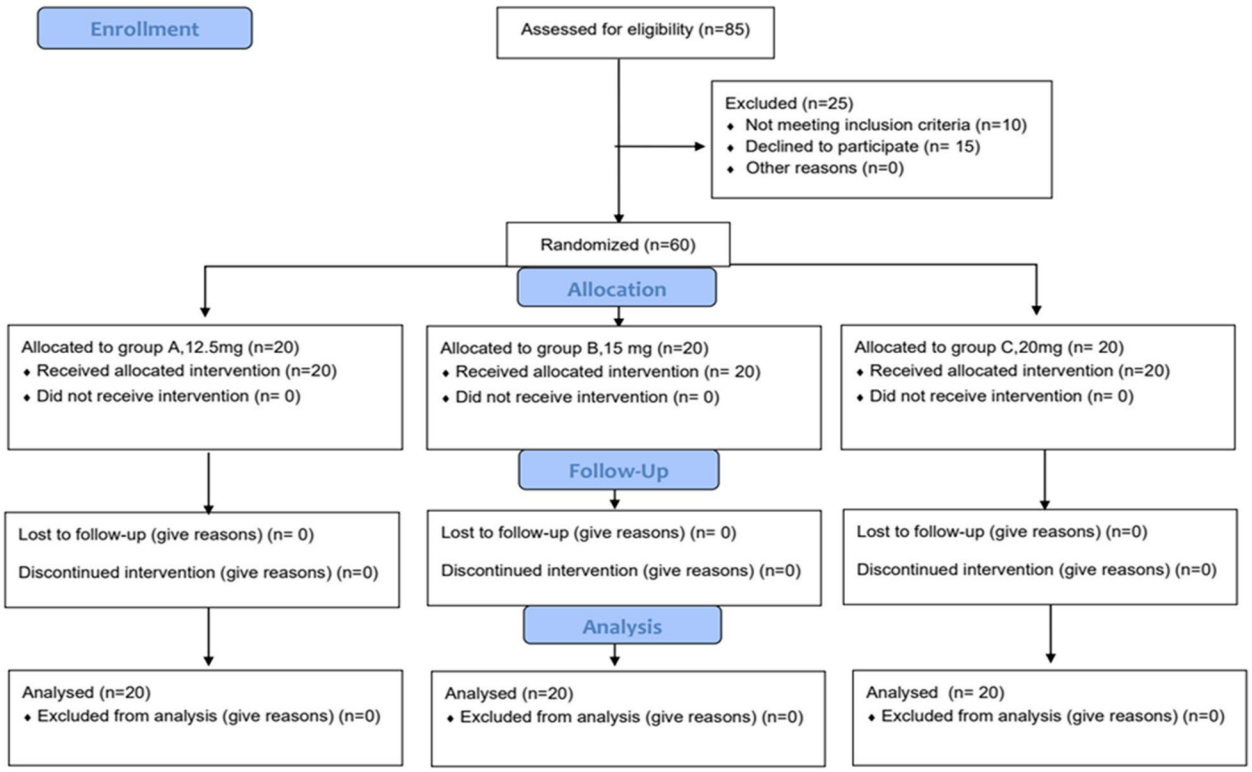

Fig. 1 Consort diagram

5ML syringes(AVA Pezeshk—Luer-lock Syringe) that were available at the hospital to maintain the accuracy of the injection dose. The rate of infusion was approximately 0.2ML/second. The room and injected solution temperature were maintained equally to assimilate the intervention into three groups. All participants received injections in Fowler's position in the L4-L5 intervertebral space. The anesthesiologist and the patients were blinded to the injected dose of the drug. Patients were immediately laid down in a supine position after injection. Patients were monitored for electrocardiography, pulse oximetry, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean blood pressure (MBP), heart rate (HR), and oxygen saturation (SpO2) (data measured with an X162 monitor (Saadat Company, Iran) by an expert physician). The sensory nerve block was assessed by a pin-prick test at the L1 dermatome and the motor nerve block was evaluated by a modified Bromage scale. Surgeries duration and type, HB-bupivacaine dosage, demographic features, and Body-mass index, for all participants were recorded in their files.

Outcome measure

Outcome variables assumed as the incidence of the adverse effect (Hypotension, Anxiety, Bradycardia, Nausea and Vomiting(N/V), Hypoventilation, and Decreased o2 saturation), and the requirement for intervention to control the unwanted reaction. Addressing that, blood pressure (BP), mean arterial pressure(MAP), heart rate(HR), oxygen saturation(O2 sat), and respiratory rate(RR) were measured before the injection and at the supine position and every 5 min up to 30 min and every 15 min up to 60 min after the injections. Atropine, saline solution with ephedrine, and oxygen were available for the management of symptomatic bradycardia, hypotension, and hypoventilation. The data of the participants with severe adverse reactions, with the need for intervention, were included just before resuscitation to minimize the effects of resuscitation on the outcome variables.

For the analysis of the results, SPSS version 26 was utilized, with a significance level set at $P \leq 0.05$. The normality of the data was assessed using the Shapiro–Wilk test. Depending on the nature of the data, either parametric (one-way ANOVA or the chi-square test) or nonparametric (Kruskal–Wallis test) were employed. Repeated measures data were analyzed using repeated measures ANOVA. Post-hoc comparisons were conducted using the Bonferroni post-hoc correction to determine associations between groups. In case of rejected assumption of sphericity, the Greenhouse- Geisser correction was utilized.

Results

Demographic features

The demographic features of the participants are presented in Table 1. 60 patients were equally distributed in three study groups (20 participants/group). The participants' mean age was 57.23(± 18.56 STD), 39 male and 21 female, with a mean BMI of 25.64 (± 3.05 STD), and mean surgery duration of 118.66 ((± 36.50 STD) minutes. The inter-group differences weren't significant regarding demographic features. The majority of each group's patients were classified as a class (II) on the ASA scale. Our sample did not contain any participants needing redosing to obtain proper anesthesia. All participants reached desirable sensory and motor nerve blocks (pin-prick perception blockage at the L1 dermatome, and a modified bromage scale score of 3 or 4 obtained).

Perioperative adverse drug reaction incidence

Precise data on adverse effects incidence is presented in Table 2. Although the observed incidences of agitation, bradycardia, and hypoventilation did not differ between our study's groups, the incidences of hypotension and nausea/vomiting showed significant variation between our study's groups (Chi^2 P-value: 0.02, and ≤ 0.001 respectively). Additionally, our data showed that the overall between-group variation of adverse drug effects was significant (Chi^2 P-value ≤ 0.001).

Baseline characteristic of the outcome measures

The baseline characteristics of the assumed variables did not have meaningful differences among the study's groups. Data on respiratory rate did not distribute normally but data on pulse rate, systolic blood pressure, diastolic blood pressure, mean arterial pressure, and O2 saturation were found to have normal distributions. Parametric or non-parametric tests were used to examine inter-group differences as appropriate. More information about the baseline characteristics of the groups is reported in Table 3.

Repeated measure results

We performed Repeated measures ANOVA to determine the possible differences between the study's groups. Total Data from 60 participants in three groups were collected. Each variable was measured 10 times according to the study's protocol (before injection, immediately after injection, every 5 min up to 30 min after injection, and at 45 and 60 min after injection). Complete data were available for all 20 participants in each study group.

Respiratory rate

Data on respiratory rate did not have a normal distribution, so we used a non-parametric test for interpretation of them at each time point. Except for 60 min after injection (P-value: 0.01) We did not find any meaningful differences in respiratory rate during the investigation between our study groups. The observed differences

Table 1 BMI: Body mass index/ ASA: American Society of Anesthesiology/ *one-way ANOVA *p*-value reported/ ** chi2 test *p*-value reported

Demographic features of the patients				
Parameter:	**Group A (12.5mg)**	**Group B (15mg)**	**Group C (20mg)**	***P*-value**
Age (Mean, STD)	57.20(21.18)	55.55(18.08)	58.95(16.98)	0.850*
Gender (Male/Female %)	70/30	70/30	55/45	0.517**
Weight (Mean, STD/Kg)	75.80(7.08)	73.90(11.53)	73.70(12.37)	0.788*
Height (Mean, STD/cm)	173.70(7.40)	169.30(8.30)	167.95(8.85)	0.078*
BMI (Kg/m^2)	25.23(3.04)	25.66(2.64)	26.02(3.63)	0.724*
ASA (I/II percent)	15/85%	25/75%	15/85%	0.641**
Surgery time/min (Mean, STD)	113.00 (36.49)	121.50 (39.80)	120.00 (34.35)	0.746*

Table 2 Incidence of adverse drug reactions

Group	Agitation	Nausea and vomiting	Hypotension	Bradycardia	Hypoventilation	Total
A	-	-	1 (5%)	1 (5%)	-	2 (10%)
B	-	8 (40%)	8 (40%)	1 (5%)	-	14 (70%)
C	1 (5%)	5 (25%)	7 (35%)	3 (15%)	-	12 (60%)
Total	1 (1.7%)	13 (21.7%)	16 (26.7%)	5 (8.3%)	0 (0%)	28 (46%)

Table 3 Baseline characteristics of outcome variables/group. SBP: Systolic blood pressure/ DBP: Diastolic blood pressure/ MAP: mean arterial pressure/ RR: Respiratory rate/ *: One-way ANOVA test/ **: Kruskal–Wallis test

	Group	Mean ± Std	P-value*	F
SBP	A	140.50 ± 12.65	0.587	0.53
	B	136.45 ± 13.42		
	C	137.90 ± 12.23		
DBP	A	80.60 ± 11	0.919	0.08
	B	80.15 ± 12.28		
	C	81.55 ± 9.45		
MAP	A	120.55 ± 11.55	0.723	0.32
	B	117.55 ± 12.72		
	C	119.05 ± 10.88		
HR	A	88.05 ± 10.82	0.721	0.32
	B	90.70 ± 8.65		
	C	89.15 ± 11.46		
O2. Saturation	A	94.65 ± 1.87	0.600	0.51
	B	94.45 ± 1.87		
	C	94.00 ± 2.42		
RR	Group	Median ± IQR	P-value**	
	A	13 ± 1	0.726	
	B	13 ± 0		
	C	13 ± 1		

were just statistically significant, and none of our participants manifested with apnea or bradypnea.

Heart rate

The Greenhouse- Geisser correction was utilized. The interaction between Time and Group was significant ($F = 10.98$, $P < 0.0001$). Post hoc comparisons indicated that between-group differences at baseline were not significant, but after 10 min of injection, all of the between-group differences were significant, with group A having lower mean heart rate levels than the other groups. The detailed data are presented in Table 4 and Fig. 2A.

Systolic blood pressure

The Greenhouse- Geisser correction was utilized. The interaction between Time and Group was significant ($F = 26.34$, $P < 0.0001$). Post hoc comparisons indicated that between-group differences at baseline were not significant, but from 10 to 30 min after injection between-group differences were statistically significant, with group A having a higher mean systolic blood pressure levels than the other groups. The detailed data are presented in Table 4 and Fig. 2B.

Diastolic blood pressure

The Greenhouse- Geisser correction was utilized. The interaction between Time and Group was significant ($F = 30.80$, $P < 0.01$). Post hoc comparisons indicated that between-group differences at baseline were not significant. Post-hoc analysis revealed that from 10 to 20 min after injection between-group differences were statistically significant, with group A having higher mean diastolic blood pressure levels than the other groups. The detailed data are presented in Table 4 and Fig. 2C.

Mean arterial pressure

The Greenhouse- Geisser correction was utilized. The interaction between Time and Group was significant ($F = 35.27$, $P < 0.0001$). Post hoc comparisons indicated that between-group differences at baseline were not significant, but from 10 to 30 min after injection between-group differences were statistically significant, with group A having higher mean arterial pressure levels than the other groups. The detailed data are presented in Table 4 and Fig. 2D.

O2 saturation

The Greenhouse- Geisser correction was utilized. The interaction between Time and Group was not significant. Post hoc comparisons did not indicate any significant between groups differences. The detailed data are presented in Table 4 and Fig. 2E.

Regression analysis

We built a binary logistic regression model to analyze the effect of age, weight, height, BMI, surgery time, ASA index, and the intervention group on the incidence of adverse effects. The model showed a significant predictive value for the Group of interventions ($P = 0.002$) and gender ($P = 0.03$). Based on a logistic model using 12.5 mg 0.5% HB-bupivacaine and female gender propose a protective effect on the incidence of adverse drug reactions (Tables 4 and 5/Fig. 3).

Discussion

We found that all three injected doses of HB-bupivacaine (A:12.5 mg/B:15 mg/C:20mg) were effective for induction of the Anesthesia required for lower limb orthopedic surgeries lasting up to 180 min. Our findings claim that the incidence of agitation, bradycardia, and hypoventilation did not vary between our study groups significantly, while for hypotension and N/V, we found an important between-group variation with a lower incidence in Group A relative to the others. Also clinically and statistically, the overall incidence

Table 4 Detailed date of the variables/group during the study (1:Kruskal–Wallis test / 2: one-way ANOVA test / 3: repeated measured ANOVA test)

	Group	Before injection	Immediate after injection	5min after injection	10min after injection	15min after injection	20min after injection	25min after injection	30min after injection	45min after injection	60min after injection	p-value [3]	
												Time effect	Time*Group
Respiratory rate (median±IQR)	A	13 ± 3	14 ± 3	14 ± 3	13 ± 2	13 ± 1	13 ±2	13 ± 1	13 ±1	13 ±0	14 ± 1		
	B	13 ±0	13 ± 3	13 ± 3	13 ± 3	13 ± 3	13 ± 1	12 ± 2	13 ± 1	13 ±2	13 ± 2		
	C	13 ± 1	13 ± 3	13 ±1	13 ± 2	13 ± 1	12 ± 1	12 ± 1	13 ± 1	13 ±1	13 ±1		
p-value [1]		0.726	0.906	0.480	0.468	0.108	0.140	0.100	0.180	0.491	**0.011**		
Heart rate (mean± Std.Eror)	A	88.05 ±2.32	91.65 ±2.99	95.35 ± 4.29	95.25 ± 4.29	93.30 ± 3.76	90.60 ±3.02	91.30 ±2.82	90.00 ±2.69	88.10 ±2.57	89.90 ± 2.57	**P<0.001**	**P<0.001**
	B	90.70 ±2.32	94.20 ±2.99	107.4 ±4.29	113.90 ±4.29	120.75 ±3.76	119.00 ±3.02	116.80 ±2.82	115.80 ±2.69	109.10 ±2.57	102.95 ±2.57		
	C	89.30 ±2.32	91.45 ±2.99	98.30 ±4.29	106.45 ±4.29	109.55 ±3.76	111.85 ±3.02	111.95 ±2.82	109.95 ±2.69	104.20 ±2.57	97.75 ± 2.57		
p-value [2]		0.721	0.770	0.127	**0.012**	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**	**P<0.001**	**0.003**		
Systolic blood pressure (mean± Std.Eror)	A	140.50 ±2.85	137.15 ±2.97	121.85 ±3.27	115.80 ±3.00	111.20 ±2.84	110.75 ±2.73	113.10 ±2.72	119.40 ±2.99	126.55 ±2.86	132.45 ±2.95	**P<0.001**	**P<0.001**
	B	136.65 ±2.85	133.35 ±2.97	116.10 ±3.27	105.45 ±3.00	101.20 ±2.84	99.55 ±2.73	102.10 ±2.72	108.15 ±2.99	122.35 ±2.86	129.00 ±2.95		
	C	137.90 ±2.85	135.60 ±2.97	115.70 ±3.27	100.50 ±3.00	95.85 ±2.84	94.90 ±2.73	98.55 ±2.72	105.75 ±2.99	126.80 ±2.86	132.50 ±2.95		
p-value[2]		0.587	0.666	0.339	**0.002**	**0.001**	**P<0.01**	**0.001**	**0.005**	0.472	0.632		
Diastolic blood pressure (mean± Std.Eror)	A	80.60 ±2.46	79.25 ±2.50	72.95 ±2.72	72.75 ±2.54	71.05 ±2.45	74.15 ±2.60	72.55 ±2.75	74.20 ±2.73	76.15 ±2.46	74.90 ±2.49	**P<0.001**	**P<0.001**
	B	80.15 ±2.46	78.95 ±2.50	71.30 ±2.72	64.85 ±2.54	60.90 ±2.45	65.95 ±2.60	66.45 ±2.75	70.50 ±2.73	75.20 ±2.46	73.90 ±2.49		
	C	81.55 ±2.46	80.70 ±2.50	71.55 ±2.72	63.85 ±2.54	59.30 ±2.45	64.05 ±2.60	64.90 ±2.75	70.10 ±2.73	73.85 ±2.46	72.15 ±2.49		
p-value [2]		0.919	0.870	0.899	**0.032**	**0.002**	**0.019**	0.126	0.508	0.803	0.733		
Mean arterial pressure (mean± Std.Eror)	A	120.55 ±2.62	117.85 ± 2.72	105.55 ±3.01	101.40 ±2.76	97.65 ± 2.65	98.55 ±2.61	99.45 ±2.64	104.40 ±2.75	109.80 ±2.60	113.25 ± 2.71	**P<0.001**	**P<0.001**
	B	117.55 ±2.62	115.35 ±2.72	101.30 ±3.01	91.95 ± 2.76	87.80 ± 2.65	88.45 ± 2.61	90.25 ± 2.64	95.60 ± 2.75	106.65 ±2.60	110.65 ±2.71		
	C	119.05 ±2.62	117.35±2.72	100.75±3.01	88.05±2.76	83.35 ±2.65	84.55± 2.61	87.05 ±2.64	93.75±2.75	109.15±2.60	112.40±2.71		
p-value[2]		0.723	0.790	0.472	**0.004**	**0.001**	**0.001**	**0.005**	**0.019**	0.668	0.789		
O2 saturation (mean± Std.Eror)	A	94.65 ±0.46	94.20 ±0.50	93.60 ±0.53	93.55 ±0.56	94.05 ±0.61	94.15 ±0.65	94.10 ±0.61	93.85 ±0.62	94.00 ±0.57	94.35 ±0.54	**P<0.001**	0.227
	B	94.45 ±0.46	93.90 ±0.50	93.25 ±0.53	93.45 ±0.56	93.90 ±0.61	93.50 ±0.65	94.05 ±0.61	93.95 ±0.62	94.25 ±0.57	93.85 ±0.54		
	C	94.00 ±0.46	93.50 ±0.50	93.00 ±0.53	93.60 ±0.56	94.25 ±0.61	93.60 ±0.65	93.95 ±0.61	93.60 ±0.62	93.55 ± 0.57	93.65 ±0.54		
p-value [2]		0.600	0.614	0.725	0.982	0.923	0.753	0.985	0.921	0.688	0.644		

rate of unwanted drug reactions was lower in group A of the participants. Our results imply that the decline of the systolic, diastolic, and mean arterial pressure are dose-dependent approximately. Conversely, respiratory rate and O2 saturation did not exhibit dose-dependent manners. Post-hoc analysis revealed that the majority of the meaningful inter-group differences happened 10–30 min after the injections, and the observed differences were more prominent between Groups A and C. Except for the injected drug dose, gender was found to be an important factor for anticipating the incidence of adverse effects. Our data suggested a protective effect of the female gender in unwanted drug reactions incidence.

Pain management during the surgical process is one of the major topics of anesthesiology. Knowing the mechanism of early surgery-related complications entails adequate pain management and faster rehabilitation. To address this method of anesthesia, anesthetic drug selection, and dose modification are the essential components.

SA is well known relatively safe method of anesthesia induction. It is widely used in lower thoracic, abdominopelvic, and lower limb surgeries. Annually, it is employed in approximately 15 million surgeries (5% of surgical interventions) around the world [1, 2]. SA was shown to have beneficial effects in the reduction of pulmonary complications, surgical site infections, the need for blood transfusion, thrombotic events, ICU admission, and inpatient care period [4].

Bupivacaine is a potent aminoacyl local anesthetic and a leading substance used for SA induction [13]. Bupivacaine blocks nerve excitation by disabling voltage-gated sodium channels and antagonizing NMDA receptors in the dorsal horn [14]. The pharmacologic features of bupivacaine are responsible for long-lasting anesthesia and sensory dissociation from motor blocks. A relatively low tachyphylaxis rate and poor placenta passage make it favorable for antinociceptive induction [15, 16]. Hyperbaric (HB) bupivacaine hydrochloride has a greater density relative to the cerebral spinal fluid. in comparison

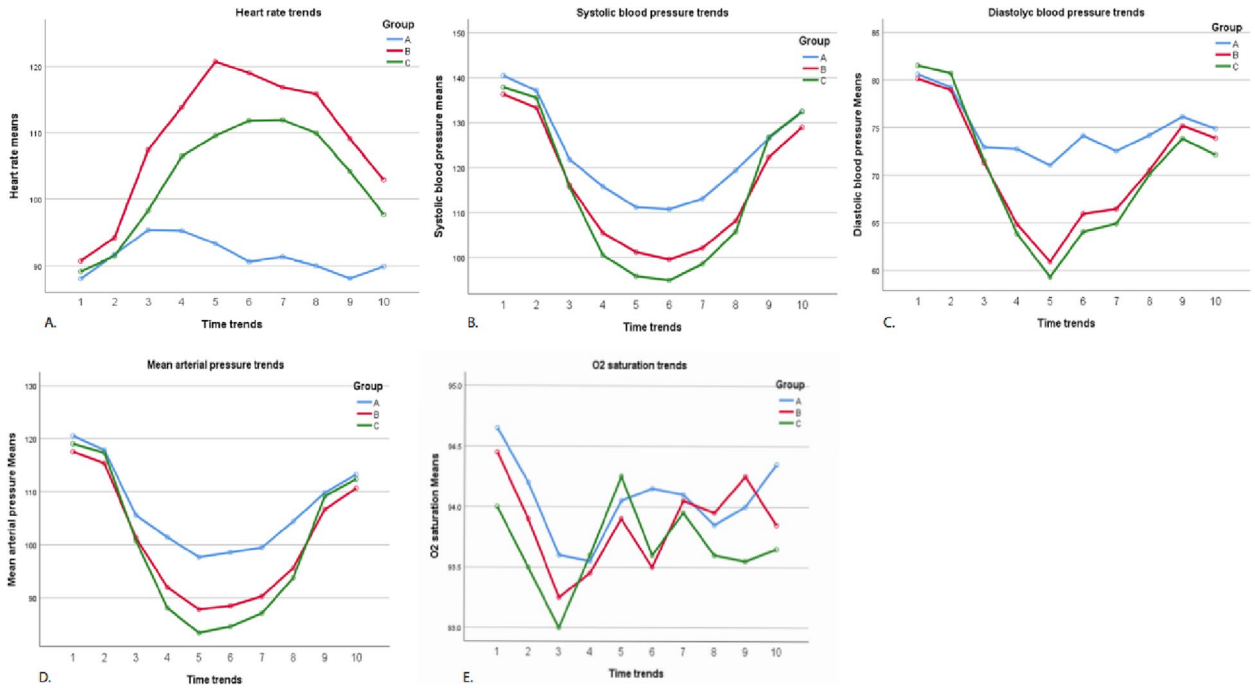

Fig. 2 A: Heart rate trends. B: Systolic blood pressure trends. C: Diastolic blood pressure trends. D:Mean arterial pressure trends. E:O2 saturation trends

Table 5 Logistic regression analysis

	P-value	Exp(B)	95% CI for Exp(B)
Intervention group	**0.002**	32.79	3.65–294.09
Gender	**0.031**	21.26	1.31–344.33
Age	0.895	0.99	0.92–1.07
Height	0.439	0.70	0.29–1.70
Weight	0.643	1.28	0.44–3.76
BMI	0.570	0.41	0.02–8.60
ASA index	0.246	0.16	0.00–3.53
Surgery time	0.124	0.98	0.96–1.00

with isobaric bupivacaine, HB-bupivacaine appeared to have brisk motor block initiation and a relatively shorter duration of sensory-motor block remission [7]. The HB form attenuates the need for conversion to general anesthesia and supplemental analgesia without increasing the incidence of adverse effects [7].

Parallel to advantages, SA has several complications. Prominent peri-operative complications of HB-bupivacaine are hemodynamic instability and respiratory depression [2]. Although individual reactions to HB-bupivacaine are idiosyncratic, more adverse reactions co-exist with higher-dose injections [8]. However an inappropriate low-dose injection of the anesthetics followed by SA failure [17]. Many efforts have been made to recognize the best dosage of HB-bupivacaine for SA, but the results are controversial.

Our findings on the efficacy of HB-bupivacaine in the induction of sensory-motor block (complete sensory-motor block without the additional intraoperative need for anesthesia) were in line with those of other studies. Picherski et.al in an RCT of lower limb orthopedic surgeries found 100% efficacy for the 15mg HB-bupivacaine solution on induction of the complete sensory-motor block. According to their results up to 73% of the patients did not need any additional intraoperative anesthesia [18]. The difference between our results and the mentioned study probably originates from the various sample sizes and unequal drug brands and injected doses. Additionally, the patient's sensitivity to pain may influence the results of the additional need for intraoperative analgesia. Considering the adequate sensory-motor block in all study groups, our results support using a lower dose (12.5 mg) of HB-bupivacaine for SA in lower limb orthopedic surgeries.

A meta-analysis has been made to investigate the efficacy and adverse reactions related to SA induction by Messina et.al [19]. 6 randomized clinical trials of lower limb orthopedic surgery were included. All of the included studies except one (using ropivacaine), using the different doses of hypo, Iso, and hyperbaric bupivacaine

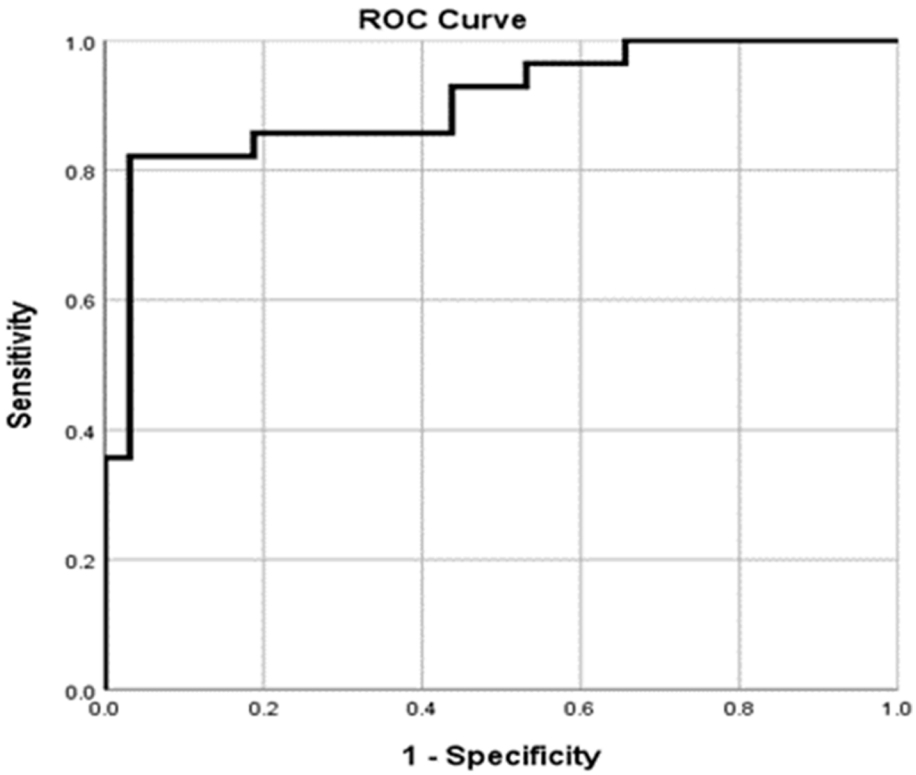

Fig. 3 ROC curve, AUC = 0.95

for SA induction. Overall, data of the 334 patients with a median age of 82yr, needed open surgical repair of hip fracture analyzed. The median surgical duration of the studies was 65 min, and the median BMI for the included studies was calculated at 23. 5 of the included studies added lipophilic opiates to local anesthesia as adjuvant therapy, and ultimately results of the meta-analysis suggested the use of 6.5mg rather than 10.5mg of local anesthesia could be reasonable to induce proper anesthesia and reduce perioperative adverse reaction. These findings claim ours in terms of decreasing the incidence of adverse reactions by administrating lower doses of SA injection. The observed differences could be addressed by the differences in mean surgical time, participants' BMI, and the use of adjuvant opiates for induction of SA. Our sample contained surgical procedures with a mean time of 118.66 min, mean participants' BMI of 25.64, mean participants' age of 57.23, and we only injected HB-bupivacaine for induction of SA without any adjuvant substances. Age is an important indicator of adverse drug reaction incidence because of the pharmacodynamic features of HB-bupivacaine. The ED50% for HB-bupivacaine is reduced by advancing in age [20]. Elderly people are more susceptible to induction of anesthesia and side effects by the use of HB-bupivacaine. In our sample surgical procedures time was noticeably higher, and our samples contained younger-aged participants. The synergism between intrathecal injection of opiates and bupivacaine makes it feasible to reduce the dose of anesthetic drugs. It also provides better cardiovascular stability and enhances early ambulation after surgery [19, 21]. However, it was demonstrated that intrathecal injection of opiates may result in urinary retention, pruritus, and respiratory depression [22].

Manouchehrian et al. in a double-blinded RCT compared the efficacy of two doses of HB-bupivacaine 0.5% (10 mg and 12 mg) in cesarean Sect. [17]. They claimed that a lower dose of HB-bupivacaine was safer and more hypotension and bradycardia were associated with a higher dose of HB-bupivacaine. they concluded that a higher dose of HB-bupivacaine had more incidence of N/V.

Arzola et al. in a meta-analysis investigated the efficacy of low-dose bupivacaine ($\leq$8 mg) in spinal anesthesia for cesarean delivery [23]. The associations of low-dose bupivacaine with a lower incidence of hypotension and N/V were concluded in this review. They also reported that low-dose bupivacaine was less effective for SA induction and associated with a higher risk of analgesic supplementation.

Prolonged immobilization after surgery is one of the most well-known risk factors for thromboembolic events.

Layson et al. demonstrated that a low-dose single shot of HB-bupivacaine provides a faster return of motor functions and better rehabilitation for patients in arthroplasty surgeries [24].

These findings necessitate more investigation to find the ideal dose of injected HB-bupivacaine for the induction of SA. Evidently, because of the multifactorial nature of adverse reactions incidence, a more precise evaluation should be conducted. Surgery duration, demographic features, patient's medical history, American Society of Anesthesiologists (ASA) physical score, spinal cord level of SA induction, and β-blocker consumption are some of the known important factors for developing adverse effects after SA induction [10, 11].

The nature of the surgical procedures, the duration of the surgery, the different doses of injection, patient characteristics, and the technical issues of the injections are potentially important variables in finding the best dose of HB-bupivacaine in SA.

We tried to equalize these parameters among our study's groups. Surgery time, demographic features, ASA score, and the spinal cord level for induction of SA didn't have any significant differences in our study's group. According to our results, injecting 12.5 mg of HB-bupivacaine for SA was a safe and efficient method for anesthesia induction in orthopedic surgeries of the lower limbs with surgery time of 45–180 min. We recommend further investigation with a lower dose of SA injection to evaluate how far we can reduce the anesthesia drug dosage.

One source of weakness in this study which could have affected the measurements of the outcomes was inadequate information about participants' past medical history and their routine drug consumption. Our information about these variables relied on patients' statements and it could affected by recall biases. Another limitation of our study is related to the sampling method. A large sample size study is needed to better evaluate HB-bupivacaine dosages' efficacy and adverse effects. All of the participants were selected from a single center, and the patients had the same ethnicity for these reasons our findings were less generalizable. Also, our study does not contain the time of onset and duration of the anesthesia, further evaluation should be made to accurately compare the efficacy of these three dosage groups for induction of anesthesia.

Conclusion

12.5 mg HB-bupivacaine seems to be the better choice for SA induction in lower limbs orthopedic surgeries lasting up to 180 minutes.

Abbreviations

ASA	American Society of Anesthesiologists
DBP	Diastolic Blood Pressure
GA	General Anesthesia
HR	Heart Rate
HB	Hyper Baric
IB	Iso Baric
MAP	Mean Arterial Pressure
N/V	Nausea and Vomiting
O2sat	O2 saturation
RR	Respiratory Rate
RICP	Raised Intracranial Pressure
SA	Spinal Anesthesia
SBP	Systolic Blood Pressure

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Authors' contributions

AA, participated in data gathering and analysis. ARS, proposed the topic and participated in generating the manuscript text. MAJ, designed the study protocol and participated in data collection. MSJ, wrote the manuscript and analyzed the data. All authors read and approved the manuscript.

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Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Data availability

The data that support the findings of this study are available in our data set and patients medical history files. the corresponding author will share the data upon the reasonable request. corresponding contact: masoudparish740@gmail.com.

Declarations

Ethics approval and consent to participate

The study was approved by the local ethics committee (IR.TBZMED.REC.1400.820) and all participants had informed consent for participation.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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References

1. Olawin AM, Das JM. Spinal Anesthesia. [Updated 2022 Jun 27]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024. Available from: https://www.ncbi.nlm.nih.gov/books/NBK537299/.
2. Cook TM, Counsell D, Wildsmith JA. Major complications of central neuraxial block: report on the Third National Audit Project of the Royal College of Anaesthetists. Br J Anaesth. 2009;102(2):179–90.
3. Kokki H. Spinal blocks. Pediatr Anesth. 2012;22(1):56–64.
4. Smith LM, Cozowicz C, Uda Y, Memtsoudis SG, Barrington MJ. Neuraxial and Combined Neuraxial/General Anesthesia Compared to General

Anesthesia for Major Truncal and Lower Limb surgery: a systematic review and meta-analysis. Anesth Analg. 2017;125(6):1931–45.
5. Carpenter RL, Caplan RA, Brown DL, Stephenson C, Wu R. Incidence and risk factors for side effects of spinal anesthesia. Anesthesiology. 1992;76(6):906–16.
6. Kumar S, Santha N. Low dose and the conventional dose of 0.5% hyperbaric bupivacaine produce comparable outcomes in the lower segment caesarean section. An observational study. Ann Afr Med. 2022;21(4):390–4.
7. Uppal V, Retter S, Shanthanna H, Prabhakar C, McKeen DM. Hyperbaric versus isobaric bupivacaine for spinal anesthesia: systematic review and meta-analysis for adult patients undergoing noncesarean delivery surgery. Anesth Analg. 2017;125(5):1627–37.
8. Tekyeh SM, Tabari M, Jahanian V. Investigation the effects and side effects of different dosage of bupivacaine in combination with sufentanil for spinal anesthesia in cesarean section. Iranian Journal of Obstetrics, Gynecology and Infertility. 2013;16(66):1–9.
9. Smiley RM, Blouin JL, Negron M, Landau R. beta2-adrenoceptor genotype affects vasopressor requirements during spinal anesthesia for cesarean delivery. Anesthesiology. 2006;104(4):644–50.
10. Kim HJ, Ahn E. Risk factors for dexmedetomidine-associated bradycardia during spinal anesthesia: a retrospective study. Medicine (Baltimore). 2022;101(43):e31306.
11. Tarkkila P, Isola J. A regression model for identifying patients at high risk of hypotension, bradycardia and nausea during spinal anesthesia. Acta Anaesthesiol Scand. 1992;36(6):554–8.
12. Shahverdi M, Sabertanha A, Nikraftar F, Mahmoudirad G. Spinal Anesthesia with a Low Dose of Hyperbaric Bupivacaine plus Fentanyl versus Hyperbaric Bupivacaine for Transurethral Resection of Prostate surgery: Hemodynamic Effects, Duration of Analgesia and Motor Block. Evidence Based Care. 2020;10(2):18–26.
13. Ashfi S, Haque A, Kumar M, Lakra L. A Comparative Study of Intrathecal Hyperbaric Bupivacaine 0.5% with Morphine and Dexmedetomidine in Lower Limb Orthopedic Surgeries: A Double-Blind Randomized Clinical Trial. Anesth Essays Res. 2022;16(3):373–7.
14. Furutani K, Ikoma M, Ishii H, Baba H, Kohno T. Bupivacaine inhibits glutamatergic transmission in spinal dorsal horn neurons. Anesthesiology. 2010;112(1):138–43.
15. Sarkar A, Bafila NS, Singh RB, Rasheed MA, Choubey S, Arora V. Comparison of Epidural Bupivacaine and Dexmedetomidine with Bupivacaine and Fentanyl for Postoperative Pain Relief in Lower Limb Orthopedic Surgery. Anesth Essays Res. 2018;12(2):572–80.
16. Sathyanarayana LA, Heggeri VM, Simha PP, Narasimaiah S, Narasimaiah M, Subbarao BK. Comparison of Epidural Bupivacaine, Levobupivacaine and Dexmedetomidine in Patients Undergoing Vascular Surgery. J Clin Diagn Res. 2016;10(1):Uc13-7.
17. Manouchehrian N, Rahimi-Bashar F, Pirdehghan A, Shahmoradi F. Comparison between 10 and 12 mg doses of intrathecal hyperbaric (0.5%) bupivacaine on sensory block level after first spinal failure in cesarean section: A double-blind, randomized clinical trial. Front Med (Lausanne). 2022;9:937–63.
18. Piacherski V, Muzyka L. Comparison of the efficacy of 0.5% isobaric bupivacaine, 0.5% levobupivacaine, and 0.5% hyperbaric bupivacaine for spinal anesthesia in lower limb surgeries. Sci Rep. 2023;13(1):2736.
19. Messina A, La Via L, Milani A, Savi M, Calabrò L, Sanfilippo F, et al. Spinal anesthesia and hypotensive events in hip fracture surgical repair in elderly patients: a meta-analysis. Journal of Anesthesia, Analgesia and Critical Care. 2022;2(1):19.
20. Chen M, Chen C, Ke Q. The effect of age on the median effective dose (ED50) of intrathecally administered plain bupivacaine for motor block. Anesth Analg. 2014;118(4):863–8.
21. Ngan Kee WD, Khaw KS, Ng FF, Ng KK, So R, Lee A. Synergistic interaction between fentanyl and bupivacaine given intrathecally for labor analgesia. Anesthesiology. 2014;120(5):1126–36.
22. Staikou C, Paraskeva A. The effects of intrathecal and systemic adjuvants on subarachnoid block. Minerva Anestesiol. 2014;80(1):96–112.
23. 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(3):308–18.
24. Layson JT, Jackson MC, Wells AJ, Mabee K, DeClaire JH, Frisch NB. Administration of Low-dose Hyperbaric Bupivacaine for Spinal Anesthesia in the Setting of Outpatient Arthroplasty. JAAOS Global Res Rev. 2024;8(5):e23.00240.

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