International Journal of Medical and Pharmaceutical Research

Online ISSN-2958-3683 | Print ISSN-2958-3675
Frequency: Bi-Monthly
Available online on: https://ijmpr.in/

Original Article

Comparative Analgesic Efficacy of Intrathecal Fentanyl versus Intrathecal Midazolam as Adjuvants to Hyperbaric Bupivacaine for Elective Caesarean Section: A Randomized Double-Blinded Clinical Trial

Gandam Raju[1], Arati Rai[2], Lhamo Dolma[3], Sofia Batool[4], Tsering Yougyal[5], Meyong Pincho Bhutia[6]

[1] Postgraduate Resident, [2,4] Associate Professor, [3,5] Assistant Professor, [6] Professor
Department of Anaesthesia.
Sikkim Manipal Institute of Medical Sciences.
Sikkim Manipal University.
5th Mile, Tadong, Gangtok, Sikkim-737102, India

OPEN ACCESS

Corresponding Author:

Dr. Arati Rai
Associate Professor,
Department of Anaesthesia
Sikkim Manipal Institute of Medical Sciences, 5th Mile Tadong, Gangtok 737102, Sikkim
Email: arati_401@yahoo.com

Received: 16-01-2026
Accepted: 12-02-2026
Available online: 19-02-2026

ABSTRACT

Background: Intrathecal adjuvants are commonly used with hyperbaric bupivacaine to enhance spinal anesthesia for caesarean section. Both fentanyl and midazolam have been shown to improve analgesic quality, but comparative evidence remains inconsistent.
Aim: To compare the analgesic efficacy of intrathecal fentanyl and intrathecal midazolam as adjuvants to hyperbaric bupivacaine in elective caesarean section.
Methods: Sixty ASA I–II parturients undergoing elective caesarean section under spinal anesthesia were randomly allocated into two groups (n = 30 each). Group A received 0.5% hyperbaric bupivacaine (1.8 mL) with fentanyl 25 µg, while Group B received 0.5% hyperbaric bupivacaine (1.8 mL) with midazolam 1 mg. Onset and duration of analgesia, postoperative analgesic consumption, hemodynamic variables, sedation score, neonatal APGAR score, and adverse effects were compared.
Results: Both groups showed comparable onset and duration of analgesia and postoperative analgesic consumption ($P > 0.05$). Early postoperative pain scores were significantly lower in the fentanyl group at 90 minutes ($P = 0.002$) and 2 hours ($P = 0.050$). The incidence of hypotension was significantly higher in the midazolam group compared with the fentanyl group (63.3% vs 33.3%, $P = 0.038$), while heart rate, sedation scores, APGAR scores, and other adverse effects were comparable between groups.
Conclusion: Both intrathecal fentanyl and midazolam are effective adjuvants to hyperbaric bupivacaine in caesarean section. Fentanyl provides superior early postoperative analgesia, whereas intrathecal midazolam serves as an effective non-opioid alternative, although careful monitoring for early intraoperative hypotension is advisable.

Keywords: *Spinal anaesthesia, Caesarean section, Intrathecal fentanyl, Intrathecal midazolam, Hyperbaric bupivacaine.*

INTRODUCTION

Caesarean delivery constitutes a major proportion of obstetric surgical procedures worldwide, and effective intraoperative anaesthesia with adequate postoperative analgesia remains essential for optimal maternal recovery and neonatal outcomes **[1].** Spinal anaesthesia remains the technique of choice for elective caesarean section because of its rapid onset, predictable block characteristics, and minimal neonatal drug exposure **[2,3].**

Hyperbaric bupivacaine is widely used for spinal anaesthesia; however, its relatively limited duration often necessitates the addition of intrathecal adjuvants to prolong analgesia and improve anaesthetic quality **[4]**. Opioids such as fentanyl provide potent analgesia through spinal opioid receptor activation but may be associated with adverse effects such as pruritus and nausea **[5]**. Intrathecal midazolam, acting via spinal GABA receptors, has emerged as a potential non-opioid alternative capable of enhancing analgesia with minimal opioid-related side effects **[6,7]**.

The present randomized double-blind clinical trial was therefore undertaken to compare the analgesic efficacy, hemodynamic effects, sedation profile, neonatal outcomes, and adverse effects of intrathecal fentanyl and intrathecal midazolam when used as adjuvants to hyperbaric bupivacaine for elective caesarean section.

MATERIALS AND METHODS

This prospective randomized double-blind clinical trial was conducted in the Department of Anaesthesiology, Sikkim Manipal Institute of Medical Sciences, Sikkim, after obtaining Institutional Ethics Committee approval (SMIMS/IEC/2022-110) and registration with the Clinical Trials Registry of India (CTRI/2023/01/048892). Written informed consent was obtained from all participants.

Based on data from Shah et al**. [8],** sixty ASA physical status I–II parturient aged 18–35 years scheduled for elective caesarean section under spinal anaesthesia were included. Patients with contraindications to spinal anaesthesia, hypersensitivity to study drugs, significant cardiovascular, neurological, hepatic, or renal disease, or those refusing participation were excluded.

Participants were randomly allocated into two equal groups (n = 30 each) using computer-generated randomization. Group A received 0.5% hyperbaric bupivacaine 1.8 mL combined with fentanyl 25 µg, while Group B received 0.5% hyperbaric bupivacaine 1.8 mL combined with preservative-free midazolam 1 mg. The total intrathecal drug volume in both groups was standardized to 2.3 mL. Study drugs were prepared by an anaesthesiologist not involved in patient management to ensure blinding of both patients and investigators.

All patients were preloaded with Ringer's lactate (10–15 mL/kg) before spinal anaesthesia. Under strict aseptic precautions, spinal anaesthesia was administered in the sitting position at the L3–L4 intervertebral space using a 25-gauge Quincke spinal needle. After confirmation of free cerebrospinal fluid flow, the study drug was injected intrathecally over 10–15 seconds, and patients were immediately positioned supine with left uterine displacement. Standard monitoring, including electrocardiography, non-invasive blood pressure, and pulse oximetry, was applied throughout the procedure.

Sensory block onset was assessed using the pinprick method, and motor block was evaluated using the Bromage scale **[9].** Hemodynamic parameters, including heart rate, systolic blood pressure, diastolic blood pressure, and mean arterial pressure, were recorded preoperatively; intraoperatively at 2, 5, 10, 15, 30, 45, and 60 minutes; and postoperatively at 2, 4, 6, 8, 10, and 12 hours. Sedation was assessed using the Ramsay Sedation Scale **[10]** at corresponding observation intervals. Pain was assessed using the Numerical Rating Scale (NRS), and duration of analgesia was defined as the time from intrathecal injection to the first request for rescue analgesia or NRS ≥ 4. Neonatal outcomes were evaluated using APGAR scores at 1 and 5 minutes.

Adverse effects such as hypotension, bradycardia, nausea, vomiting, pruritus, respiratory depression, and excessive sedation were recorded and managed according to institutional protocol.

Statistical analysis was performed using SPSS software (IBM Corp., USA). Continuous variables were compared using the unpaired *t*-test, while categorical variables were analysed using the chi-square test or Fisher's exact test as appropriate. Non-normally distributed continuous data were analysed using the Mann–Whitney *U* test. A p-value < 0.05 was considered statistically significant.

RESULTS

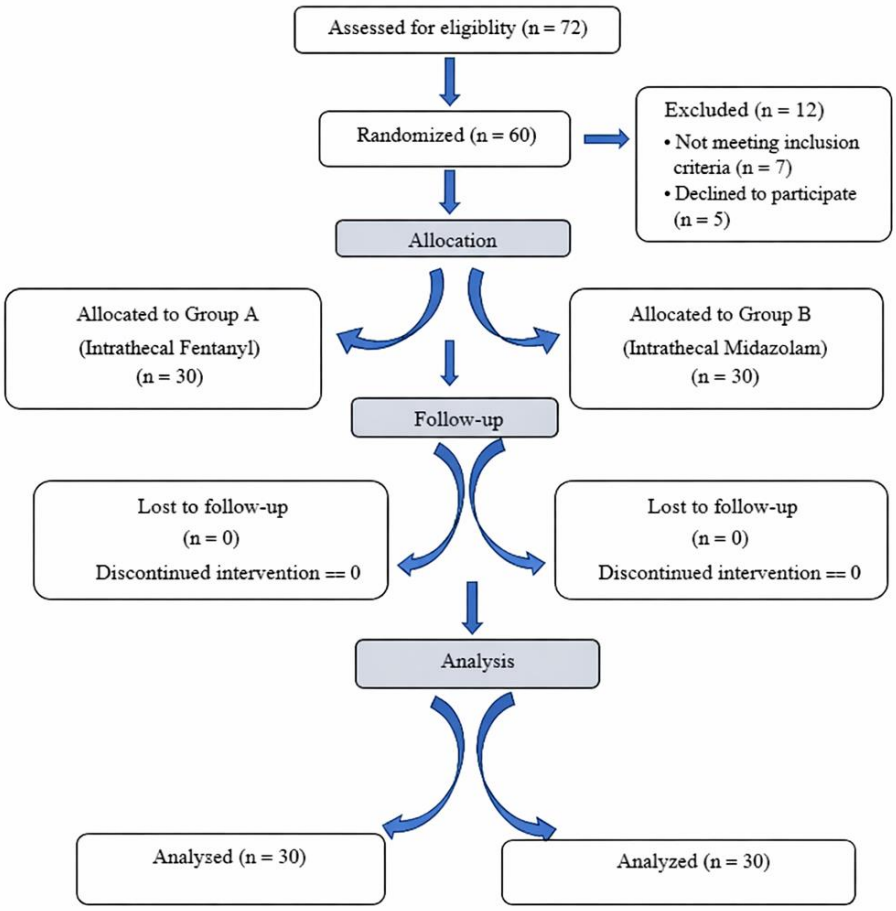

Figure 1: CONSORT flow diagram of patient selection, randomization, and analysis

Demographic Characteristics

Both groups were comparable with respect to demographic and obstetric characteristics. There were no statistically significant differences between Group A (Fentanyl) and Group B (Midazolam) in age distribution, parity, number of previous pregnancies, living children, or abortions (all $P \geq 0.05$) (Table 1). Mean gestational age was also comparable between groups (38.2 ± 0.96 weeks vs 37.4 ± 2.9 weeks; $P = 0.143$) (Table 2). The prevalence of comorbidities, including diabetes, hypertension, hypothyroidism, anaemia, and intrahepatic cholestasis of pregnancy (IHCP), did not differ significantly between groups (all $P > 0.05$) (Table 3).

Table 1. The demographic data with parity of each group showed no statistical significance.

Variables		Group A		Group B		Chi-square test P value
		N	%	N	%	
Age	</=30	16	53.3%	15	50.0%	0.796
	>30	14	46.7%	15	50.0%	
	Mean+/-SD	30.2+/-3.8		30.5+/-3.5		
G (Parity)	1	10	33.3%	8	26.7%	0.601
	2	13	43.3%	16	53.3%	
	3	7	23.3%	5	16.7%	
	4	0	0.0%	1	3.3%	
P (Previous Pregnancies)	0	10	33.3%	11	36.7%	0.116
	1	16	53.3%	19	63.3%	
	2	4	13.3%	0	0.0%	
L (Live children)	0	11	36.7%	11	36.7%	0.196
	1	16	53.3%	19	63.3%	
	2	3	10.0%	0	0.0%	
A (Abortions)	0	27	90.0%	22	73.3%	0.173
	1	3	10.0%	6	20.0%	
	2	0	0.0%	2	6.7%	

Table.2 The mean and standard deviation of gestational age among the groups do not have statistical significance.

Variables	Group A		Group B		Unpaired t-test P value
	Mean	SD	Mean	SD	
Gestational age	38.2	0.96	37.4	2.9	0.143

Table 3. The comorbidities among the group have no statistical significance

Variables		Group A		Group B		Fisher's exact test P value
		N	%	N	%	
Diabetes	Yes	3	10.0%	6	20.0%	0.472
	No	27	90.0%	24	80.0%	
Hypertension	Yes	5	16.7%	3	10.0%	0.706
	No	25	83.3%	27	90.0%	
Hypothyroidism	Yes	6	20.0%	5	16.7%	1.000
	No	24	80.0%	25	83.3%	
Anemia	Yes	0	0.0%	1	3.3%	1.000
	No	30	100.0%	29	96.7%	
IHCP	Yes	2	6.7%	2	6.7%	1.000
	No	28	93.3%	28	93.3%	

Onset of Analgesia

The onset of analgesia was comparable between the groups, with Group A demonstrating a mean onset time of 2.13 ± 0.78 minutes and Group B 1.87 ± 0.78 minutes (P = 0.188) (Table 4).

Table 4. The onset of analgesia among the fentanyl and midazolam groups

Variable	Group A		Group B		Unpaired t-test P value
	Mean	SD	Mean	SD	
Onset of analgesia – pin prick minutes	2.13	0.78	1.87	0.78	0.188

Duration of Analgesia

The median duration of analgesia was similar between the two groups (300 minutes [Q1: 180, Q3: 540] in Group A vs 240 minutes [Q1: 180, Q3: 600] in Group B; P = 0.514) (Table 5).

Table 5: The duration of analgesia with Group A and Group B.

	Group A			Group B			Mann-Whitney U test P value
	Median	Q1	Q3	Median	Q1	Q3	
Duration of analgesia	300	180	540	240	180	600	0.514

Numerical Rating Scale (NRS) Scores

Pain scores were comparable at most postoperative time points (P > 0.05). However, significantly lower NRS scores were observed in the fentanyl group at 90 minutes (P = 0.002) and 2 hours (P = 0.050) postoperatively (Table 6).

Table 6: Comparison of NRS score between two groups.

NRS	Group A		Group B		Unpaired t-test P value
	Mean	SD	Mean	SD	
30MIN	.0	.0	.0	.0	NA
1HR	.0	.0	.1	.4	0.321
1HR30MIN	.0	.0	.6	1.0	0.002
2HR	.9	1.6	1.8	1.9	0.050
3HR	3.4	2.4	3.4	2.0	0.954
4HR	4.0	1.8	3.4	1.7	0.172
5HR	3.6	1.3	4.0	1.8	0.368
6HR	3.8	.9	4.1	1.7	0.295
7HR	3.9	1.1	4.1	1.6	0.515

8HR	3.8	1.3	3.8	1.4	0.924
9HR	3.7	1.2	3.9	1.8	0.497
10HR	3.9	1.1	4.4	2.0	0.242
11HR	4.0	1.7	3.9	2.1	0.840
12HR	3.7	1.6	4.1	2.3	0.430

Haemodynamic parameters.

Heart rate remained comparable between the groups throughout the perioperative period ($P > 0.05$). In contrast, systolic, diastolic, and mean arterial pressures were significantly lower in the midazolam group at 5 minutes after spinal anaesthesia (SBP: $P = 0.047$; DBP: $P = 0.001$; MAP: $P = 0.006$), with MAP also remaining significantly lower at 10 minutes ($P = 0.044$). At all other intraoperative and postoperative time points, blood pressure parameters were comparable between groups. (Figure 2)

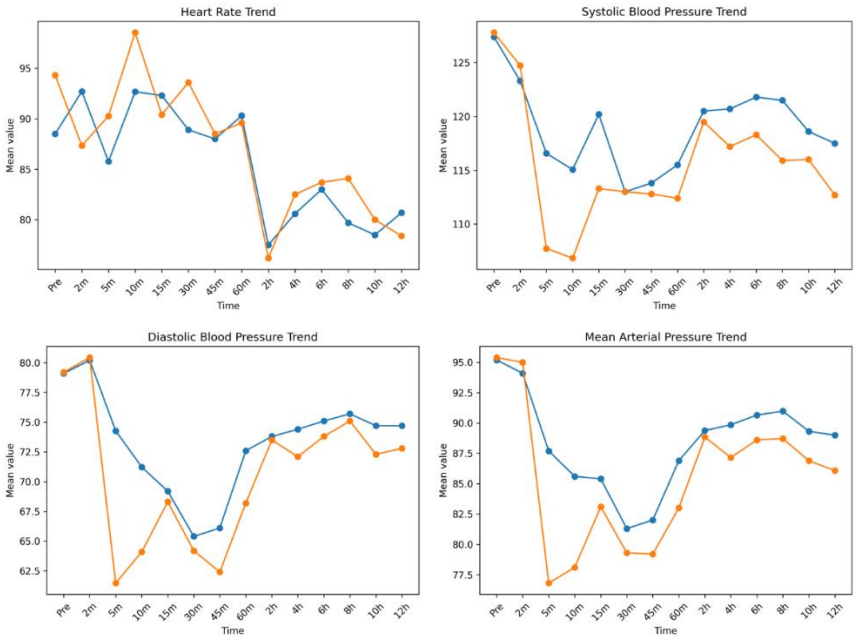

Figure 2: Comparison of haemodynamic parameters.

Analgesic Consumption

Postoperative analgesic consumption was comparable between the groups, with no statistically significant difference observed ($P > 0.05$) (Figure 3).

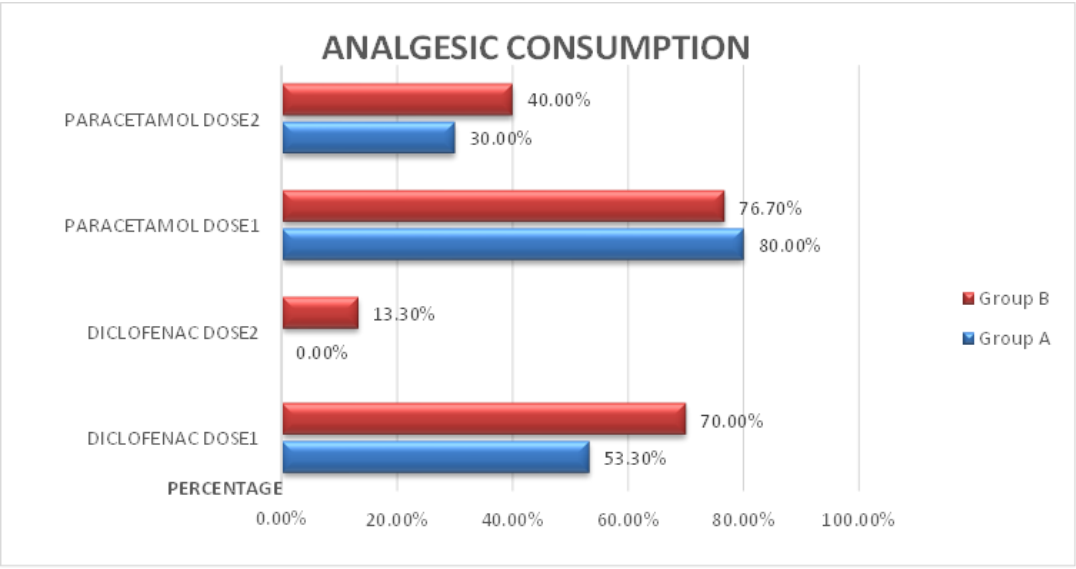

Figure 3: Analgesics consumption between two groups.

Sedation Score

Sedation scores were similar between the groups at all observation times, with most patients maintaining Ramsay sedation scores between 2 and 3 and no clinically significant sedation requiring intervention (P > 0.05) (Table 7).

Table 7: Maternal Sedation Score

SEDATION OF MOTHER	GROUP A			GROUP B			Mann Whitney U test P value
	Median	Q1	Q3	Median	Q1	Q3	
0HR	1.00	1.00	1.00	1.00	1.00	1.00	1.000
1HR	1.00	1.00	2.00	1.00	1.00	1.00	0.394
2HR	1.00	1.00	2.00	1.00	1.00	2.00	0.421

Adverse effects

The overall incidence of adverse effects was comparable between the groups (P > 0.05). However, hypotension occurred more frequently in the midazolam group (63.3% vs 33.3%, P = 0.038), while pruritus was observed only in the fentanyl group (Table 8).

Table 8: The adverse effects encountered in both groups

Adverse effects		Group A		Group B		Fisher's exact test P value
		N	%	N	%	
Hypotension	Yes	10	33.3%	19	63.3%	0.038
	No	20	66.7%	11	36.7%	
Bradycardia	Yes	0	0.0%	0	0.0%	NA
	No	30	100.0%	30	100.0%	
Pruritus	Yes	3	10.0%	0	0.0%	0.237
	No	27	90.0%	30	100.0%	
Nausea/vomiting	Yes	3	10.0%	3	10.0%	1.000
	No	27	90.0%	27	90.0%	
Shivering	Yes	1	3.3%	2	6.7%	1.000
	No	29	96.7%	28	93.3%	
Respiratory depression	Yes	0	0.0%	0	0.0%	NA
	No	30	100.0%	30	100.0%	

APGAR Score

Neonatal APGAR scores at birth, 1 minute, and 5 minutes were comparable between the groups, with no statistically significant differences observed (all P > 0.05) (Table 9

Table 9: APGAR score of neonates

APGAR	Group A		Group B		Unpaired t-test P value
	Mean	SD	Mean	SD	
APGAR at birth	7.3	.5	7.2	.4	0.597
APGAR at 1 minute	7.6	.7	7.4	.5	0.083
APGAR at 5 minutes	8.2	.6	8.2	.6	1.000

DISCUSSION

The present randomized double-blind clinical trial compared the analgesic efficacy and safety of intrathecal fentanyl and intrathecal midazolam when used as adjuvants to hyperbaric bupivacaine for elective caesarean section. The findings of this study demonstrated that both agents produced comparable onset and duration of analgesia, postoperative analgesic consumption, and neonatal outcomes. However, fentanyl was associated with significantly lower early postoperative pain scores, whereas the midazolam group demonstrated a higher incidence of early intraoperative hypotension.

The onset of analgesia was slightly faster in the midazolam group, although the difference was not statistically significant. Similar observations have been reported in earlier clinical studies evaluating intrathecal midazolam as an adjuvant to spinal anaesthesia **[11].** Although the fentanyl group demonstrated a numerically longer duration of analgesia in the present study, the difference was not statistically significant, which is consistent with the findings of Shah et al. [8] and Bhushanam et al. **[12],** who also observed comparable durations of analgesia between intrathecal fentanyl and midazolam when added to bupivacaine. In contrast, Fawaz et al. **[13]** reported a longer duration of analgesia with fentanyl, suggesting variability among studies that may be related to differences in adjuvant doses and local anaesthetic concentrations.

Early postoperative pain scores were significantly lower in the fentanyl group, indicating superior early analgesic quality. This effect may be attributed to activation of spinal μ-opioid receptors by fentanyl, resulting in enhanced inhibition of nociceptive transmission at the dorsal horn level. Previous studies evaluating fentanyl as an intrathecal adjuvant have similarly demonstrated improved early postoperative analgesia and prolonged sensory blockade when compared with bupivacaine alone **[14,15**], reinforcing the established role of intrathecal opioids in enhancing the quality of spinal anaesthesia.

Hemodynamic analysis revealed comparable heart rate trends between the two groups, whereas systolic, diastolic, and mean arterial pressures were significantly lower in the midazolam group during the early intraoperative period, indicating a greater tendency toward early hypotension. The relatively higher incidence of early hypotension observed with intrathecal midazolam may be related to GABA-mediated attenuation of sympathetic outflow following intrathecal administration, although the precise mechanism remains incompletely understood. Similar findings were reported by Shaikh et al. **[16],** who observed a higher incidence of hypotension in the intrathecal midazolam group compared with the fentanyl group. Despite these early differences, hemodynamic parameters stabilized later in the intraoperative and postoperative periods, suggesting that both agents are hemodynamically safe when appropriate monitoring and management are provided.

Adverse effects were minimal and comparable between the groups, with pruritus observed only in the fentanyl group, consistent with the known side-effect profile of intrathecal opioids. Importantly, neonatal APGAR scores were comparable between the two groups, supporting the safety of both intrathecal fentanyl and midazolam in obstetric anaesthesia. Similar maternal and neonatal safety profiles have been reported in systematic reviews evaluating intrathecal midazolam as an adjuvant for caesarean section anaesthesia **[17].** Sedation scores were also comparable between groups, indicating that the addition of either fentanyl or midazolam in the studied doses did not result in clinically significant sedation.

Overall, the findings of the present study are consistent with earlier literature demonstrating that both intrathecal fentanyl and midazolam effectively enhance spinal anaesthesia when added to hyperbaric bupivacaine. While fentanyl appears to provide superior early postoperative analgesia, intrathecal midazolam represents a viable non-opioid alternative, particularly in patients where opioid-related adverse effects such as pruritus are undesirable. Nevertheless, careful intraoperative monitoring is advisable due to the higher incidence of early hypotension observed with midazolam.

CONCLUSION

Both intrathecal fentanyl and intrathecal midazolam are effective adjuvants to hyperbaric bupivacaine for spinal anaesthesia in elective caesarean section. Fentanyl provides superior early postoperative analgesia, whereas midazolam serves as a useful non-opioid alternative with careful monitoring for early intraoperative hypotension.

LIMITATIONS

The present study had a relatively modest sample size and postoperative follow-up limited to 12 hours, which restricted evaluation of long-term analgesic outcomes. In addition, patient satisfaction scores were not assessed, which could have provided further insight into the subjective quality of analgesia. The study evaluated only a single dose of each intrathecal adjuvant; therefore, dose–response relationships could not be examined. Furthermore, long-term neonatal neurobehavioral outcomes were not evaluated, and the single-centre design may limit the generalizability of the findings.

CLINICAL IMPLICATIONS

Intrathecal fentanyl remains a reliable opioid adjuvant for improving early postoperative analgesia in caesarean section, while intrathecal midazolam may be considered an effective non-opioid alternative when avoidance of opioid-related adverse effects is desired.

DECLARATION

Conflicts of interests: The authors declare no conflicts of interest.
Author contribution: All authors have contributed in the manuscript.
Author funding: Nill

REFERENCES

1. Betran AP, Ye J, Moller AB, Souza JP, Zhang J. Trends and projections of caesarean section rates: global and regional estimates. **BMJ Glob Health.** 2021;6(6):1-8.
2. Watson SE, Richardson AL, Lucas DN. Neuraxial and general anaesthesia for caesarean section. **Best Pract Res Clin Anaesthesiol.** 2022;36(1):53-68.
3. Swain A, Nag DS, Sahu S, Samaddar DP. Adjuvants to local anesthetics: current understanding and future trends. **World J Clin Cases.** 2017;5(8):307-313.
4. Wilson DJ, Douglas MJ. Spinal anaesthesia for caesarean section. **J Obstet Gynaecol Can.** 1998;20(8):754-761.
5. Stoelting RK, Hillier SC. Opioid agonists and antagonists. In: **Stoelting's Pharmacology and Physiology in Anesthetic Practice.** 6th ed. Philadelphia: Elsevier; 2022.

6. Stoelting RK, Hillier SC. Benzodiazepines. In: **Stoelting's Pharmacology and Physiology in Anesthetic Practice.** 6th ed. Philadelphia: Elsevier; 2022.
7. Shadangi BK, Garg R, Pandey R, et al. Effects of intrathecal midazolam in spinal anaesthesia: a prospective randomized case-control study. **Singapore Med J.** 2011;52(6):432-435.
8. Shah VR, Mehta S, Khan DA. Comparative study of intrathecal fentanyl with bupivacaine and fentanyl-midazolam with bupivacaine in spinal anaesthesia. **Indian J Clin Anaesth.** 2021;8(2):302-309.
9. Bromage PR. A comparison of the hydrochloride and carbon dioxide salts of lidocaine and prilocaine in epidural analgesia. **Acta Anaesthesiol Scand.** 1965;9:55-69.
10. Ramsay MAE, Savege TM, Simpson BRJ, Goodwin R. Controlled sedation with alphaxalone-alphadolone. **Br Med J.** 1974;2:656-659.
11. Aasim SA, Reddy V, Reddy M, et al. Comparative study of the effects of intrathecal midazolam and fentanyl as additives to hyperbaric bupivacaine. **J Evid Based Med Healthc.** 2015;2(56):8845-8848.
12. Bhushanam MR, et al. Comparative study of intrathecal midazolam (1 mg) and fentanyl (25 μg) as additives to hyperbaric bupivacaine. **J Chalmeda Anand Rao Inst Med Sci.** 2019;17(1):1-5.
13. Fawaz A, Elie T, Abdelwahab W, Mattar A. Comparative study between intrathecal fentanyl and midazolam as adjuvant to local anesthetics in elective cesarean section. **Ain Shams Med J.** 2020;71(4):841-852.
14. Ebrie AM, Mohammed A, et al. Hemodynamic and analgesic effect of intrathecal fentanyl with bupivacaine in elective cesarean section. **PLoS One.** 2022;17(7):e0268318.
15. Ferrarezi WP, Braga AFA, Ferreira VB, et al. Spinal anesthesia for elective cesarean section: bupivacaine associated with different doses of fentanyl—randomized clinical trial. **Braz J Anesthesiol.** 2021;71(6):642-648.
16. Shaikh SI, Govindaraju C, Hegade G. Comparison of intrathecal fentanyl and midazolam for cesarean section under spinal anesthesia. **J Clin Diagn Res.**
17. Hung TY, Huang YS, Lin YC. Maternal and neonatal outcomes with intrathecal midazolam as an adjuvant to spinal anesthesia in cesarean delivery: a systematic review and meta-analysis. **J Clin Anesth.** 2022;80:110786.
18. Cenkowski MJ, Maguire D, Kowalski S, et al. Hemodynamic effects of low-dose bupivacaine spinal anesthesia for cesarean section: a randomized controlled trial. **Saudi J Anaesth.** 2019;13(3):208-214.
19. Miller RD, editor. **Miller's Anesthesia.** 9th ed. Philadelphia: Elsevier; 2020.
20. Stoelting RK, Hillier SC. Local anesthetics. In: **Stoelting's Pharmacology and Physiology in Anesthetic Practice.** 6th ed. Philadelphia: Elsevier; 2022.