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ORIGINAL INVESTIGATION

Dexmedetomidine versus sufentanil as adjuvants to bupivacaine for brachial plexus block during upper extremity surgery: a randomized clinical trial

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Abstract
Background: Brachial plexus block (BPB) has been accepted as a reliable alternative for general anesthesia in upper limb surgeries. Adding adjuvant drugs like dexmedetomidine and sufentanil has been shown to have clinical and pharmacologic advantages. In this randomized parallel clinical trial, we aim to compare the effects of these two adjuvants for bupivacaine in BPB.
Methods: In this double-blinded study, by using computer-assisted block randomization, 40 patients ranged from 20 to 65 years old and scheduled for elective upper limb surgeries were assigned to two equal study groups (n = 20), receiving 1 mL of 5 $\mu g.mL^{-1}$ sufentanil (group S) or 1 mL of 100 $\mu g.mL^{-1}$ dexmedetomidine (group D) in adjunction to 30 mL of 0.5% bupivacaine for supraclavicular BPB under the guidance of ultrasonography. Characteristics of local anesthesia and postoperative analgesia were evaluated (n = 40).
Results: The duration of blocks significantly improved in group S (sensory: estimated median difference (EMD) [95%CI] = 100.0 [70.0∼130.0], $p < 0.001$; motor: EMD [95%CI] = 120.0 [100.0∼130.0], $p < 0.001$). Group S also had significantly longer postoperative analgesia and lower opioid consumption within 24 hours after the surgery (EMD [95%CI] = 4.0 [3.0∼7.0], $p < 0.001$; EMD [95%CI] = -5.0 [-5.0∼-5.0], $p < 0.001$; respectively). None of the patients showed adverse effects concerning vital signs, nausea, or vomiting.
Conclusion: Our study showed that during ultrasound-guided supraclavicular BPB, sufentanil is a fairly better choice than dexmedetomidine as an adjuvant for bupivacaine and can provide preferable sensory and motor blocks. No significant side effects were seen in either of the study groups.

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Introduction

As a reliable alternative to general anesthesia, peripheral nerve blockade has attracted acceptance among specialists. Brachial plexus block (BPB) has been commonly performed for patients undergoing upper limb surgeries.[1] Regarding its less adverse effects, BPB has been considered an ideal choice for patients with underlying cardiopulmonary diseases.[2]

There are various approaches to perform BPB, depending on the patient's condition and the medical team's expertise.[3] The supraclavicular approach is an efficient and acceptable method for BPB.[4] Given the ease of procedure, high success rates, fast blockade onset time,[2] and high single-shot efficient blockade rates, the supraclavicular approach under ultrasound guidance is a suitable choice for BPB.

The addition of various drugs as adjuvants to the local anesthetic has been shown to have clinical and pharmacologic merits.[5–7] Prolonged duration of analgesia, faster blockade onset, and decreased total anesthetic usage, thus an extended safety margin of the block, are among the advantages.[8]

Alpha-2 adrenoreceptor agonists and opioids have been widely studied as adjuvant drugs.[9–11] Bupivacaine (known widely by its brand name, Marcaine®, Pfizer) is a local anesthetic that blocks Na^+ influx and thereby depolarization of nerve cells and has been widely used for peripheral nerve blockade. In this study, we aim to compare the effects of dexmedetomidine, an α-2 agonist, with sufentanil, a synthetic opioid, as adjuvants for bupivacaine. The onset and the duration of sensory and motor blocks and postoperative analgesia were evaluated and analyzed.

Material and methods

The ethics committee of the university approved the study protocol before the initiation of the study, and it was registered under the same code in the National Committee for Ethics in Biomedical Research, which is the official registry for the clinical trials of medical universities in the country. This study was registered retrospectively on the German Clinical Trials Register (DRKS) under the ID number DRKS00024182. Before obtaining written informed consent, the study protocol was described to each patient, and we answered their questions. Subsequently, written consent was obtained from all the individuals. None of the patients revoked their consent during or after the study.

This randomized, double-blinded, parallel (1:1), monocenter clinical trial was performed during October and November 2019. Forty patients aged 20 to 65 years and scheduled for elective upper limb surgeries were included. Their physical status was equivalent to the American Society of Anesthesiologists (ASA) I or II. Patients with prior brachial plexus injury or a history of allergic reactions to the study drugs were previously excluded.

Using computer-generated random numbers, one research assistant allocated the patients in blocks of 4 participants. Another assistant was separately responsible for enrolling the patients into blocks. A third assistant was responsible for assigning the patients to either of the study groups: S, receiving 1 mL of 5 μg.1 mL^{-1} sufentanil added to 30 mL of 0.5% bupivacaine; or D, receiving 1 mL of 100 μg.mL^{-1} dexmedetomidine added to 30 mL of 0.5% bupivacaine. The groups were initially named A and B, and the names S and D were assigned to the groups after the data collection. The volume of the solutions was equal in both groups. The drug type was masked from the patients and the anesthesia assistant who prepared the study drugs. One anesthesiologist performed nerve blocks and data registrations in the entire study. The drug type was also masked from the anesthesiologist. None of the patients experienced an unsuccessful block, and all of the enrolled patients were included in the analysis. The enrollment process was designed according to the CONSORT guideline, and flow diagram of the study is shown in Figure 1.

Before entering the operation room (OR), patients were medicated with 2 mg of midazolam using an intravenous (IV) line obtained from the non-injured upper limb. They were told to fast eight hours before surgery. Upon their arrival to the OR, patients' standard monitoring, including noninvasive measurement of peripheral O2 saturation (O2 sat), heart rate (HR), respiratory rate (RR), and noninvasive mean arterial pressure (MAP) was initiated. The registration of vital signs began at the anesthetic injection time and repeated 5, 15, and 30 minutes after the injection (start of surgery), and every 15 minutes until the end of surgery.

As sufentanil and dexmedetomidine have sedative characteristics, no intraoperative sedative was administered to the patients. However, if the administration of the sedative was indicated, 100 μg fentanyl would be injected intravenously, and the patient would be excluded.

The patients underwent nerve blockade under ultrasound guidance (SonoAce™ R5 Ultrasound Machine [Samsung] with LN5-12/40© Linear Probe [Samsung]) while their head was rotated at an angle of 45° to the opposite of the operation side in the supine position. After proper sterilization of the skin and anesthetization of the cutaneous tissue by injecting 3 ml of 2% lidocaine, brachial plexus was spotted in the supraclavicular fossa using ultrasound guidance. Delivery of the anesthetic solution was performed via a single injection to the brachial plexus using a 22G needle.

Sensory block was described using the pinprick test. Compared with the non-operative upper limb, the pinprick test has three scores: 2, indicating the normal sensation, 1, indicating the sensation loss to pinprick, and 0, indicating the sensation loss to fine touch. Achieving the score of 0 in the innervated regions of the five main branches of the brachial plexus (axillary, median, radial, musculocutaneous, and ulnar nerves) was considered a complete sensory block. Motor block was evaluated using modified Lovett's rating scale, which consists of 6 scores: 0 for complete paralysis, 1 for almost total paralysis, 2 for substantial movement impairment, 3 for slight movement impairment, 4 for a reduction in muscular force, and 5 for normal muscular force. The complete motor block was defined as reaching a score of 0 in the primary motor nerves of the upper limb innervated areas. The time interval between the completion of injection and the resultant complete block was defined as the onset of block. The time interval between the initiation of the complete block and its full restoration to the normal state was defined as the duration of the block.

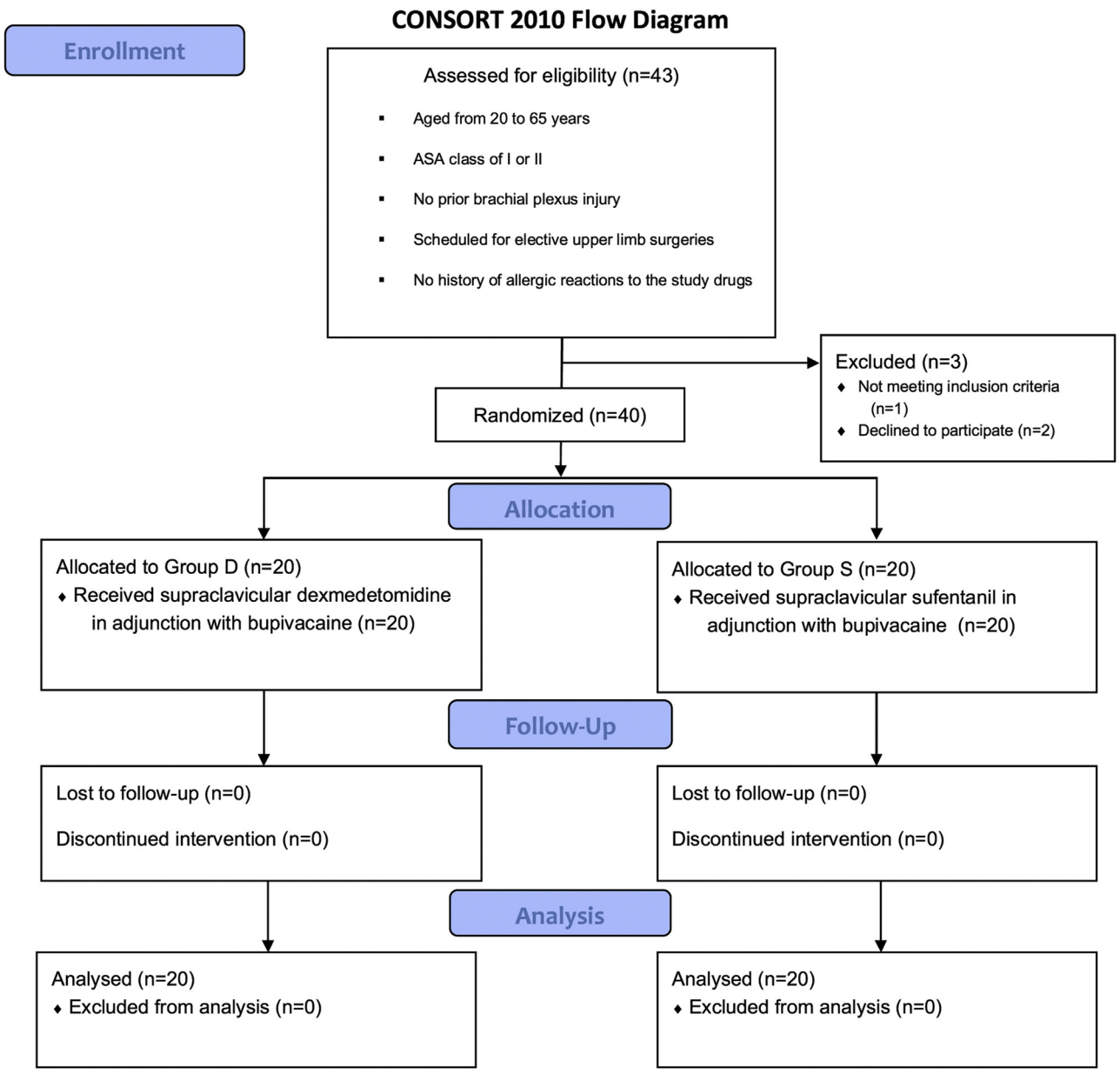

Figure 1 The CONSORT flow of the study.

Patients' MAP, HR, RR, and O2 saturation were recorded up to the end of surgery. In the recovery room, patients were observed for 30 minutes regarding postoperative side effects including itching, nausea, or vomiting.

Pain levels were evaluated before, during, and after the surgery using the Visual Analog Scale (VAS), that ranges from 0, indicating no pain, to 10, reflecting the worst pain possible. The patients were familiarized with the scale before entering the OR. Pain levels were recorded at 30, 15, 10, and 5 minutes before, once during, and 6, 12, 18, and 24 hours after the surgery. The VAS score at 30 minutes before surgery was registered concurrently with the injection time. For postoperative VAS score more than 4, 5 mg of IV morphine sulfate was administered. Also, the first opioid (IV morphine sulfate) request time (FORT) and total postoperative opioid consumption in the first 24 hours (TPOC24) were recorded using patients' folders and nursing notes. The mean TPOC24 value in each group was determined as the primary indicator of postoperative analgesia. If the patient requested opioids after the first 24 hours, the time would be registered, and the total opioid consumption would be considered zero.

Finally, patients were asked about their satisfaction with the surgery. Overall satisfaction rates were evaluated using a scale from 1, meaning a terrible experience, to 5, which showed an excellent experience.

The primary outcome of this study was sensory block duration. The secondary outcomes included the onset of blocks, the duration of motor block, FORT, TPOC24, VAS scores, and patients' vital signs. The null hypothesis was that there would be no difference between the groups concerning the sensory block duration.

Based on the values taken from a study conducted by Farooq et al.,[12] the sample size was calculated n = 20 for each group using PASS© 11 software. The level of statistical significance throughout the data analysis was assumed $p < 0.05$ for a two-sided *t*-test. Type 1 and type 2 errors were assumed 0.05 and 0.20, respectively. The primary outcome, sensory block duration, was treated as a continuous variable. The difference that was expected to be detected between the means of the two groups was 47.4.

Data analysis was performed using IBM® SPSS® Statistics version 25. Given the small sample size of the study groups, the Mann-Whitney U test was used and summary statistics are presented as median and interquartile range (IQR). Besides, categorical variables are reported as absolute and relative frequencies, and the Chi-square test was performed to compare them. Vital signs' data were analyzed using a Linear Mixed Model (LMM). For each vital sign variable, a maximum of 13 timepoints, including 30 (baseline), 25, and 15 minutes before, at the beginning, and every 15 minutes up to the end of the surgery (maximum surgery time = 135 minutes) were extracted. Due to different surgery durations, a LMM analysis was performed to compare these values. Regarding the small sample size, restricted maximum likelihood (REML) was chosen for LMM. All of the variables were modeled by using the Unstructured covariance type. Ultimately, due to multiple comparisons, the Holm-Bonferroni (HB) method was used for the correction of the family-wise error rate of 0.05.

Results

Demographic information and ASA classifications of both groups are summarized in Table 1. They were comparable between the groups. In the sufentanil group (S), the sensory and motor block duration was significantly longer compared to the other group. After adjustment of the study's α level by applying the HB method, significant differences between the onset of the blocks were ultimately revealed to be insignificant. The difference between the medians of the onset of sensory and motor blocks was approximately 1 minute and can be considered clinically irrelevant. Study groups were comparable regarding the duration of surgery. Detailed results for these variables are depicted in Table 2.

As presented in Table 2, there were significant differences in the patients' postoperative FORT and TPOC24 levels. The patients in group S had significantly lower TPOC24 levels, thus, a longer period of analgesia. Besides, the patients in group S had also significantly longer FORT values.

Regarding the VAS scores, there was a small but statistically significant difference at various timepoints. However, after applying HB method, the initial statistically significant differences at 15 and 10 minutes before surgery and 18 hours post-surgery were corrected to insignificant (p = 0.014 [0.002[1] p = 0.026 [0.002•], and p = 0.041 [0.003•], respectively). As shown in Figure 2, VAS was slightly, but significantly lower in group S at 12 hours post-surgery, and roughly the same at the rest of the timepoints.

[1] • HB adjusted α level

There was no incidence of nausea or vomiting in either of the groups.

In LMM for the vital signs, type III tests of fixed effects showed no statistically significant difference among the groups. Further details are depicted in Figure 3.

Moreover, patients' overall satisfaction rate was comparable among the groups (p = 0.054).

Discussion

The popularity of peripheral nerve blockade is rising. With fewer complications and more feasibility, it is an outstanding replacement to conventional general anesthesia during limb surgery. The supraclavicular approach under the guidance of ultrasound is among the most reliable and successful methods.

Like most local anesthetics, various drugs have been studied as adjuvants for bupivacaine. Dexmedetomidine is a well-known α-2 adrenoreceptor agonist and eight times more selective than clonidine for $\alpha 2/\alpha 1$ receptors.[8] Many studies have evaluated both its intravenous[13] and local[1,2,8,12,14,15] effects on regional nerve block. Sufentanil, a semi-synthetic fentanyl analog, is believed to be 5 to 15 times more potent than fentanyl and has been used in various types of anesthesia, including as an adjuvant to local anesthetics.[11,16–18] Sufentanil has been shown to prolong the duration of local analgesia when used as an adjuvant,[10,11] however, some studies suggest otherwise.[19] Since a limited number of studies have been done a head-to-head comparison of dexmedetomidine and sufentanil as adjuvants for local anesthetic during BPB, we compared these two drugs in our study. It is noteworthy that the use of ultrasonography can reduce not only the likelihood of supraclavicular BPB side-effects including phrenic nerve palsy but also the probability of intravenous or intra-arterial bolus injection of the anesthetic solution. Moreover, as elderly patients are more likely to benefit from BPB, probable bradycardia resulted from IV or intra-arterial dexmedetomidine,[20,21] or a clinically significant decrease in O2 saturation following intravenous sufentanil injections could be catastrophic.[22]

In our study, the duration of surgery was comparable between the study groups. Similar findings were observed in previous studies.[23–25] The duration of sensory and motor block was significantly improved in the sufentanil group. However, the onset of sensory and motor blocks was roughly similar among the groups. There were statistically significant differences concerning both TPOC24 and FORT, indicating better postoperative analgesia in the sufentanil group. Moreover, using VAS at various timepoints before and after the surgery, we observed significantly lower pain levels in the sufentanil group 12 hours after the surgery. Although it is plausible to assume that the considerable difference in TPOC24 levels might be due to the significant difference of VAS levels at 12 hours post-surgery, further follow-up data on the postoperative opioid consumption would be more helpful to establish a clearer understanding. Overall, the adjunction of sufentanil to the anesthetic solution seems to lower the postoperative pain slightly more than dexmedetomidine. This observation probably can be explained by the immense analgesic potency and the rapid onset of action of sufentanil. In this study, comparing the vital signs among

Table 1 Description of demographics and ASA classification among the groups.

Parameter		Groups		Total
		D (n = 20)	S (n = 20)	
Sex (n%)	Male	13 (65%)	15 (75%)	28 (70%)
	Female	7 (35%)	5 (25%)	12 (30%)
Median age (IQR[a]) (years)		38.00 (13)	41.00 (17)	40.00 (13.00)
Median height (IQR[a]) (cm)		178.00 (13)	175.50 (12)	176.00 (13)
Median weight (IQR[a]) (kg)		74.50 (12)	75.00 (15)	75.00 (14)
Median BMI (IQR[a])		23.46 (1.15)	23.09 (2.25)	23.16 (1.21)
ASA (n%)	I	13 (65%)	13 (65%)	26 (65%)
	II	7 (35%)	7 (35%)	14 (35%)

ASA, American Society of Anesthesiologists physical status.
[a] Interquartile range.

Table 2 Description and comparison of onset and duration of blocks (minutes), First Opioid Request Time after the surgery (h), and Total Postoperative Opioid Consumption within 24 h (mg) among the groups.

Parameter	Groups		The estimate of Median Difference[a]	95% Confidence Interval[a]		Two-tailed *p*-value[b]
	D (n = 20)	S (n = 20)		Lower	Upper	
Median sensory block onset (IQR)	16.00 (1)	14.00 (1)	−1.0	−2.0	0.0	0.005
Median sensory block duration (IQR)	530.00 (65)	647.50 (45)	100.0	70.0	130.0	< 0.001
Median motor block onset (IQR)	18.00 (0)	17.00 (2)	−1.0	−2.0	0.0	0.033
Median motor block duration (IQR)	470.00 (38)	590.00 (18)	120.0	100.0	130.0	< 0.001
Median duration of surgery (IQR)	60.00 (30)	67.50 (56)	0.0	−15.0	15.0	0.813
Median FORT (IQR)	16.00 (4)	20.00 (4)	4.0	3.0	7.0	< 0.001
Median TPOC24 (IQR)	10.00 (0)	5.00 (5)	−5.0	−5.0	−5.0	< 0.001

FORT, First Opioid Request Time; TPOC, Total Postoperative Opioid Consumption; IQR, Interquartile range.
[a] Mann–Whitney U test.
[b] Hodges–Lehman Estimator were used.

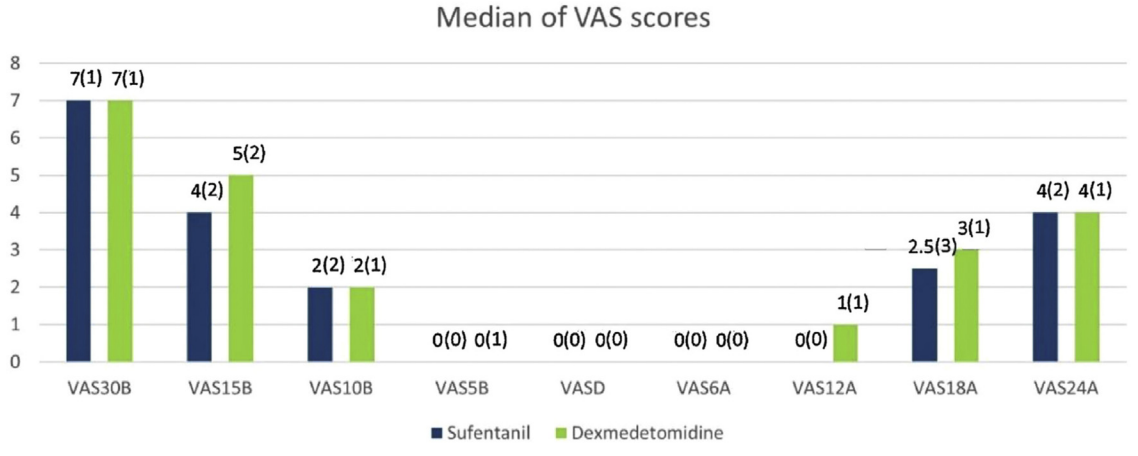

Figure 2 Description and comparison of VAS (interquartile range) at specific time intervals among the groups.

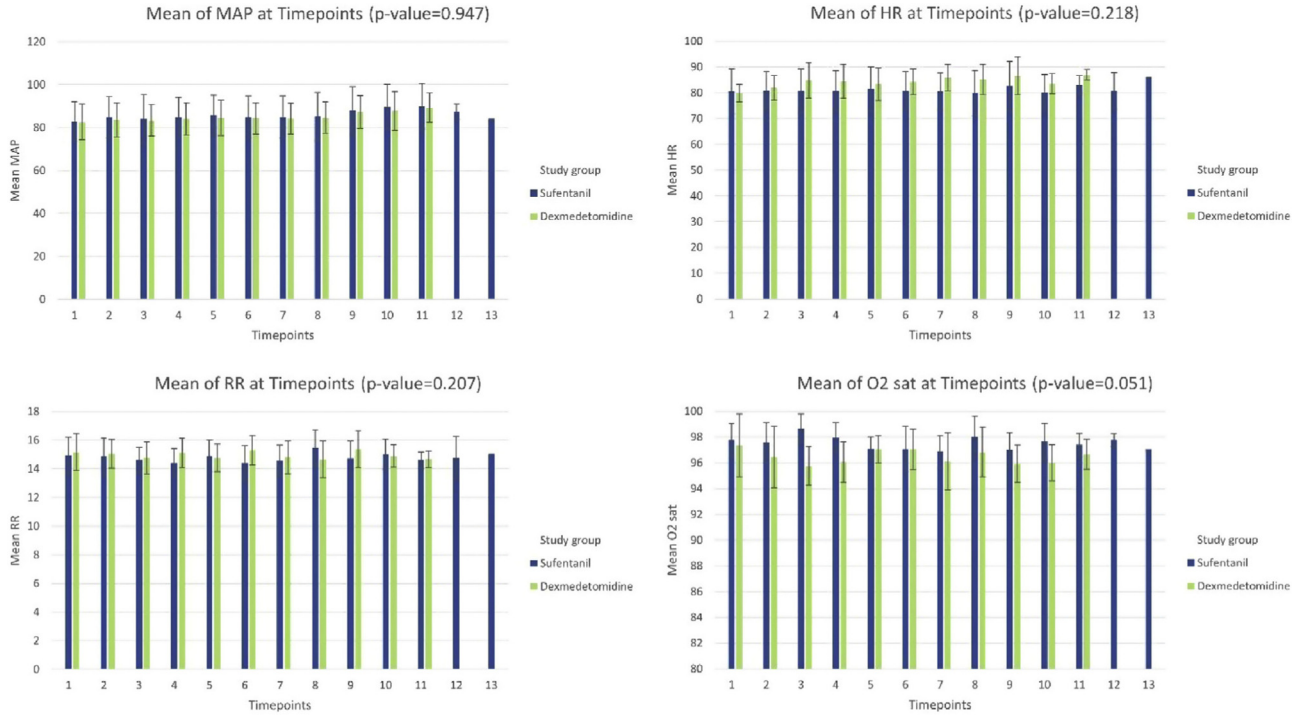

Figure 3 Comparison of mean vital sign variables between the groups using a Linear Mixed Model (*p*-values are the significancy for Type III Tests of Fixed Effects of Timepoint.
* Study group by using the Unstructured covariance type. Error bars represent ± SD).

the groups did not render significant differences. There were no incidences of cardiopulmonary complications among the patients. No patient reported itching, nausea, or vomiting. Besides, patients' satisfaction rates were comparable between the groups.

It has been shown that both the concentration and volume of the anesthetic solution are influential to attain desirable local anesthesia.[26] Although there were studies with lower concentrations of local anesthetic,[14,23] given the nature of dexmedetomidine and the potency of sufentanil, studying low concentrations of bupivacaine could hypothetically alter the effects of sufentanil or dexmedetomidine in an unbalanced fashion. Hence, we chose 0.5% bupivacaine concentration.

Farooq et al. conducted a randomized trial on 105 patients undergoing supraclavicular brachial plexus block. They compared three groups of patients receiving either normal saline added to 3 $mg.kg^{-1}$ of 0.75% ropivacaine, 1 $\mu g.kg^{-1}$ of fentanyl added to 3 $mg.kg^{-1}$ of 0.75% ropivacaine, or 1 $\mu g.kg^{-1}$ of dexmedetomidine added to 3 $mg.kg^{-1}$ of 0.75% ropivacaine. Their results showed better onset and duration of blocks in the fentanyl group. They reported no significant difference between the groups concerning postoperative analgesia and observed no side effects in the groups.[12]

Dharmarao and Holyachi showed that the addition of 1 $\mu g.kg^{-1}$ of dexmedetomidine compared with the addition of 1 $\mu g.kg^{-1}$ of fentanyl to 0.5% ropivacaine during the ultrasound-guided supraclavicular BPB does not make a significant difference regarding the onset of blocks. On the other hand, the duration of blocks was significantly longer in the dexmedetomidine group. While they concluded that the postoperative analgesia was longer in the dexmedetomidine group, they report no significant difference concerning the administered rescue analgesics. Interestingly, even though they used 1 $\mu g.kg^{-1}$ of dexmedetomidine, the researchers reported more sedation, bradycardia, nausea, and vomiting incidences in the dexmedetomidine group that was statistically insignificant.[27]

In separate studies, Kaur et al. and Hamed et al. found that dexmedetomidine significantly improves the onset and duration of sensory and motor blocks with significantly longer postoperative analgesia compared with fentanyl.[2,28]

Hamed et al. compared three groups of patients receiving either 1.5 $mg.kg^{-1}$ 0.5% bupivacaine, the same dose of bupivacaine plus 1 $mg.kg^{-1}$ dexmedetomidine, or the same dose of bupivacaine plus 1 $mg.kg^{-1}$ fentanyl. Despite their reported statistically significant differences between the groups regarding HR and MAP variables, they concluded that dexmedetomidine is a better adjuvant for bupivacaine without substantial adverse effects.[2]

Kaur et al. compared 1 $\mu g.kg^{-1}$ of dexmedetomidine with 1 $\mu g.kg^{-1}$ of fentanyl as adjuvants for 25 mL 0.5% levobupivacaine. They reported no statistically significant side effects in the study except for grade 2 sedation in the dexmedetomidine group.[28]

Dexmedetomidine is shown to be more effective than morphine on the onset and duration of sensory and motor block in epidural anesthesia.[29] Moreover, regarding a study by Barzin et al., as an adjuvant to local anesthetic during BPB, sufentanil is significantly more effective on postoperative analgesia than morphine and buprenorphine.[10] It is noteworthy that the addition of fentanyl to local anesthetic has been shown to increase the duration of sensory block.[30] A similar result showing prolonged analgesia with sufentanil

is reported in a study by Antonucci.[16] Since sufentanil is an analgesic 5 to 15 times more potent than fentanyl,[17,18] the discrepancy of the results between our study and the mentioned studies on dexmedetomidine and fentanyl is possibly due to this considerable difference in drugs' potency. The difference in the dosage of the drugs between the current and the previously mentioned studies is yet another possible factor. However, due to the lesser sample size of our study, there might be no adequate material for challenging those findings.

A relatively low number of subjects was a noticeable limitation of our study. Due to logistic constraints, we had limited postoperative monitoring of the patients and no follow-up for the patients' analgesic consumption after their discharge. Further studies with larger sample sizes, different study groups, and better patient monitoring are mandatory for a better understanding of the subject.

Conclusion

In summary, our study showed that during ultrasound-guided supraclavicular brachial plexus block, the addition of sufentanil as an adjuvant for bupivacaine can provide more desirable sensory and motor block than dexmedetomidine. In this study, no significant side effects were observed.

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Conflicts of interest

The authors declare no conflicts of interest.

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