The Effect of Dexmedetomidine, Magnesium Sulfate or Midazolam as Adjuvant to Bupivacaine in Ultrasound Guided Supraclavicular Brachial Plexus Block

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Abstract:

Background: Different adjuvant have been used to improve the quality of regional anesthesia.

The aim of the study: It is evaluation and comparing the effects of dexmedetomidine, magnesium sulfate and midazolam when added as adjuvant to bupivacaine on the quality of US-guided supraclavicular brachial plexus block.

Patients and methods: This prospective, randomized controlled trial was conducted on 100 patients undergoing upper limb surgery under US-guided supraclavicular brachial plexus block. These patients were randomized into 4 equal groups. 15 ml of 0.5% bupivacaine plus each of 5ml normal saline, 1µg/kg dexmedetomidine, 3 mg/kg of 10% magnesium sulfate and 50µg/kg of midazolam were used in the control (B/S) group, dexmedetomidine (B/D) group, magnesium sulfate (B/MgS) group and midazolam (B/M) group, respectively. Onset and duration of sensory and motor blocks, time to first analgesic request, total postoperative analgesic consumption, hemodynamic changes, and the associated side effects were recorded.

Results: The block onset times, intraoperative analgesic potency, duration of postoperative analgesia and rates of the associated side effects in B/D, B/MgS, and B/M groups were significantly better than in B/S (Control) group ($P < 0.001$) and in B/D group they were significantly better than in B/MgS and B/M groups ($P = 0.042$) and in B/MgS group they were significantly better than that in B/M group.

Conclusion: Addition of Dexmedetomidine, Magnesium sulfate and midazolam as adjuvant to bupivacaine are efficient in improving the characteristics of supraclavicular brachial plexus block but Dexmedetomidine is the most efficient one that followed by Magnesium sulfate and then by midazolam.

Keywords: Bupivacaine; Dexmedetomidine; Magnesium sulfate; Midazolam; Supraclavicular brachial plexus block; Ultrasound-guided regional anesthesia.

Introduction:

Brachial plexus block is a cornerstone technique in regional anesthesia for upper limb surgeries, providing both intraoperative anesthesia and postoperative analgesia. Several approaches are available including interscalene, infraclavicular, axillary, and supraclavicular, each offering distinct advantages depending on the surgical site. Among these, the supraclavicular approach is often considered the most

effective for anesthesia of the upper limb distal to the shoulder. The injection is administered at the level of the distal trunks and the origin of the divisions, where the brachial plexus is densely arranged over the first rib. At this point, nearly all sensory, motor, and sympathetic fibers of the upper limb except for the uppermost medial aspect of the arm (T2) are encompassed. Hence, this block is sometimes referred to as the *"spinal of the arm"* **[1]**

The traditional, landmark-guided supraclavicular block was historically associated with complications such as pneumothorax, vascular puncture, and nerve injury. However, the advent of ultrasound guidance has revolutionized peripheral nerve blockade by allowing real-time visualization of neural, vascular, and pleural structures. This innovation has markedly enhanced the accuracy, safety, and success rate of the supraclavicular approach **[2].**

Bupivacaine, a long-acting amide local anesthetic, is commonly used for brachial plexus blocks because of its prolonged duration of action (6–9 hours). Despite its reliability, bupivacaine alone may be limited by a relatively delayed onset of sensory and motor blockade, moderate postoperative analgesic duration, and potential systemic toxicity at higher doses **[3].**

To overcome these limitations, various adjuvants have been investigated to improve the onset, quality, and duration of peripheral nerve blocks. Examples include combinations of local anesthetics (e.g., lidocaine with bupivacaine), alkalinizing agents (such as sodium bicarbonate), and pharmacologic additives such as opioids, ketamine, clonidine, dexmedetomidine, magnesium sulfate, midazolam, neostigmine and dexamethasone **[4,5].** These adjuvants enhance anesthetic efficacy primarily by potentiating neural blockade or by providing additional analgesic mechanisms **[6].**

However, most of these agents are associated with undesirable side effects, including hypotension, bradycardia, respiratory depression, sedation, or. nausea and vomiting. Despite extensive investigation, no ideal adjuvant has yet been identified—one that optimizes block characteristics without compromising patient safety. The search for a safe and effective adjuvant therefore remains a topic of ongoing clinical interest **[7].**

The aim of the work is a comparison between the effects of Dexmedetomidine, Magnesium Sulfate and Midazolam as Adjuvant to Bupivacaine on the quality of the produced anesthesia by ultrasound guided supra-clavicular brachial plexus block to find out the most effective one with the least side effects.

Patients and methods:

Study design and ethics

This prospective randomized controlled clinical trial was carried out at Zagazig University Hospitals, Egypt, from June 1, 2022, to June 30, 2024. Ethical approval was obtained from the Institutional Review Board of Zagazig University, and written informed consent was secured from all participants. The study was conducted in accordance with the Declaration of Helsinki and relevant national regulations.

Sample size:

According to the study conducted by **Laiq et al., [8],** the mean duration of sensory block (hours) in group 1 (Control group) was 6.2±3 h and in group II (bupivacaine/midazolam group) was 9.3 ±7h. Using the Open EPI system to calculate the sample size with a power of 80 % and confedence level of 95%, the calculated sample size was 84 patients. For compensation of the dropped cases, the sample size was increased to 100 patients.

Inclusion criteria: Patient aged 21–60 years, with body mass index (BMI) of 18.5–35, and ASA physical status classes I and II undergoing elective upper limb surgery that did not exceeding 120 min.

Exclusion criteria: Refusal or inability to cooperate, allergy to study drugs, peripheral neuropathy or neuromuscular disorders, pregnancy, local infection or coagulopathy, significant hepatic, renal, or cardiac conduction pathology.

Randomization:

According to a computer generated randomization chart, the patients were assigned to one of the 4 equal groups (i.e. 25 patients in each group) as the following:

1. **Bupivacaine/Saline (B/S or Control) group (n=25):** The patients received 15 ml of 0.5% bupivacaine plus 5ml normal saline.

2. **Bupivacaine/Dexmedetomidine (B/Dex) group (n=25)**: The patients received 15 ml of 0.5% bupivacaine plus 1µg /kg dexmedetomidine.

3. **Bupivacaine/Magnesium sulfate (B/MgS) group (n=25):** The patients received 15 ml of 0.5% bupivacaine plus 3mg/kg of 10% magnesium sulfate.

4. **Bupivacaine/ Midazolam (B/M) group (n=25):** The patients received 15 ml of 0.5% bupivacaine plus 50µg/kg of Midazolam.

The volume of each adjuvant was increased to 5ml by normal saline before adding to Bupivacaine.

The addition of 5ml normal saline or 5ml of each adjuvant to 0.5% Bupivacaine decreased its concentration to 0.375%.

Each local anesthetic mixture with either saline or adjuvant was prepared in syringe by another study anesthesiologist than who performed the block and assess the pain and the effect of block.

Preoperatively, all of patients were visited at the night before the surgery for assessment, preparation and taking an informed consent on the type of anesthesia and to find out any exclusion criteria of the technique. The technique of Ultrasound guided supraclavicular brachial plexus block was explained to the patients. The patients were examined clinically and their baseline Heart Rate (HR), Mean Arterial Blood Pressure (MABP), Respiratory Rate (RR), and peripheral arterial oxygen saturation (SpO_2) were recorded. Also all patients were educated about the assessment of perioperative pain using the 0-10 cm visual analogue scale (VAS) **[9]**. where 0 corresponding to no pain and 10 to the worst pain imaginable. The patient was instructed to make a mark along the line to represent the intensity of pain currently

being experienced. The patients were allowed to take water and solid foods till midnight and clear fluids until 2 hours before operation. Premedications was not given to prevent factors that may have or potentiate the effects of the tested drugs.

Technique of establishment of Ultrasound guided supraclavicular brachial plexus block:

On arrival to the operating room, a 20-gauge intravenous cannula was inserted in the non-operating limb. Ringer Lactate solution was started at a rate of 5 ml/kg/h and patients were monitored with standards monitoring including electrocardiography, pulse oximetry, and noninvasive blood pressure. O_2 was administered through nasal sponges at a rate of 5 L/min.

The block was achieved with the patient in the supine position, 45° table head up (beach-chair position), and with the head rotated toward the non-operative side. The lateral aspect of the neck was disinfected with a 10%. povidone-iodine solution and draped. A linear high frequency (8-13 MHz) probe (covered with a sterile dressing) was used in the study.

The probe was placed in the supra-clavicular fossa in coronal oblique plane aiming scanning at different angles to obtain the best image of the subclavian artery, brachial plexus, first rib and pleura. Brachial plexus trunks and/or divisions were visualized as a group of round or oval hypoechoic nodules (honey comb appearance) surrounded by a hyper-reflective fascial sheath, superior to the first rib and lateral to the round pulsating hypoechoic subclavian artery. Subclavian artery was seen sitting on the hyperechoic line of the first rib or pleura. The subclavian vein was seen medial to the artery.

First rib was seen as hyperechoic line without sliding movement during respiration. The pleura was seen as the hyperechoic line with sliding movement during respiration.

The needle entry point was infiltrated via 25- to 27-gauge needle with 2ml of %1 lidocaine.

A sterile short bevel, 50-mm 18-G intravenous cannula was inserted along the longitudinal axis of the ultrasound probe (in-plane needle approach)**.**

The needle was advanced toward the junction of the subclavian artery and first rib. This area, which is inferomedial to the plexus, posterolateral to the subclavian artery, and superior to the first rib, is commonly referred to as ‘‘the corner pocket’’

After negative aspiration, 1-2 ml of the local anesthetic (LA) was injected to document the proper needle placement, then remaining volume was slowly injected. High injection pressures may indicate intra-neural needle placement. In this case injection was stopped and readjustment of needle position was performed.

Primary outcome of the study is evaluation of the onset and duration of sensory and motor block Secondary outcomes are evaluation of intraoperative and postoperative pain severity via visual analog scale (VAS), hemodynamic changes, the time to the

first request of analgesia, the total analgesic requirements, and the associated side effects.

Sensory block (SB) and motor block (MB) were assessed every 3 min in the first 30 min after LA injection and every 30 min postoperatively till the end of supraclavicular block. SB was assessed using both cold test by alcohol swab and pinprick test by blunt 26-gauge needle in the dermatomal areas corresponding to the median nerve, ulnar nerve, radial nerve, and musculocutaneous nerve **[10].** SB was graded: 0 = normal sensation; 1 = loss of sensation to pinprick (analgesia); and 2 = loss of touch sensation (anesthesia).

Onset of SB is defined as the time interval between the end of total local anesthetic injection and complete SB. The duration of the SB is the time interval between the onset of the complete SB and complete resolution of the SB. Duration of analgesia is the time interval between the onset of the complete SB and the first dose of postoperative analgesia.

MB was assessed by Modified Bromage Scale. The Motor block was graded according to modified Bromage scale: 0 = normal motor function, 1 = ability to move only fingers, 2 = complete motor block with inability to move the elbow and/or wrist and/or finger **[10].** Onset of MB is the time interval between injection of LA and time of the complete MB. The duration of MB is the time interval between the onset of the complete MB and complete resolution of the MB.

The block was considered successful when the SB is 2 and MB is 0 within 30 min after injection of the LA. Otherwise, the block was considered as failed or inadequate block and the patients would receive general anesthesia or analgesia to complete the surgical intervention. These patients were excluded from the study.

Intraoperative mean arterial blood pressure (MAP) and heart rate (HR) were recorded preoperatively and every 15 min after the administration of LA solution till the end of surgery.

Postoperative pain was assessed using a 0-10-cm visual analog scale (VAS): 0= no pain to 10= worst pain imaginable and recorded at admission to postoperative care unit and 1, 2, 4, 6, 8, 12, 18, and 24 h postoperative.

Patients received postoperative analgesia in the form of diclofenac sodium (75 mg intramuscular) every 12 h, and if the patient still complained of pain, pethidine 1 mg/kg was given i.v. as rescue analgesia. The first dose of diclofenac sodium was given when VAS was >3. Total consumption of rescue analgesia was recorded.

Any intraoperative or postoperative complications were recorded such as vascular puncture, pneumothorax, Horner syndrome, local anesthetic toxicity, bradycardia (HR <50 beats/min and managed by atropine 0.5 mg), and hypotension (defined as a decreased of blood pressure >25% of the baseline and managed by i.v. fluids and ephedrine 10 mg bolus if no response to fluid administration), nausea/vomiting that was assessed using a 4 point score: 1= no nausea nor vomiting , 2= mild nausea, no vomiting , 3= excessive nausea or vomiting , 4= vomiting 2 times or more **[11]**,and **sedation**, that was assessed using **Ramsay sedation score [12]** (1 = anxious, agitated, and restless, 2 = cooperative, oriented, and tranquil, 3 = responsive to commands

only, 4 = asleep but has brisk response to light glabellar tap or loud auditory stimulus, 5 = sluggish response to light glabellar tap or loud auditory stimulus, and 6 = no response to light glabellar tap or loud auditory stimulus).

Statistical Analysis:

The collected data was computerized and statistically analyzed using the SPSS software (Statistical Package for Social Science) version 27.0 (IBM, 2020).

The Shapiro-Wilk test was used to check the normality of the data distribution. Normally distributed continuous variables were expressed as mean ± SD while categorical variables were expressed as number and percentage. Student t-test was used for continuous data. A Chi-square or Fisher's Exact tests, post hoc test and one-way ANOVA test were used for statistical analysis. All tests were conducted with a 95% confidence interval. P [probability] value < 0.05 was considered statistically significant.

Results:

A total of 113 patients were assessed for eligibility. Thirteen patients were excluded because they either declined participation or did not meet the inclusion criteria. Consequently, 100 patients were randomized equally into four groups (n = 25 each). The participant flow is illustrated in Figure 1, following the *CONSORT* guidelines.

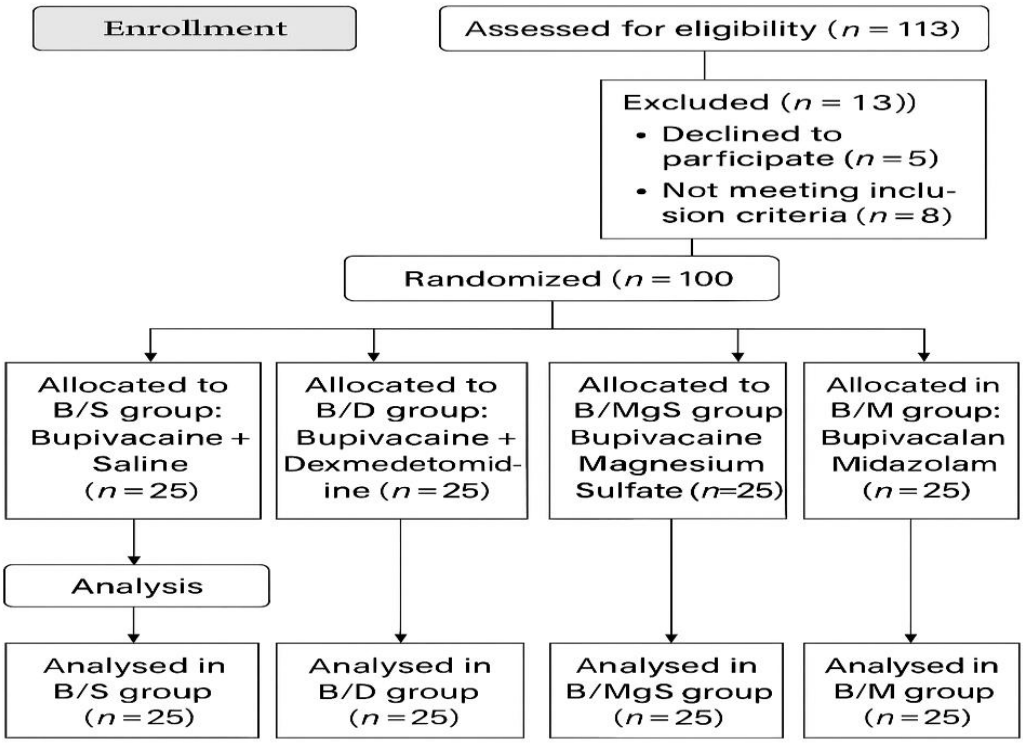

Figure (1): CONSORT flow diagram demonstrating the randomization.

The demographic profile (age, sex), anthropometric parameters (weight, height, BMI), ASA physical status classes, the distribution of the various types of operations, tourniquet time, and duration of surgery of the four groups were comparable **(Table 1).**

Table (1): Patients' demographic data, distribution of the various types of operations, tourniquet time, and duration of surgery in the four studied groups.

	B/S group (n=25)	B/D group (n=25)	B/MgS group (n=25)	B/M group (n=25)	ANOVA Test f
Age (years).	**34.2±8.07**	**37.1±15.1**	**33.68±11.3**	**38.2±15.5**	**0.540**
Weight (kg).	**80.8±6.5**	**80.2±8.05**	**83.92±8.6**	**83.16±8.1**	**0.277**
Height (cm).	**174.1±6.3**	**173.5±6.1**	**174.8±4.9**	**173.9±5.0**	**0.869**
BMI (kg/m2)	**26.7±2.6**	**26.6±2.9**	**27.4±2.7**	**27.5±2.7**	**0.580**
Sex ratio (M:F).	**20:5**	**18:7**	**21:4**	**19:6**	**0.88**
ASA ps classes ratio (I/II).	**20:5**	**18:7**	**19:6**	**17:8**	**0.74**
Distribution of the various types of operations [N (%)]:					
ORIF distal humerus.	**2 (8%)**	**3 (12%)**	**3 (12%)**	**3 (12%)**	
ORIF BB forearm.	**7 (28%)**	**8 (32%)**	**9 (36%)**	**8 (32%)**	**0.935**
Cut wrist repair.	**8 (32%)**	**6 (24%)**	**6 (24%)**	**6 (24%)**	
ORIF radius.	**2 (8%)**	**3 (12%)**	**2 (8%)**	**2 (8%)**	
ORIF Ulna.	**2 (8%)**	**2 (8%)**	**2 (8%)**	**3 (12%)**	
- K Wires distal radius.	**4 (16%)**	**3 (12%)**	**3 (12%)**	**3 (12%)**	
Tourniquet time (min).	**55.1± 7.4**	**55.7± 5.6**	**56.3±7.9**	**58.3±7.9**	**0.31**
Surgery duration (min.)	**65.4±18.7**	**67.8±15.5**	**66.4±17.04**	**68.2±18.2**	**0.288**

Data are expressed as Mean ± Standard Deviation (SD) or numbers (%). n = Group number.
N (%) = number (%) of each operation type in each group. f = one way ANOVA test.
B/S group=Bupivacaine/Saline (Control) group.
B/D group = Bupivacaine /Dexmedetomidine group.
B/MgS group=Bupivacaine/Magnesium sulphate group.
B/M group = Bupivacaine/Midazolam group.
ASA ps class = American Society of Anesthesiology physical status class.
P> 0.05 means Non significant difference.

The onset times of sensory and motor blocks in all tested groups were statistically highly significant faster than in control (B/S) group (P <0.001). Among the tested groups, B/D group showed the faster onset that followed by B/MgS and then by B/M groups **(Table 2).**

Table (2): Onset times of each of sensory and motor block after establishment of US-guided Supra-clavicular block in the four studied groups.

	B/S group (n=25)	B/D group (n=25)	B/MgS group (n=25)	B/M group (n=25)	ANOVA Test f	Post hoc P
Onset time of sensory block (min).	**19.5±1.9**	**12.8±1.4**	**15.4±1.4**	**16.8±1.2**	**0.001**	**P1=0.001 P2=0.001 P3=0.001 P4=0.001 P5=0.001**

						P6=0.002
Onset time of motor block (min).	**24.2±1.9**	**17.5±1.8**	**20.1±1.5**	**21.28±1.7**	**0.001**	**P1=0.001 P2=0.001 P3=0.001 P4=0.001 P5=0.001 P6=0.001**

Data are expressed as Mean ± Standard Deviation (SD). n = Group number.
f = One way ANOVA test. B/Sgroup=Bupivacaine/Saline (Control) group.
B/D group = Bupivacaine/Dexmedetomidine group.
B/MgS group=Bupivacaine/Magnesium sulphate group.
B/M group = Bupivacaine/Midazolam group.
P1= B/S (Control) against B/D group, P2= B/S (Control) against B/MgS group, P3= B/S (Control) against B/M group, P4= B/D against B/MgS group, P5= B/D against B/M group, P6= B/MgS group against B/M group, P= 0.005 means highly significant difference.

The mean of surgical pain scores in all tested groups were statistically highly significant less than that in control (B/S) group and in B/D group it was significantly less than that in B/MgS and B/M group and in B/MgS group it was significantly less than that in B/M group **(Table 3).**

Intraoperative fentanyl consumptions (µg/patient) in all tested groups were statistically highly significant less than that in control (B/S) group and in B/D group it was significantly less than that in B/MgS and B/M groups and in B/MgS it was significantly less than that in B/M group **(Table 3).**

Durations of tolerance to tourniquet pain in the tested groups were highly significant longer than that in control (B/S) group. Among the tested groups, B/D group demonstrated the longest durations of tolerance to tourniquet pain followed by B/MgS and then B/M groups **(Table 3).**

Table (3): Intra-operative analgesic potency of US-guided Supra-clavicular block in the four studied groups.

	B/S group (n=25)	**B/D group (n=25)**	**B/MgS group (n=25)**	**B/M group (n=25)**	**ANOVA Test P**	**Post hoc P**
Intraoperative surgical pain score (VAS values).	**2.9 ± 0.81**	**1.33 ±0.35**	**59±0.55**	**2.1± 0. 45**	**0.001**	**P1=0.001 P2=0.001 P3=0.001 P4=0.04 P5=0.001 P6=0.002**
Total intra-operative fentanyl consumption (µg/patient).	**100.5±10.7**	**53.8± 8.17**	**63.7±9.04**	**70.1±9.33**	**0.001**	**P1=0.001 P2=0.001 P3=0.001 P4=0.001 P5=0.001 P6=0.01**

Duration of tolerance to tourniquet pain (min.).	**14.7±3.8**	**27.4±4.06**	**22.5±4.15**	**19.5±4.15**	**0.001**	**P1=0.001 P2=0.001 P3=0.001 P4=0.001 P5=0.001 P6=0.01**

Data are expressed as Mean ± Standard Deviation (SD). n = Group number
f =one-way ANOVA.
B/S group= Bupivacaine/Saline (Control).
B/D group= Bupivacaine/Dexmedetomidine group.
B/MgS group= Bupivacaine/Sulfate of magnesium group.
B/M group=Bupivacaine/Midazolam group.
P1= B/S (Control) against B/D group, P2= B/S (Control) against B/MgS group, P3= B/S (Control) against B/M group, P4= B/D against B/MgS group, P5= B/D against B/M group, P6= B/MgS group against B/M group, P= 0.005 means highly significant difference.

Durations of sensory and motor block in all tested were statistically highly significant longer than in control (B/S) group (P <0.001). Among the tested groups, the B/D group demonstrated the longest block duration, followed by B/MgS and then B/M groups **(Table 4).**

Table (4): Duration of sensory and motor block after establishment of US-guided supra-clavicular block in the four studied groups.

	B/S group (n=25)	**B/D group (n=25)**	**B/MgS group (n=25)**	**B/M group (n=25)**	**ANOVA Test P**	**Post hoc P**
Duration of sensory block (min)	**278.6±38.1**	**655.2±45.2**	**549.2±41.6**	**366.8±36.8**	**0.001**	**P1=0.001 P2=0.001 P3=0.001 P4=0.001 P5=0.001 P6=0.001**
Duration of motor block (min)	**220.8±27.3**	**561.4±44.9**	**466.6±42.6**	**289.5±32.3**	**0.001**	**P1=0.001 P2=0.001 P3=0.001 P4=0.001 P5=0.001 P6=0.001**

Data are expressed as Mean ± Standard Deviation (SD). n=Group number.
f = one way ANOVA test. B/S group=Bupivacaine/Saline (Control) group.
B/D group=Bupivacaine/Dexmedetomidine group.
B/MgS group=Bupivacaine/Magnesium sulphate group.
B/M group= Bupivacaine/Midazolam group
P1= B/S (Control) against B/D group, P2= B/S (Control) against B/MgS group, P3= B/S (Control) against B/M group, P4= B/D against B/MgS group, P5= B/D against B/M group, P6= B/MgS group against B/M group, P= 0.005 means highly significant difference.

The times to the 1st request to postoperative analgesia in all tested groups were statistically highly significant longer than in control (B/S) group (P <0.001). Among the tested groups, the B/D group demonstrated the longest time, followed by B/MgS and then B/M groups **(Table 5).**

The consumed amounts of diclofenac sodium to relief pain in the 1st 24 hours post-opertatively in the tested groups were statistically highly significant lesser than in control (B/S) group (P <0.001). Among the tested groups, the B/D group demonstrated the lesser consumed amount followed by B/MgS and then B/M groups **(Table 5).**

Table (5): The time to ask for the 1st post operative analgesia and the consumed amount of diclofenac sodium to relief pain in the 1st 24 hours postopertatively in the three studied groups.

	B/S group (n=25)	B/D group (n=25)	B/MgS group (n=25)	B/M group (n=25)	ANOVA Test P	Post hoc P
Time to ask for post operative analgesia (min).	**340.2±36**	**757.1±46.9**	**631.1±41.5**	**434.4±41.3**	**0.001**	**P1=0.001 P2=0.001 P3=0.001 P4=0.001 P5=0.001 P6=0.001**
The consumed amount of diclofenac sodium during the 1st 24 hrs postoperatively (mg/patient)	**177.5±48.9**	**81.5 ± 13.1**	**111.25±15.2**	**125.35±21.2**	**0.001**	**P1=0.001 P2=0.001 P3=0.001 P4=0.001 P5=0.001 P6=0.01**

Data are expressed as Mean ± Standard Deviation (SD). n = Group number
f = one way ANOVA test. B/S group=Bupivacaine/Saline (Control) group.
B/D group=Bupivacaine/Dexmedetomidine group.
B/MgS group=Bupivacaine/Magnesium sulphate group.
B/M group=Bupivacaine/Midazolam group.
P1= B/S (Control) against B/D group, P2= B/S (Control) against B/MgS group, P3= B/S (Control) against B/M group, P4= B/D against B/MgS group, P5= B/D against B/M group, P6= B/MgS group against B/M group, P= 0.005 means highly significant difference.

There were no significant differences in the mean arterial blood pressure **(Figure 2)**, heart rate **(Figure 3),** respiratory rate and SpO_2 at the different times of measurement among the all groups.

The recorded side effects were hypotension, bradycardia, nausea and vomiting and sedation. Statistically, the incidences of each of bradycardia in B/D group, nausea and vomiting in control (B/S) and sedation in both B/D and B/M groups were significantly higher than in the other groups (**Table 6).**

Table (6): The incidences of the various associated side effects in the four studied groups.

	B/S group (n=25)	B/D group (n=25)	B/MgS group (n=25)	B/M group (n=25)	ANOVA Test f	Post hoc P
Hypotension [N(%)]:	**0(0.0%)**	**3(12%)**	**0(0.0%)**	**1(4.0%)**	**0..101**	
Bradycardia [N(%)]:	**0(0.0%)**	**7(28%)**	**1(4.0%)**	**1(4.0%)**	**0.002**	**P1=0.012 P2=0.601 P3=0.601 P4=0.002 P5=0.002 P6=1**
Nausea and vomiting [N(%)]:	**4(16.0%)**	**0(0.0%)**	**0(0.0%)**	**0(0.0%)**	**0.006**	**P1=0.003 P2=0.003 P3=0.003 P4=1 P5=1 P6=1**
Sedation (i.e. patient with sedation score more than 2) **[N(%)]:**	**0(0.0%)**	**6(24%)**	**1(4.0%)**	**7(28%)**	**0.006**	**P1=0.012 P2=0.671 P3=0.004 P4=0.036 P5=0.671 P6=0.012**

Data are expressed as numbers and percent. n=Group number.
N (%) = number (%) of each side effect in each group. f = one way ANOVA test.
B/S group=Bupivacaine/Saline (Control) group.
B/D group=Bupivacaine/Dexmedetomidine group.
B/MgS group=Bupivacaine/Magnesium sulphate group.
B/M group= Bupivacaine/Midazolam group.
P1= B/S (Control) against B/D group, P2= B/S (Control) against B/MgS group, P3= B/S (Control) against B/M group, P4= B/D against B/MgS group, P5= B/D against

B/M group, P6= B/MgS group against B/M group, P= 0.005 means highly significant difference.

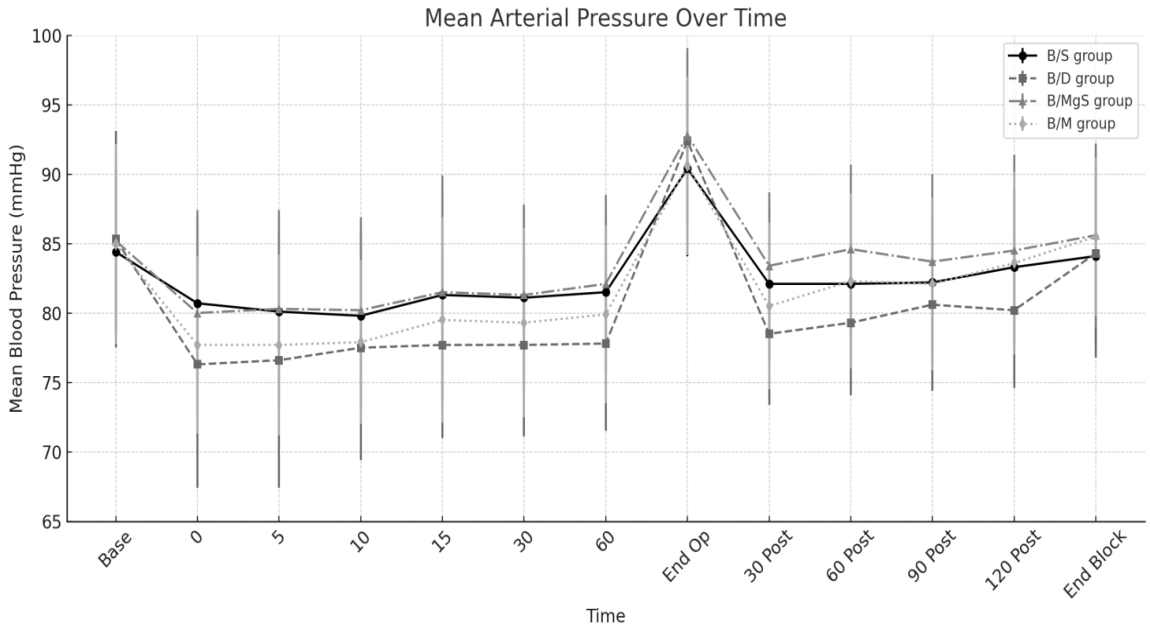

Figure (2): Mean blood pressure changes at the different times of measurement in the four studied groups.

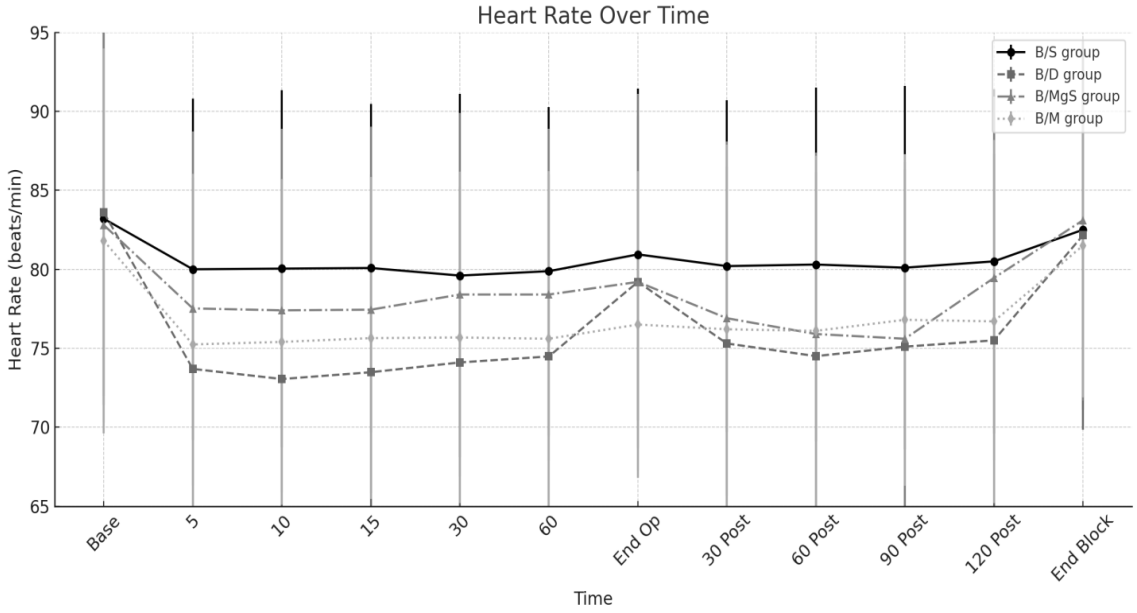

Figure (3): Heart rate changes at the different times of measurement in the four studied groups.

Discussion:

From the present study, it was found that, dexmedetomidine, magnesium sulfate or midazolam are efficient adjuvants in improving the block characteristics with minimal associated side effects when added to bupivacaine for supraclvicular block with superiority of dexmedetomidine, over magnesium sulfate and superiority

of magnesium sulfate over midazolam. They resulted in the early onset of sensory and motor blocks and prolonged the duration of sensory and motor blocks. prolonged duration of analgesia, and reduction of postoperative rescue analgesia consumption, better patient's satisfaction, preservation of hemodynamics and minimal associated side effects than bupivacaine alone.. Moreover, the onset times of sensory block and motor block were the fastest and the durations of sensory, motor block and analgesia were the longest, patient satisfaction score was the best for B/D group, followed by B/$MgSO_4$ then by B/M group and lastly by control (B/S) group.

The detected efficiency of dexmedetomidine when added to bupivacaine in improving its block characteristics is in consistence with the reported findings of many workers. **Esmaoglu et al.,** reported that, addition of dexmedetomidine to levobupivacaine for axillary brachial plexus blockade resulted in shortening of block onset time and prolongation of sensory block duration and postoperative analgesia and bradycardia was reported as a side effect in their study **[13]**. **Ammar and Mahmoud** concluded that, the addition of dexmedetomidine (0.75 µg/kg) to bupivacaine (0.33%) for infraclavicular BPB in 60 patients undergoing upper extremity surgery hastened the onset of sensory and motor block, prolonged the duration of postoperative analgesia, and decreased opioid requirements with lower pain assessment scale, but there were no side effects documented in their study **[14]**. **Das et al.,** revealed that, the use of dexmedetomidine (100 µg) as an adjuvant to ropivacaine 0.5% for supraclavicular brachial plexus block prolonged the sensory and motor block durations and the duration of postoperative analgesia and decreased total analgesic need with no adverse effects **[15]**. **Hassan et al.,** reported that, adding 100mcg of dexmedetomidine in 1ml volume to 24ml volume of a local anesthetic mixture (lidocaine 2% plus bupivacaine 0.5%, 1:1 mixture) for US -guided brachial plexus block is more effective in enhancing the onset for sensory and motor blocks, prolongation of their durations. And the time to the 1st analgesic request **[16]**.

The detected efficiency of magnesium sulfate when added to bupivacaine in improving its block characteristics is in consistence with the reported findings of many workers. **Lee et al**., proved that the use of 2 ml of magnesium sulfate (10%) as an adjuvant to bupivacaine 0.5% with epinephrine (1:200,000) for the interscalene nerve block in 66 patients underwent arthroscopic rotator cuff repair increased the duration of analgesia and reduced the postoperative pain**. [17]**. **Mukherjee et al.,** reported that, addition of magnesium sulfate to ropivacaine for supraclavicular brachial plexus block resulted in prolongation of the sensory and motor block durations, the time for the first analgesic request as well as decreased total analgesic consumption without side effects **[18] Haghighi et al.,** in their study on 60 patients undergoing orthopedic surgery of the upper extremities concluded that, the addition of 3mL of 20% magnesium sulfate to lidocaine (5 mg/kg) lengthened the duration of MB and SB of the axillary BPB [**19]**. **Abu Elyazed and Mogahed** reported that Magnesium sulfate is a useful adjuvant to ropivacaine for infraclavicular BPB in lengthening the duration of analgesia.**[20]**. **Jie et al.,** from meta-analysis and systemic review they found that, magnesium sulfate effectively prolonged the total duration of sensory blockade, reducing Visual Analog Scale pain scores at 6 hours and 12 hours postsurgery, effectively reduced postoperative analgesic use within 24 hours postsurgery and reduced the incidence of nausea and vomiting **[21]** . **Senapathi**, **et al.** in a study of 28 patients scheduled for hemodialysis vascular access surgery, observed that adding magnesium sulfate to bupivacaine in supraclavicular block resulted in a

faster achievement of complete sensory and motor block compared with bupivacaine alone **[22]**. In contrast, **Bassiony et al.,** evaluated magnesium sulfate as an adjuvant to bupivacaine in supraclavicular block and found that although the onset time was faster than the control group, the difference was not statistically significant **[23]**. This discrepancy may be explained by the lower dose used in their study (150 mg) compared with the higher mean dose

The detected efficiency of midazolam when added to bupivacaine in improving its block characteristics is in consistence with the reported findings of many workers. **Gulec et al.** also noticed bupivacaine midazolam to provide prolonged postoperative analgesia compared to bupivacaine-morphine combination when given caudally **[24]**. **Batra et al.,** reported that addition of midazolam to intrathecal bupivacaine lower visual analogue score as compared to bupivacaine alone **[25]**. **Mahajan et al.,** reported that, addition of midazolam to caudally administered bupivacaine prolongs post-operative analgesia compared to bupivacaine alone without causing any adverse effects **[26]**. **Jarbo et al.,** reported that, addition of midazolam to bupivacaine for brachial plexus block hastened onset of sensory and motor block, and improved postoperative analgesia without producing any adverse events **[27]**. **Laiq et al.,** reported that addition of midazolam 50 µg·kg–1 to 30 ml of 0.5% of bupivacaine for supraclavicular brachial plexus block enhanced the onset of sensory and motor blocks. It also improved quality of analgesia as manifested by lower pain scores, a prolonged effect and reduced requirements for rescue analgesics with stable hemodynamic and minimal rise in sedation score **[8]**. **Moharam, et al.,** reported that, addition of midazolam to bupivacaine for supraclavicular brachial plexus block fastens the onset and prolongs the duration of both sensory and motor block, and postoperative analgesia. Moreover, it provides a favorably mild degree of sedation **[28]**.

The detected superiority of dexmedetomidine over magnesium sulfate when added to bupivacaine in improving its block characteristics is in agreement with the findings of many workers. **Hassan et al.,** reported that, adding 100mcg of dexmedetomidine in 1ml volume to 24ml volume of a local anesthetic mixture (lidocaine 2% plus bupivacaine 0.5%, 1:1 mixture) is more effective in various aspects than adding 1ml volume of 100mg magnesium sulphate to the same LAs mixture for US -guided brachial plexus block. Dexmedetomidine provided more rapid onset for sensory and motor block and prolonged their durations. Also, Dexmedetomidine prolonged the time to the 1st analgesic request more than magnesium sulphate.**[16]**. **Abu Elyazed and Mogahed** reported that Magnesium sulfate or dexmedetomidine is a useful adjuvant to ropivacaine for infraclavicular BPB in lengthening the duration of analgesia. Dexmedetomidine provided quicker onset and longer duration of both SB and MB and longer duration of analgesia with lesser consumption of postoperative rescue analgesia than Magnesium sulfate **[20]**. **Mohamed and Genidy [29]** reported the superiority of dexmedetomidine over magnesium sulphate in improving the block characteristics when added to local anesthetic mixture (lidocaine 2% and bupivacaine 0.5%) for peribulbar anesthesia in the operations of phacoemulsification of cataract and intraocular lens implantation. dexmedetomidine enhanced onset of globe anesthesia, akinesia of the globe and the lid, prolonged the duration of globe akinesia, lid akinesia, increased the time to 1st analgesic request, and enhanced the satisfaction of the patients and quality of the operative conditions significantly more than magnesium sulphate. **Abu Elyazed and Mogahed [20]** reported that, dexmedetomidine is more effective than magnesium

sulphate as an adjuvant to ropivacaine in infraclavicular brachial plexus block. **Hassan, et al.,** reported that, dexmedetomidine is more effective than magnesium sulphate as an adjuvant to LAs in US guided Brachial plexus block. Dexmedetomidine provide more rapid onset for sensory and motor block and prolong their duration. Also, dexmedetomidine provide duration of analgesia longer than magnesium sulphate **[16]**. **Shukla et al.,** investigated 60 patients undergoing upper limb orthopedic procedures using 0.5% ropivacaine with either magnesium sulfate or dexmedetomidine as adjuvants. Their results showed that dexmedetomidine not only produced a faster onset of block but also prolonged sensory and motor blockade, reduced the need for rescue analgesia, and extended analgesia duration when compared with magnesium sulfate **[30]**. **Youssef et al.,** also found that dexmedetomidine accelerated the onset of block when combined with 0.5% ropivacaine in supraclavicular brachial plexus block **[31]**. **Usha et al.,** reported that addition of dexmedetomidine or $MgSO_4$ to ropivacaine resulted in the early onset of sensory and motor blocks and prolonged the duration of sensory and motor blocks when compared with control group (ropivacaine alone). Also they reported that, the onset of sensory block and motor block was fastest and the duration of sensory and motor block was the longest for dexmedetomidine group, followed by $MgSO_4$ group and then by control group **[32]**. **Wu et al.** reported that, dexmedetomidine took longer than magnesium sulfate to start analgesic demands, according to research on the effects of various local anesthetic adjuvants for supraclavicular brachial plexus block. Additionally, the dexmedetomidine group consumed much fewer opioids after surgery **[33]**.

The detected superiority of dexmedetomidine over midazolam when added to bupivacaine in improving its block characteristics is in consistence with **Youssef et al. [31]** They reported that, adding of dexmedetomidine to bupivacaine for ultrasound-guided supraclavicular brachial plexus block upon 90 patients scheduled for upper-limb vascular surgeries was more effective than adding midazolam in prolonging the duration of both sensory and motor block.

In the present study, the detected side effects were hypotension in 0, 3, 0 and 1 patients in B/S**,** B/D, B/MgS and B/M groups respectively, bradycardia in 0, 7, 1 and 1 patients in B/S**,** B/D, B/MgS and B/M groups respectively, nausea and vomiting in 4 patients in B/S group only and sedation in 0, 6, 1 and 7 patients in B/S**,** B/D, B/MgS and B/M groups respectively. Statistically, the incidences of each of bradycardia in B/D group, nausea and vomiting in B/S and sedation in both B/D and B/M groups were significantly higher than in the other groups.

These associated side effects are in agreement with some and in disagreement with other reported findings. Hassan et al., reported that, adding 100mcg of dexmedetomidine in 1ml volume to 24ml volume of a local anesthetic mixture (lidocaine 2% plus bupivacaine 0.5%, 1:1 mixture) provided a favorably mild degree of sedation **[16]**. **Abu Elyazed and Mogahed [20]** comparing of the effect of adding of magnesium sulfate and dexmedetomidine to 0.5% ropivacaine in infraclavicular brachial plexus block. They discovered that dexmedetomidine group had higher rates of bradycardia (7 patients out of 35) and hypotension (5 patients out of 35). Furthermore, three patients in the dexmedetomidine group and one in the magnesium sulphate group showed sedation. **Rao et al.** investigated the effect of addition of magnesium sulfate to 0.5% bupivacaine for supraclavicular brachial

plexus block. They found that, patients in magnesium sulfate group had no associated side effects **[34]**. **Ammar and Mahmoud** investigated the effect of addition dexmedetomidine (0.75 µg/kg) with bupivacaine (30 mL of 0.33% concentration) for infraclavicular brachial plexus block. The associated side effects in dexmedetomidine group were only nausea and vomiting in four out of thirty patients with neither hypotension nor bradycardia. The associated side effects in the control group were sedation in seven out of thirty patients.. Additionally, four out of thirty patients in the dexmedetomidine group had nausea and vomiting, which is different from the current study. In contrast, seven of the thirty patients in the control group had these side effects, which is in line with what we found **[14]**.

The causes of the differences between the rates of occurrence of the associated side effects in the current study and the other workers may be attributed to the different sample sizes, the different adjuvant doses, the different types of the local anesthetic, the effect of premedication (if used), different brachial block approach, and different types and duration of the surgical procedures.

The mechanism by which dexmedetomidine enhances the quality of regional anesthesia when used as an adjuvant to LAs can be explained by two peripheral mechanisms **[35]** and central-mediated analgesia **[36]**.

The first is the vasoconstrictor effect around the site of injection which leads to delay of the absorption of the LAs and prolong the duration of the LAs effect. The second mechanism is the direct action of dexmedetomidine on the activity of peripheral nerve. Dexmedetomidine may inhibit the compound action potentials that results in direct inhibition of nerve conduction **[37].**

The mechanism of the analgesic effects of magnesium sulfate on the peripheral nerve (PN) may be by the NMDA receptors antagonist effect that causes prevention of central sensitization from peripheral nociceptive stimulation, as well as magnesium reduced release of acetylcholine through the competitive block of the calcium entry in presynaptic endings Another possible mechanism for the action of magnesium sulfate on the PN is the surface charge theory **[17].**

The modulation of the external magnesium concentration bathing a nerve bundle can enhance the PNB caused by LAs, as well as the high concentration of magnesium attracted by the negative charges of the outer membrane surface affected Na+ channel gating and could cause hyperpolarization which results in inhibition of nerve conduction **[18].**

The mechanism by which midazolam causes prolonged analgesia could be due to its action on GABA-A receptors present in the brachial plexus and thus producing antinociception. The action of midazolam on GABA receptors is well-established. Various researchers have demonstrated the presence of GABA receptors in peripheral nerves. The presence of GABA receptors within the temporomandibular joint were observed by **Cairns et al.** and that its activation could decrease the transmission of nociceptive signals **[38].** In vitro autoradiography of lamina-II of the dorsal horn in the human spinal cord has shown the presence of high density of benzodiazepine (GABA-A) receptors suggesting a possible role in pain modulation. **[39].**

Limitations of this study were the following: **First,** it is a single center study. **Second,** sample size was relatively modest per group, limiting the power to detect rare adverse events. **Third,** the study was limited to one type of local anesthetic (bupivacaine) and one concentration. **Fourth,** the long-term outcomes such as nerve safety were not evaluated**. Lastly,** the design of the work did not include a group that received dexmeditomidine intravenously as adjuvant to bupivacaine for suraclavicular brachial plexus block to prove or disprove that the analgesic effects of dexmedetomidine are due to its systemic absorption.

Future multicenter studies with larger cohorts, varied drug doses, and extended follow-up are recommended to validate these findings and explore underlying mechanisms.

Conclusion: Addition of Dexmedetomidine, Magnesium sulfate and midazolam as adjuvant to bupivacaine are efficient in improving the characteristics of supraclavicular brachial plexus block but Dexmedetomidine is the most efficient one that followed by Magnesium sulfate and then by midazolam.

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