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The Effect of Adding Ketamine or Midazolam to Bupivacaine for Ultrasound-Guided Supraclavicular Brachial Plexus Block for Upper Extremity Surgeries

MOHAMED Z. WFA, M.Sc.; MONA BLOUGH EL-MOURAD, M.D.; AYMAN A. YOUSEF, M.D. and NADEA H. FETOUH, M.D.

The Department of Anesthesia, Surgical Intensive Care and Pain Management, Faculty of Medicine, Tanta University, Tanta, Egypt

Abstract

Background: The use of supraclavicular brachial plexus block is one of the most effective anesthetic techniques in operations for the upper extremity. The use of ultrasound guidance for regional anesthesia became popular owing to detection of anatomical variants, painless performance and correct needle placement. Aim of the study is to evaluate the value of adding ketamine or midazolam to bupivacaine when used for ultrasound guided supraclavicular brachial plexus block in upper extremity surgical procedures as regard the quality of surgical anesthesia and post-operative analgesia.

Patients and Methods: Seventy adult patients of both sexes aged (18-60) years with ASA physical status I/II scheduled for elective surgical procedure of the elbow, forearm, wrist and hand. Patients divided into two groups thirty-five patients were given 30ml total volume of 0.5% bupivacaine with midazolam 50μg/kg injected around brachial plexus cluster (Group A) and thirty-five patients were given 30ml general volume contained 0.5% bupivacaine with ketamine 2mg/kg injected around brachial plexus cluster (Group B).

Results: There was no significant difference among both groups according to demographic data, hemodynamic changes, onset of motor and sensory block, sedation score, total doses of rescue analgesia and incidence of complications. There was significant prolongation in duration of sensory and motor block, significant decrease in VAS and significant delay in first request of rescue analgesia in Group A.

Conclusion: The addition of midazolam (50μg/kg) when used as adjuvants to bupivacaine in ultrasound guided brachial plexus block produced prolongation of sensory and motor block, providing desirable sedation, improved quality of postoperative analgesia and decreased necessities of rescue analgesics in post-operative period.

Key Words: *Bupivacaine – Midazolam – Ketamine – Supraclavicular brachial plexus block – Ultrasound guided.*

Correspondence to: Dr. Mohamed Z. Wfa,
E-Mail: Dr.mohamedzakarea@gmail.com

Introduction

SUPRACLAVICULAR brachial plexus block is the most effective anesthetic procedure in surgeries of the upper extremity, it has surgical, and therapeutic purpose in interventional pain management [1].

It blocks the brachial plexus with much less requirement of anesthetic solution and rapid onset of action. The use of ultrasound has become popular due to its ability to come across the anatomical variants, painless performance and more correct needle placement [1].

Bupivacaine used frequently for supraclavicular nerve block because of its long duration of action 3-6hr. [2]. Numerous adjuvants had been used in brachial plexus block to improve the quality of duration of anesthesia and perioperative analgesia [3].

Ketamine is a noncompetitive antagonist of the N-Methyl-D Aspartate Receptor (NMDAR). It's used for sedation, it has central, regional, local anesthetic and analgesic effect [4].

Midazolam potentiates the impact of local anesthesia when used in neuroaxial block. It acts on Gamma Aminobutyric Acid-A (GABA-A) receptors which also found in peripheral nerves [5].

The objective of our study was to evaluate the impact of adding ketamine or midazolam to bupivacaine in ultrasound guided supraclavicular brachial plexus block in upper extremity procedures as regard the quality of surgical anesthesia and postoperative analgesia.

Patients and Methods

After approval of Institutional Ethical Committee of Faculty of Medicine Tanta University. This study was registered in Pan African Clinical Trial Registry with unique identification number PACTR201706002029303. This study was carried out in Tanta University Hospitals between January 2016 and March 2017 on 70 adult patients of both sexes scheduled for optional surgical procedure of the elbow, forearm, wrist or hand, a written informed consent was obtained from all patients participated in the study.

Patients with neurological deficit of upper limbs, bleeding disorders or patients on anticoagulant therapy, intellectual dysfunctions, history of drug abuse, chronic analgesic use, hypersensitivity to local anesthetics or any of the study drugs and pregnant or lactating patients were excluded from the study. Patients were randomly allocated into two groups with the use of sealed envelopes. Thirty-five patients received ultrasound guided supraclavicular brachial plexus block using 30ml overall volume contained 0.5% bupivacaine with midazolam 50µg/kg (Group A). Thirty-five patients ultrasound guided supraclavicular brachial plexus block using 30ml overall volume contained 0.5% bupivacaine with ketamine 2mg/kg (Group B).

Ordinary monitoring which includes ECG, non-invasive mean arterial blood pressure and pulse oximetry (SPO_2) were implemented to the patient and intravenous line was established using 18G cannula, in the non-operated arm. Hemodynamics (MAP, HR) were measured at arrival to operating theatre then every 5 minutes till 30 minutes then every 15 minutes until 60 minutes, at recovery, at 30 and 60 minutes post-operatively.

The skin was disinfected with betadine solution 10%. And a high frequency 12MHz (SonoScape®, SSI-6000, China) linear probe, protected with the aid of sterilized gloves was placed firmly over the supraclavicular fossa, the probe was positioned within the transverse plane advanced to the clavicle at approximately its midpoint. The probe was tilted caudally to achieve a move-sectional view of the subclavian artery. The brachial plexus become visible as a collection of hypoechoic oval structures lateral and superficial to the artery.

The patients were assessed for sensory block using pinprick test [6] (grade 0: Sharp pin felt, grade 1: Analgesia, dull sensation felt, grade 2: Anesthesia, no sensation). The onset of sensory block was recorded as the time taken from the end of the injection to the first dull response to pinprick (Grade 1) in the distribution of the sensory nerves in the hand. Duration of sensory block was recorded as the time taken from injection of the drug till the first experience of Grade 0 (sharp pin felt).

The degree of motor block was assessed according to modified Bromage scale of upper extremities [6] (grade 0: Normal motor function with full flexion and extension of elbow, wrist and fingers, grade 1: Decrease motor strength with ability to move the fingers only, grade 2: Complete motor block with inability to move fingers). The onset of motor block was recorded as the time taken from end of injection until onset of complete loss of the motor power. We checked the degree of motor block every 5min up to 30min.

The duration of motor block was recorded as the time taken between injection of the drug till the first experience of postoperative motor power recovery (Grade 0).

The patients were familiarized with a 10-point Visual Analog Scale (VAS) for pain [7], that ranged from (0=no pain) to (10=the worst imaginable pain). Patients with VAS score ≥4 received rescue analgesia in the form of meperidine 25mg increments.

Sedation was measured using sedation score as follow [8] (grade 1: Awake and alert, grade 2: Responding to verbal stimulus, grade 2: Responding to verbal stimulus, grade 3: Responding to mild physical stimulus, grade 4: Responding to moderate-or-severe physical stimulus).

Technique:

Using a 25-gauge needle, 1 to 2mL of lidocaine was injected into the skin 1cm lateral to the probe to decrease the discomfort for the duration of needle insertion. The needle must be inserted not deeper than 1 cm to keep away from inadvertent puncture of subclavian artery. The needle became superior alongside the long axis of the probe in the same plane of the ultrasound beam so the shaft and tip of the needle can be visualized when directed in the direction of the targeted nerves. The volume was injected under direct vision of ultrasound beams according to the respective groups.

Our primary outcome was quality of onset and duration of sensory and motor blockade and secondary outcome measurements were the onset of 1st request of analgesia, degree of post-operative analgesia (VAS score), the need of rescue analgesia and sedation score.

Statistical analysis:

Parametric data were analyzed using Student's *t*-test while non-parametric data were analyzed using χ^2-tests or fisher exact test. Data were presented as mean and standard deviation. A *p*-value of less than 0.05 was considered significant.

Patients were randomly classified into two equal groups, the sample size calculation was estimated at N>33 in each group, so we enrolled 35 patients per group, based on the following criteria: 95% confidence limit, 80% power of study, ratio of Group A to Group B 1:1, and the expected outcome in Group A compared to Group B ranged 30% change according to the measurements.

Results

There was no significant difference between both groups regarding demographic data (age, gender, ASA physical status, types and duration of operation) (Table 1). There were no significant differences were detected in both groups as regards hemodynamic parameters (heart rate and blood pressure) (Tables 2,3).

Regarding onset sensory block there was no significant difference between both groups in Group A the onset of sensory block was 13.09±1.95min. in comparison to 14.31±3.14min in Group B (*p*=0.053), while there was significant prolongation of the duration of sensory block in Group A which was 11.09±3.76hrs. compared to 3.54±0.74 hrs. in Group B (*p*=0.0001), and there was no significant difference between both groups regarding onset of motor block in Group A 12.086±1.422min. compared to 12.6±2.5min. in Group B (*p*=0.2941). There was significant prolongation of motor blockade duration in Group A it was 11.97±3.69hrs. compared to 3.63±0.69hrs. in Group B (*p*=0.0001) (Table 4).

There was significant delay in 1st request of rescue analgesia in Group A (*p*=0.0001) and there was no significant difference between both groups regarding the total doses of rescue analgesia needed (*p*=0.5201) (Table 5).

There was a significant decrease in VAS in Group A at 4 ,6, 8 and 10hrs. post-operatively (*p*= 0.0001, 0.0001, 0.0001 and 0.006) respectively while there was no significant change in sedation score between both groups (Table 6).

Only two patients in Group A evolved chest discomfort compared to one patients in Group B, while one patient in each groups evolved horner's syndrome (Table 7).

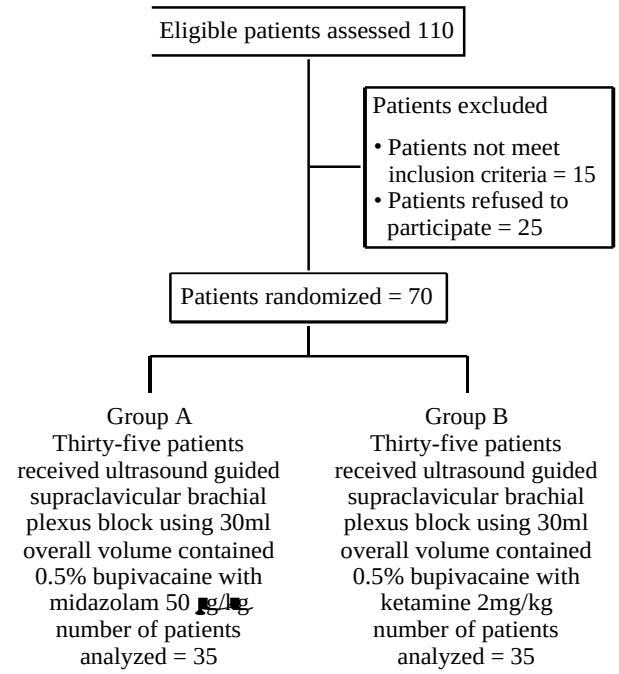

Fig. (1): Patients flow throughout the study.

Table (1): Demographic data of both groups.

Demographic data	Group A (n=35)	Group B (n=35)	Test of sig. (*t*-test- Chi square)	*p*-value
• *Age (years):* Mean ± SD	36.14±12.27	40.14±12.59	1.35	0.18
• *Sex:* F/M	10/25	9/26	0.0722	0.79
• *Wt. (Kg):* Mean ± SD	75.4±11.25	79.06±12.65	1.28	0.21
• *ASA:* II/I	11/24	14/21	0.2489	0.62
• *Duration of operation (min):* Mean ± SD	86.57±19.52	94.57±17.84	1.7898	0.0779

Table (2): Mean values of mean arterial blood pressure in studied groups.

	Group A Mean ± SD (n=35)	Group B Mean ± SD (n=35)	Unpaired *t*-test	*p*-value
Pre-operative	87.4±3.8	88.9±4.07	1.54	0.13
10min	84.5±2.8	85.7±2.9	1.88	0.07
30min	87.9±2.5	88.2±1.7	0.51	0.61
45min	89.8±2.1	90±2.8	0.34	0.74
60min	89.7±2.44	89.6±2.6	0.19	0.85
Recovery	89.8±2.92	90.14±2.7	0.47	0.64
60min	90.5±2.5	91.1±2.32	0.99	0.324

Table (3): Mean values of heart rate changes in studied groups.

	Group A Mean ± SD (n=35)	Group B Mean ± SD (n=35)	Unpaired *t*-test	*p*-value
Pre-operative	84.22±6.17	83.7±6.5	0.14	0.75
10min	80.37±5.21	82.3±4.5	1.7	0.098
30min	83.3±3.8	83.3±4.4	0.058	0.95
45min	84.5±3.98	84.6±4.26	0.058	0.95
60min	83.6±3.7	85±3.7	1.6	0.122
Recovery	81.02±4.4	82.34±4.64	1.22	0.22
60min	79.3±2.3	79.2±2.22	0.211	0.834

Table (4): Onset and duration of sensory and motor block.

	Group A (n=35)	Group B (n=35)	Test of sig. (*t*-test- Chi square)	*p*-value
• Onset of sensory block	13.09±1.95	14.31±3.14	1.97	0.053
• Onset of motor block	12.086±1.422	12.6±2.5	1.057	0.2941
• Duration of sensory block	11.09±3.76	3.54±0.74	11.64	0.0001
• Duration of motor block	11.97±3.69	3.63±0.69	13.12	0.0001

Table (5): Onset of 1 st dose and total doses of rescue analgesia.

	Group A (n=35)		Group B (n=35)		Test of sig. (*t*-test- Chi square)	*p*-value
• Mean of 1st dose of rescue analgesia (hrs.)	15±3.2		6.8±1.03		8.3	0.0001
• Mean values of rescue analgesia (mg).	28.13±8.84		31.25±11.31		0.656	0.5201
• *Number of patients need rescue analgesia:*	No.	Percentage	No.	Percentage		
Yes	8	22.9%	12	34.3%	0.63	0.427
No	27	77.1%	23	65.7%		
• *Number of rescue analgesia doses:*						
Rescue analgesia	9	25.7%	15	42.8%	1.78	0.18
No rescue	27	77.1%	23	65.7%		

Table (6): Mean values of sedation score in standard groups.

	Group A (n=35)				Group B (n=35)				Chi-square	*p*-value
	G1	G2	G3	G4	G1	G2	G3	G4		
Intraoperative	10	25	0	0	7	28	0	0	0.311	0.29
Post-operative										
Arrival to recovery unit	35	0	0	0	35	0	0	0	–	1
4h	35	0	0	0	35	0	0	0	–	1
8h	35	0	0	0	35	0	0	0	–	1
12h	35	0	0	0	35	0	0	0	–	1
18h	35	0	0	0	35	0	0	0	–	1

Table (7): Complications of both groups.

Complication	Group A (n=35)		Group B (n=35)		Chi-square	*p*-value
	N	%	N	%		
Horner's syndrome	1	2.8	1	2.8	–	1
Chest discomfort	2	5.7	1	2.8	0.35	0.56
Pneumothorax	0	0	0	0	–	1
Voice changes	0	0	0	0	–	1
Total complications	3	8.51	2	5.6	0.22	0.64

Discussion

Regional anesthesia techniques are often used to provide not only anesthesia but also post-operative analgesia after surgery. Brachial plexus block is a versatile and reliable regional anesthesia technique and suitable alternative to general anesthesia for upper limb surgery. Adjuvants to local anesthetics have been added in order to shorten the onset time, increase the quality and duration of brachial plexus block resulting in smooth post-operative outcome.

The study was designed to compare the effect of adding midazolam as and ketamine as adjuvants to bupivacaine and the study showed significantly increase in the duration of sensory and motor block, significant lower postoperative visual analogue score at (4h, 6h, 8h, 10h and 18h), significant increase the onset of 1 st dose of analgesic requirement, increasing number of patients needed analgesia post-operatively and there was no statistically significant difference in sedation scores between both groups.

We claim that our results were due to midazolam, a water soluble, short acting benzodiazepine which produces analgesia by acting on gamma amino butyric acid (GABA) receptors. Extra synaptic receptors for GABA are present on myelinated axons of peripheral nerves. Various studies demonstrated the efficacy of midazolam as an adjuvant to local anesthesia in intrathecal [9], caudal [10] and epidural routes as it prolongs post-operative analgesia [11]. While the mechanism by which ketamine acts by blocking N-Methyl-D-Aspartate (NMDA) receptor. Various studies demonstrated the efficacy of ketamine when used in premedication [12], sedation [13], induction, and maintenance of general anesthesia [14].

According to hemodynamics our results showed agreement with Nalwaya et al., [15] compared between two groups one group received bupivacaine (0.5%), Lignocaine (2%) with Adrenaline (1: 2,00,000) versus midazolam in addition to these drugs using ultrasound guided supraclavicular

brachial plexus block showed no statistically significant distinction in mean arterial blood pressure and heart rate, in addition Lashgarinia **[16]** sixty adult patients undergoing supraclavicular brachial plexus block ultrasound guided for surgeries of the elbow, forearm, wrist or hand, randomly allocated in two groups of 30 patients each. Ketamine group received 5mg/kg lidocaine 1.5% plus 2mg/kg ketamine, the other group received 5mg/kg lidocaine 1.5% and saline confirmed no statistically considerable difference in mean arterial blood pressure and heart rate between ketamine with bupivacaine versus bupivacaine only. Studies showed agreement with our study according to onset of sensory and motor block as Shaikhl et al., **[17]** added midazolam to bupivacaine in comparison to saline with bupivacaine showed no statistically significant difference in onset of sensory and motor block, Senel et al. **[18]** compared tramadol with ropivacaine compared to ketamine with ropivacaine, and there was no statistically significant difference in onset of motor and sensory block, Panda NB et al., **[19]** was in agreement with our study as he added midazolam as an adjuvant to bupivacaine in brachial plexus block compared to bupivacaine and showed prolongation of the duration of sensory block in group received midazolam, and according to ketamine Lee et al. **[20]** compared between ropivacaine, ropivacaine with ketamine as adjuvants and ropivacaine with 30mg ketamine intravenous showed no significant change between both groups regard duration of sensory and motor block, there was lower visual analogue score in group received midazolam and this was in agreement to Shaikh et al. **[17]** added midazolam to bupivacaine in comparison to saline with bupivacaine confirmed lower visual analogue score in group received midazolam, according to 1 st dose of analgesia in group received midazolam Nalwaya D et al., **[15]** study showed that 1 st dose of analgesia was significantly higher in group received midazolam and according to group received ketamine Senel AC et al., **[18]** showed that onset of 1 st dose of analgesia needed in ketamine group was shorter than the other two groups. In agreement to our study regarding requirements of analgesia Shaikh et al. **[17]** added midazolam to bupivacaine in comparison to saline with bupivacaine showed reduction in requirement of analgesia in patients received midazolam. Panda et al. **[19]** showed agreement to our results as midazolam used as an adjuvant to bupivacaine and sedation score in group received midazolam was higher than the other group. Nalwaya et al. **[15]** proven that no patients suffered airway compromise or required airway guide. Our study had some limitations. First; the sample size wasn't large. Second, although our study was a randomized clinical trial, we didn't have a control group, which makes it difficult to put our results into perspective.

We concluded the addition of midazolam with dose (50 tg/kg) was better than ketamine with dose (2mg/kg) when both used as adjuvants to bupivacaine in ultrasound guided brachial plexus block as demonstrated by prolongation duration of sensory block, improved quality of post-operative analgesia and reduced requirements of rescue analgesics in post-operative periods and providing desirable sedation without any side effects. We recomend to use higher concentration of ketamine as an adjuvant to local anesthetics in brachial plexus block to enhance the onset and duration of sensory and motor block.

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تآثير إضافة الكيتامين آو الميدازولام للبيوبيفيكين فى التخدير الجزئى فوق الترقوة بإستخدام الموجات فوق الصوتية فى جراحات الطرف العلوى

تخدير كتلة الضفيرة فوق الترقوة العضدية هى واحدة من إجراءات التخدير الآكثر فعالية فى عمليات الطرف العلوى، وقد آصبح تخدير فوق الترقوة العضدية له آهمية كبيرة فى الجراحات التشخيصية والعلاجية وفى تسكين الآلم. وإنتشر إستخدام التخدير الجزئى بالتوجيه بالموجات فوق الصوتية بسبب الآداء الغير مؤلم والآكثر دقة فى الإسترشاد نحو حزمة وعائية عصبية لتجنب إصابة الشرايين والآوردة المجاورة ورصد إنتشار المخدر فى المكان الصحيح وتجنب حدوث إستروا ح الصدر وثقب الشرايين والتلف المباشر للآعصاب.

الهدف من هذه الدراسة هو تقييم تآثير إضافة الكيتامين والميدازولام للبيوبيفيكين عند إستخدامها فى تخدير فوق الترقوة العضدية معتمدا على الموجات فوق الصوتية وتحديد بداية ومدة التخدير العصبى والعضلى ودرجة تآثيرهم كمسكن ما بعد العملية وتم تنفيذ هذه الدراسة فى مستشفيات جامعة طنطا على ٧٠ مريض من كلا الجنسين ما بين آعمار (١٨–٦٠) وتم إجراء عمليات جراحية على الكوع، الساعد، الرسغ آو اليد بعد الحصول على الموافقة الخطية من المريض حيث تم تقسيم المرضى لمجموعتين كل مجموعة ٣٥ مريض، المجموعة الآولى: ٣٠مللل من ٠.٥٪ بيوبيفيكين وميدازولام بتركيز ٥٠ميكروجرام/كجم تم حقنها حول الكتلة الضفيرة فوق الترقوة العضدية والمجموعة الثانية: ٣٠مللى من ٠.٥٪ بيوبيفيكين وكيتامين بتركيز ٢مجم/كجم تم حقنها حول كتلة الضفيرة فوق الترقوة العضدية وكانت نتيجة هذه الدراسة توصلنا إلى آن إستخدام الميدازولام كمساعد للبيوبيفيكين كان آفضل من الكيتامين كمساعد للبيوبفكين حيث كانت هناك إطالة فى مدة التخدير الحسى والعضلى وإنخفاض فى معدلات الآلم بعد العملية وتآخر فى الإحتياج لآول جرعة مسكن.