Palestinian Medical and Pharmaceutical Journal

Dexmedetomidine as an Adjuvant to Local Anesthesia in Supraclavicular Brachial Plexus Block: A Randomized Controlled Trial

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Received: 15th May. 2024, Accepted: 28th Jul. 2024, Published: ××××, DOI: https://doi.org/××.xxxx

Accepted Manuscript, In press

ABSTRACT: Purpose: This research aims to examine the effects of dexmedetomidine on the analgesia, duration of the sensory and motor blocks, and hemodynamics in the supraclavicular brachial plexus block when used in conjunction with local anesthetic Bupicavine in a group of patients having surgeries on their upper limbs. Methodology: A randomized control trial was conducted at An-Najah National University Hospital. A control group received bupivacaine alone, and an intervention group received bupivacaine and dexmedetomidine. Patients were monitored for sensory and motor blocks, heart rate, and blood pressure intraoperatively. In addition, they were evaluated for pain, somnolence, nausea, heart rate, and blood pressure postoperatively. Results: The study included 112 participants: 56 in the intervention group and 56 in the control group. The intervention group, which received dexmedetomidine in addition to bupivacaine, demonstrated significantly accelerated onset of sensory and motor blocks, prolonged duration of these blocks, and extended duration of analgesia compared to the control group. Specifically, the median duration of analgesia was significantly longer in the intervention group (337.50 ± 314.17 - 408) compared to the control group (188.75 ± 145 – 241.67). Additionally, dexmedetomidine was associated with a significant reduction in the median systolic blood pressure of 145.66 ± (135.88 - 153.67) compared to the systolic blood pressure in the control group of 151.08 ± (147.27 ± 156.24), and the diastolic blood pressure showed significantly lower median values in the dexmedetomidine group compared to the control group with a p-value of >.001. The heart rate readings did not show a statistically significant increase in the intervention group compared to the control group. Although the control group had significantly higher systolic and diastolic blood pressure readings compared to the intervention group, there was no significant difference between each of those groups intraoperatively or postoperatively. Conclusion: Dexmedetomidine enhances anesthesia and analgesia without compromising hemodynamics. Adding dexmedetomidine to bupivacaine increased analgesia, expedited onset, and extended sensory and motor blocks. Dexmedetomidine reduced heart rate and blood pressure during and after surgery. It decreased postoperative nausea. More research is needed to completely understand the clinical potential of dexmedetomidine.

Keywords: Dexmedetomidine, Bupivacaine, Supraclavicular Brachial Plexus Block, Sensory Block, Motor Block, Analgesia.

INTRODUCTION

Over the last few decades, the area of anesthesia has advanced significantly [1], with efforts aimed at improving hospital care and patient satisfaction [2] and decreasing morbidity and mortality. Many types of anesthesia have been established, including general, local, regional, spinal, and epidural anesthesia [3]. The preferred type of anesthesia depends on the type of surgery, medical condition [4], and sometimes the patient's preferences. In general, anesthesia has various side effects, such as nausea, dizziness, faintness, coldness, headaches, itching, bruising, soreness, urination difficulty, and pain [5].

Although some studies found no significant differences in postoperative morbidity and mortality between general and local anesthesia [6], regional anesthesia is still preferable for specific surgeries, such as distal vascular surgery. In this procedure, a local anesthetic creates localized numbness without causing loss of consciousness [7]. This type of anesthesia was first employed in 1882, and later adjuvants were added to extend the length of the block and analgesic effect [8]. The accuracy of local anesthesia is increased by accurate needle placement, visualization of the spread of the anesthetic, and elimination of intraneural injections. Besides, image interpretation techniques such as ultrasound can adjust for anatomical variations [9].

Previous literature has highlighted the role of regional anesthesia in decreasing morbidity and mortality and perioperative and postoperative pain, early mobilization, fewer side effects, and improved blood pressure control in previous studies [10–12]. It also has the advantage of lowering hospital stays and costs [13].

The supraclavicular brachial plexus block focuses on the brachial plexus, a complex network of nerves extending from the spinal cord roots of C5 to T1. As part of the block procedure, a local anesthetic is injected in the supraclavicular fossa close to the nerve roots that make up the brachial plexus [14]. Targeting the plexus's trunks and divisions, the supraclavicular brachial

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plexus block causes anesthesia throughout the upper limb and that's why SBPB is used for postoperative pain control in surgeries involving the upper extremities, such as arteriovenous fistula creation, closure, and hand and orthopedic surgeries [15].

Dexmedetomidine is a highly selective α2-adrenoceptor agonist, leading to hyperpolarization and decreased neuronal excitability. This results in an enhanced blockade of nerve conduction when used as an adjuvant to local anesthetics. The drug's vasoconstrictive properties also limit systemic absorption, prolonging the duration of the local anesthetic. Moreover, dexmedetomidine's sedative and analgesic effects are mediated through its action on the locus coeruleus in the brainstem, which decreases the release of norepinephrine and increases inhibitory GABAergic activity [9, 16]. Its sedative, anxiolytic, analgesic, sympatholytic, and hemodynamic stabilizing properties without causing respiratory depression offer a promising adjunct to local anesthetic [16]. Apart from its analgesic effect, dexmedetomidine may protect against cardiac surgery-associated acute kidney injury [17], and reduce postoperative mortality, mechanical ventilation duration, intensive care unit stay, hospital stay, and the prevalence of delirium atrial fibrillation, and cardiac arrest [18].

Dexmedetomidine was first approved for use as a sedative in the intensive care unit, but it is now being administered in peripheral nerve blocks [19]. Many studies have shown that dexmedetomidine can improve the effectiveness of local anesthetics [16,18,20]. For example, a meta-analysis of eighteen randomized controlled trials (1092 patients) concluded that when used as an adjuvant to local anesthetic for brachial plexus blockade, dexmedetomidine can shorten the onset time and prolong the blockade duration [21]. Doses used in various studies range from 0.5 to 1 µg/kg [16 - 17]. Esmaoglu et al. (2010) reported that a dose of 1 µg/kg significantly prolonged analgesia in axillary brachial plexus block, though with increased bradycardia incidence [16]. These studies underscore the importance of dose optimization.

Dexmedetomidine was also found to increase the incidence of hypotension, bradycardia, and somnolence in another meta-analysis of eighteen randomized controlled trials (1014 patients) [12,20]. Bradycardia results from the activation of alpha-2 adrenoceptors, reducing sympathetic outflow and increasing vagal activity, leading to a lower heart rate. The drug's initial vasoconstrictive effect causes transient hypertension, followed by reflex bradycardia [22]. Somnolence results from dexmedetomidine's central action on the locus coeruleus, which induces sedation by inhibiting norepinephrine release [23]. Understanding these mechanisms is crucial to balancing the therapeutic benefits and side effects when using dexmedetomidine in clinical practice.

Dexmedetomidine administration was shown to improve patient satisfaction and comfort [24]. Its analgesic properties resulted in a decrease in the dosage of analgesics like opioids, as well as a decrease in their adverse effects [25].

In this study, we compared the effects of dexmedetomidine combined with bupivacaine to bupivacaine alone. It's worth mentioning that this is the first of its kind in Palestine and its neighboring countries, as well as one of the few that compares dexmedetomidine combined with bupivacaine in supraclavicular brachial plexus block.

The primary objective of this study is to compare the analgesic effect of combined dexmedetomidine and bupivacaine, as well as the onset and duration of anesthesia in the supraclavicular brachial plexus block to bupivacaine alone. We also aim to compare the incidence of side effects on heart rate, blood pressure, somnolence, and nausea between the intervention and control groups during and after the operation.

The main hypothesis of our study is that combining dexmedetomidine with the anesthetic bupivacaine would prolong analgesia longer than bupivacaine alone in supraclavicular plexus block anesthesia.

METHODOLOGY

Study design and population

This is a parallel, single-blinded, randomized controlled trial investigating the effect of dexmedetomidine in supraclavicular brachial plexus block as an adjuvant to bupivacaine, a local anesthetic.

This study was conducted at the An-Najah National University Hospital (NNUH) in Nablus between October 2020 and November 2023. The research committee of the medical school at An-Najah National University approved the study and the Institute Review Board of An-Najah National University-Nablus provided ethical approval (approval number F.Med. 25th August 2020/10). The trial is registered through the ClinicalTrials.gov Protocol Registration and Results System (PRS) with identifier number (NCT04981951).

During our study, participants were enrolled at the NNUH for upper limb procedures using supraclavicular brachial plexus block anesthesia and were assessed for eligibility. Every patient aged 18 to 75 who was classified as having a physical status grade of 1 or 2 according to the American Society of Anesthesiology Classification of Physical Status was invited to participate in the clinical trial. After being fully informed, Consent was obtained from both capable and willing to participate. Patients who had a confirmed allergic reaction to bupivacaine or dexmedetomidine, uncontrolled diabetes mellitus, uncontrolled hypertension, coagulopathy, cardiac arrhythmias, pregnancy, peripheral neuropathy, psychiatric problems, infection at the site of injection, and those taking beta-blockers were not included in the study.

According to prior research, we calculated that a total of 110 participants were needed to detect a difference between the two groups using a two-sided 5% significant level and 80% power. The study comprised a total of 112 participants, with 56 individuals assigned to the intervention group and 56 individuals assigned to the control group.

Block randomization was used to create the randomization schedule by a research team member who was not directly involved in participant selection or intervention administration to maintain balance across treatment arms. There were four people in each block. To hide allocation, pre-printed randomization sequences were kept in sealed envelopes.

Study Intervention and Outcomes

After signing informed consent, each participant received a general physical examination, including a patient history and blood sampling for red, white, and coagulation markers. ECG, blood pressure, heart rate, and other tests were done to prove study eligibility. 112 participants, 56 per group, were blindly assigned into two groups: A (bupivacaine alone) and B (with dexmedetomidine).

Before surgery on the targeted hand, an 18-gauge venous cannula was placed on the opposite hand in the morning. During the procedure, pulse oximetry, non-invasive blood pressure, and an ECG were attached.

Bupivacaine (30 ml) alone for group A and dexmedetomidine (1 mcg/kg) for group B were the study medications. Under ultrasound guidance, anatomy and needle placement were monitored, improving SBPB safety. A needle was inserted into

the brachial plexus sheath posterior to the subclavian artery to inject local anesthesia around the trunks and divisions.

Patients were assessed for sensory and motor block onset every 3 minutes after injection, at 15, 30, 45, 60, 90, and 120 minutes, and subsequently hourly (even after surgery) until resolution. All dermatomes innervated by the brachial plexus (C5-T1) in the median, radial, ulnar, and musculocutaneous nerve distributions were pinprick tested with a blunt 25-G hypodermic needle. Upper extremity motor blockage was measured using the Modified Bromage Scale (MBS). Heart rate and noninvasive blood pressure were taken every 15 minutes during surgery and every 2 hours for 6 hours afterward. A Ramsay Sedation Scale score used to assess the somnolence 30 minutes following the operation. The first analgesia order assessed postoperative pain.

Primary Outcomes

The duration of analgesia is defined as the period from when the anesthetic block begins until the participant requests additional pain relief. The onset of anesthesia encompasses the onset of sensory and motor blocks. Specifically, the onset of the sensory block is measured from the end of total local anesthetic administration to when the participant first experiences a dull sensation to a pinprick, known as sensory block grade 1. The motor block's onset is determined by the local anesthetic injection until the participant reaches a Bromage score of 2, which indicates a significant reduction in motor function but not complete paralysis.

For sensory response assessment, the pinprick sensation test is used, where a grade of 0 indicates a sharp pin sensation is felt, grade 1 denotes only a dull sensation felt (analgesia), and grade 2 means no sensation is felt (anesthesia). The Modified Bromage Scale (MBS) evaluates motor block severity with four grades: grade 0 allows the participant to fully raise the extended arm to 90 degrees for 2 seconds; grade 1 allows bending of the elbow and movement of fingers but not the extended arm; grade 2 permits finger movement but no elbow flexion; and grade 3 shows no movement of the arm, elbow, or fingers.

The duration of anesthesia is determined by the duration of sensory and motor blocks. The intraoperative duration of the sensory block is the time from the onset until partial recovery in all dermatomes that do not reach a pinprick test grade of 0. The intraoperative duration of the motor block is from its onset to partial recovery, where motor power does not reach a Bromage Test Grade 0. The total duration of the sensory block is from its onset until complete recovery from anesthesia in all dermatomes, achieving a pinprick test grade of 0. The total duration of the motor block is the time taken from the onset until the full return of motor power, marked by achieving a Bromage test grade of 0.

Secondary Outcomes

Heart rate and noninvasive blood pressure are carefully documented both during surgery and in the postoperative period. A 20% drop in systolic blood pressure from the baseline is indicative of hypotension. A heart rate of less than 60 beats per minute is referred to as bradycardia, and a heart rate of more than 100 beats per minute is referred to as tachycardia. Postoperative nausea is described as the participants' subjective feeling of discomfort in the stomach, accompanied by an urge to vomit, experienced after the procedure.

Somnolence, which refers to feelings of drowsiness or dizziness, is evaluated using the Ramsay Sedation Scale. On this scale, a score of 4 or higher indicates that the patient is somnolent. The full Ramsay Sedation Scale includes: 1 for patients who are anxious, agitated, and restless; 2 for those who are cooperative, oriented, and tranquil; 3 for patients who respond only to commands; 4 for those with a brisk response to a light glabellar tap or loud noise; 5 for a sluggish response to these stimuli; and 6 for no response at all. Furthermore, background characteristics such as age, gender, and body mass index (BMI) are collected to provide comprehensive data on the patient demographic being studied.

Analysis plan

For data analysis, IBM SPSS Statistics for Windows, version 25 (IBM Corp., Armonk, NY, USA) was used. To describe the patients' characteristics, we employed analytical statistics such as mean and standard deviation. We performed a chi-square test for categorical data such as gender and nausea. To test normally distributed data, the unpaired t-test was performed (BMI, heart rates). For the remainder of the information, the Mann-Whitney U test was used to test non-normally distributed data.

RESULTS

A total of 123 patients were assessed for eligibility, and 112 were enrolled in the study and randomized into two groups, as shown in (Figure 1).

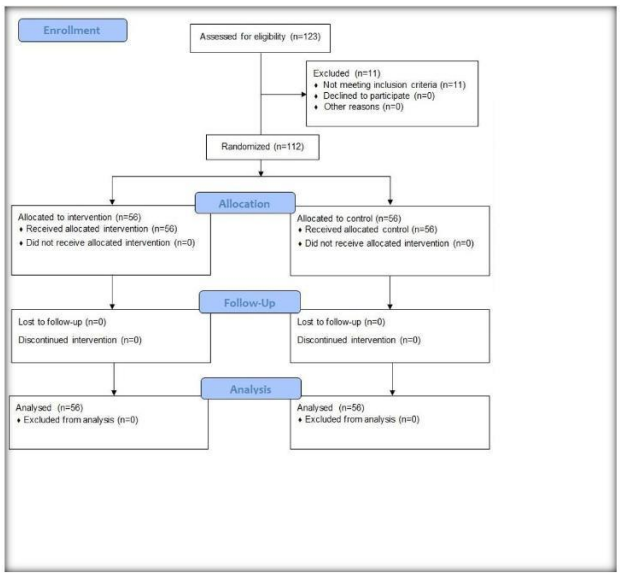

Figure (1): Consort Flow-Chart of Participants.

Study Population

The patients' demographic information was distributed as shown in the table below. The median ages of the intervention and control groups were 58 ± (50.25- 62.75) and 60 ± (55.25- 62) years, respectively. The male-to-female ratio in the two groups was varied, with the intervention group having a 2.5:1 ratio and the control group having a 2.1:1 ratio. The results of the body mass index differed slightly between the two groups. (Table 1)

Table (1): Background Characteristics of Participants (n=112).

	Intervention (n=56)	**Control (n=56)**	**P-value**
Age **	58 ± (50.25- 62.75)	60 ± (55.25- 62)	. 328
Gender*** Male female	 40 (71.4 %) 16 (28.6 %)	 38 (67.9 %) 18 (32.1%)	.681
BMI	27.16±2.92	28.59±2.63	.053

*Unpaired t-test **Mann–Whitney U test ***Chi-square test

Sensory and Motor Onset, Duration and Termination

The study's findings revealed a significant difference in the onset of sensory and motor loss. The onset of sensory loss medians for the intervention and control groups were 3.68 (2.55- 5.13) and 5.15 (3.18- 7.96), respectively. The difference in the duration and ends of sensory and motor blocks, as shown in the table, also yielded clear results. The study found a clear difference in support of the intervention group with a median of 337.50 ± (314.17 - 408) compared to the control group with a median of 188.75 ± (145–241.67) in the most relevant element for the study, which is the duration of analgesia. (Table 2).

Table (2): Effect of combined Dexmedetomidine and Bupivacaine on sensory and motor onset, duration, and termination of anesthesia and analgesia in SCPB compared to Bupivacaine alone.

	Intervention (n=56)	Control (n=56)	P-value*
The onset of sensory loss	3.68 ± (2.55- 5.13)	5.15 ± (3.18- 7.96)	.001
Duration of sensory block	143.2 ± (134- 156.25)	107.25 ± (82.50- 125.33)	<.001
The end of sensory loss	146.67 ± (138.46 - 160.75)	113.33 ± (89 – 129.75)	<.001
The onset of motor block	5.95 ± (4.68 - 8)	9.78 ± (7.95-12)	<.001
Duration of motor block	117.4 ± (97.5 - 131.67)	77 ± (57.4 - 94)	<.001
The end of motor loss	123.93 ± (106.7-135.83)	88.89 ± (69 – 103.75)	<.001
End of sensory block 2	314.59 ± (241.58 - 359.19)	157.14 ± (115.71 -220)	<.001
End of motor block 2	283.64 ± (194 – 343)	141.43 ± (84 – 217.50)	<.001
Duration of sensory block 2	468.66 ± (382.5 - 497.75)	249.66 ± (212 – 311.5)	<.001
Duration of motor block 2	398.5 ± (308.37 - 452.95)	214 ± (156 – 261)	<.001
Duration of analgesia	337.50 ± (314.17 - 408)	188.75 ± (145 – 241.67)	<.001

*Mann–Whitney U test.

Effects of Dexmedetomidine and Bupivacaine on Vitals and Side Effects

Intra-operatively and post-operatively, the intervention group had somewhat reduced heart rates. Systolic blood pressure readings in the intervention group were significantly lower intraoperatively and postoperatively. Diastolic blood pressure readings were significantly lower in the intervention group intraoperatively and postoperatively. While Somnolence was slightly but not significantly decreased in the intervention group, Nausea was significantly decreased in the intervention group compared to the control group. (Table 3)

Table (3): Effect of combined Dexmedetomidine and Bupivacaine on heart rate, blood pressure, intraoperatively and postoperatively, as well as somnolence and nausea.

	Intervention (n=56)	Control (n=56)	P-value*
HR intraoperatively	71.19 ± 6.14	72.84 ±6.10	.155
SBP intraoperatively	145.66 ± (135.88 - 153.67)	151.08 ± (147.27 ± 156.24)	.002
DBP intraoperatively	78.44 ± (73.77 - 83.25)	82.53 ± (80.24 - 86.66)	<.001
HR postoperatively	71.90 ± 5.53	73.38 ± 5.35	.157
SBP postoperatively	145 ± (137.12 - 154.43)	150 ± (146.56 - 155.31)	.028
DBP postoperatively	77.91 ± (73.08 - 81.08)	81.08 ± (78.15 - 84.84)	<.001
Somnolence	2.02 ± (1.50 - 2.53)	2.06 ± (2 – 2.56)	.407
Nausea No nausea	1 (1.8%) 55(98.2%)	23 (41.1%) 33(58.9%)	<.001

*Unpaired t-test, Mann–Whitney U test, and Chi-square test; HR= Heart Rate; SBP= Systolic Blood Pressure; DPB= Diastolic Blood Pressure

While postoperative heart rate readings were slightly higher. The control group's systolic and diastolic blood pressure measurements were somewhat higher intraoperatively. (Figure 2)

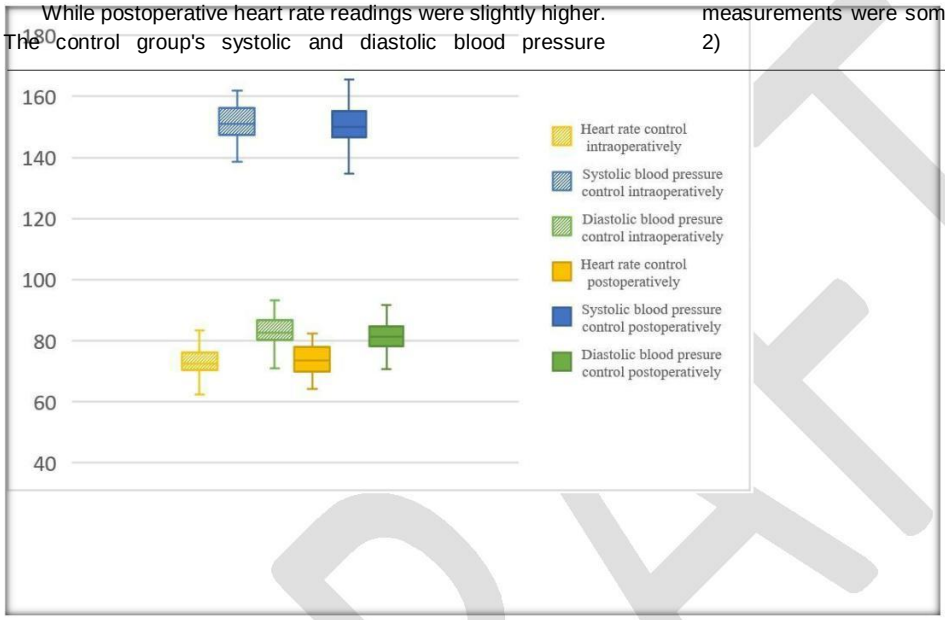

Figure (2): Heart rates and blood pressures of Bupivacaine alone group intraoperative and postoperative.

The intervention group's heart rate, systolic, and diastolic blood pressure values were not considerably different intraoperatively and postoperatively. (Figure 3)

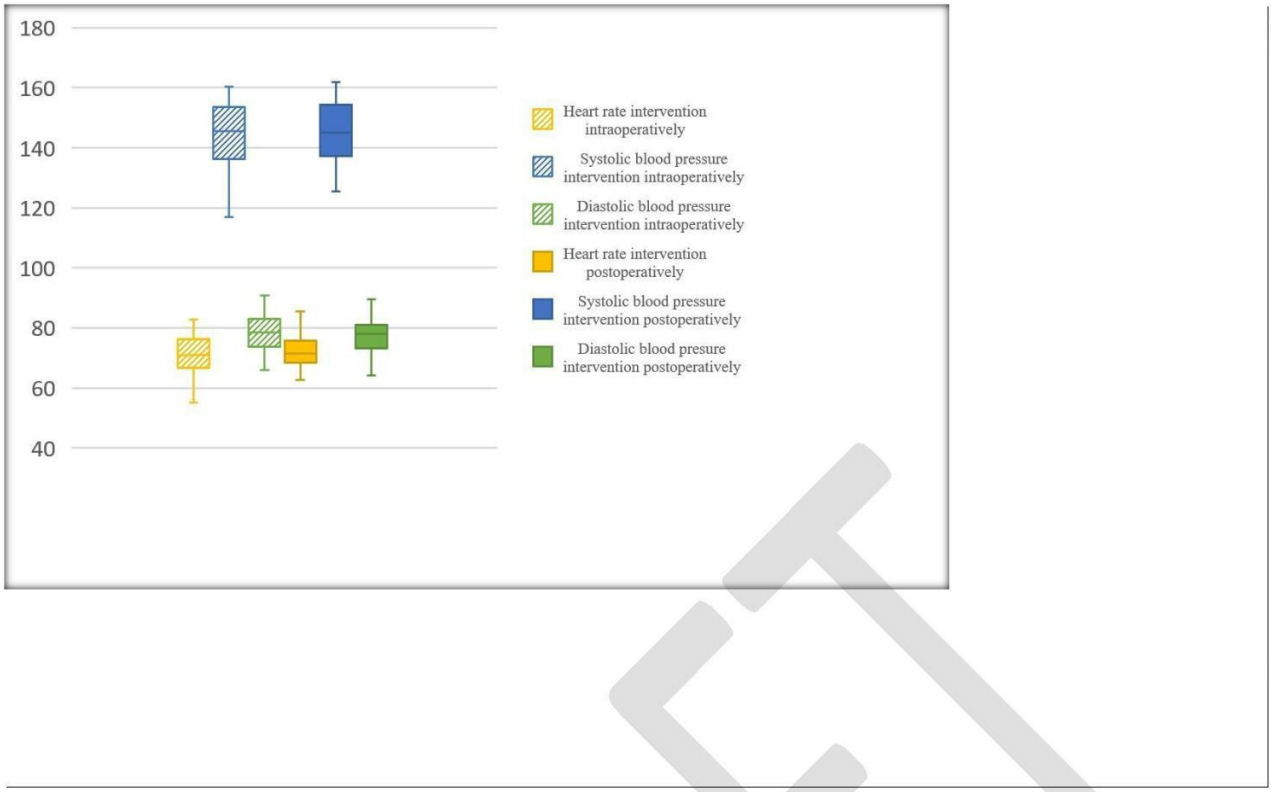

Figure (3): Heart rates and blood pressures of combined Dexmedetomidine and Bupivacaine group intraoperative and postoperative.

DISCUSSION

Using adjuvants is a common practice in anesthesia that intends to enhance the quality of the anesthesia. Adjuvants also decrease the side effects of the primary anesthetics due to lower needed doses of the primary medications to reach the desired outcome. Several medications have been used as adjuvants in the world of anesthesia; the class of alpha-2 adrenergic receptor blockers such as epinephrine and clonidine showed promising outcomes, enhancing the quality of the onset and duration of anesthesia as well as the quality of analgesia [22].

Dexmedetomidine is a relatively selective alpha2-adrenergic agonist that was initially approved by the FDA in 1999 for many applications, for example, sedation for intubated and not-intubated patients [26]. It was first used as a local anesthetic adjuvant in IV regional anesthesia in 2004. A study that was published in 2008 ruled out the potential neurotoxic effects of the newly emerging adjuvant in a study on rats. Subsequently, several studies have investigated its beneficial outcomes and established its effect by shortening the onset and increasing the duration of anesthesia. The dexmedetomidine effect on analgesia quality was also established. However, the favorable outcomes of dexmedetomidine come with a price of potential side effects, and several questions have been raised about its safety [11,22-23,27].

There are several proposed mechanisms of action for dexmedetomidine. Its alpha-2 adrenergic receptor blocking activity leads to vasoconstriction at the site of injection, leading to limited systemic absorption of the primary anesthetic; hence, the lower doses needed and decreased side effects of the primary anesthetic. Despite the fact that dexmedetomidine alone does not cause any motor or sensory block [11], it has antinociceptive properties by decreasing the release of substance P through the blockage of sodium channels and neuronal potassium current [22,28].

In this study, we investigated the use of the anesthetic dexmedetomidine as an adjuvant to local anesthesia in the supraclavicular brachial plexus block. It included 112 patients who satisfied the inclusion criteria.

Our study showed that the duration of analgesia, the onset, and the duration of both sensory and motor blocks in each group differed significantly, with the dexmedetomidine and bupivacaine group outperforming the bupivacaine alone group, which will encourage physicians to use dexmedetomidine as a novel addition to local anesthesia with a significant effect in the core targets of anesthesia such as the onset, end, and duration.

Two meta-analyses of randomized controlled trials studying dexmedetomidine as an adjuvant to local anesthetics in brachial plexus blocks showed that adding dexmedetomidine significantly prolonged the duration of sensory, motor block, and analgesia, as well as a significant decrease in the time to onset of sensory and motor blocks. However, both studies revealed concern over the safety of dexmedetomidine regarding hemodynamics, mostly bradycardia [11,28].

Bradycardia following dexmedetomidine administration can be explained as the vasoconstrictive activity leading to transient hypertension followed by a reflex bradycardia [17, 27]. Management strategies for bradycardia include the administration of atropine or glycopyrrolate to counteract the decreased heart rate [22]. Monitoring patients closely during the perioperative period and adjusting the dosage of dexmedetomidine can help mitigate these risks [17, 29]. Implementing these strategies in clinical practice is essential to ensure patient safety and maximize the benefits of dexmedetomidine as an adjuvant in regional anesthesia. In our study, we encountered two cases of intraoperative bradycardia in the intervention group (n=56). No reversal agents were used, as the heart rates for those two participants were 55 and 58. However, several studies have reported a greater incidence of these potential side effects and the possibility of reversing the bradycardia by medications such as atropine. Esmaoglu et al. studied the prolongation of axillary brachial plexus block when dexmedetomidine was added to levobupivacaine, they reported bradycardia (defined as heart rate less than 50 bpm) as a side effect in seven out of 30 participants in the intervention group [16].

Systolic and diastolic blood pressure readings were significantly lower intraoperatively and postoperatively in the intervention group. However, we didn't report any hypotensive cases intraoperatively or postoperatively in either study group.

We reported a significant increase in the duration of postoperative analgesia in the dexmedetomidine intervention group, matching several studies. Our study also demonstrated that dexmedetomidine reduces postoperative nausea significantly. A plausible explanation is the link between postoperative nausea and postoperative pain. Dexmedetomidine was reported as an effective substance to

reduce postoperative nausea in a randomized controlled trial including eighty-eight subjects. Another study also reported the advantage of decreasing nausea in general anesthesia [30].

Although, regarding the novel contributions of the current research, there are several important limitations; the COVID-19 pandemic limited the number of elective surgeries that affected our data collection. Another limitation was the unavailability of ultrasounds all the time, which coerced us to exclude some cases from the study. Dexmedetomidine was not always available in the hospital as the study was conducted in a developing country.

One distinguishing characteristic of our study is its large sample size in comparison to previous research studies. It is one of the few research projects in the region that addresses the study's objective. Furthermore, the existing literature on the safety of using dexmedetomidine as an adjuvant to local anesthetics in supraclavicular brachial plexus blocks is limited.

CONCLUSION

The findings of this randomized controlled trial indicate that the addition of dexmedetomidine to bupivacaine as a local anesthetic adjuvant in supraclavicular brachial plexus block results in prolonged durations of analgesia, sensory block, and motor block. As well, it increases the time needed for the onset of sensory and motor blocks. Additionally, these benefits are achieved with a minimally increased risk of hypotension and no significant impact on heart rate. However, further studies with larger sample sizes investigating the safety of this use of dexmedetomidine are needed.

Ethics approval and consent to participate

Ethical approval was obtained from An-Najah National University Institutional Review Board (IRB) to conduct the research. Informed consent was required and obtained from all participants.

Consent for Publication

Consent for publication was obtained from each participant in this study. The participants were informed of the study's details and the objective of publishing the findings. Written consent was obtained from all participants to ensure that they understood the publication of their anonymized data. To maintain privacy, all personal information has been anonymized.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request. Any materials used in the study can also be provided upon reasonable request to the corresponding author.

Author's contribution

Layan Abu Alya: conceptualization, writing-original draft, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing review & editing. **Leen Sabbooba:** conceptualization, writing-original draft, data curation, investigation, methodology, project administration, resources, supervision, validation, and visualization. **Ikhlas Alfoqaha:** conceptualization, writing-original draft, data curation, investigation, methodology, project administration, resources, supervision, and validation. **Walaa Abualia:** conceptualization, writing-original draft, project administration, resources, and supervision. **Basil Jalamneh:** revision. **Wael Sadaqa:** conceptualization, data curation, investigation, project administration, resources, supervision, and validation. **Zaher Nazzal:** conceptualization, writing-original draft, data curation, formal analysis, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing review & editing. The students Layan Abu Alya, Leen Sabbooba, and Ikhlas Alfoqaha conducted this study.

Competing Interests

The authors declare that they have no competing interests.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Acknowledgment

The authors would like to thank all participants of the study for their cooperation and contribution.

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