

ORIGINAL RESEARCH

REGIONAL ANESTHESIA

Fentanyl versus tramadol as an adjunct to bupivacaine in ultrasound-guided supraclavicular brachial plexus blockade: pros and cons

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Abstract

Background & objective: There have been a lack of consensus among the anesthetists regarding the utility of different opioids as adjuvants in brachial plexus blockade (BPB). The results vary and there is no agreement. We studied the utility of fentanyl versus tramadol as an adjunct to local anesthetic bupivacaine in ultrasound-guided supraclavicular BPB.

Methodology: The study was conducted on 71 patients who were randomized in three groups for ultrasound-guided supraclavicular brachial plexus block. Group B: received 20 ml bupivacaine 0.5% plus normal saline 2 ml; Group F received 20 ml of bupivacaine 0.5% plus fentanyl 100 µg in 2 ml and Group T received 20 ml bupivacaine 0.5% plus tramadol 100 mg in 2 ml. Data was collected for the onset and duration of sensory and motor block, time to first request for rescue analgesia and the total analgesic consumption in first 24 h postoperatively.

Results: The onset of sensory blockade in Group T (8.36 ± 1.59 min) was significantly shorter compared to Group B [15.91 ± 3.21 min ($p = 0.011$)] and to Group F [10.64 ± 1.86 min ($p = 0.011$)]. The onset of motor blockade was also shorter in Group T (10.36 ± 1.92) compared to Group B [20.91 ± 3.22 min ($p = 0.001$)] and Group F [13.36 ± 1.29 ($p = 0.001$)] respectively. The time to first analgesic requests was significantly longer in the Groups T and F than in the Group B ($p = 0.001$ and $p = 0.021$, respectively) and significantly longer in the tramadol group compared to the fentanyl group ($p = 0.041$).

Conclusion: Tramadol as an adjuvant to bupivacaine in ultrasound-guided supraclavicular BPB, when compared to bupivacaine alone or with fentanyl, has a shorter onset of sensory and motor blockade and produces a significantly prolonged analgesia.

Key words: Adjuvants; Analgesia; Bupivacaine; Fentanyl; Tramadol; Ultrasound-guided supraclavicular block

Abbreviations: BPB – brachial plexus blockade; VAS – visual analog scale; MBP – mean blood pressure; HR – heart rate; SpO₂ – peripheral oxygen saturation; LSD – test Least Significant Difference test

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1. Introduction

Supraclavicular brachial plexus block (BPB) is an alternative technique to general anesthesia. It is a fast onset and reliable block of the brachial plexus.¹ The use of ultrasound for the performance of

supraclavicular block has been the gold standard since it enables the clinician to deposit the local anesthetic close to the nerves and observe the spread of the injectate in the real-time, thus improving the success rate with an enhanced safety margin.²

Adjuvants are added to the local anesthetic in supraclavicular BPB to improve the quality of the nerve blocks and prolong the duration of analgesia. The addition of opioids as adjuvants not only affects the block properties by activating opioid receptors outside the central nervous system but also decreases the need for postoperative opioids in patient controlled intravenous analgesia thereby reducing the potential side effects of opioids such as nausea, vomiting, and respiratory depression.³

Tramadol is a synthetic 4-phenylpiperidine analog of codeine that has a unique mode of action. It stimulates the μ receptor and to a lesser extent the δ and κ -opioid receptors. By its non-opioid mechanism, it motivates spinal inhibition of pain by decreasing the reuptake of norepinephrine and serotonin from nerve endings and strengthens the effect of local anesthetics when mixed in peripheral regional nerve block. It has far less respiratory depressant effect than the opioids due to weak μ receptor affinity.⁴

Fentanyl is a potent synthetic μ -receptor stimulating opioid. The addition of fentanyl to local anesthetics has different effects on the quality of brachial plexus blocks.⁵ Many controversies have been noted among the previous studies for the use of different opioids as adjuvants in BPB,⁶ Moreover, only a few studies compared the use of fentanyl versus tramadol as an adjunct to bupivacaine supraclavicular BPB.

We investigated the analgesic efficacy of fentanyl versus tramadol as an adjunct to bupivacaine in patients undergoing elbow and forearm surgery using ultrasound-guided supraclavicular BPB.

2. Methodology

After approval from the institutional review board and Clinical Trials Registry (NCT04666337), this prospective, randomized, double-blinded controlled study was conducted on 71 patients who were scheduled for elbow and forearm surgeries. The patients had been taught about the study and gave their consent in a written form.

Patients aged between 18 and 60 y, of both genders, and belonging to the ASA physical status I/II were included in the study. Patients who had bleeding disorders, received opioid analgesics before surgery, had a history of seizures, respiratory or cardiac diseases, local infections at the site where needle for the block was to be inserted, pregnant women or patients with unsatisfactory

block effect requiring supplementary anesthesia were excluded from the study.

Preoperatively, the procedure was explained to the patient in order to ensure cooperation and acceptance of being awake during surgery. Patients were shown a visual analog scale (VAS), which consisted of a straight 10 cm line of which one end represented 'no pain' (0 cm) and the other end represented 'The worst pain imaginable' (10 cm).

All patients were fasting for at least 6 h before the procedure. On arrival at the operating room, standard monitoring was connected and peripheral intravenous (I.V.) line with an 18G cannula was secured in the contralateral hand. Ringer lactate infusion started, and midazolam 0.05 mg/kg was given intravenously for sedation. We measured the mean blood pressure (MBP), heart rate (HR), peripheral oxygen saturation (SpO₂) before the block (0 min) and at 5, 10, 15, and 30 min then at 1, 2, 3, 6, 12, 18, and 24 h after the block.

2.1. Randomization and blinding

Patients were randomly divided into three groups using computer-generated randomization tables and the group allocation was hidden in sealed opaque envelopes.

Group B (bupivacaine group): patients received 20 ml bupivacaine 0.5 % + 2 ml normal saline.

Group F (fentanyl group): patients received 20 ml bupivacaine 0.5 % + fentanyl [100 μ g (2 ml)].

Group T (tramadol group): patients received 20 ml bupivacaine 0.5 % + tramadol [100 mg (2 ml)].

One of the authors who was not involved in the conduct of the study received serially numbered sealed envelopes indicating the B, F, or T codes for preparing the anesthetic mixture to be administered. The surgeon, attending anesthesiologists, data collecting personnel and the patient were blinded to the group assignment

Ultrasound-guided supraclavicular brachial plexus block⁷ was performed using a 5–10 MHz linear probe.

2.2. Patient evaluation

The primary outcome was the onset time of sensory and motor blockade. The onset of sensory blockade was checked with a gauze piece soaked in iced normal saline with a three-point scale⁴: Grade 0 = normal sensation; Grade 1 = loss of cold sensation (analgesia), Grade 2 = loss of touch sensation (anesthesia). Every patient was checked for the onset of motor blockade

using the modified Bromage scale (three-point scale)⁸; Grade 0: Normal motor function; Grade 1: Decreased

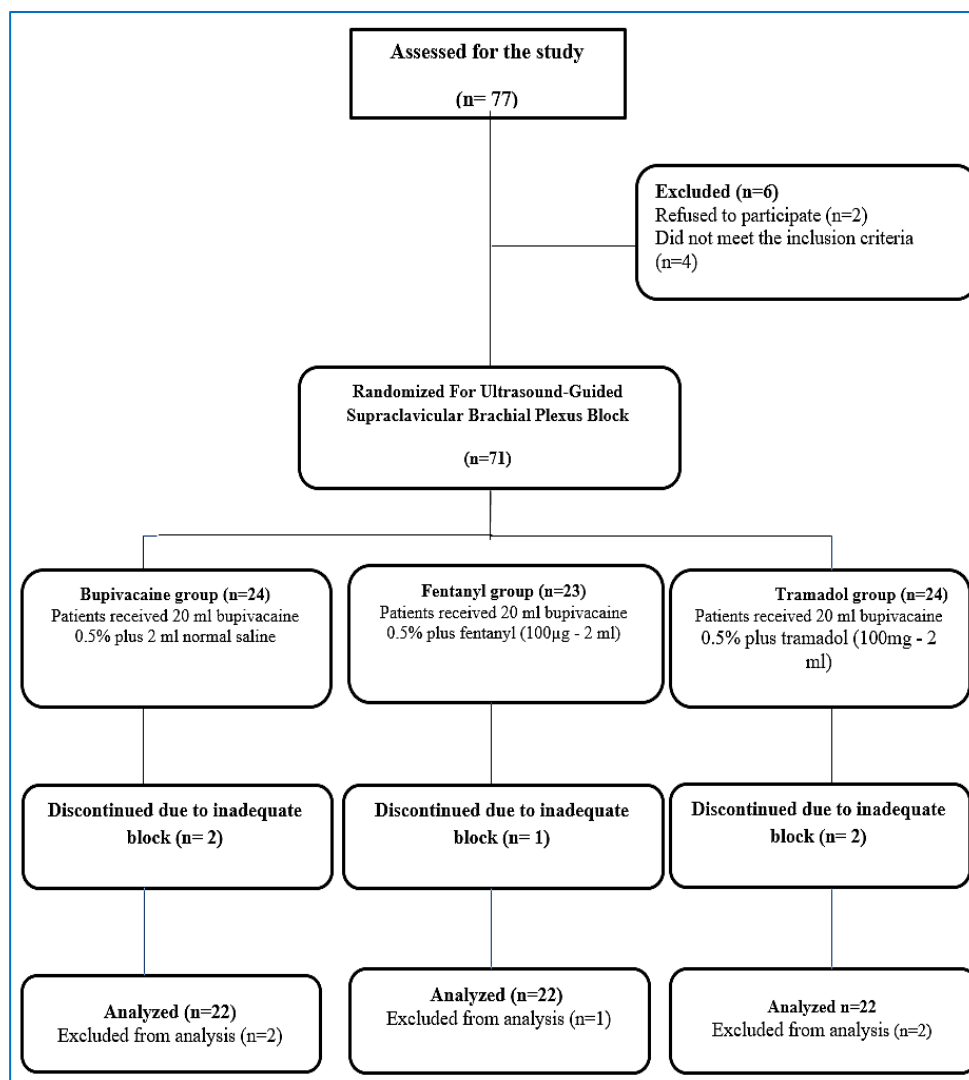


Figure 1: The study flowchart.

motor strength with the ability to move the fingers only; Grade 2: Complete motor block with inability to move the fingers.

Patients were evaluated in terms of secondary outcomes for:

- Duration of sensory block (h): Time from sensory block onset to the time of restoration of sensation at the surgical site.
- Duration of motor block (h): Time from motor block onset to the restoration of global mobility in the hand and the wrist.
- Visual analog scale (VAS) for the first 24 h: Patients were asked to rate their pain intensity at 1, 2, 4, 6, 12, 18, and 24 h after the block.

- First request for rescue analgesia, which was taken from the time of complete sensory block to the request for rescue analgesia when VAS \geq 4 cm.

- Rescue analgesia in the form of 0.05 mg/kg morphine sulfate intravenously and the total morphine consumption in the first 24 h were recorded.

- Mean blood pressure (MBP), heart rate (HR), peripheral oxygen saturation (SpO₂) were measured before the block (0 min) and at 5, 10, 15, 30 min then 1, 2, 3, 6, 12, 18 and 24 h after the block.

- Any adverse effects were recorded.

2.3. Statistical analysis

We calculated the sample size using the G-Power version 3.1.3 to detect a significant difference in the mean value of sensory blockade onset time

between three independent groups under the study. Based on the next parameters one-tailed, effect size 0.4, alpha error 0.05, power 0.80, and 1:1 allocation ratio, we calculated the sample size to be 58 and after taking into consideration the dropout rate, the total sample size was projected to be 66 (Twenty-two patients in each group)⁹

Data were analyzed by statistical package for the social sciences (SPSS) program for statistical analysis (version 26; SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean \pm SD. Qualitative data were expressed as frequency and percentage. F test (one-way analysis of variance) was applied for the comparison of more than two independent quantitative variables normally distributed with Fisher LSD (Least Significant Difference) test used as a post-hoc test. Chi-square χ^2 -test was used for comparison between two or more independent qualitative variables. A $p < 0.05$ was considered statistically significant.

Table 1: Patients' characteristics and surgical profile of the study groups

Parameters	Group B (N = 22)	Group F (N = 22)	Group T (N = 22)	P-value	LSD post hoc
Age (years): Mean \pm SD	31.12 \pm 8.3 9	30.18 \pm 8.16	33.4 \pm 10.38	0.126	Pa = 0.764 Pb = 0.110 Pc = 0.095
Gender					
Male [n (%)]	16 (72.7)	14 (63.6)	12 (54.5)	0.071	0.071
Female [n (%)]	6 (27.3)	8 (36.4)	10 (45.5)		
Weight (kg) Mean \pm SD	67.72 \pm 6.19	66.73 \pm 5. 92	69.27 \pm 5.84	0.094	Pa = 0.568 Pb = 0.091 Pc = 0.075
ASA classification					
ASA -I [n (%)]	15 (68.2)	20 (90.9)	13 (59.1)	0.066	
ASA - II [n (%)]	7 (31.8)	2 (9.1)	9 (40.9)		
Duration of surgery (min) (Mean \pm SD)	86.6 \pm 14.3	88.5 \pm 15.5	87.7 \pm 17.4	0.845	Pa = 0. 446 Pb = 0. 231 Pc = 0.555
<i>Group B: bupivacaine alone group; Group T: tramadol group; Group F: fentanyl group; LSD: least significant difference; ASA: American Society of Anesthesiologist. Pa: Control versus fentanyl; Pb: Control versus tramadol; Pc: Fentanyl versus tramadol.</i>					

Table 2: Sensory and motor block characteristics after drug administration in the study groups

Parameters	Group B (N = 22)	Group F (N = 22)	Group T (N = 22)	p-value	LSD post hoc
Sensory block onset time (min)	15.91 \pm 3.21	10.64 \pm 1.86	8.36 \pm 1.59	0.011	Pa = 0.012 Pb = 0.001 Pc = 0.045
Sensory block duration (h)	5.73 \pm 1.12	8.27 \pm 1.21	12.51 \pm 1.66	0.032	Pa = 0.040 Pb = 0.021 Pc = 0.015
Motor block onset time (min)	20.91 \pm 3.221	13.36 \pm 1. 29	10.36 \pm 1.92	0.001	Pa = 0.001 Pb = 0.001 Pc = 0.022
Motor block duration (h)	5.023 \pm 0.95	6.09 \pm 1.11	7.11 \pm 1.16	0.072	Pa = 0.056 Pb = 0.041 Pc = 0.051
<i>Group B: bupivacaine group; Group T: tramadol group; Group F: fentanyl group; LSD: least significant difference. Pa: bupivacaine group versus fentanyl group; Pb: bupivacaine group versus tramadol group; Pc: fentanyl group versus tramadol group. Data given as Mean \pm SD</i>					

3. Results

We assessed seventy-seven patients for eligibility in the present study. Six patients were excluded, two of whom refused to participate, and four patients did not meet the inclusion criteria. Also, five patients who required general anesthesia due to inadequate block were omitted from the data analysis. Figure 1 depicts

study flowchart.

Patients' characteristics and other operative data are summarized in Table 1. There was no significant difference in age, gender distribution, or weight of the patients in the study groups. Also, ASA status and duration of surgery were comparable in the three groups and there was no statistical significance.

Table 3: First time for rescue analgesia and total analgesic consumption in the study groups

Parameters	Group B (N = 22)	Group F (N = 22)	Group T (N = 22)	p-value	LSD post hoc
	Mean ± SD (Range)	Mean ± SD (Range)	Mean ± SD (Range)		
The first time for rescue analgesia (h):	4.55 ± 1.42 (3–7)	7.33 ± 2.22 (5–9)	9.52 ± 3.01 (6–12)	0.042	Pa = 0.021 Pb = 0.001 Pc = 0.041
Total morphine sulfate consumption (mg) in 1 st 24 h postoperatively	9.05 ± 1.5 (3 – 15)	5.91 ± 1.43 (3–10)	3.72 ± 0.51 (0–5)	0.022	Pa = 0.011 Pb = 0.001 Pc = 0.045

Group B: bupivacaine group; **Group T:** tramadol group; **Group F:** fentanyl group; **LSD:** least significant difference. **Pa:** bupivacaine group versus fentanyl group; **Pb:** bupivacaine group versus tramadol group; **Pc:** fentanyl group versus tramadol group.

The mean time for the onset of sensory block in Group B, Group F, and Group T was 15.91 ± 3.21 min, 10.64 ± 1.86, and 8.36 ± 1.59 min, respectively. The LSD post

hoc showed that the time for onset of sensory block in Group T was significantly faster compared to Group B (p = 0.001), and Group F (p = 0.045) (Table 2). The mean

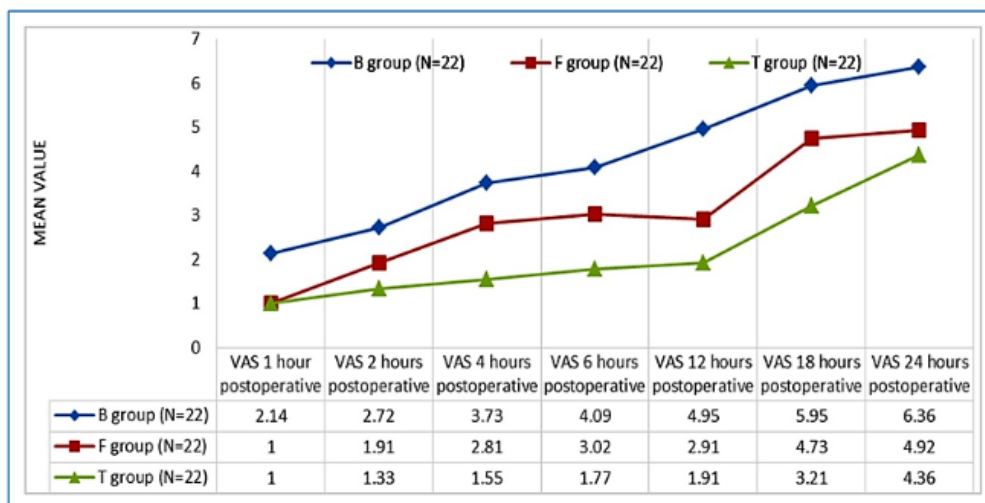


Figure 2: Visual analog scale (VAS) in the three groups over the postoperative times

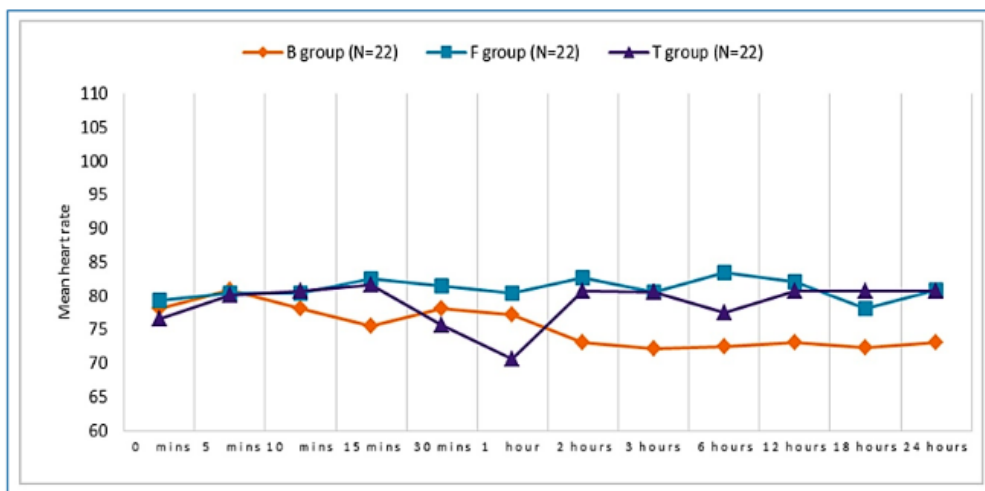


Figure 3: Heart rate of the three study groups at various time intervals

time for the duration of sensory block in Group T was significantly prolonged compared to Group B (p = 0.021) and Group F (p = 0.015), as shown in Table 2.

The mean time for the onset of motor block was different in the study groups. The mean time for Group B was 20.91 ± 3.21, Group F was 13.36 ± 1.29 and Group T was 10.36 ± 1.92 min (Table 2). Statistical analysis by The LSD post hoc showed that the mean time for the onset of motor block in Group T was significantly faster compared to bupivacaine and fentanyl groups (p < 0.001, p < 0.022, respectively). The mean time for the

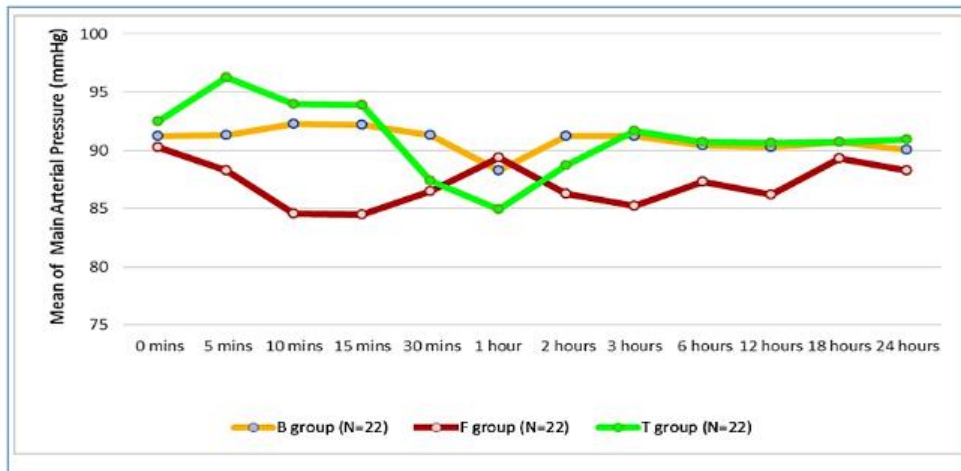


Figure 4: Mean arterial pressures in the three study groups at various time intervals

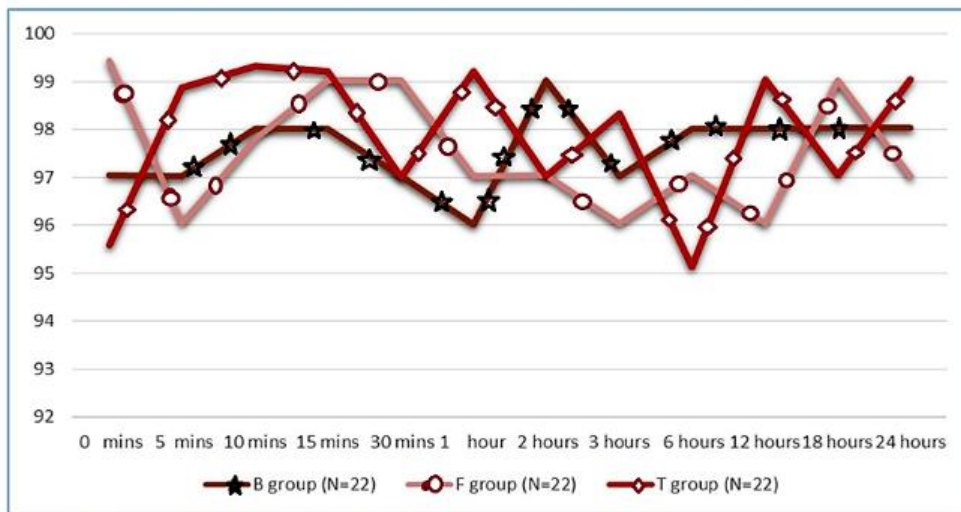


Figure 5: Arterial oxygen saturation (%) of the study groups at various time intervals

duration of the motor blockade between the three groups showed no statistically significant difference ($p = 0.072$) but statistical analysis by the LSD post hoc showed that the duration of the motor blockade was prolonged in Group T compared to Group B ($p = 0.041$) as shown in Table 2.

The statistical analysis by ANOVA test showed that the mean VAS score among the three groups differed significantly at the 4th ($p < 0.033$), 6th ($p < 0.031$), 12th ($p < 0.011$), and at the 24th ($p < 0.001$) hours after surgery.

The three groups had an average VAS score below 4 cm in the first 4 h after completion of surgery and required no rescue analgesia (Figure 2). Time taken for the first rescue analgesic dosage was significantly prolonged in tramadol and fentanyl groups compared to the bupivacaine group ($p = 0.001$, $p = 0.021$, respectively),

and significantly prolonged in the tramadol group compared to the fentanyl group ($p = 0.041$).

The ANOVA test showed that the total consumed doses of morphine sulfate in the first 24 h were statistically significant ($p = 0.022$) among the three study groups. LSD post hoc analysis revealed that patients in the tramadol group received fewer analgesic doses than those in the bupivacaine and fentanyl groups ($p = 0.001$ and $p = 0.045$, respectively) (Table 3).

As shown in the graph, there was no significant difference in heart rate ($p > 0.05$) between the three

groups as shown in (Figure 3). The mean arterial blood pressure between the three study groups was comparable, with no significant difference ($p > 0.05$), as shown in Figure 4. The statistical analysis by ANOVA 'F' test showed that there was no significant difference in arterial oxygen saturation between the three groups ($p > 0.05$) (Figure 5).

There were no significant differences in side effects between the three groups. The side effects were transient and did not require any therapeutic intervention.

4. Discussion

Supraclavicular BPB provides complete and reliable anesthesia for the upper limb surgeries. It has been associated with a shorter hospital stay, low financial burden, and it avoids complications associated with general anesthesia. Bupivacaine, when used alone for

supraclavicular BPB provides perfect operative situations with a brief duration of postoperative analgesia. Hence, the ideal adjuvant to achieve quick, dense block with prolonged postoperative analgesia is still being investigated.

Earlier studies used empirical single doses of perineural tramadol ranging from 50-100 mg and fentanyl ranging from 50-100 µg with significant differences in outcomes; however, the optimal doses that provide the greatest improvement in block parameters with the fewest side effects remain unknown.⁹⁻¹⁵ In our clinical trial, we investigated the pros and cons of 100 µg (1 µg/kg) fentanyl versus 100 mg (1 mg/kg) tramadol as a bupivacaine adjunct in ultrasound-guided supraclavicular brachial plexus blockade.

The main findings of our study show that the onset of sensory blockade was significantly faster in the tramadol group compared to bupivacaine and fentanyl groups ($p = 0.001$ and $p = 0.045$; respectively) and earlier in the fentanyl group than the bupivacaine group ($p = 0.012$). Patients in the tramadol group have a longer time for the first rescue analgesic dosage with a prolonged analgesia time than patients in fentanyl and bupivacaine groups. Also, the total duration of sensory block in the tramadol group was significantly longer than in the fentanyl and bupivacaine groups ($p = 0.015$, $p = 0.021$; respectively). Sensory prolongation was also observed in the fentanyl group compared to the bupivacaine group ($p = 0.040$).

Consistent with our results, Nagpal et al. in their study confirmed that when tramadol plus bupivacaine were injected perineurally for supraclavicular brachial plexus block, they sped up the onset of sensory block, motor block and prolonged the time to rescue analgesia as compared to the other two groups in which tramadol was either injected intravenously (systemic group) or was not given at all (control group).⁴

Shin et al. in a systematic review and meta-analysis included 16 studies that examined the impact of the addition of tramadol to local anesthetics (LA) for BPB and indicates that use of tramadol as an adjuvant to LA in BPB prolongs the duration of sensory block, motor block, and shortens the time to onset of sensory block and motor block without any change in adverse effects.¹⁰

Matching with previous results, Kumaran and Haribaskar¹ evaluated the efficacy of tramadol (2 mg/kg) as an adjuvant to bupivacaine (0.25%) in the supraclavicular block in a study of 60 patients undergoing upper limb surgery. They found that patients in tramadol (BT) group had a shorter time of onset and a longer duration of sensory and motor blockade than the bupivacaine alone (B) group. In addition, the mean

duration of analgesia in BT (7.06 ± 2.894 h) was longer than Group B (3.42 ± 0.283 h).

The earlier onset of sensory block and prolonged analgesia in the fentanyl group compared to the bupivacaine group in the current study is also consistent with Kaniyil and Radhakrishnan observations.¹¹ They noticed that the total duration of analgesia was also significantly prolonged ($p < 0.001$) in fentanyl group compared to bupivacaine group.

Rajkhowa et al.¹² found that using fentanyl as an adjuvant in BPB extends sensory and motor duration by 3 h, and they speculate that the mechanism of fentanyl in prolonging analgesia could be due to the presence of peripheral functional opioid receptors.

However, Kiran et al.¹³ discovered that the onset time of the sensory block in the fentanyl group was delayed compared to the control group ($p = 0.01$). This difference from our results could be explained by the different local anesthetics (bupivacaine 0.5% 20 mL + lignocaine 2% 20 mL) and dose of fentanyl (50 µg) used during their work. Likewise, Kaniyil and Radhakrishnan¹¹ noticed that the onset time of complete sensory and motor block was significantly prolonged in the fentanyl group and compared to the bupivacaine group. This discrepancy could potentially be attributed to the varied local anesthetics (10 ml 1.5% lignocaine with adrenaline + 20 ml 0.25% bupivacaine) and fentanyl (50 µg) doses employed during their work.

Allene et al. compared the efficacy of 100 mg tramadol versus 50 µg fentanyl as an adjuvant to 0.25% bupivacaine for axillary block and founded that the onset of complete sensory and motor block was shorter in the fentanyl group compared to both the tramadol and bupivacaine groups ($P < 0.001$).¹⁴ Furthermore, the tramadol group had significantly longer mean duration of sensory and motor blockade. The most likely explanation for this dissimilarity from our results is due to factors related to the difference in the approach of axillary approach versus supraclavicular BPB.

Our findings are consistent with those of Nagpal et al.⁴ who observed that most patients who received perineurally tramadol for supraclavicular brachial plexus block required their first analgesic dose after 6 h of surgery, and that the delayed requirement of analgesia postoperatively in these patients was statistically significant compared to control group. The prolonged analgesia in the tramadol group could be due to the local anesthetic effect of tramadol on peripheral nerves as demonstrated by Yu-Chan Tsai et al.¹⁵

There was no significant difference in the hemodynamic parameters between the study groups. This finding was consistent with what Suman Chattopadhyay et al. had

discovered.¹⁶ Likewise, no major side effects such as respiratory depression, pneumothorax, signs, or symptoms of local anesthetic toxicity were observed in any study group.

5. Limitations

It is a small, single-center study. Large-scale multicenter studies are recommended to highlight the differences between fentanyl and tramadol in supraclavicular brachial plexus blockade.

6. Conclusion

We conclude that tramadol as an adjuvant to bupivacaine shortens the onset time of both sensory and motor blocks and prolongs the analgesia time when compared to fentanyl in supraclavicular brachial plexus block. Moreover, its hemodynamic stability and fewer perioperative side effects favor it as an adjuvant for nerve blocks.

7. Acknowledgments

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8. Conflict of interest

No potential conflict of interest relevant to this article was reported

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