ISSN: 1607-8322, e-ISSN: 2220-5799 Anaesthesia, Pain & Intensive Care
Vol 27(4); August 2023 DOI: 10.35975/apic.v27i4.2160

ORIGINAL RESEARCH REGIONAL ANESTHESIA

Effect of height-based spinal anesthetic dose versus conventional dose on hemodynamics in lower limb surgeries in geriatric patients: a randomized controlled trial

Ramy M. Alkonaiesy[1], Shereen Mostafa Amin[2], Nasr M. Abdallah[3], Sherif Ismail Muhammad[4], Haitham Hassan[5]

Author affiliation:

1. Ramy M. Alkonaiesy, MD; Department of Anesthesia, Surgical Intensive Care & Pain Management, Faculty of Medicine, Cairo University, Cairo, Egypt; 11562; E-mail: ramyalkonaiesy@gmail.com
2. Shereen Mostafa Amin, MD; Department of Anesthesia, Surgical Intensive Care & Pain Management, Faculty of Medicine, Cairo University, Cairo, Egypt; 11562; E-mail: Alyandfarah@gmail.com
3. Nasr M. Abdallah, MD; Department of Anesthesia, Surgical Intensive Care & Pain Management, Faculty of Medicine, Cairo University, Cairo, Egypt; 11562; E-mail: sief.nasr@yahoo.com
4. Sherif Ismail Muhammad, MSc; Department of Anesthesia, Surgical Intensive Care & Pain Management, Faculty of Medicine, Cairo University, Cairo, Egypt; 11562; E-mail: sherif.abbas38244@postgard.kasralainy.edu.eg
5. Haitham Hassan, MD; Department of Anesthesia, Surgical Intensive Care & Pain Management, Faculty of Medicine, Cairo University, Cairo, Egypt; 11562; E-mail: Haitham_eltrabily@yahoo.com

Correspondence: Ramy M. Alkonaiesy; E-mail: ramyalkonaiesy@gmail.com; Phone: +201224883990

ABSTRACT

Background: An adequate dose of spinal anesthetic is very crucial in elderly surgical patients. The routine method to calculate the dose in a particular patient is usually based upon the weight of the patient, but the effect cannot always be predictable. We evaluated the efficacy and safety of the height-based dose of spinal anesthetic versus the conventional dose on intraoperative hemodynamics and spinal block characteristics in geriatric patients scheduled for lower limb surgeries.

Methodology: This single-blinded, parallel-group, randomized, clinical trial enrolled 56 patients, aged 60 y or above who were scheduled for lower limb orthopedic surgeries under spinal anesthesia. The patients were randomly divided into two groups. In the height-based group, 0.06 mg of 0.5% hyperbaric bupivacaine/cm height of the patient was administered intrathecally. The control group received a fixed dose of 12.5 mg of 0.5% hyperbaric bupivacaine intrathecally. All patients received 25 µg of fentanyl (0.1 mg / 2 ml) intrathecally. The incidence of hypotension was the primary outcome. The incidence of bradycardia, highest sensory level, onset and duration of sensory and motor block, incidence of shivering, the total dose of bupivacaine, total amount of fluid infused, vasopressors needed, and blood loss were the secondary outcomes.

Results: The incidence of hypotension was significantly reduced in patients receiving height-based spinal dose compared to those in which standard dose was administered (57.1% vs. 82.1%, P = 0.042). The duration of sensory blocks was significantly shorter in height-based group compared to the control group (116 ± 32.77 vs. 90.59 ± 19.66 min; P = 0.001) as was the duration of the motor block (153.18 ± 42 and 117 ± 25.37 min; P < 0.001).

Conclusion: In geriatric patients undergoing orthopedic lower limb surgery, the height-based dose of spinal anesthesia was effective and safe in reducing the incidence of hypotension with fast recovery from sensory and motor block.

Abbreviations: ASA- American Society of Anesthesiologists; COPD- Chronic Obstructive Pulmonary Disease; CSF- Cerebrospinal Fluid; DVT- Deep Venous Thrombosis; IQR- Interquartile range- n: Numbers; SD- Standard Deviation; SA- Spinal Anesthesia

Key words: Bromage scale; Elderly; Height; Hypotension; Orthopedics; Anesthesia, Spinal

Citation: Alkonaiesy TM, Amin SM, Abdallah NM, Sherif Ismail Muhammad SI, Hassan H. Effect of height-based spinal anesthetic dose versus conventional dose on hemodynamics in lower limb surgeries in geriatric patients: a randomized controlled trial. Anaesth. pain intensive care 2023;27(4):565−572; DOI: 10.35975/apic.v27i4.2160

Received: February 20, 2023; **Reviewed:** May 16, 2023; **Accepted:** June 16, 2023

1. INTRODUCTION

Geriatric patients frequently have several co-morbid diseases that must be considered in the perioperative anesthetic regimen. However, there is currently insufficient data to suggest a single anesthetic strategy that works best for the elderly.[1]vity, which lowers the vasomotor tone, preload, afterload, and ultimately cardiac output, especially in the elderly. Hemodynamic instability and intraoperative hypotension are largely influenced by autonomic nervous system function.[2] Intraoperative hypotension is a well-known cause of postoperative complications. higher mortality rates were associated with lower intraoperative hypotension as a result of high volumes of the intrathecal local anesthetic.[3] Vasopressors and intravenous fluids are frequently used to control spinal hypotension. For the older population with coronary disease, this regimen is debatable[1] Thus, an effective and safe method of spinal anesthesia (SA) is needed for the elderly.

Several factors can affect SA including the age, vertebral column length, position of the patient, and spinal curvature etc.[4] Many studies employed the standard dose of bupivacaine as a spinal local anesthetic. These studies defined the standard dose as 12.5 mg to 15 mg of hyperbaric bupivacaine 0.5%, with or without an additive. It is still uncertain how much intrathecal local anesthetic is to be used in the elderly and in pregnant women.[2] It is supposed that the block level depends on the patient's height. Moreover, reduction of the local anesthetic dose could reduce the incidence of intraoperative hypotension without compromising analgesia.[5]

In obstetric practice, variable regimens have been tried to adjust the intrathecal bupivacaine dose according to patients' height. Using the height-based formula may result in better hemodynamic parameters perioperatively when compared to conventional dosing regimen.[5, 6]

We aimed to evaluate the efficacy and safety of the height-based dose of SA regarding the intraoperative hemodynamics and spinal block characteristics in elder patients scheduled for lower limb orthopedic operations.

2. METHODOLOGY

The study was conducted following approval by the Ethics Committee of the Faculty of Medicine, Cairo University, Egypt. This trial was registered at the Pan African Clinical Trials Registry (ID: PACTR202301868522124). Each participant gave written informed permission. The information of each participant was kept private. This single-blind, parallel-group, randomized, clinical trial was conducted at Cairo University Hospitals, Egypt between August 2020 and June 2021.

We included 56 geriatric patients of both genders, aged more than 60 y, who were ASA physical status I or II and scheduled for lower limb orthopedic surgeries under SA.

Patients with any of the following conditions were excluded: height less than 150 cm; history of allergy to the used medications; opioid abuse; coagulopathy; sepsis; hypovolemia; increased intracranial pressure; autonomic neuropathy; intermediate neurologic disease; or infection at the puncture site.

Patients were randomly allocated to two groups, with 28 patients in each group. The control group received 12.5 mg of bupivacaine 0.5% (Sunnypivacaine Sunny Pharmaceutical, Egypt) (2.5 ml) and 25 µg of fentanyl (fentanyl Hameln Pharmaceutical, Germany) (0.5 ml) to make a total volume of 3 ml. The height-based group received 0.06 mg of bupivacaine per cm height of the patient added to 25 µg of fentanyl (0.5 ml). Using the procedure of sequentially numbered, opaque, sealed envelopes, randomization and allocation concealment was ensured.[7]

2.1. Anesthetic management

All patients were subjected to detailed history taking and thorough physical examination. Complete blood count, prothrombin time, partial tissue thromboplastin time, international normalized ratio, and random blood sugar were among the standard preoperative tests carried out. Chest X-ray and 12-lead electrocardiography were done.

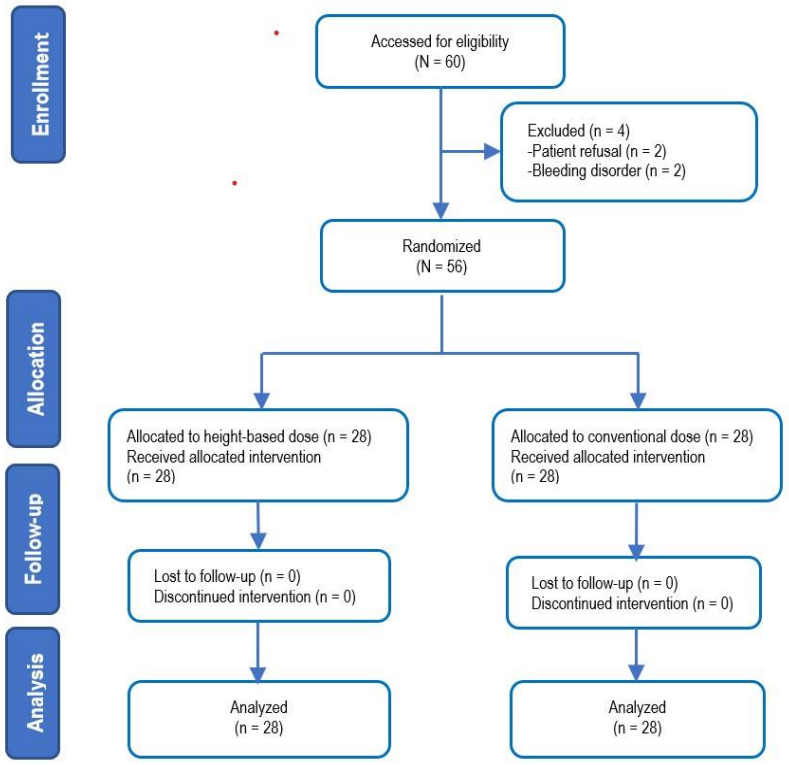

Figure 1: The CONSORT flow diagram of the trial

Upon arrival to the operating room, intravenous line was maintained, ECG, peripheral oxygen saturation, and non-invasive arterial blood pressure were monitored. Blood pressure was recorded before the anesthesia twice (taking average reading), then at 5 min intervals for half an hour and every 15 min thereafter.

The dose of bupivacaine was calculated and withdrawn in 3-ml syringe, and SA was done under complete aseptic conditions in the sitting position at L3-L4 or L4-L5 intervertebral space.

The patients were placed in the supine posture following SA. A pin prick test was used to gauge the sensory level following 5 min of SA. The measurements included the onset of the sensory block (time from intrathecal injection of drugs to reach T10 sensory level). The highest dermatomal level was recorded and the time for the first analgesic request was measured [8]. The Bromage scale was used to evaluate the motor block [9]. The onset of the motor block (time from intrathecal injection to Bromage scale 3) and the duration of the motor block (time from complete block till Bromage scale 0) were recorded.

When the mean arterial blood pressure diminished by 20% lower than the baseline level or even less than 65 mmHg, an intermittent dose of 5 mg of ephedrine was administered and repeated if hypotension continued for 5 min or recurred, every 2 min up to 150 mg total dose. If hypotension persisted, norepinephrine infusion at 0.05 µg/kg/min was given. If the HR decreased ≤ 60 beats/min without hypotension, 0.5 mg atropine was administered intravenously. Supplemental oxygen was applied if oxygen saturation decreased below 94%. Fluid management consisted of crystalloid co-load and hourly intraoperative maintenance fluid in a dose of 4 mL/kg/h in addition to blood loss replacement by 3:1 rule (3 mL of crystalloid for each ml blood loss). Balanced crystalloid solution (Ringer's lactate solution) was administered. Volume overload was avoided.

2.2. Outcomes

The primary outcome was the incidence of hypotension. The incidence of bradycardia, highest sensory level, the characteristics of sensory and motor blocks (onset and duration), intraoperative shivering, and the total dose of bupivacaine, amount of fluid consumption, vasopressors used, and the blood loss were secondary outcomes.

2.3. Sample size

The sample size was calculated using the MedCalc software version 14 (MedCalc software bvba, Ostend, Belgium), with a unilateral α of 0.05 and power to 0.80. According to Gohiya et al. [10], the incidence of hypotension was 83%. The calculated sample size was 25 patients per group for a relative risk reduction of 50% in the incidence of hypotension. In order to make up for the lost, the final sample size was increased to 28 patients each group (total sample size was 56 patients).

2.4. Statistical analysis

The Statistical Package for Social Sciences (IBM SPSS Statistics) for Windows, version 25, was used to conduct the statistical analysis. The data were summarized as mean ± standard deviation or median (interquartile range), and groups were compared using unpaired t test. Qualitative data were summarized as frequencies, and associations were tested using Mann-Whitney test and Pearson's Chi-square test. The data were considered significant if P value was equal to or less than 0.05.

Table 1: Demographic data of the patients

Variables		Height-based group (n = 28)	Control group (n = 28)	P-value
Gender	Male	10 (35.7)	8 (28.6)	0.567
	Female	18 (64.3)	20 (71.4)	
Age (y)		69.79 ± 6.62	69.29 ± 6.92	0.783
Height (cm)		163.18 ± 8.96	161.86 ± 9.29	0.590
Weight (kg)		77.64 ± 10.22	78.25 ± 9.76	0.821

Data presented as n (%) or mean ± standard deviation

3. RESULTS

Sixty patients were enrolled in the study. Four patients were excluded due to refusal to participate in the study and bleeding disorders. Fifty-six patients were randomly allocated to two groups (Figure 1).

The age, height, or body weight were not statistically different between the two groups (Table 1). Co-morbid conditions were comparable in the two group with statistically no difference (Table 2).

The incidence of hypotension requiring ephedrine was significantly lower in the height-based group compared to the control group (57.1% vs 82.1%, P = 0.042). The incidence of bradycardia and the highest sensory level of SA, shivering, and total amount of noradrenaline were not significantly different between the two groups (P = 0.491, 0.133, 0.485, and 1 respectively) (Table 3).

The total volume of the used spinal anesthetic was smaller in height-based group than the control group (2.47 ± 0.1 ml vs 3 ± 0 ml, P = 0.001). The mean dose of intrathecal bupivacaine of the height-based group was significantly reduced compared to the control group (9.79 ± 0.54 mg vs 12.5 ± 0 mg, P = 0.001). The onsets of sensory and motor block were comparable in the groups (P = 0.133 and 0.085, respectively). The duration of sensory and motor anesthesia and the first analgesic request were significantly reduced in the height-based group compared to the control group (P = 0.001). The total amount of administered crystalloids, total blood loss, and total amount of ephedrine were comparable between the two groups (P = 0.082, 0.109, and 0.090 respectively, Table 4).

4. DISCUSSION

Spinal anesthesia frequently causes hypotension and bradycardia. These side effects are particularly evident in elderly patients, increasing the risk of postoperative morbidity and mortality.[11] We evaluated the efficacy and safety of the height-based dose of spinal anesthetic

Table 2: Comparative morbid conditions of patients in two groups

Morbid conditions		Height based group (n = 28)	Control group (n = 28)	P-value
Hypertension		13 (46.4)	14 (50.0)	0.789
Diabetes mellitus		9 (32.1)	6 (21.4)	0.365
Ischemic heart diseases		3 (10.7)	0 (0.0)	0.236
Neurological	Stroke	2 (7.1)	0 (0.0)	0.491
	Alzheimer's disease	0 (0.0)	1 (3.6)	
	Stroke and Alzheimer's disease	0 (0.0)	1 (3.6)	
Renal		1 (3.6)	0 (0.0)	1
Hepatic	Mild cirrhosis and hepatitis C virus	0 (0.0)	1 (3.6)	1
Chest	bronchial asthma	1 (3.6)	2 (7.1)	1
	COPD	1 (3.6)	0 (0.0)	
Hematological	Deep venous thrombosis	1 (3.6)	0 (0.0)	1
	DVT, pulmonary embolism 5 y ago	0 (0.0)	1 (3.6)	
Rheumatology	Systemic lupus erythematosus	0 (0.0)	1 (3.6)	1
	Rheumatoid arthritis	1 (3.6)	1 (3.6)	

n: numbers; DVT: deep venous thrombosis; COPD: chronic obstructive pulmonary disease

Table 3: Comparative incidences of complications in two groups

Variables, n (%)		Height-based (n = 28)	Control group (n = 28)	P-value
Hypotension		16 (57.1)	23 (82.1)	0.042*
Bradycardia		0 (0.0)	2 (7.1)	0.491
Shivering		4 (14.3)	6 (21.4)	0.485
Ephedrine use		16 (57.1)	23 (82.1)	0.042*
Total amount of used noradrenaline, µg	0	28 (100.0)	27 (96.4)	1
	10	0 (0.0)	1 (3.6)	
Data presented as n (%): significant at P ≤ 0.05*				

on intraoperative hemodynamics and spinal block characteristics in geriatric patients scheduled for lower limb orthopedic operations. Our findings indicated that the height-based spinal anesthetic dose was associated with a lower incidence of hypotension compared to the conventional SA. This was indicated by reduction in the incidence of ephedrine use in the height-based group. Furthermore, the mean dose of bupivacaine used in the height-based SA was significantly reduced that was associated with significant rapid recovery from

Table 4: Comparative block characteristics and the drugs used

Variables		Height based group (n = 28)	Control group (n = 28)	P-value
Drugs used				
Total volume of spinal anesthetic (ml)		2.47 ± 0.10	3.00 ± 0.00	< 0.001*
Bupivacaine used (mg)		9.79 ± 0.54	12.50 ± 0.00	< 0.001*
Total dose of ephedrine used (mg)		22.5 (10-60)	55 (25-60)	0.090
Total amount of consumed crystalloids (ml)		1641.07 ± 447.43	1855.36 ± 455.90	0.082
Total blood loss (ml)		400 (250-500)	250 (200-500)	0.109
Sensory block characteristics				
Onset of sensory anesthesia (min)		3 (2-5.5)	3 (2-3)	0.133
Duration of sensory anesthesia and time to first analgesic request (min)		116.00 ± 32.77	153.18 ± 42.00	0.001*
Onset of sensory anesthesia (min)		3 (2-5.5)	3 (2-3)	0.133
Highest sensory level of spinal anesthesia	T 2	1 (3.6)	3 (10.7)	0.133
	T 4	9 (32.1)	8 (28.6)	
	T 5	1 (3.6)	0 (0.0)	
	T 6	4 (14.3)	11 (39.3)	
	T 7	0 (0.0)	1 (3.6)	
	T 8	7 (25.0)	3 (10.7)	
	T 9	2 (7.1)	0 (0.0)	
	T 10	4 (14.3)	2 (7.1)	
Duration of sensory anesthesia and time to first analgesic request, min		116.00 ± 32.77	153.18 ± 42.00	0.001*
Motor block characteristics				
Onset of motor block, min		5 (4-17)	4.5 (2-7)	0.085
Duration of motor block, min		90.59 ± 19.66	117.00 ± 25.37	< 0.001*
*Data presented as mean ± SD or median (IQR); * significant at P ≤ 0.05*				

anesthesia. Similarly, Huang et al. reported that the height-based dose adjustment was effective in the cesarean section with less maternal hypotension.[5] Numerous variables influence SA, including height, patient positioning during and after the administration of SA, patient's age, spinal curvature, intra-abdominal pressure, pregnancy, and cerebrospinal volume.[4] It was debatable if the block level for SA was related to the

patient's height. Evidence of statistical relationship between block level and height is scarce; however, statistical association between height and vertebral column length has been reported. Norris found that 10.6% of the difference in spine length is associated with the total height.[12] Hence, the block level could depend on height.[13,14] According to Huang et al., as the local anesthetic dose decreased in SA, intraoperative hypotension diminished with sufficient analgesia.[5]

Several studies found that low doses of bupivacaine with fentanyl were effective in reducing hypotension incidence and analgesic use in lower limb surgeries in elderly patients.[2,10,15,16] Xiao et al. reported that reduction of the bupivacaine dose could lower the incidence of maternal hypotension in patients undergoing elective cesarean section under spinal epidural anesthesia.[17] The intrathecal opioids have paradoxical behavior, where they could block conduction in sympathetic pathways and somatosensory evoked potentials but generate analgesia by inhibiting synaptic transmission in nociceptive afferent pathways.[18]

Sadegh et al. and Seetharam and Bhat found no significant difference in hypotension incidence when fentanyl was added to bupivacaine in elderly patients scheduled for lower limb surgeries.[19,20] This inconsistency with our findings might result from the small sample size in these studies and the difference in hypotension definition. Białowolska et al. found no reduction of the incidence of hypotension with the height-based dose adjustment in cesarean section under SA.[21] The disagreement with our findings can be explained by the difference in the inclusion criteria where Białowolska et al. included only middle-aged females. Moreover, hypotension was identified by reduction of systolic blood pressure to less than 85 mmHg or drop of more than 30% in the mean arterial pressure.

In the current study, the incidence of bradycardia was comparable in the two groups. Likewise, Some researchers found that low dose of bupivacaine and fentanyl did not significantly affect the incidence of bradycardia when compared to bupivacaine alone in geriatric patients.[15,22] Contrary to these findings, Gohiya et al. showed that the incidence of bradycardia increased with the high bupivacaine dose compared to the low dose.[10] They included higher age group (more than 65 y) than those in our study. A higher age group is known to be more susceptible to hemodynamic disturbances.

The highest sensory level was not significantly different between the groups. There was a non-exact linear relationship between the bupivacaine dose and the block height.[23] Carpenter et al. revealed a good correlation between the cephalic spread of local anesthetic and the volume of lumbosacral cerebrospinal fluid (CSF).[24] There was a large variability in the CSF volume among different patients with large unpredictability and great variations in local anesthetic spread and maximum sensory block height.

In our study, the incidence of shivering was comparable in the two groups. Some other studies also reported no difference between bupivacaine-fentanyl mixture and ropivacaine-fentanyl mixture regarding shivering.[25,26] A systematic review and meta-analysis by Subramani et al. concluded that intrathecal fentanyl diminished the incidence of shivering in female patients undergoing cesarean section under SA.[27] In our study, the same dose of fentanyl was added to bupivacaine in all patients clarifying the comparable incidence of shivering.

In our height-based group, the duration of sensory and motor blocks and the time of first analgesic request were significantly reduced. Liu et al. compared different doses of hyperbaric bupivacaine and concluded that the lower dose was associated with the lower duration of effective analgesia.[28] As a general rule in pharmacology, increasing the dose could increase the duration of action provided other factors are kept constant.[29] In cesarean sections a prolonged time to sensory and motor block with the conventional bupivacaine dose has been reported, indicating a deeper sympathetic block with a higher incidence of hypotension in comparison to the height-based dose.[5]

Other researchers demonstrated that the low dose of bupivacaine added to fentanyl had comparable analgesic effect to the conventional dose of bupivacaine alone.[30] The discrepancies could be attributed to the differences in the study design, the small sample size, and the time to first analgesic request was not measured in the ward.

The blood loss and intravenous fluids were not markedly different in our study groups. Olofsson et al. noticed that the blood loss was significantly reduced intraoperatively but not the fluid administration.[15] The inconsistency with our results could be attributed to the difference in the bupivacaine doses used in the two studies.

The total amounts of ephedrine and noradrenaline were comparable in both groups of our study, as reported by some earlier studies.[31,32] Ben-David et al., however, found a significant decline of the total amount of the vasopressor ephedrine in geriatric patients who received 4 mg bupivacaine added to fentanyl compared to 10 mg bupivacaine only in hip operations.[33] The incompatible findings might be due to the great difference between the two used doses of bupivacaine (10 vs. 4 mg) by them, while we used 12.5 vs. 9.79 mg of bupivacaine.

5. LIMITATION

This study was conducted at only one institution and had a limited sample size. There is a need for larger, multicenter, randomized, controlled trials, to validate our findings, so that general recommendations regarding the choice od the spinal anesthetic can be offered.

6. CONCLUSION

In geriatric patients undergoing orthopedic lower limb surgery, the height-based dose of spinal anesthetic was effective and safe in reducing the incidence of hypotension and improving the sensory and motor anesthetic characteristics.

7. Data availability

The numerical data generated during this research is available with the authors.

8. Acknowledgement

We gratefully thank Faculty of Medicine, Cairo University, Cairo, Egypt.

9. Conflict of interest

Authors declare no conflict of interest. The study utilized the hospital resources only, and no external or industry funding was involved.

10. Authors' contribution

RA: Concept, conduction of the study work, data analysis, and manuscript editing

SA, SM: Design, conduction of the study work, and manuscript drafting

NA: Design, data interpretation, and manuscript editing

HH: Concept, data analysis, and manuscript editing

All authors approved the final version of the manuscript to be published and agreed to be accountable for all aspects of this work.

11. REFERENCES

1. Lim BG, Lee IO. Anesthetic management of geriatric patients. Korean J Anesthesiol. 2020;73:8-29. [PubMed] DOI: 10.4097/kja.19391
2. 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. J Anesth Analg Crit Care. 2022;2:19. [PubMed] DOI: 10.1186/s44158-022-00047-6
3. White SM, Moppett IK, Griffiths R, Johansen A, Wakeman R, Boulton C, et al. Secondary analysis of outcomes after 11,085 hip fracture operations from the prospective UK Anaesthesia Sprint Audit of Practice (ASAP-2). Anaesthesia. 2016;71:506-514. [PubMed] DOI: 10.1111/anae.13415
4. She YJ, Liu WX, Wang LY, Ou XX, Liang HH, Lei DX. The impact of height on the spread of spinal anesthesia and stress response in parturients undergoing caesarean section: a prospective observational study. BMC Anesthesiol. 2021;21:298-298. [PubMed] DOI: 10.1186/s12871-021-01523-2
5. Huang Q, Wen G, Hai C, Zheng Z, Li Y, Huang Z, et al. A Height-Based Dosing Algorithm of Bupivacaine in Spinal Anesthesia for Decreasing Maternal Hypotension in Cesarean Section Without Prophylactic Fluid Preloading and Vasopressors: A Randomized-Controlled Non-Inferiority Trial. Front Med. 2022;9:858115. [PubMed] DOI: 10.3389/fmed.2022.858115
6. Danelli G, Zangrillo A, Nucera D, Giorgi E, Fanelli G, Senatore R, et al. The minimum effective dose of 0.5% hyperbaric spinal bupivacaine for cesarean section. Minerva Anestesiol. 2001;67:573-577. [PubMed]
7. Doig GS, Simpson F, Delaney A. A review of the true methodological quality of nutritional support trials conducted in the critically ill: time for improvement. Anesth Analg. 2005;100:527-533. [PubMed] DOI: 10.1213/01.ANE.0000141676.12552.D0
8. Chen X, Wang F, Zhang Y, Ma X, Cao P, Yuan L, et al. Fusion gene map of acute leukemia revealed by transcriptome sequencing of a consecutive cohort of 1000 cases in a single center. Blood Cancer J. 2021;11:112. [PubMed] DOI: 10.1038/s41408-021-00504-5
9. Bromage PR. Epidural analgesia: WB Saunders Company; 1978.
10. Gohiya S, Gohiya V, Singh N. Study of addition of fentanyl to bupivacaine in subarachnoid block administered for cemented bipolar prosthesis in geriatric patients population. Indian J Clin Anaesth. 2018;5:501. DOI: 10.18231/2394-4994.2018.0096
11. Ferré F, Martin C, Bosch L, Kurrek M, Lairez O, Minville V. Control of Spinal Anesthesia-Induced Hypotension in Adults. Local Reg Anesth. 2020;13:39-46. [PubMed] DOI: 10.2147/LRA.S240753
12. Norris MC. Patient variables and the subarachnoid spread of hyperbaric bupivacaine in the term parturient. Anesthesiology. 1990;72:478-482. [PubMed] DOI: 10.1097/00000542-199003000-00015
13. Yu X, Zhang F. The effect of parturient height on the median effective dose of intrathecally administered ropivacaine. Ann Saudi Med. 2016;36:328-333. [PubMed] DOI: 10.5144/0256-4947.2016.328
14. Siddiqui KM, Ali MA, Ullah H. Comparison of spinal anesthesia dosage based on height and weight versus height alone in patients undergoing elective cesarean section. Korean J

Anesthesiol. 2016;69:143-148. [PubMed] DOI: 10.4097/kjae.2016.69.2.143

15. Olofsson C, Nygårds EB, Bjersten AB, Hessling A. Low-dose bupivacaine with sufentanil prevents hypotension after spinal anesthesia for hip repair in elderly patients. Acta Anaesthesiol Scand. 2004;48:1240-1244. [PubMed] DOI: 10.1111/j.1399-6576.2004.00504.x
16. Desai D, Bumiya P, Mr, Upadhyay, Vashishtha A. Spinal anesthesia with low dose bupivacaine and fentanyl for femur surgeries in elderly patients. J Anesth Crit Care Open Access. 2019;11:60-64. DOI: 10.15406/jaccoa.2019.11.00412
17. Xiao F, Xu WP, Zhang XM, Zhang YF, Wang LZ, Chen XZ. ED 50 and ED 95 of intrathecal bupivacaine coadministered with sufentanil for cesarean delivery under combined spinal-epidural in severely preeclamptic patients. Chin Med J (Engl). 2015;128:285-290. [PubMed] DOI: 10.4103/0366-6999.150083
18. Kumamoto E, Mizuta K, Fujita T. Opioid Actions in Primary-Afferent Fibers—Involvement in Analgesia and Anesthesia. Pharmaceuticals (Basel). 2011;4:343-365. DOI: 10.3390/ph4020343
19. Sadegh A, Tazeh-Kand NF, Eslami B. Intrathecal fentanyl for prevention of shivering in spinal anesthesia in cesarean section. Med J Islam Repub Iran. 2012;26:85-89. [PubMed]
20. Seetharam KR, Bhat G. Effects of isobaric ropivacaine with or without fentanyl in subarachnoid blockade: A prospective double-blind, randomized study. Anesth Essays Res. 2015;9:173-177. [PubMed] DOI: 10.4103/0259-1162.152149
21. Białowolska K, Horosz B, Sękowska A, Malec-Milewska M. Fixed Dose versus Height-Adjusted Conventional Dose of Intrathecal Hyperbaric Bupivacaine for Caesarean Delivery: A Prospective, Double-Blinded Randomised Trial. J Clin Med. 2020;9:3600. [PubMed] DOI: 10.3390/jcm9113600
22. Doger C, Yüksel BE, Canoler O, Ornek D, Emre C, Kahveci K. Effects of intrathecal bupivacaine and bupivacaine plus sufentanil in elderly patients undergoing transurethral resection. Niger J Clin Pract. 2014;17:149-153. [PubMed] DOI: 10.4103/1119-3077.127423
23. Alston RP, Littlewood DG, Meek R, Edström HH. Spinal anaesthesia with hyperbaric bupivacaine: effects of concentration and volume when administered in the sitting position. Br J Anaesth. 1988;61:144-148. [PubMed] DOI: 10.1093/bja/61.2.144
24. Carpenter RL, Hogan QH, Liu SS, Crane B, Moore J. Lumbosacral cerebrospinal fluid volume is the primary determinant of sensory block extent and duration during spinal anesthesia. Anesthesiology. 1998;89:24-29. [PubMed] DOI: 10.1097/00000542-199807000-00007
25. Teoh WH, Thomas E, Tan HM. Ultra-low dose combined spinal-epidural anesthesia with intrathecal bupivacaine 3.75 mg for cesarean delivery: a randomized controlled trial. Int J Obstet Anesth. 2006;15:273-278. [PubMed] DOI: 10.1016/j.ijoa.2006.03.004
26. Leo S, Sng BL, Lim Y, Sia AT. A randomized comparison of low doses of hyperbaric bupivacaine in combined spinal-epidural anesthesia for cesarean delivery. Anesth Analg. 2009;109:1600-1605. [PubMed] DOI: 10.1213/ANE.0b013e3181b72d35
27. Subramani Y, Nagappa M, Kumar K, Fochesato LA, Chohan MBY, Zhu YF, et al. Effect of intrathecal lipophilic opioids on the incidence of shivering in women undergoing cesarean delivery after spinal anesthesia: a systematic review and bayesian network meta- analysis of randomized controlled trials. BMC Anesthesiol. 2020;20:214. [PubMed] DOI: 10.1186/s12871-020-01116-5
28. Liu SS, Ware PD, Allen HW, Neal JM, Pollock JE. Dose-response characteristics of spinal bupivacaine in volunteers. Clinical implications for ambulatory anesthesia. Anesthesiology. 1996;85:729-736. [PubMed] DOI: 10.1097/00000542-199610000-00007
29. Holford N. Holford NHG and Sheiner LB "Understanding the Dose-Effect Relationship-Clinical Application of Pharmacokinetic-Pharmacodynamic Models", Clin Pharmacokin 6:429-453 (1981)-The Backstory. AAPS J. 2011;13:662-664. [PubMed] DOI: 10.1208/s12248-011-9306-5
30. Halvadia SH, Halvadia HB, Joshi RM, Upadhyaya DP. Low Dose Bupivacaine - Fentanyl Vs. Conventional Dose Of Bupivacaine In Spinal Anesthesia For Orthopaedic Procedures In Elderly Patients. Natl J Integr Res Med. 2013;4:50-56. [FreeFullText]
31. Lilot M, Meuret P, Bouvet L, Caruso L, Dabouz R, Deléat-Besson R, et al. Hypobaric spinal anesthesia with ropivacaine plus sufentanil for traumatic femoral neck surgery in the elderly: a dose-response study. Anesth Analg. 2013;117:259-264. [PubMed] DOI: 10.1213/ANE.0b013e31828f29f8
32. Cenkowski MJ, Maguire D, Kowalski S, Al Gurashi FA, Funk D. Hemodynamic effects of low-dose bupivacaine spinal anesthesia for cesarean section: A randomized controlled trial. Saudi J Anaesth. 2019;13:208-214. [PubMed] DOI: 10.4103/sja.SJA_799_18
33. Ben-David B, Levin H, Solomon E, Admoni H, Vaida S. Spinal bupivacaine in ambulatory surgery: the effect of saline dilution. Anesth Analg. 1996;83:716-720. [PubMed] DOI: 10.1097/00000539-199610000-00009

