

Should the Paramedian Approach be the First Choice in Spinal Anesthesia of Geriatric Patients? Prospective Randomized Clinical Trial

Geriatrik Hastaların Spinal Anestezisinde Paramedyan Yaklaşım İlk Tercih Olmalı mı? Prospektif Randomize Klinik Çalışma

✉ Kadir Arslan, ✉ Ayça Sultan Şahin

University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey

Abstract

Objective: There are significant technical difficulties in spinal anesthesia for geriatric patients. Spinal anesthesia can be applied with a median or paramedian approach. This study aimed to evaluate the success rates and intraoperative complications of two approaches in spinal anesthesia for geriatric patients.

Method: This prospective randomized study included 110 patients aged 60 years and older with ASA II-III status. The patients were randomly divided into the median (M) and paramedian (P) groups. Spinal anesthesia was performed on the patients at the L3-4 level. In case of failure in both approaches despite three attempts, an alternative method was applied. The patients' demographic data, the number of interventions, the duration of the procedure, bone contact during the process, the need for an alternative approach, and intraoperative complications were recorded.

Results: While the success rate at the first attempt was 56.6% in group M, it was 78.1% in group P. The duration of spinal anesthesia was significantly lower in group P (18 ± 13 vs. 41 ± 27 seconds, $p < 0.001$). The mean number of attempts and bone contact were also significantly lower in group P (1.1 ± 0.3 vs. 1.4 ± 0.7 , $p = 0.02$, 30.9% vs. 52.8%, $p = 0.02$, respectively). No significant difference was observed in terms of intraoperative complications.

Conclusion: This study showed that the procedure time was significantly shortened in the paramedian approach in spinal anesthesia in geriatric patients, and there was less bone contact during the procedure. We think the paramedian approach may be the first choice in spinal anesthesia for geriatric patients.

Keywords: Geriatrics, regional anesthesia, spinal anesthesia

Öz

Amaç: Geriatrik hastaların spinal anestezisinde önemli teknik zorluklar mevcuttur. Spinal anestezi median veya paramedian yaklaşımla uygulanabilir. Bu çalışmada, geriatrik hastaların spinal anestezisinde iki farklı yaklaşımın başarı oranlarını ve intraoperatif komplikasyonlarını değerlendirmek amaçlanmıştır.

Yöntem: Prospektif randomize bu çalışmaya ASA II-III statüsüne sahip 60 yaş ve üzeri 110 hasta dahil edildi. Hastalar randomize olarak grup median (M) ve grup paramedian (P) olarak ikiye ayrıldı. Tüm hastalara L3-4 seviyesinde spinal anestezi uygulandı. Her iki grupta üç denemeye rağmen spinal anestezide başarısız olunması durumunda diğer yaklaşım uygulandı. Hastaların demografik verileri, girişim sayıları, işlem süresi, işlem sırasındaki kemik teması, alternatif yaklaşım ihtiyacı ve intraoperatif komplikasyonları kaydedildi.

Bulgular: Demografik veriler gruplar arasında benzerdi. Grup M'de ilk denemede başarı oranı %56,6 iken grup P'de %78,1 idi. Spinal anestezi süresi grup P'de anlamlı olarak düşüktü (18 ± 13 'e karşın 41 ± 27 saniye, $p < 0,001$). Ayrıca girişim sayıları ve kemik teması da grup P'de anlamlı olarak düşük bulundu (sırasıyla, $1,1 \pm 0,3$ 'e karşın $1,4 \pm 0,7$, %30,9'a karşın %52,8, $p = 0,02$). İntraoperatif komplikasyonlar açısından anlamlı farklılık gözlenmedi.

Sonuç: Bu çalışmada geriatrik hastaların spinal anestezisinde paramedian yaklaşımında işlem süresinin anlamlı olarak kısaldığı ve işlem sırasında daha az kemik teması olduğu gösterilmiştir. Geriatrik hastaların spinal anestezisinde paramedian yaklaşımın ilk tercih olabileceğini düşünüyoruz.

Anahtar kelimeler: Geriatrik, reyoner anestezi, spinal anestezi



Address for Correspondence: Kadir Arslan, University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital, Clinic of Anesthesiology and Reanimation, İstanbul, Turkey

E-mail: kdrarslanmd@gmail.com **ORCID:** orcid.org/0000-0003-4061-0746 **Received:** 13.06.2022 **Accepted:** 12.08.2022

Cite this article as: Arslan K, Şahin AS. Should the Paramedian Approach be the First Choice in Spinal Anesthesia of Geriatric Patients? Prospective Randomized Clinical Trial. Bagcilar Med Bull 2022;7(3):240-246

©Copyright 2022 by the Health Sciences University Turkey, Bagcilar Training and Research Hospital
Bagcilar Medical Bulletin published by Galenos Publishing House.

Introduction

Spinal anesthesia (SA), also known as subarachnoid block, is a low-cost neuraxial anesthesia method that can be applied, which has a high success rate and allows rapid mobilization. It is frequently preferred in lower abdomen, inguinal, urogenital, rectal, and lower extremity operations. Compared to general anesthesia, it has advantages such as rapid recovery, early mobilization and discharge, lower pulmonary embolism and venous thrombosis, less surgical bleeding and transfusion need, and early return of bowel functions (1).

SA can be performed with the median approach (MA) or the paramedian approach (PA). Although MA is most frequently preferred in routine practice, its application becomes difficult due to changes in the vertebrae of geriatric patients. The PA has been reported to be more successful due to the decreased joint distances with aging, limitation of joint movements, highly calcified interspinous ligament, and osteophyte formation (2). However, there are limited studies on the median and PAs in SA of geriatric patients in the literature.

This study was conducted to compare the effectiveness of the median and PAs in SA of geriatric patients regarding success rates, difficulties, advantages, and early complications.

Materials and Methods

This prospective randomized study was conducted at the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital after the approval of the Local Ethics Committee (date: 09.02.2022, number: 19). The principles of the Declaration of Helsinki complied with the study. The study included one hundred ten patients with the American Society of Anesthesiologists (ASA) II-III status, who underwent elective orthopedic operation under SA and obtained an informed consent form.

The study's inclusion criteria included patients aged 60 years and over and were scheduled for elective surgery under SA in the sitting position. Exclusion criteria of the study included patients who did not accept SA, who were under the age of 60 years, who would undergo SA in the lateral decubitus position, who were allergic to any drug in SA, for whom SA was contraindicated, and who were not successful in SA despite repeated attempts. After creating two sets of 55 unique numbers from 1 to 110 for each group using an internet-based program (www.randomize.org), the patients were randomly allocated to one of the two groups as group median (M) (n=55, SA with a MA) and group paramedian (P) (n=55, SA with PA). A flow chart demonstrating patient selection is presented in Figure 1.

After 8 hours of fasting, the patients were taken to the operating table for the procedure. Standard ASA monitoring was applied throughout the process, including the non-invasive arterial blood pressure, heart rate, and pulse oximetry. A peripheral intravenous cannula (18-20 G) was placed. A crystalloid infusion was started. Routine iv fluid loading was not performed before SA in our clinic. Before the procedure, patients were premedicated with 0.02-0.5 mg kg⁻¹ midazolam.

The puncture site of the patients, placed in a sitting position by the healthcare personnel, was cleaned under aseptic conditions. The classical method, connecting the tops of both iliac crests (Tuffier's line), was used to determine the level at which SA would be applied. This level was accepted as L4 spinous process or L4-L5 vertebral space, and the first intervention level was determined as L3-L4 in all patients. For group M, SA was performed using 25 µg fentanyl and 10-15 mg bupivacaine heavy, according to the operation, using 22 G Quincke needles at the L3-4 level with the MA. L4-L5 levels were optionally used as an alternative in patients whose first attempt failed. The PA was tried in group M patients when SA could not be performed despite three attempts.

For group P, 22 G Quincke needles were advanced 10-15 degrees medially and 60 degrees cephalad from 1 cm lateral and 1 cm caudal distance of the interspinous space at the L3-4 level. The operation performed SA with 25 µg fentanyl and 10-15 mg bupivacaine heavy. Likewise, L4-L5 levels were optionally used as an alternative in patients who failed the first attempt. The MA was tried in group P patients with a similar method when SA could not be performed despite three attempts. Surgery was allowed after adequate block levels were achieved. General anesthesia was started when the procedure was unsuccessful or there was not enough block.

The same anesthesiologist performed all SA interventions, and the same anesthesia technician recorded the procedure times. The demographic data of the patients, the number of interventions, the duration (seconds) of the procedure after skin disinfection, the success rates according to the groups, the levels of vertebrae used for SA, bone contact during the process, and the transition to an alternative approach were recorded. In addition, hypotension, bradycardia,

The same anesthesiologist performed all SA interventions, and the same anesthesia technician recorded the procedure times. The demographic data of the patients, the number of interventions, the duration (seconds) of the procedure after skin disinfection, the success rates according to the groups, the levels of vertebrae used for SA, bone contact during the process, and the transition to an alternative approach were recorded. In addition, hypotension, bradycardia,

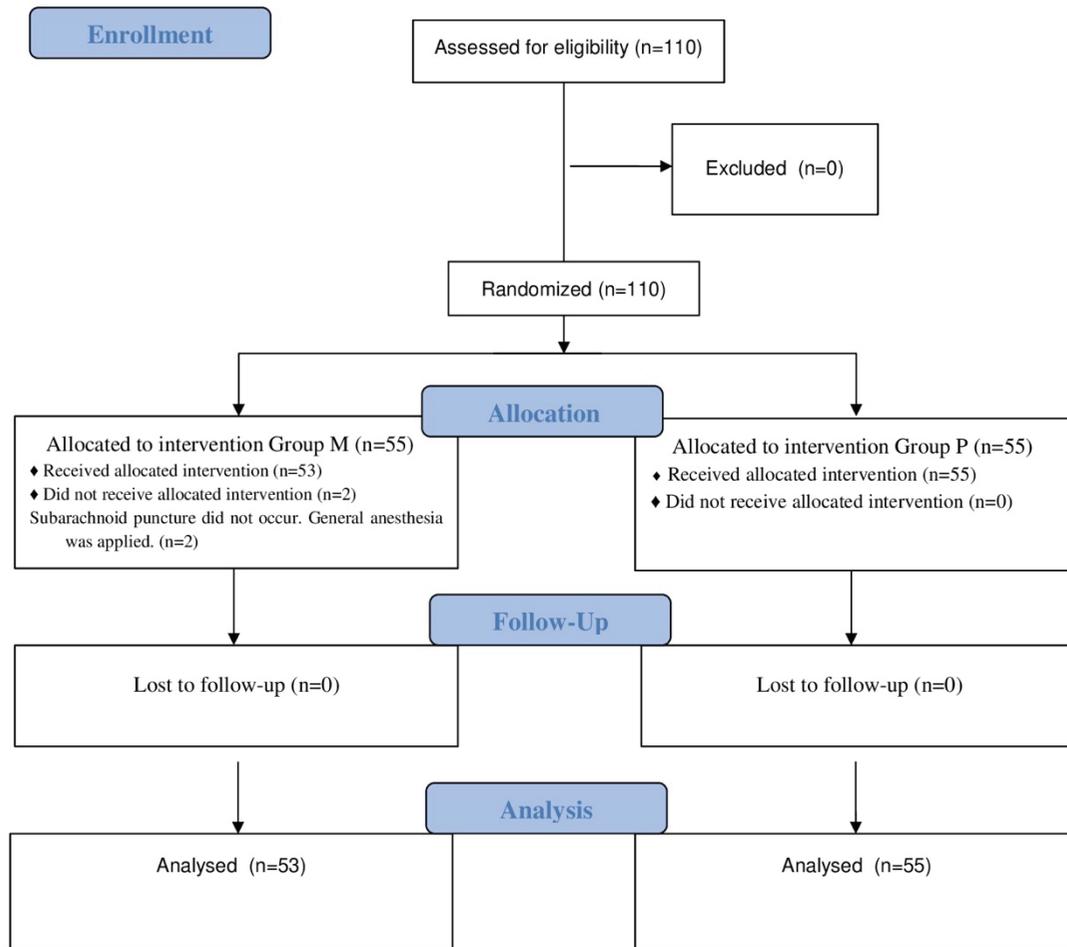


Figure 1. Flow chart of the study

nausea-vomiting, total or high spinal block, cardiac arrest, hemorrhagic tap due to venous puncture, failure in SA, and paresthesia development were recorded between the groups.

Statistical Analysis

G*Power 3.1 program was used to calculate the sample size. For t-tests, with an effect size of 0.5, α : 0.05, and study power (1- β): 0.8, 51 patients in each group were evaluated. One-hundred ten patients, 55 from both groups, were included in our study.

The IBM SPSS 22 statistical package program was used for data analysis. The Shapiro-Wilk test and histogram were used to examine the compatibility of the data for normal distribution. Categorical data were expressed as absolute and relative frequencies. Continuous variables were expressed as means and standard deviation. The chi-square and Fisher's Exact test were used to compare categorical

variables between the two groups. The Mann-Whitney U test was used to analyze quantitative data that did not show normal distribution. An independent sample t-test was used to compare the normally distributed quantitative data. $p < 0.05$ was considered statistically significant.

Results

One hundred ten patients, including 55 patients in each group, were included in the study. General anesthesia was applied since subarachnoid puncture did not occur in 2 patients in group M. As a result, 108 patients, 53 in group M and 55 in group P, were included in the study (Figure 1). The characteristics of patients and findings related to SA are presented in Table 1. There was no significant difference between the groups regarding age, gender, ASA status, and body mass index [$p=0.52$, $p=0.54$ ($\chi^2:0.36$, $df:1$), $p=0.34$ ($\chi^2:0.88$, $df:1$), $p=0.49$ respectively].

Table 1. The characteristics of patients and findings related to spinal anesthesia

	All population (n=108)	Group M (n=53)	Group P (n=55)	p	χ^2
Age (years)	70.4±8.3	70.4±9.3	70.4±7.3	0.52*	
Gender, n (%)				0.54†	0.36
Female	60 (55.6)	31 (58.5)	29 (52.7)		
Male	48 (44.4)	22 (41.5)	26 (47.3)		
ASA, n				0.34†	0.88
II	64	29	35		
III	44	44	20		
BMI (kg/m ²)	27.5±4.7	27.5±5.6	27.6±3.5	0.49‡	
Duration of process (sec)	30.0±24.3	41.7±27.8	18.8±13.0	<0.001*	
Number of attempts	1.3±0.5	1.4±0.7	1.1±0.3	0.02*	
Touching the bone? n (%)				0.02†	5.33
Yes	45 (41.7)	28 (52.8)	17 (30.9)		
No	63 (58.3)	25 (47.2)	38 (69.1)		

Data are given as mean ± standard deviation, number of patients (n), and percentage.

ASA: American Society of Anesthesiologists status, BMI: Body mass index, sec: Seconds, data obtained by using the chi-square (χ^2) are given in the analysis. *Mann-Whitney U test, †Chi-square test, ‡Independent sample t-test

The duration of SA was significantly lower in group P (p<0.001). The rate of a successful subarachnoid block at the first attempt was 56.6% in group M and 78.1% in group P. The number of SA interventions was significantly lower in group P (p=0.02). Attempts to achieve SA in the groups are shown in Table 2.

Bone contact rate was significantly lower in group P (p=0.02, χ^2 :5.33, df:1) (Table 1). The alternative level L4-L5 range was used in 18.8% (n=10) of the patients in group M and 12.7% (n=7) of the patients in group P. Although the need for SA from a different level was less in group P, no significant difference was found (p=0.38).

Hypotension was accepted as a 25% decrease in the patient's baseline blood pressure. Hypotension was resolved quickly by administering 5-10 mg of ephedrine hydrochloride as a vasoconstrictor and fluid resuscitation. There was no significant difference between the groups regarding hypotension and bradycardia (p=0.74, p=1.00, respectively). Complications observed during SA of the patients are shown in Table 3.

Discussion

The subarachnoid block is widely used in the lower abdomen and lower extremity operations because it reduces postoperative morbidity and complications. The MA is the most commonly used method. At the same time, it has technical advantages, such as requiring less frequent three-dimensional imaging and easier detection of the

Table 2. Number of attempts for spinal anesthesia

Number of attempts	Group M	Group P
First attempt	30 (56.6%)	43 (78.1%)
Second attempt	8	9
Third attempt	5	0
Another approach	10	2

Data are given as the number and percentage of patients

Table 3. Complications observed in spinal anesthesia

Complications	Group M	Group P	p
Hypotension	5	4	0.74*
Bradycardia	4	4	1.00*
Cardiac arrest	-	-	-
Total or high spinal anesthesia	-	-	-
Hemorrhagic tap	3	2	-
Nausea-vomiting	1	1	-
Inadequate spinal anesthesia	2	2	-
Paresthesia	0	0	-

Data are given as the number of patients (n). *Fisher's Exact test

operation site since the broadest part of the ligamentum flavum is in the median part (3). However, this approach is problematic in elderly patients due to degenerative changes in the structural elements of the spine. In the MA, the supraspinous, interspinous ligaments, and ligamentum flavum are passed after the skin, and subcutaneous tissue is given. After passing the skin and subcutaneous tissue, the ligamentum flavum is directly reached in the PA. Since the paravertebral muscles are replaced by the supraspinous

and interspinous ligaments, difficulties due to degenerative change can be avoided in elderly patients (4).

Bayındır et al. (4) reported the success rate of SA as 70% with the PA and 95% with the MA in young patients aged 30-40 years. In contrast, Singh et al. (5) found a success rate of 100% in the PA and 90% in the MA. Similarly, Kartal et al. (6) reported the success of SA in geriatric patients as 79.1% with the MA and 90.5% with the PA. In our study, the success rate of SA was 81.1% with the MA and 96.3% with the paramedian method. Cerebrospinal fluid (CSF) flow was not observed in 18.8% (n=10) of the patients in group M after three attempts. SA was performed with the PA. In the PA, CSF flow was not observed in 3.6% (n=2) of the patients despite three attempts, and successful SA was achieved with the MA. The incidence of SA with the other approach was significantly higher in group M ($p=0.01$). In our study, the success of SA was found to be higher with the PA in the geriatric population, which is consistent with the literature. Bayındır et al. (4) reported higher success of the MA in their study. We think this is related to the patient population being in the young-middle age range.

Rabinowitz et al. (2) reported that the procedure time was short in the PA with continuous SA in elderly patients. However, no significant difference was observed. Kartal et al. (6) reported that the application time of SA was significantly shorter in the PA compared to the median approach. In our study, the application time of SA was 41 ± 27 seconds in group M and 18 ± 13 seconds in group P. Consistent with the literature, we found that the procedure time was significantly shorter in the PA (<0.001). As stated in the literature, we think that in the PA, bypassing the interspinous and supraspinous ligaments and avoiding stenosis and degeneration in the interspinous space shorten the procedure time. At the same time, the difficulty in positioning during the procedure in the geriatric population also contributed to the shorter procedure time in the PA (2,4,6).

Singh et al. (5) reported the success rate in the first trial as 70% in the MA and 90% in the PA. In another study, the success rate in the first attempt was 68% in the MA and 92% in the PA (7). In our research, the success rate in the first trial was 56.6% in the MA and 78.1% in the PA. Consistent with the literature, the PA had a higher success rate in the first attempt.

Bayındır et al. (4) compared the number of interventions and the duration of SA in SA performed with the median and PAs. They found that the number of interventions

and the duration of SA were higher in the MA (4). Kartal et al. (6) reported that while there was no significant difference in the number of interventions, the duration of SA administration was significantly higher. In our study, the number of interventions and the time of application were substantially lower in the paramedian group, consistent with the literature ($p=0.02$, $p<0.001$, respectively).

It is difficult and uncomfortable to place geriatric patients in a forward flexion position during subarachnoid block application. The contact of the spinal need with the bone at the intervention site may also cause pain. Podder et al. (8) reported that young patients with lower extremity trauma felt less pain with the PA approach in SA. Kartal et al. (6) said that patients had lower bone contact rates in the paramedian method but it was not significantly different. In their study, 60% of the patients who underwent the PA did not have bone contact. In our study, bone contact was not observed in 69% of the patients who underwent the PA. Consistent with the literature, bone contact was significantly lower in the PA ($p=0.02$).

Positioning for SA in elderly patients is difficult, especially in orthopedic surgery because the procedure is painful and positioning is difficult. Similar to the studies in the literature, a sitting position was preferred for SA in our study (6-8). Rabinowitz et al. (2) reported that the intervention rate from another space was 5% with PA and 30% with MA due to failure in SA applied in the lateral decubitus position. Kartal et al. (6) reported that intervention from another space was performed at 27% with PA and 36.8% with MA. Our study performed SA at the L4-L5 level, an alternative level, in 18.8% in the MA and 12.7% in the PA. Considering that the higher success rate of the PA reduces the need for intervention from another level, this difference was not significant in our study ($p=0.38$).

Hypotension is a common complication of SA. The literature's improvement rate varies between 8.2% and 57.9%. The rate of cardiac arrest due to SA has been reported to be between 0.018% and 0.029% (9). One of the acute effects of the sympathetic blockade after SA is that it triggers reflexes and causes bradycardia with a decrease in cardiac venous return. A study evaluating 612 SA cases reported complications in 148 patients, including bradycardia in 25.7%, nausea and vomiting in 13.5%, post-spinal headache in 29.1%, urinary retention in 2.7%, hypotension in 21.6%, 3.4% inadequate SA was found in 2% and unsuccessful application in 2% (10). In our study, hypotension was observed at a rate of 8.3% and bradycardia at a rate of 7.4%,

while no significant difference was observed between the groups ($p=0.74$, $p=1.00$, respectively). Respiratory arrest and cardiac arrest were not observed in any patient.

During the procedure, nausea and vomiting in SA often develop due to hypotension or retraction of the peritoneum. Hypotension that occurs should be treated with fluid resuscitation or vasoconstrictor agents. In our study, it was seen in 1.8% of the patients. It was resolved in a short time with fluid resuscitation and vasoconstrictor administration. We think that the geriatric patients in our study resulted in lower rates of nausea and vomiting than in the literature.

Post-spinal headache (PSHA) is one of the common complications of SA. Its incidence increases with younger age, increased needle size, use of sharp-pointed needles, and recurrent puncture of the dura mater. Its incidence varies between 0.1% and 36% (3). Firdous et al. (1) applied SA with two different approaches using a pencil-tipped needle in 120 patients undergoing cesarean section. They found the incidence of PSHA in the PA lower than in the MA (1.6% vs. 5%). However, no significant difference was observed (1). In their study, Haider et al. (11) found the incidence of PSHA with the PA as significantly lower than with the MA. In another study conducted on 150 middle-aged patients undergoing orthopedic surgery, the incidence of PSHA was reported to be similar to the two approaches (12). Kartal et al. (6) did not register PSHA in their study with geriatric patients. PSHA was not evaluated because our study focused on the success of the median and PAs and was rarely seen in old orthopedic surgery in our hospital.

In a study investigating the causes and failures of neuraxial blocks, the failure rate in SA was reported as 3.9% in 6966 patients (13). In our study, SA was inadequate in 3.7% ($n=2$) of the patients in group M and 3.6% ($n=2$) of the patients in group P. In these cases, spontaneous breathing is preserved, and the depth of anesthesia is increased with intravenous analgesics, or general anesthesia is started.

Study Limitations

This study has several limitations. First, this study was conducted in a single center. Secondly, our study focused on the success of SA. Early intraoperative complications of SA were investigated, but late complications were not evaluated. In addition, diseases such as ankylosing spondylitis and anatomical variations of the vertebral column, which limit vertebral movements, were not determined.

Conclusion

As a result, SA in geriatric patients is complex due to anatomical changes in the vertebrae and patient compliance. The PA makes direct access to the dura possible from the paravertebral muscles without encountering the supraspinous and interspinous ligaments. This study showed that the procedure time was significantly shortened in the PA in SA of geriatric patients, and there was less bone contact during the procedure. Anesthesiologists' experience in SA approaches can also affect the duration and success of the procedure. We think that the PA may be the first choice in SA for geriatric patients.

Ethics

Ethics Committee Approval: After the approval of the University of Health Sciences Turkey, Kanuni Sultan Süleyman Training and Research Hospital Ethics Committee, a prospective placebo-controlled randomized study was started (date: 09.02.2022, number: 19).

Informed Consent: An informed consent form was obtained from the patients participating in the study.

Peer-review: Internally and externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: K.A., Concept: K.A., A.S.Ş., Design: K.A., A.S.Ş., Data Collection or Processing: K.A., Analysis or Interpretation: K.A., A.S.Ş., Literature Search: K.A., A.S.Ş., Writing: K.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Firdous T, Siddiqui MA, Siddiqui SM. Frequency of post-dural puncture headache in patients undergoing elective cesarean section under spinal anesthesia with median versus paramedian approach. *Anaesth Pain & Intensive Care* 2016;20(2):165-170.
2. Rabinowitz A, Bourdet B, Minville V, Chassery C, Pianezza A, Colombani A, et al. The Paramedian technique: a superior initial approach to continuous spinal anesthesia in the elderly. *Anesth Analg* 2007;105(6):1855-1857.
3. Wantman A, Hancox N, Howell PR. Techniques for identifying the epidural space: a survey of practice amongst anaesthetists in the UK. *Anaesthesia* 2006;61(4):370-375.
4. Bayındır S, Özcan S, Koçyiğit F, Hanbeyoğlu O. Which Approach is preferred in spinal anesthesia: median or paramedian? Comparison of early and late complications. *Istanbul Med J* 2017;18(4):205-209.

5. Singh P, Agrawal SK, Dwivedi S, Yadav A. A comparative evaluation between median and paramedian approaches for sub-arachnoid block in elderly patients. *Int J Res Med Sci* 2016;4(6):2069-2072.
6. Kartal S, Kongur E, Aşçı SS, Aydın HR, Aydın PD, Şen A. Evaluation Of The Median And Paramedian Approach In Spinal Anesthesia In Elderly Patients. *Dicle Med J* 2020;47(2):243-249.
7. Ali SM, Dash S, Mohapatra R. Spinal anaesthesia with the median and paramedian approach in geriatric patients undergoing lower limb surgery. *IJMAS* 2016;3(3):130-135.
8. Podder S, Kumar N, Yaddanapudi LN, Chari P. Paramedian lumbar epidural catheter insertion with patients in the sitting position is equally successful in the flexed and unflexed spine. *Anesth Analg* 2004;99(6):1829-1832.
9. Chinachoti T, Tritrakarn T. Prospective Study of Hypotension and Bradycardia during Spinal Anesthesia with Bupivacaine: Incidence and Risk Factors. *J Med Assoc Thai* 2007;90(3):492-501.
10. Eryeğen H, Yüksel E, Kokulu S, Doğan Bakı E, Gül Sıvacı R. Hastanemizdeki Spinal Anestezi Uygulamalarının Retrospektif Değerlendirilmesi. *Kocatepe Medical Journal* 2012;13(2):69-77.
11. Haider S, Butt KJ, Aziz A, Qasim M. Post dural puncture headache a comparison of midline and paramedian approaches. *Biomedica* 2005;21:90-92.
12. Mosaffa F, Karimi K, Madadi F, Khoshnevis SH, Daftari Besheli L, Eajazi A. Post-dural Puncture Headache: A Comparison Between Median and Paramedian Approaches in Orthopedic Patients. *Anesth Pain Med* 2011;1(2):66-69.
13. Özdemir H, Kayhan Z. Failure of Neuraxial Blocks and Etiologic Factors. *J Turk Anaesth Int Care* 2011;39(4):198-206.