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Analgesic Effect of Three Different Adjuvants to Bupivacaine in Transversus Abdominis Plane Block after Caesarean Section: A Randomized Controlled Trial.

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ABSTRACT:

Background: A vital component of enhanced recovery programs is optimal pain management after cesarean section (CS). Transversus abdominis plane block (TAPB) is recommended to reduce post-CS pain.

Methods: The study evaluated three different adjuvants to bupivacaine in TAPB after CS. The primary endpoint was the time to the first rescue analgesia. The secondary endpoints were the visual analog scale (VAS) for pain, the total opioid consumption, the post-operative vital signs, and patient satisfaction with analgesia. The patients were assigned to four groups regarding the additives to bupivacaine (dexamethasone, Dexmedetomidine (DEX), tramadol, and control groups). The study included 240 patients planned for elective lower-segment CS underneath spinal anesthesia. After surgery, a bilateral posterior ultrasound-guided TAPB was performed.

Results: The first request for analgesia in dexamethasone group was delayed significantly compared to control group (p-value = 0.041). Still, it was statistically insignificant compared to the DEX and Tramadol groups. The opioid analgesic requirement in the dexamethasone group was reduced substantially in comparison to control group (p-value = 0.006). However, it was statistically insignificant compared to the DEX and Tramadol groups. The dexamethasone group had significantly lower VAS ratings from 8 to 24 hours than the other additives. However, VAS scores between 30 minutes and 4 hours and patient satisfaction with analgesia were comparable among groups.

Conclusion: adding dexamethasone, dexmedetomidine, or tramadol to TAPB improved postoperative analgesia without inciting severe adverse effects after CS. The dexamethasone significantly reduced the opioid analgesic requirements and prolonged analgesia for up to 24 hours.

Keywords: Dexamethasone, dexmedetomidine, tramadol, postoperative analgesia, transversus abdominis plane block, Ultrasound-guided.

INTRODUCTION

Postoperative pain management is challenging, as improper pain control leads to increased incidences of chronicity, patient discomfort, increased hospital stay, and complications. Optimal pain management following cesarean section (CS) is a significant issue in the enhanced recovery after surgery (ERAS) program and is even more challenging because the patient must ambulate early and be alert to take care of the newborn. (1, 2)

Although opioids effectively control postoperative pain, they are associated with dose-dependent unpleasant pruritus, nausea, and respiratory depression. (3-5) Intravenous or neuraxial opioids would be restricted to individuals with intolerable pain or not eligible for oral medications due to serious adverse effects. (6-8)

Post-caesarean delivery analgesia can be achieved by multimodal approach by combining different techniques and medications. Compared to using a single analgesic, multimodal analgesia offers improved pain control and decreases opioid consumption and complications. (9)

Transversus abdominis plane block (TAPB) targets the sensory supply of anterior abdominal wall (ventral rami of the spinal nerves T7 to L1) by local anesthetic deposition just above the transversus abdominis muscle. Using ultrasound (US) guidance increases the blocks' efficacy, safety, and accuracy. (10) There are several approaches for US-guided TAPB including lateral, posterior, and subcostal approaches. The posterior TAPB is associated with prolonged action and better analgesic coverage, which may be explained by local anesthetic (LA) diffusion posteriorly to the lumber paravertebral

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space. (11, 12)

Different adjuvants can be administered with local anesthetics, including opioids, dexamethasone, ketamine, dexmedetomidine (DEX), and clonidine, to enhance efficacy and extend the duration of the block. (13)

Long-acting corticosteroid dexamethasone reduces ectopic nociceptive C-fiber discharge and prevents the synthesis of inflammatory mediators. (14) Even though the exact process by which dexamethasone acts perineurally is not entirely clarified, several trials have determined that perineural dexamethasone enhances sensory block. (15)

DEX (a selective alpha-2 agonist) has an inhibitory effect on hyperpolarization-activated cation channels perineurally. (16, 17) Tramadol is a mild opioid agonist with local anesthetic-like action. It also blocks the reuptake of norepinephrine and serotonin, which potentiate the inhibitory action of the descending pain tracts, therefore suppressing pain propagation at the spinal level. (18, 19)

This trial aimed to evaluate and compare the impact of adding three distinct adjuvants, dexamethasone, DEX, and tramadol, to bupivacaine in TAPB on postoperative pain after CS. Our primary endpoint was the time for the first request for analgesia. The secondary outcomes were visual analog scale (VAS) scores for pain, total opioid consumption, postoperative hemodynamic stability, patient satisfaction with analgesia, and complications.

Methods, Randomization, and Blinding.

The current trial was approved by the Pan African Clinical Trial Registry (**PACTR202001534185026)**. It was a prospective, randomized, controlled study designed after ethical authorization from the Faculty of Medicine (IRB NO: 00012098, FWA NO: 00018699, Serial Number: 0304482**)**. Participants, investigators, and outcome assessors were all blinded. This research followed the CONSORT 2010 standards for clinical trials.

The Department of Medical Statistics computed the minimal sample size using IBM SPSS software (IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). According to previous studies, the sample size is sufficient to achieve 90% power to determine a medium-sized effect (Cohen's d = 0.25) using one-way ANOVA at the 0.05 significance level. A minimum required number of 240 patients (60 patients /group) achieved 90% statistical power to detect differences between the groups. (20-22)

The study included 240 pregnant participants ASA II, who were scheduled for elective CS under the effect of spinal anesthesia (Figure 1). Patients were randomly assigned to four distinct groups via a computer-generated model. The exclusion criteria were twin pregnancy, complicated or emergency CS, contraindications for spinal anesthesia, failed spinal anesthesia, history of allergy to any of the studied medications, local infection, and morbid obesity.

Bilateral US-guided posterior TAPB was performed with 20 mL of bupivacaine (0.25%), and the patients were arbitrarily allocated according to the additives to local anesthetic:

1. **In the dexamethasone Group:** Dexamethasone (4 mg) on each side.
2. **In the Dexmedetomidine Group:** DEX (0.5 µg/kg) per side.
3. **In the Tramadol Group:** Tramadol (50 mg) per side.
4. **In the Control Group:** Received bupivacaine (0.25%) without adjuvants.

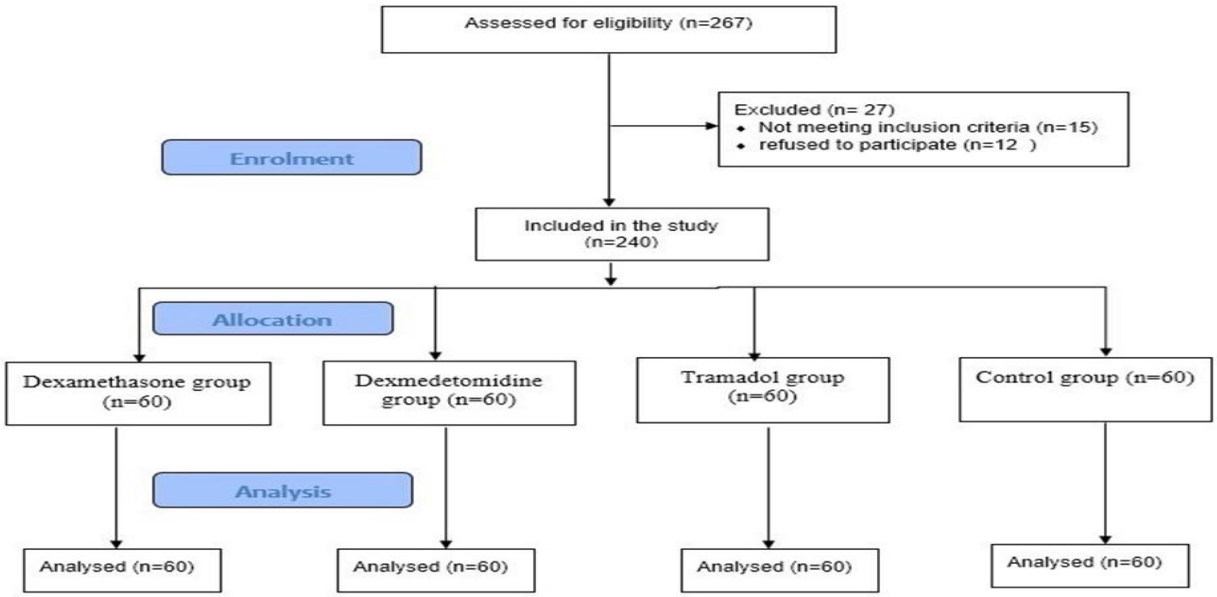

Figure (1): Flow chart of patient recruitment.

Block technique: Bilateral US-guided posterior TAPB was performed in the supine position after cesarean section under a strict aseptic technique. The linear transducer was oriented transversely in the flank along the anterior axillary line until the three muscle layers (external and internal oblique and transversus abdominis) were detected. The transducer was shifted posteriorly till the transversus abdominis transformed into aponeurosis. The LA mixture was injected above the

aponeurosis after verifying the needle tip position with normal saline. All patients received 1g of paracetamol every 6 hours and 30 mg of ketorolac every 8 hours postoperatively.

Measurements

1. The duration from the block's end until the first rescue analgesia dose and the number of patients who required rescue analgesia were recorded.
2. Total opioid requirements (mg) during the first 24 hours were calculated.
3. Preoperative basal heart rate (HR) and mean arterial blood pressure (MAP). The patient's HR, MAPB, and VAS scores were assessed at 30 minutes, 1 and 4 hours, and then every 4 hours in the first 24 hours postoperatively. If the VAS was ≥ 4, patients received repeated increments of 2 mg of morphine until the VAS score was < 4 and not to exceed 0.05 mg /kg/dose.
4. Patients were closely monitored for severe side effects or complications (such as hematoma formation, local infection, or visceral injury).
5. Patient satisfaction was surveyed using the Likert scale (23), where one equals very dissatisfied, and five equals very satisfied.
6. The age and weight.

Statistical analysis

Data was entered and analyzed using the IBM SPSS software package version 20.0. (Armonk, NY: IBM Corp). The Kolmogorov–Smirnov test was employed to confirm the normality of the data distribution. The chi-square test (Monte Carlo) was used to compare categorical variables. ANOVA was used to compare the four studied groups, followed by a Post Hoc test (Tukey) for pairwise comparison. ANOVA with repeated measures was utilized to analyze normally distributed quantitative data across multiple intervals, and the Post Hoc test (Bonferroni adjusted) was used for pairwise comparisons. The Kruskal-Wallis test was applied to analyze abnormally distributed quantitative data, followed by a Post Hoc test (Dunn's test for multiple comparisons) for pairwise comparisons. The Friedman test was employed to analyze abnormally distributed quantitative data across various intervals, and the Post Hoc Test (Dunn's test) was used for pairwise comparisons. The significance of the results obtained was determined at the 5% level.

Results:

The first request for analgesia in the dexamethasone group was delayed significantly compared to the control group (p-value = 0.041). Still, it was statistically insignificant compared to the DEX and Tramadol groups (p-values = 0.961 and 1.000, respectively) (Table I). The number of patients who requested rescue analgesia was decreased significantly in the dexamethasone group compared to the tramadol and control groups (p-values = 0.032 and 0.020, respectively); however, it was statistically insignificant in comparison to the DEX group (p-values = 0.673). The opioid analgesic requirement in the dexamethasone group was significantly decreased compared to the control group (p-value = 0.006). However, it was statistically insignificant compared to the DEX and Tramadol groups (p-values = 0.123 and 0.618, respectively) (Table I).

Table (I): Comparison among the four studied groups regarding rescue analgesia, total morphine consumption, and patient satisfaction

	Dexamethasone (n = 60)	**Dexmedetomidine (n = 60)**	**Tramadol (n = 60)**	**Control (n = 60)**	**P**
Time to first request for morphine (hours)					
Mean ± SD.	12.71 ± 3.93	12.0 ± 3.92	12.72 ± 4.73	9.15 ± 3.15	0.007*
p_0		0.961	1.000	0.041*	
Significance among Groups		p_1=0.942, p_2=0.118, p_3=0.010*			
	n (%)	**n (%)**	**n (%)**	**n (%)**	
The number of patients required Rescue analgesia.					
No	46 (76.7%)	44 (73.3%)	35 (58.3%)	34 (56.7%)	0.038*
Yes	**14 (23.3%)**	**16 (26.7%)**	**25 (41.7%)**	**26 (43.3%)**	
p_0		0.673	0.032*	0.020*	
Significance among Groups.		p_1=0.083, p_2=0.056, p_3=0.853			
Total morphine consumption (mg)/day					
2	9 (64.3%)	4 (25%)	14 (56%)	4 (15.4%)	^{MC}p = 0.012*
4	3 (21.4%)	8 (50%)	9 (36%)	17 (65.4%)	
6	2 (14.3%)	4 (25%)	2 (8%)	5 (19.2%)	
p_0		^{MC}p = 0.123	^{MC}p = 0.618	^{MC}p = 0.006*	
Significance among Groups		$^{MC}p_1$ = 0.131, $^{MC}p_2$ =0.612, MCp_3 = 0.010*			
Patient Satisfaction					
3	3 (5%)	3 (5%)	4 (6.7%)	6 (10.0%)	^{MC}p = 0.540
4	12 (20%)	19 (31.7%)	11 (18.3%)	15 (25.0%)	
5	45 (75%)	38 (63.3%)	45 (75%)	39 (65.0%)	

SD: **Standard deviation** **F**: **F for One-way ANOVA test**, pairwise comparison bet. every two groups were done using the **Post Hoc Test (Tukey)**
c^2: **Chi-square test** MC: **Monte Carlo**
p: p-value for comparing the four studied groups
p_0: p-value for comparing the **Dexamethasone** and each other groups
p_1: p-value for comparing the **Dexmedetomidine** and **Tramadol**
p_2: p-value for comparing the**Dexmedetomidine** and **Control**
p_3: p-value for comparing **Tramadol** and **Control**
*: $p \leq 0.05$ (Statistically significant)

The VAS scores significantly increased over 24 hours in the four groups compared to the baseline VAS scores at 30 minutes. Regarding inter-group comparison, the VAS scores at 8 hours, 12 hours, 16 hours, 20 hours, and 24 hours were significantly lower in the dexamethasone group compared to the other three groups. From 30 minutes until 4 hours postoperatively, the differences in the VAS among the four groups were insignificant (Table II).

Table (1I): Comparison of VAS Scores among the four studied groups.

VAS	Dexamethasone (n = 60)	Dexmedetomidine (n = 60)	Tramadol (n = 60)	Control (n = 60)	H (p)
30 min					
Mean ± SD.	0.32 ± 0.57	0.32 ± 0.47	0.13 ± 0.34	0.37 ± 0.55	7.690
Median (Min. – Max.)	0 (0 – 2)	0 (0 – 1)	0 (0 – 1)	0 (0 – 2)	(0.053)
1 hr.					
Mean ± SD.	0.65 ± 0.73	0.75 ± 0.57	0.55 ± 0.59	0.83 ± 0.64	7.299
Median (Min. – Max.)	$0.5^{\#}$ (0 – 2)	$1^{\#}$ (0 – 2)	$0.5^{\#}$ (0 – 2)	$1^{\#}$ (0 – 2)	(0.063)
4 hrs.					
Mean ± SD.	1.28 ± 0.88	1.45 ± 0.62	1.4 ± 0.69	1.23 ± 0.59	6.586
Median (Min. – Max.)	$1^{\#}$ (0 – 5)	$1^{\#}$ (0 – 4)	$1^{\#}$ (0 – 4)	$1^{\#}$ (1 – 4)	(0.086)
8 hrs.					
Mean ± SD.	1.45 ± 0.67	2.12 ± 0.49	1.88 ± 0.8	1.92 ± 1.01	29.193^{*}
Median (Min. – Max.)	$1^{\#}$ (0 – 3)	$2^{a\#}$ (1 – 4)	$2^{a\#}$ (1 – 4)	$2^{a\#}$ (1 – 5)	($<0.001^{*}$)
12 hrs.					
Mean ± SD.	1.63 ± 0.88	2 ± 0.78	2.03 ± 1.12	2.03 ± 0.94	13.062^{*}
Median (Min. – Max.)	$1^{\#}$ (1 – 4)	$2^{a\#}$ (1 – 5)	$2^{a\#}$ (1 – 5)	$2^{a\#}$ (1 – 5)	(0.005^{*})
16 hrs.					
Mean ± SD.	1.52 ± 0.83	1.77 ± 0.77	1.83 ± 0.87	2.03 ± 0.99	13.518^{*}
Median (Min. – Max.)	$1^{\#}$ (0 – 5)	$2^{a\#}$ (1 – 5)	$2^{a\#}$ (1 – 5)	$2^{a\#}$ (1 – 5)	(0.004^{*})
20 hrs.					
Mean ± SD.	1.33 ± 0.71	1.78 ± 0.85	1.78 ± 0.9	1.72 ± 0.94	15.978^{*}
Median (Min. – Max.)	$1^{\#}$ (0 – 5)	$2^{a\#}$ (1 – 4)	$2^{a\#}$ (1 – 5)	$1.5^{a\#}$ (1 – 5)	(0.001^{*})
24 hrs.					
Mean ± SD.	1.33 ± 0.66	1.67 ± 0.48	1.82 ± 0.89	1.87 ± 0.85	21.318^{*}
Median (Min. – Max.)	$1^{\#}$ (0 – 4)	$2^{a\#}$ (1 – 2)	$2^{a\#}$ (1 – 5)	$2^{a\#}$ (1 – 5)	($<0.001^{*}$)

SD: **Standard deviation**
H: H for **Kruskal-Wallis test,** pairwise comparison bet. Every two groups were analyzed using a **Post Hoc Test (Dunn's test for multiple comparisons)**
p: p-value for comparisons between the four studied groups
#: Significant with **30 min** for Post Hoc Test **(Dunn's) for Friedman test.**
a: Significantly different from **Dexamethasone**
*: $p \leq 0.05$ (Statistically significant)

Patient satisfaction with analgesia in the present trial was comparable (p-value = 0.540) (Table I). There were insignificant variations regarding patients age or weight (p-values =0.381 and 0.137, respectively) (Table III). Similarly, there were no significant variations in postoperative HR or MAPB among groups in the first 24 hours (Figures 2 and 3). We did not report any complications in the studied groups.

Table (III): Demographic Data.

	Dexamethasone (n = 60)	Dexmedetomidine (n = 60)	Tramadol (n = 60)	Control (n = 60)	P value
Age (years) (Mean ± SD).	29.52 ± 4.18	28.33 ± 3.96	29.53 ± 5.02	28.82 ± 4.59	0.381
Weight (kg) (Mean ± SD).	84.68 ± 6.04	85.18 ± 6.29	86.60 ± 5.62	84.05 ± 6.66	0.137

SD: **Standard deviation** **F**: **F for ANOVA test**
p: p-value for comparing the four studied groups

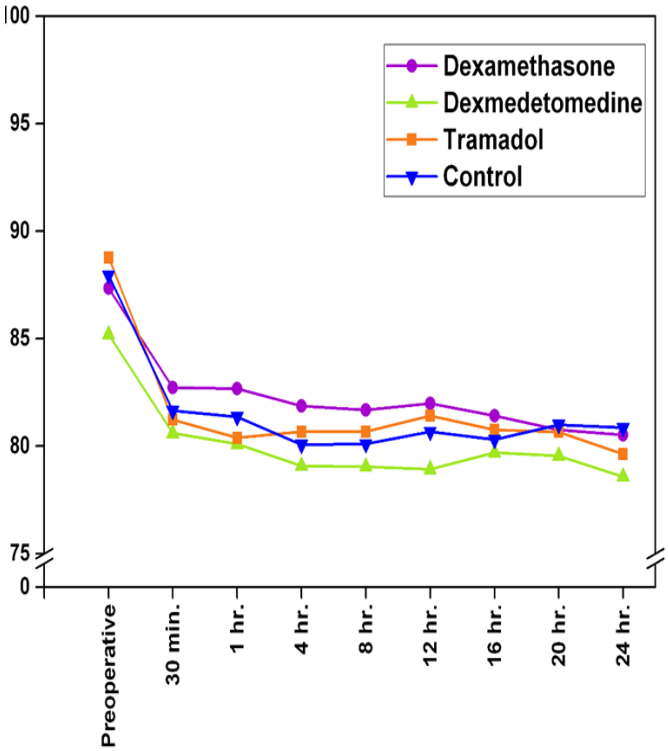

Figure (2): Comparison of postoperative heart rate (beat/minute) among the four studied groups

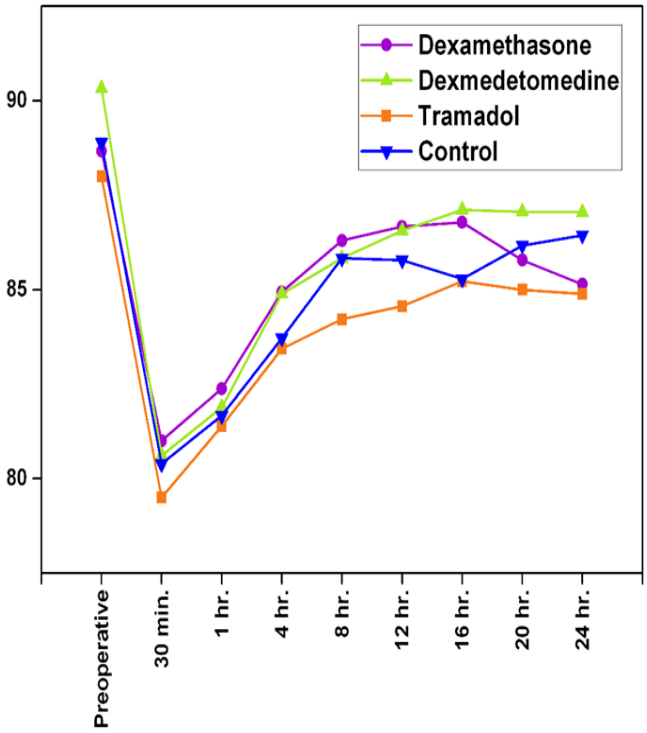

Figure (3): Comparison of postoperative Mean arterial blood pressure (mmHg) among the four studied groups

Discussion:

Effective management of post-caesarean section pain is crucial. Inadequate pain management is associated with increased opioid requirements, prolonged hospital stay, and delayed ambulation with an increased risk of thromboembolism. (8, 24) TAPB is a regional block that is simple and achieves adequate pain control with rare complications. (25, 26) In the current study, we evaluated the analgesic effects of adding three adjuvants, dexamethasone, DEX, and tramadol, to bupivacaine in posterior US-guided TAPB in comparison to the control group (bupivacaine only without additives).

In the present study, while the initial request for analgesia in the dexamethasone group was comparable to the DEX and Tramadol groups, it was significantly delayed compared to control group. The opioid consumption in the dexamethasone group was comparable to the DEX and Tramadol groups; however, it was substantially decreased in comparison to control group. The percentage of patients who requested rescue analgesia in dexamethasone group significantly decreased in comparison to tramadol and control groups, yet it remained comparable to the DEX group. Moreover, dexamethasone provided prolonged analgesia and significantly decreased the VAS scores from the 8th to the 24th hours in comparison to the other groups. Its potent anti-inflammatory and inhibition of neural discharge and nociception c-fibers transmission might be the reason why dexamethasone is a potent co-analgesic and local anesthetic adjuvant. (27) Several meta-analyses revealed that peri-neural dexamethasone, when compared to placebo, resulted in prolonged sensory block and significantly decreased postoperative pain. (15, 28) Sharma et al. (21), Gupta et al. (29), and others (27) reported that adding dexamethasone to TAPB considerably decreased pain and prolonged the duration of postoperative analgesia up to 24 h after cesarean section with a reduction in analgesic requirements.

Several studies (17, 30-33) revealed that tramadol and DEX as adjuvants improved VAS scores throughout the first 6 to 8 hours postoperatively. Bansal et al. (34) reported delayed requests for analgesia and reduced VAS scores in the DEX

group compared to local anesthetic-only TAPB after CS. A systematic review (35), including 1212 participants, concluded that peri-neural DEX significantly decreased VAS values (at rest for 8 hours and at movement for 4 hours postoperatively) and opioid consumption. However, it did not affect the incidence of side effects. Almarakbi (36) studied adding DEX to bupivacaine in TAPB for abdominal hysterectomy compared to control group. During the first 8 hours, The VAS at rest and during cough decreased considerably in the DEX group.

Kiran et al. (37) compared tramadol and dexamethasone when added to ropivacaine for TAPB in open cholecystectomy. The overall 24-hour VAS and analgesic consumption were decreased in dexamethasone group. Korkutata et al. (30) reported that dexmedetomidine and tramadol as TAPB adjuvants were comparable regarding the duration of analgesia, analgesic requirements, and adverse effects.

Contrary to our results, Singla et al. (38) reported prolonged analgesia and decreased analgesic requirement in dexmedetomidine compared to dexamethasone in bilateral TAP block following CS. His different methodology may explain his results since he used intrathecal fentanyl 25 µg with spinal anesthesia and lateral TAPB. Moreover, Kiran et al. (37) reported a comparable requirement and time for the first (paracetamol) and second (tramadol) rescue analgesia between tramadol and dexamethasone adjuvantsin subcostal TAPB for open cholecystectomy. However, coinciding with our findings, rescue opioid consumption, and VAS scores at 24 hours were significantly decreased in dexamethasone group. These findings may be attributed to the distinctive characteristics of visceral pain of open cholecystectomy, and patients in this study received general anesthesia with unilateral subcostal TAPB, which may have increased the need for analgesia in both groups.

Sinha et al. (39) studied dexamethasone and dexmedetomidine in US-TAPB for total abdominal hysterectomy. In the DEX group, they reported statistically decreased VAS scores at 6, 9, and 12 hours. However, at 18 to 24 hours, the VAS scores were comparable. A significant decrease in MABP and HR was found in the DEX group at 1, 12, and 18 hours. The DEX group had delayed the first request for analgesia and reduced opioid consumption. These different results may be explained by different surgery and the study's small sample size (37 participants in each group).

We reported insignificant differences among the four groups regarding postoperative heart rate (HR) and blood pressure. Adding the three adjuvants to LA in TAPB resulted in comparable patient satisfaction with analgesia.

Multiple researchers (30, 36, 40, 41) who used DEX in the regional blocks reported a significant decrease in the heart rate and MAPB, especially at higher doses (DEX≥ 1 µg/kg). The DEX (0.5 µg/kg) used in the present trial had a minor effect on vital signs.

Conclusion

Dexamethasone, tramadol, or DEX as adjuvants to bupivacaine in the TAPB extended postoperative analgesia and lowered analgesic needs after CS without serious adverse effects. The bupivacaine-dexamethasone TAPB mixture following CS significantly prolonged analgesia up to 24 hours. The percentage of patients who requested analgesia was more significant in the tramadol and control groups than in the dexamethasone group.

Competing interests and funds: none

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