Available online at website: https://ejournal.undip.ac.id/index.php/janesti

JAI (Jurnal Anestesiologi Indonesia), Volume 18 (3), 2026

***RESEARCH***

# Comparison of the Effectiveness and Side Effects of Spinal Anesthesia: Bupivacaine-Fentanyl vs. Bupivacaine-Fentanyl-Clonidine in Caesarean Section Patients

Astria Yuliastri Permana[✉*], Retnosari Andrajati[**], Rafidya Indah[***], Ulvi Nur Rista[****]

[*]Faculty of Pharmacy, Universitas Indonesia, Depok, Indonesia
[**]Department of Clinical Pharmacy, Universitas Indonesia, Depok, Indonesia
[***]Department of Anesthesiology, Bethsaida Hospital, Tangerang, Indonesia
[****]Department of Pharmacy, Bethsaida Hospital, Tangerang, Indonesia

[✉]Correspondence: permanaastria@gmail.com

*Received: 13th April 2026; Revised: 5th November 2026; Accepted: 11th November 2026*
*Available online: 12th November 2026; Published regularly: November 2026*

## ABSTRACT

**Background:** Spinal anesthesia is the regional technique of choice for caesarean section procedures. Achieving adequate block duration, however, often necessitates higher doses of local anesthetics, which carry an increased risk of complications. Fentanyl is commonly added as an adjuvant to reduce this dose requirement, but it carries a substantial side-effect burden — particularly nausea, vomiting, and pruritus. Clonidine has been proposed as an alternative or additive adjuvant for its analgesic, antiemetic, and sedative properties without these opioid-related effects; however, direct comparative data on the triple combination (bupivacaine–fentanyl–clonidine) against standard bupivacaine–fentanyl practice remain limited, particularly in Indonesian clinical settings.

**Objective:** This study aimed to compare the effectiveness (sensory and motor block duration) and side effect profiles of bupivacaine–fentanyl versus bupivacaine–fentanyl–clonidine spinal anesthesia in patients undergoing caesarean section, addressing the current lack of local comparative evidence for this combination.

**Methods:** This prospective cohort study was conducted at Bethsaida Hospital from December 2019 to February 2020. Fifty patients were divided into two groups (n=25 each): the bupivacaine-fentanyl (BF) group (bupivacaine 12.5 mg + fentanyl 25 mcg) and the bupivacaine, fentanyl, and clonidine (BFC) group (bupivacaine 12.5 mg + fentanyl 25 mcg + clonidine 30 mcg). Data were analyzed using T-tests and Mann-Whitney tests.

Result: Motor block duration was significantly longer in the BFC group (213.14 min) than in the BF group (189.84 min), with an approximate difference of 23 minutes ($p < 0.05$). Sensory block duration similarly favored the BFC group (342.08 min vs. 204.08 min), representing a mean difference of 138 minutes ($p < 0.05$). Although nausea and vomiting rates were lower in the BFC group (16% vs. 44%), no statistically significant between-group difference was found in the overall incidence of side effects. Multivariate analysis identified age and body weight as significant predictors of motor block duration.

**Conclusion:** The combination of BFC significantly prolongs both sensory and motor block durations compared to the BF combination, without a significant increase in the clinical incidence of side effects.

**Keywords:** bupivacaine; clonidine; effectiveness; fentanyl; side effects; spinal anesthesia


JAI_83503_2026 Copyright © 2026, e-ISSN 2089-970X

Copyright© 2026 by the authors, published by the Indonesian Association of Anesthesiology and Intensive Therapy Specialist Chapter Jawa Tengah in collaboration with the Faculty of Medicine, Universitas Diponegoro. This is an open access article under the CC BY-SA License (https://creativecommons.org/licenses/by-sa/4.0).

**Permalink/DOI:** https://doi.org/10.14710/jai.v0i0.83503

## INTRODUCTION

Spinal anesthesia, or subarachnoid block (SAB), is the mainstay regional technique for patients undergoing caesarean section. Its success depends on achieving an adequate duration of sensory and motor block throughout the procedure, thereby ensuring patient comfort while limiting the risk of adverse events.[1] However, achieving the expected duration using local anesthetics alone often requires large doses, which may lead to complications or failure. A 2022 multicenter prospective cohort study of 794 patients found that spinal anesthesia failure in caesarean section remains a persistent clinical problem, often requiring conversion to general anesthesia when local anesthetic dosing is inadequate. [2]

To overcome these limitations, low-dose bupivacaine is frequently combined with adjuvants such as opioids or clonidine. A systematic review and meta-analysis confirmed that adjuvant combinations with intrathecal bupivacaine continue to be actively investigated for their ability to improve block quality while limiting local anesthetic dose.[3] Fentanyl is a widely used opioid adjuvant that can significantly prolong subarachnoid blocks.[4] Its clinical utility is, however, tempered by a recognized adverse effect profile encompassing respiratory depression, emesis, and pruritus, as confirmed in a 2022 systematic review and meta-analysis of randomized studies.[5] A prospective cohort study similarly reported that nausea, vomiting, and pruritus remain common complications among patients receiving intrathecal fentanyl with bupivacaine, which can significantly impact patient comfort and necessitate additional therapy.[6]

As a potential solution to these side effects, recent clinical studies have recommended clonidine, a selective $\alpha_2$-adrenoceptor agonist. Unlike opioids, clonidine provides longer sensory and motor blocks while offering antiemetic and sedative properties. It also reduces shivering and anxiety without the risk of pruritus or respiratory depression associated with fentanyl.[7] Despite these theoretical advantages, there is a lack of direct comparative data in local clinical settings, particularly regarding the triple combination of bupivacaine, fentanyl, and clonidine (BFC).

Therefore, this study aimed to compare the effectiveness and side effects of spinal anesthesia using bupivacaine–fentanyl versus bupivacaine–fentanyl–clonidine in patients undergoing caesarean section, addressing this gap in local comparative evidence.

## METHOD

This study used a prospective cohort design and was conducted at Bethsaida Hospital, Tangerang, Indonesia, from December 2019 to February 2020. The study population consisted of patients undergoing caesarean section under spinal anesthesia. A total of 50 patients were included and divided into two


Copyright © 2026, e-ISSN2089-970X

groups: 25 patients in the bupivacaine–fentanyl group (BF group) and 25 patients in the bupivacaine–fentanyl–clonidine group (BFC group).

Patients in the BF group received spinal anesthesia comprising bupivacaine 12.5 mg combined with fentanyl 25 mcg, while those in the BFC group received bupivacaine 12.5 mg combined with fentanyl 25 mcg and clonidine 30 mcg. Spinal anesthesia was administered in accordance with standard clinical procedures.

The inclusion criteria were patients with American Society of Anesthesiologists (ASA) physical status I or II who underwent spinal anesthesia using a 27-gauge needle at the L3–L4 intervertebral space in the sitting position, with no failed spinal anesthesia attempts.

The exclusion criteria were a history of uncontrolled hypertension or cardiac disorders, known allergies to bupivacaine, fentanyl, or clonidine, and spinal deformities.

The independent variable in this study was the type of spinal anesthesia combination administered. The dependent variables were the duration of sensory block, duration of motor block, and the incidence of side effects. Potential confounding variables included age, body weight, height, patient position during injection, and injection site.

For the duration of motor block, multivariate analysis was performed using a stepwise regression approach. The analysis consisted of three steps (Models 1, 2, and 3), with Model 3 (Step 3) representing the final model. In this final model, age and the type of spinal anesthesia combination were retained as independent predictors of motor block duration, while height and weight were excluded during the stepwise selection process.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 22. Normality of data distribution was assessed using the Kolmogorov–Smirnov test. Differences between groups were analyzed using an independent t-test for normally distributed data and a Mann–Whitney test for non-normally distributed data. A p-value of less than 0.05 was considered statistically significant.

This study was approved by the Ethics Committee of Bethsaida Hospital, Tangerang, with ethical approval number 218/BETH/MED/6/2020.

## RESULTS

A total of 50 patients undergoing caesarean section with spinal anesthesia at Bethsaida Hospital were enrolled and divided into two groups (n=25 each): the BF group and the BFC group. Subject characteristics, summarized in Table 1, showed a mean age of 31 years (range: 23–42 years).

The mean height was 158 cm (range: 144–170 cm), while the mean weight was 69 kg (range: 47–100 kg). Previous studies concluded that height is not a factor influencing cephalad spread of anesthesia; rather, it is the hip-to-shoulder ratio that may affect the spread[8]. In the present study, hip-to-shoulder ratio measurement was not performed.

The clinical effectiveness of the two regimens regarding block duration is presented in Table 2 and Table 3. The independent-samples t-test for motor block duration showed a significant


Copyright © 2026, e-ISSN2089-970X

difference between groups, with the BFC group (213.14 min) exhibiting a significantly longer duration compared to the BF group (189.84 min). Similarly, Mann-Whitney U analysis for sensory block duration revealed that the BFC group (342.08 min) was significantly longer than the BF group (204.08 min), representing a mean difference of approximately 138 minutes.

Postoperative side effect frequencies are illustrated in Figure 1. The BF group showed a higher incidence of pruritus and nausea/vomiting compared to the BFC group. Conversely, back pain, leg pain, and conjunctival injection (red eyes) occurred only in the BFC group. Despite these trends, bivariate analysis indicated no statistically significant differences between the BFC and BF groups regarding the incidence of pruritus, nausea, vomiting, back pain, leg pain, or conjunctival injection ($p > 0.05$). Furthermore, variables such as age, weight, and height did not significantly influence the occurrence of these side effects. The BFC group was found to be 1.222 times less likely to cause pruritus compared to the BF group.

Multivariate analysis was performed to identify independent predictors of block duration. As shown in Table 4, the final regression model demonstrated that age and body weight were significant factors influencing the duration of the motor block. These findings suggest that while the anesthetic combination is the primary driver of effectiveness, individual physiological characteristics significantly modulate the pharmacokinetic response in spinal anesthesia.

**Table 1**. Distribution of subject characteristics

| Characteristics | BFC group (n=25) | BF group (n=25) |
|---|---|---|
| Age (years) | | |
| Young adult (15-20) | 1 (2%) | 0 (0%) |
| Adult (21-30) | 7 (14%) | 9 (18%) |
| Middle age (31-50) | 17 (34%) | 16 (32%) |
| Min | 23 | 25 |
| Max | 42 | 37 |
| Mean | 31 | 31.56 |
| Median | 32 | 31 |
| Body mass indeks (kg/m$^2$) | | |
| Obese (BMI >30) | 6 (12%) | 6 (12%) |
| Overweight (BMI 25-29.9) | 5 (10%) | 14 (28%) |
| Normal (BMI 18.5-24) | 14 (28%) | 5 (10%) |
| Min | 19.74 | 23.05 |
| Max | 40.06 | 38.57 |
| Mean | 26.38 | 28.68 |
| Median | 24.84 | 28.30 |
| Height (cm) | | |
| Tall (>158 cm) | 15 (30%) | 11 (22%) |
| Average-short (<146 -158 cm) | 10 (20%) | 14 (28%) |
| Min | 144 | 150 |
| Max | 170 | 160 |
| Mean | 158.36 | 157.52 |
| Median | 160 | 158 |


Copyright © 2026, e-ISSN2089-970X

**Table 2**. Comparison of motor block duration

| Anesthetic group | Mean duration (minutes) | *P-value* |
|---|---|---|
| BFC | 213.14 | .024 |
| BF | 189.84 | .026 |

**Table 3**. Comparison of sensory block duration (Mann-Whitney U Test)

| Anesthetic group | Mean duration (minutes) | *P-value* |
|---|---|---|
| BFC | 342.08 | .000 |
| BF | 204.08 | .000 |

**Table 4**. Multivariate analysis of motor block duration predictors

| Model (Step 3) | | Unstandardized coefficients (B) | Std. error | Standardized coefficients (Beta) | P-value | 95.0% Confidence interval | |
|---|---|---|---|---|---|---|---|
| | | | | | | Lower | Upper |
| Step 1 | Constant | 109.156 | 35.554 | | .004 | 37.547 | 180.765 |
| | Age | 20.025 | 8.776 | .265 | .027 | 2.350 | 37.700 |
| | Height | 6.598 | 9.076 | .090 | .471 | -11.682 | 24.878 |
| | Weight | 25.244 | 6.078 | .523 | .000 | 13.003 | 37.486 |
| | Spinal anesthesia | -14.567 | 8.793 | .199 | .105 | -32.277 | 3.143 |
| Step 2 | Constant | 120.974 | 31.457 | | .000 | 57.656 | 184.293 |
| | Age | 20.015 | 8.731 | .265 | .027 | 2.441 | 37.588 |
| | Weight | 23.856 | 5.741 | .494 | .000 | 12.301 | 35.412 |
| | Spinal anesthesia | -14.911 | 8.715 | .191 | .115 | -31.553 | 3.531 |
| Step 3 | Constant | 93.424 | 26.821 | | .001 | 39.468 | 147.380 |
| | Age | 20.771 | 8.864 | .275 | .023 | 2.939 | 38.602 |
| | Spinal anesthesia | 26.067 | 5.667 | .540 | .000 | 14.667 | 37.467 |

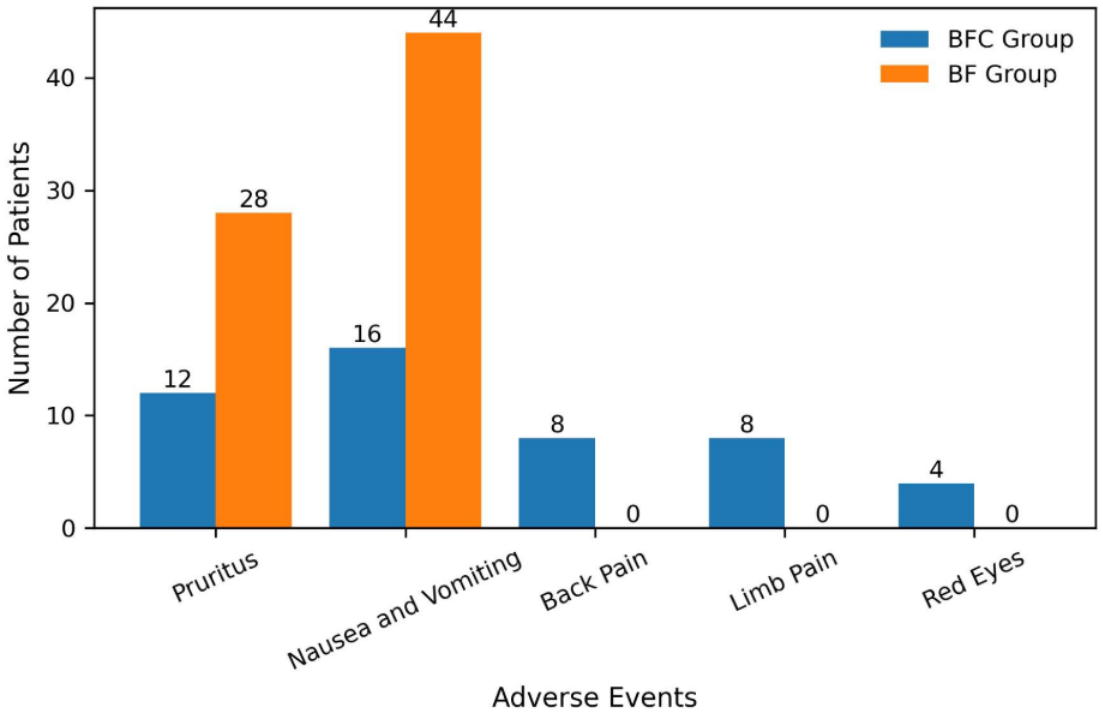



**Figure 1**. Comparison of side effect frequency between BFC and BF groups


Copyright © 2026, e-ISSN2089-970X

## DISCUSSION

The findings of this study directly address the research question by demonstrating that intrathecal clonidine, when added to a bupivacaine–fentanyl spinal regimen, significantly extends both motor (approximately 23 minutes) and sensory block durations (approximately 138 minutes) relative to the dual-agent combination.

In addition to the anesthetic combination, individual patient characteristics may influence the distribution and effectiveness of spinal anesthesia. Clinical observations suggest that anesthetic spread may occur more rapidly in older patients due to anatomical, neurophysiological, and cardiovascular changes. Previous studies have indicated that height alone does not significantly influence the cephalad spread of spinal anesthesia; rather, the hip-to-shoulder width ratio may affect anesthetic distribution.[8] However, the hip-to-shoulder width ratio was not measured in the present study. Body weight may also influence the administration and effectiveness of spinal anesthesia. In obese patients, obscured anatomical landmarks and reduced cerebrospinal fluid (CSF) space due to epidural fat accumulation may complicate the procedure.[9] These patient-related factors may contribute to variations in spinal anesthesia outcomes and should be considered when interpreting the findings.

The pharmacodynamic basis for clonidine's adjuvant effect lies in its partial agonism at α2-adrenoreceptors, through which it amplifies local anesthetic-induced sensory and motor blockade. This occurs through a spinal potentiation mechanism involving the inhibition of neuronal activity and the release of Substance P, norepinephrine, and acetylcholine in the dorsal horn of the spinal cord. The downstream consequence is direct inhibition of impulse conduction in Aδ fibers alongside enhanced potassium conductance. These mechanisms collectively stabilize neurons and prevent central sensitization to painful stimuli.[10] This mechanistic pathway accounts for the significantly prolonged sensory and motor block durations observed in the BFC group compared to the BF group.

The analgesic effect following intrathecal administration is mediated spinally through the activation of postsynaptic α2-receptors in the substantia gelatinosa of the spinal cord. This action blocks conduction in C-fibers and Aδ fibers, increases potassium conductance in isolated neurons in vitro, and intensifies the conduction block provided by local anesthetics.[11] Chemically, clonidine is an imidazoline derivative (Benzenamine, 2,6-dichloro-N-2-imidazolidinylidene monohydrochloride), whose imidazole ring stimulates α2-adrenoreceptors in the brain and spinal cord, reducing sympathetic outflow and consequently lowering peripheral resistance, heart rate, cardiac output, and blood pressure.[7] These findings are consistent with those of Singh et al., who reported that the BFC triple combination extended both sensory and motor block durations in lower limb surgery patients.[5]

The combination of opioids and α2-agonists enhances the effectiveness of local anesthesia and improves postoperative analgesia. When clonidine and fentanyl are administered together, they produce greater antinociception. Previous studies have identified mu (μ) and delta (δ) opioid receptors as candidate receptors capable of interacting synergistically with α2-agonists.[12]


Copyright © 2026, e-ISSN2089-970X

Postoperative side effects in this study were predominantly nausea, vomiting, and pruritus. Pruritus occurred in 12% of BFC subjects versus 28% in the BF group, and was mild in all cases, requiring no pharmacological management. The precise mechanism underlying opioid-induced pruritus remains incompletely understood; proposed explanations involve activation of itch-processing centers in the CNS, modulation of the dorsal horn, inhibition of inhibitory transmitters, and engagement of serotonergic pathways. Pain and pruritus share unmyelinated C-fiber transmission pathways. The release of prostaglandins PG $E_1$ and PG $E_2$ increases C-fiber transmission, which subsequently triggers pruritus.

Nausea and vomiting occurred in 44% of the BF group compared to 16% in the BFC group. This suggests that the inclusion of clonidine may reduce the incidence of emetic side effects compared to a bupivacaine-fentanyl combination alone. In the CNS, the chemoreceptor trigger zone (CTZ) and the central vomiting centre (CVC), located in the medulla, coordinate the vomiting reflex. Opioids like fentanyl activate receptors in these regions. Efferent signals from the CTZ are sent to the CVC, which then triggers a series of sympathetic and parasympathetic reactions via the vagus nerve.[13] The CTZ contains receptors for various neuroactive compounds. Emetic stimuli can originate from gastrointestinal, vestibulo-ocular, or higher cortical afferents. Opioids activate μ receptors in the CTZ and may increase vestibular sensitivity, directly stimulate the CTZ, and delay gastric emptying, all of which contribute to nausea and vomiting.[14]

Other adverse events, including back pain and transient neurologic symptoms (TNS), were recorded exclusively in the BFC group. Post-spinal back pain is frequently attributed to mechanical trauma involving ligamentous, fascial, or osseous structures, with potential contributions from localized bleeding or nerve root irritation. Established risk factors encompass prolonged immobilization beyond 2.5 hours, lithotomy positioning, BMI ≥32 kg/m², and the specific injection site.[15] In this study, two BFC patients had BMI values exceeding 32 kg/m², likely contributing to their back pain. TNS presents as dull, radiating pain or dysesthesia in the lower extremities following block regression. Its etiology is not fully established but has been associated with neurotoxicity in some reports; notably, bupivacaine — the local anesthetic used in this study — carries a substantially lower risk of TNS than lidocaine.[16]

Despite the occurrence of these events, bivariate analysis confirmed no statistically significant difference between groups ($p > 0.05$), indicating that the safety profile of the BFC combination is comparable to that of the BF combination. Multivariate analysis was feasible for motor block duration but not for sensory block duration, owing to the non-normal distribution of sensory data. Using the backward elimination approach, age and body weight were retained in the final model (Step 3), confirming their role as significant predictors of motor block duration.

The primary limitation of this study is that postoperative observations were limited to the first 24 hours. However, a significant strength of this research is its prospective cohort design, which allowed for direct and accurate observation of the subjects.


Copyright © 2026, e-ISSN2089-970X

## CONCLUSION

Intrathecal clonidine, when incorporated into a bupivacaine–fentanyl spinal regimen, demonstrably extends both sensory and motor block durations in patients undergoing caesarean section. The triple-drug regimen provides a superior duration of anesthesia compared to the standard dual-agent combination, particularly in extending the sensory blockade for postoperative relief, without a corresponding increase in adverse events. The comparable side effect profiles between groups support the safety of this approach in obstetric anesthetic practice.

**Acknowledgment**

The authors would like to express their sincere gratitude to the Faculty of Pharmacy, Universitas Indonesia, particularly to the thesis supervisors, Prof. Dra. Retnosari Andrajati, M.S., Ph.D., Apt. and dr. Rafidya Indah, Sp.An., for their invaluable guidance, advice, and academic support. The authors also gratefully acknowledge the management and staff of Bethsaida Hospital, Tangerang, particularly Dr. Bina Ratna K.F., Prof. dr. Marzuki Suryaatmadja, Sp.PK(K), Apt. Siti Daljinah, and Apt. Ulvi Nur Rista, for granting permission and providing assistance and support throughout the research process. Finally, the authors extend their appreciation to all individuals who contributed to the successful completion of this study.

**Conflict of Interest**

The authors declare no conflict of interest to disclose.

**Declaration of Use of Artificial Intelligence (AI)**

During manuscript preparation, the authors used AI to assist with proofreading and translation. The authors reviewed and edited the AI-assisted text and take full responsibility for the final content of the manuscript.

## REFERENCES

1. Seljogi D, Wolff AP, Scheffer GJ, Van Geffen GJ, Bruhn J. Correlation of bupivacaine 0.5% dose and conversion from spinal anesthesia to general anesthesia in cesarean sections. Acta Anaesthesiol Belg. 2016;67(1):36-42.
2. Bekele Z, Jisha H. Type, management, and associated factors of failed spinal anesthesia in cesarean section. Prospective cohort study. Ann Med Surg (Lond). 2022;77:103616. doi:10.1016/j.amsu.2022.103616
3. Kumar S, Choudhury B, Varikasuvu SR, Singh H, Kumar S, Lahon J, Saikia D. A Systematic Review and Meta-analysis of Efficacy and Safety of Dexmedetomidine Combined With Intrathecal Bupivacaine Compared to Placebo. Cureus. 2022;14(12):e32425. doi:10.7759/cureus.32425
4. World Health Organization. WHO recommendation on epidural analgesia for pain relief during labour. Geneva: World Health Organization; 2018.
5. Singh R, Kundra S, Gupta S, Grewal A, Tewari A. Effect of clonidine and/or fentanyl in combination with intrathecal bupivacaine for lower limb surgery. J Anaesthesiol Clin Pharmacol. 2015;31(4):485-490. doi:10.4103/0970-9185.169069
6. Ebrie AM, Woldeyohanis M, Abafita BJ, Ali SA, Zemedkun A, Yimer Y, Ashebir Z, Mohammed S. Hemodynamic and analgesic effect of intrathecal fentanyl with bupivacaine in patients undergoing elective cesarean section; a prospective cohort study. PLoS One. 2022;17(7):e0268318. doi:10.1371/journal.pone.0268318


Copyright © 2026, e-ISSN2089-970X

7. Whizar-Lugo VM, Flores-Carrillo JC, Preciado-Ramírez S. Intrathecal clonidine as spinal anaesthesia adjuvant — is there a magical dose? 2014:97-121. doi:10.5772/58712
8. Shivashankar, Bhat R, et al. Evaluation of Effect of Hip/Shoulder-Width Ratio on the Sensory Level of Spinal Anesthesia — A Prospective Observational Study. Anesth Essays Res. 2022;16(1):80-83. doi:10.4103/aer.aer_146_21
9. Mahrous R, Alalfy M, Abdalgeleel SA, Abdelnasser A, Abd Elfattah DA, Hassen H, Ibrahim Ogila A, Ibrahim MA. The relation between body mass index and difficulty in inducing spinal anesthesia in elective cesarean section. Egyptian Journal of Anaesthesia. 2021;37(1):373-376.
10. Schuster DJ, Stone LS, Wilcox GL. Analgesic synergy between opioid and α2-adrenoceptors. Br J Pharmacol. 2015;172(2):427-439. doi:10.1111/bph.12695
11. Singh RB, Chopra N, Choubey S, Tripathi RK. Role of clonidine as adjuvant to intrathecal bupivacaine in patients undergoing lower abdominal surgery: A randomized control study. Anesth Essays Res. 2014;8(3):307-312. doi:10.4103/0259-1162.143119
12. Chabot-Doré AJ, Millecamps M, Stone LS. The delta-opioid receptor is sufficient, but not necessary, for spinal opioid-adrenergic analgesic synergy. J Pharmacol Exp Ther. 2013;347(3):773-780. doi:10.1124/jpet.113.206581
13. Smith HS, Smith JM, Seidner P. Opioid-induced nausea and vomiting. Ann Palliat Med. 2012;1(2):121-129. doi:10.3978/j.issn.2224-5820.2012.07.08
14. Koch KL, Hasler WL. Nausea and Vomiting: Diagnosis and Treatment. New York: Springer; 2016. doi:10.1007/978-3-319-34076-0
15. Lee JH, Yoon DH, Heo BH. Incidence of newly developed postoperative low back pain with median versus paramedian approach for spinal anesthesia. Korean J Anesthesiol. 2020;73(6):518-524. doi:10.4097/kja.19409.
16. Forget P, Borovac JA, Thackeray EM, Pace NL. Transient neurological symptoms (TNS) following spinal anaesthesia with lidocaine versus other local anaesthetics in adult surgical patients: a network meta-analysis. Cochrane Database Syst Rev. 2019;12:CD003006. doi:10.1002/14651858.CD003006.pub4


Copyright © 2026, e-ISSN2089-970X