Ain-Shams Journal of Anesthesiology

ORIGINAL ARTICLE Open Access

The efficacy of adjuvants to bupivacaine in ultrasound-guided supraclavicular block: a comparative study between dexmedetomidine, ketamine, and fentanyl

Reham Mustafa Hashim[1,2*] and Rasha Mahmoud Hassan[1]

Abstract

Background: Ultrasound-guided supraclavicular block is of increasing importance in upper limb surgeries as it provides excellent pain control and reduced side effects. The search for the ideal adjuvant is still present. In this study, we aim to evaluate the efficacy and safety of dexmedetomidine, ketamine, and fentanyl when added to bupivacaine in ultrasound-guided supraclavicular block.

Patients and methods: A total of 60 patients with American Society of Anesthesiologists (ASA) I and II scheduled for upper limb surgeries were randomly assigned into three groups (20 patients each): group DB received 38 ml bupivacaine 0.5% with 2 ml (100ug) dexmedetomidine. Group KB received 38 ml bupivacaine 0.5% with 2 ml (100 mg) ketamine. Group FB received 38 ml of bupivacaine 0.5% with 2 ml (100ug) fentanyl. We measured sensory/motor block, sedation level, adverse effects, the total amount of rescue analgesia, and post-operative pain.

Results: There was a significant increase in the duration of sensory and motor block in the DB group with no difference in the onset. The mean blood pressure and heart rate were lower in the DB group. Analgesic effects of dexmedetomidine were higher, followed by ketamine and lastly fentanyl. Post-operatively visual analogue scale (VAS) and rescue analgesia results indicated that dexmedetomidine and ketamine provided adequate post-operative analgesia.

Conclusion: Addition of dexmedetomidine was more effective in prolongation of the sensory and motor duration as well as providing adequate intra-operative analgesia when compared to ketamine and fentanyl. Dexmedetomidine and ketamine are effective and safe in post-operative analgesia.

Keywords: Dexmedetomidine, Fentanyl, Ketamine, Ultrasound-guided supraclavicular block

Background

The techniques of regional anesthesia have become very popular as they provide several advantages in comparison with general anesthesia and systemic analgesia. They provide perfect pain control, decreased complications, and reduced post-anesthesia care unit stay (Abdallah and Brull 2013).

Regional anesthesia provides more patient safety and better outcomes, which led to the fact that ultrasound-guided regional anesthesia became more popular. Ultrasound provides clinicians with real-time images which are useful for better identification of the anatomical structures, safe needle placement, and adequate local anesthetic spread (Hanumanthaiah et al. 2013).

Surgeries of the upper limb are commonly done using peripheral blocks such as the supraclavicular brachial plexus block which provides effective anesthesia (Hanumanthaiah et al. 2013; Swami et al. 2012). Seeking for adequate adjuvants to the regional nerve block is still under research, with medication that increases the time of analgesia but with lesser side effects (Swami et al. 2012). Drugs such as opioids, naloxone, clonidine, midazolam, dexmedetomidine, epinephrine, and recently dexamethasone have been used along with local anesthetics for this purpose with varying degrees of success (Lashgarinia et al. 2014).

* Correspondence: Dr_reham80@yahoo.com; reham_mustafa@med.asu.edu.eg
[1]Faculty of Medicine, Ain Shams University, Cairo 11591, Egypt
[2]Cairo, Egypt

Dexmedetomidine is an effective α2 adrenoceptor agonist, which is almost eight times more selective towards the α2 adrenoceptor than clonidine, having sedative and analgesic, peri-operative sympatholytic, and cardiovascular stabilizing effects. These effects result in adequate opioid-sparing effects as well as a reduction in requirement of inhalational anesthetics. Dexmedetomidine is also proven to increase the duration of various blocks and provide post-operative analgesia when added to local anesthetic (Swami et al. 2012).

Ketamine is a noncompetitive antagonist of the *N*-methyl-D-aspartate receptor (NMDAR). It has various uses including premedication and sedation, and also induction and maintenance of general anesthesia. Ketamine induces its effects through central, regional, and local anesthetic and analgesic properties. Intravenous (IV) administration of low-dose ketamine decreases postoperative opioid use and improves analgesia (Lashgarinia et al. 2014). Its addition is reported to increase the duration of regional anesthesia and post-operative analgesia when added to epidural lidocaine or bupivacaine (Sethi et al. 2011).

Opioids such as fentanyl mediate their analgesic/antinociceptive effect primarily at the central and/or spinal cord level (Rajkhowa et al. 2016). An increase in the duration of the block and in the success rate of brachial plexus block on addition of opioid adjuvants has been reported by many studies (Nishikawa et al. 2000). The mechanism of action of fentanyl is mostly by binding directly with opioid binding sites on the dorsal neve roots aided with axonal transport or by diffusing into surrounding tissues and subsequently into the epidural and subarachnoid spaces. Fentanyl may also have local anesthetic-like action, and systemic absorption may also mediate central opioid receptor effects (Rajkhowa et al. 2016).

The purpose of this research is to study the safety and efficacy of different additives, namely dexmedetomidine, ketamine, or fentanyl, when added to bupivacaine in ultrasound-guided supraclavicular block as regards to the onset and duration of sensory and motor block, sedation score, pain scale, and side effects.

Patients and methods

This is a prospective, randomized, double-blinded study. It was done after the approval of our hospital ethical committee. Written informed consent was taken from 60 patients undergoing elective upper limb surgery including arm, forearm, and hand fractures lasting less than 120 min; with American Society of Anesthesiologist (ASA) I and II; of both sexes; and age range from 18–50 years. Patients with a history of neuromuscular, pulmonary, neurological, cardiovascular, renal, or hepatic diseases were excluded from the study. Also, patients with bleeding disorders, any known allergy to the studied drugs, and failure of the block were excluded.

All patients included were allocated randomly (using computer-generated number lists and opaque sealed envelopes) into three groups. Patients' assessment and observation were recorded by a second blinded researcher both in the operating theatre and recovery room. Patients were randomly allocated into the following groups: group DB received 38 ml bupivacaine 0.5% with 2 ml (100 μg) dexmedetomidine. Group (KB) received 38 ml bupivacaine 0.5% with 2 ml (100 mg) ketamine. Group (FB) received 38 ml of bupivacaine 0.5% with 2 ml (100 μg) fentanyl. The three solutions of the studied drugs were prepared by a staff anesthetist who was not involved in the study.

All patients fasted overnight and received 150 mg ranitidine and 4 mg ondansetron slowly intravenously through an 18G cannula which was inserted peripherally 30 min before the block in the unaffected limb. They were pre-medicated with intravenous midazolam 0.02 mg/kg. A standard monitor (non-invasive blood pressure, five-lead electrocardiography, and pulse oximetry probe) was connected, and baseline vital readings were recorded before performing the block. Intravenous lactated Ringer's solution infusion 6–8 ml/kg was started. Oxygen was supplied with a nasal catheter intra-operatively.

Supraclavicular brachial plexus block was performed by ultrasound technique using Honda electronics HS-2100 Portable ultrasound machine with linear probe 6–12 MHz probe. The brachial plexus and its relation to the surrounding structures were viewed while the patient was supine and the head turned 45° to the contralateral side. In the supraclavicular fossa, the probe was placed in the coronal plane to visualize the subclavian artery and the brachial plexus in a transverse sectional view. The subclavian artery was viewed as a pulsating hypoechoic structure on top of the hyperechoic first rib, lateral to it was the brachial plexus in the form of a cluster of hypoechoic nodules. After skin sterilization and local anesthetic administration, a 50-mm 22-gauge insulated needle was then introduced lateral to the ultrasound probe and parallel to the long axis of the probe, following the in-plane technique. Once the needle penetrated the brachial plexus cluster, the local anesthetic mixture was injected incrementally after negative aspiration for blood or air just next to the artery, then the needle was repositioned to inject on the upper pole of the artery. Local anesthetic dispersion at the time of injection was seen by ultrasound.

Intra-operative parameters included assessment of the sensory, motor, sedation, and side effects. Sensory block was examined by the pinprick test every minute in the dermatomal areas corresponding to the median, radial, ulnar, and musculocutaneous nerves after complete drug injection till full sensory blockade. Sensory onset was considered when the patients experienced dull sensation to pinprick along the dermatomal areas of any of the previously mentioned nerves. When there was a complete loss of sensation to pinprick, complete sensory block was

considered. Sensory block was graded as follows: grade 0 when sharp pin felt, grade 1 if analgesia and dull sensation felt, and grade 2 when the patients felt no sensation. The time between the complete sensory block and the first postoperative pain was defined as the duration of sensory block and was recorded.

Assessment of the motor block was performed by the same observer at each minute until complete motor blockade after drug injection. A modified Bromage scale was used for evaluation of the upper extremities on a 3-point scale; grade 0 indicated normal motor function with full flexion and extension of the joints of the upper limb, namely the elbow, wrist, and fingers. Grade 1 identified when there was a decrease in motor strength with the patients able to move the fingers only. Grade 2 considered when there was complete motor block and the patients were unable to move their fingers. Grade 1 indicated the onset of motor blockade. Peak motor block was considered when there was a grade 2 motor blockade. The time between the complete motor paralysis and complete recovery of motor function was defined as the duration of motor block and was recorded.

Intra-operative monitoring of vital parameters as heart rate, mean blood pressure, and oxygen saturation were performed every 5 min for the first 30 min and thereafter every 15 min till the end of surgery. The mean of all these measurements taken throughout the observation period was statistically calculated and compared between the three groups.

Sedation level was assessed intra-operatively 20 min after starting surgery for each patient using a 4-point scale as follows: grade 1 when patient was awake, grade 2 when he was drowsy but responsive to verbal command (mild sedation), grade 3 when patient was drowsy but responsive to physical stimulus (moderate sedation), and grade 4 when the patient was unresponsive to verbal or physical stimulus (deep sedation).

Adverse effects were also noted which compromised of the following: hypotension (i.e., 20% decrease in mean blood pressure relative to baseline) which was treated with intravenous increments of ephedrine 3 mg till normal blood pressure is regained, bradycardia (heart rate < 50 beats per minute) which was treated by intravenous atropine 0.5 mg till regaining pulse of at least 60 beats per minute, and nausea, vomiting, and hypoxemia (oxygen saturation < 90%) which were also recorded and managed in the form of 10 mg metoclopramide for nausea and vomiting and increase in Fi O2 and oxygen supplementation for hypoxemia.

Postoperative assessment included analgesia which was assessed at 1 h and at 6 h postoperatively using visual analogue scale (VAS) (0 is no pain at all; 10 cm is maximum imaginable pain) which was explained to all patients in their preoperative visit. The time for the first request of analgesia and the total amount of rescue analgesic medication given over the first 24 h (at VAS 40 or more) were as also recorded. The rescue analgesic medication was provided with intravenous injection of 0.5 mg/kg pethidine.

Sample size calculation

According to previous studies done by Swaro et al. (Swaro et al. 2016) and Lashgarinia et al. (Lashgarinia et al. 2014), 18 patients would be required to achieve an alpha error of 5% and a beta error of 3%. Thus, 18 patients for each group were considered sufficient for such data types (IBM SPSS Sample Power, V. 3, July 2010, IBM SPSS statistics, IBM Corp., USA). Twenty patients were included in each group to replace dropouts.

Statistical methods

IBM SPSS statistics (V. 24.0, IBM Corp., USA, 2016) was the statistical program used for analysis. Data were tested for normal distribution and expressed as mean ± SD for quantitative parametric measures in addition to both number and percentage for categorized data.

The following tests were done:

1. Comparison between more than 2 groups for parametric data using analysis of variance (ANOVA) and post hoc test.
2. Chi-square test to study the association between every 2 variables or comparison between 2 independent groups.
3. The probability of error at 0.05 was considered significant, while at 0.01 and 0.001 are highly significant.

Results

This study was done in Ain Shams University hospitals on 60 patients divided equally into three groups, receiving dexmedetomidine (DB), ketamine (KB), and fentanyl (FB) respectively with bupivacaine in supraclavicular plexus block (Fig. 1). As regards to the demographic data and ASA classification, there was no statistically significant difference between groups. Also, the type and duration of surgery showed no significant difference between the three groups.

Concerning the sensory and motor block onset, there was no significant difference between the three groups (p value 0.244 and 0.23 respectively). As regards the sensory block duration, the differences were highly significant with a p value of 0 which was significantly longer in the group DB than group KB with a p value of 0. Group KB was also significantly longer in duration than group FB with a p value of 0. Motor block duration also showed a statistically significant increase in the DB group when compared with the other two groups with a p value of 0. The duration was significantly longer in the group KB than group FB (p value 0.043) (Table 1).

On measuring the mean blood pressure throughout the surgical procedure, the results showed a significant difference between the three groups with a p value of 0.

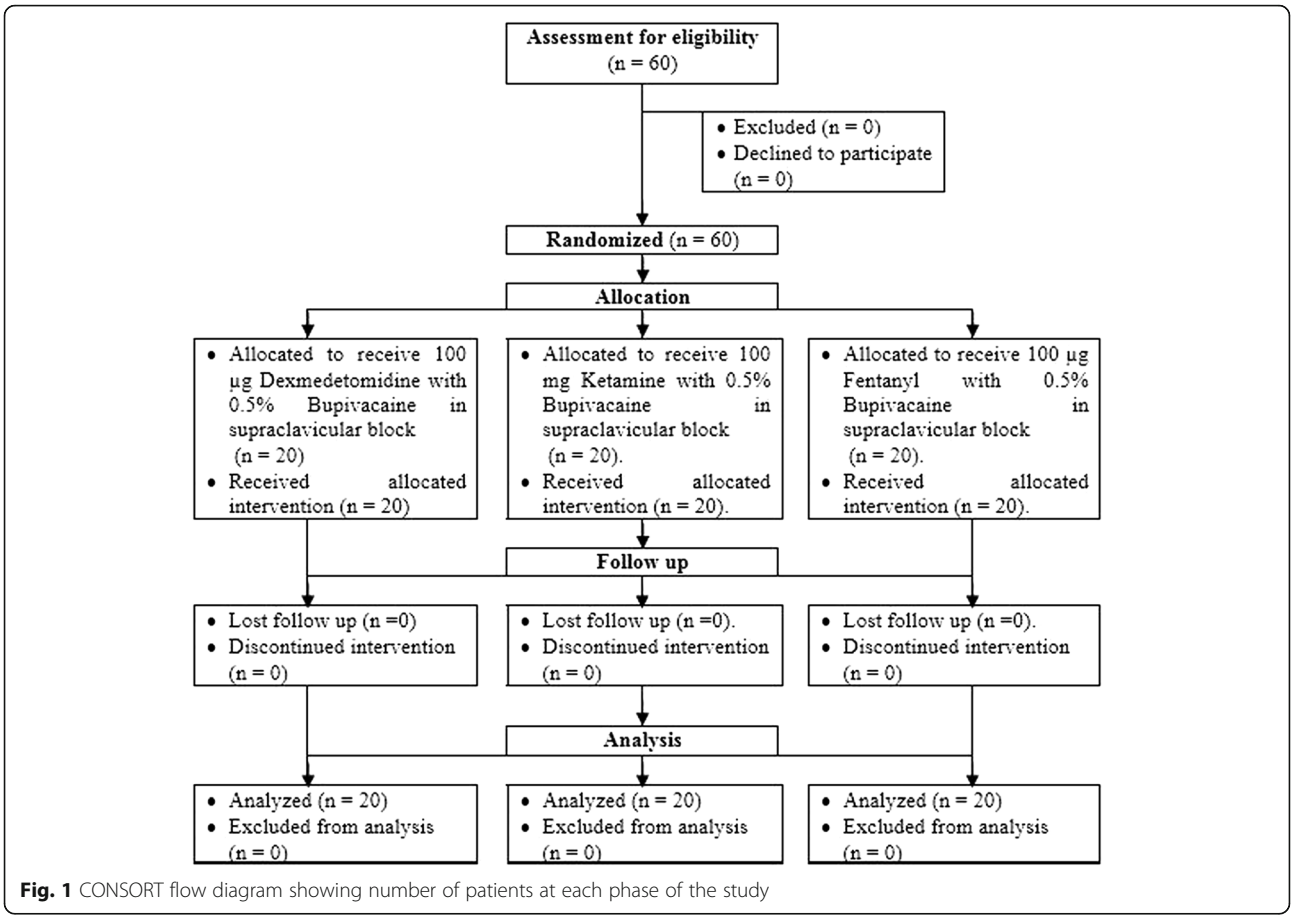

Fig. 1 CONSORT flow diagram showing number of patients at each phase of the study

The mean blood pressure measured was significantly lower in the dexmedetomidine group than the ketamine group and fentanyl group with a *p* value of 0. Meanwhile, it showed no significant difference between ketamine and fentanyl group with a *p* value of 0.822. The mean heart rate throughout the procedure was significantly lower in the dexmedetomidine group than the KB group and no significant difference between KB and FB groups (*p* value 0.688) (Table 2). Oxygen saturation was above 95% in all patients in the three groups throughout the observation period with no significant difference and *p* value of 1.

Assessment of intra-operative sedation level using a 4-point scale was recorded for each patient throughout the procedure and presented as a percentage of the number of patients in each group experiencing each scale. Sedation level showed a significant difference between the 3 groups (*p* value of 0.0). Patients in the DB group represented 20% in scale 4, 70% scale 3, 10% scale 2, and no patients at all scale 1. Group KB showed no patients in scale 4 and 30% in scale 3 and 2, while 40% in scale 1. Patients in the FB group showed different results where no patients experienced scale 4 or 3, 30% scale 2, and the highest number of patients 70% were in scale 1. These results indicate that the optimum sedative effect was with dexmedetomidine followed by ketamine then fentanyl group (Fig. 2).

Complications that occurred intraoperatively included hypotension, bradycardia, and nausea and vomiting.

Table 1 Sensory and motor block onset and duration

Block	Variable	Group DB (*n* = 20)	Group KB (*n* = 20)	Group FB (*n* = 20)	*P* value	Sig.
		Mean ± SD	Mean ± SD	Mean ± SD		
Sensory	Onset (min)	11.5 ± 2.71	14 ± 2.55	15 ± 3.01	0.244	NS
	Duration (min)	723.4 ± 32.5	244.7 ± 36.5	195.9 ± 21.6	0.00	HS
Motor	Onset (min)	15.8 ± 1.98	17.1 ± 2.45	16.3 ± 2.67	0.23	NS
	Duration (min)	665.4 ± 41.2	272.4 ± 30.5	249.7 ± 31.1	0.00	HS

Table 2 Mean blood pressure and heart rate

Variable	Group DB (n = 20)	Group KB (n = 20)	Group FB (n = 20)	P value	Sig.
	Mean ± SD	Mean ± SD	Mean ± SD		
Mean BP (mm Hg)	65.9 ± 5.9	78.9 ± 9.6	79.5 ± 9.3	0.00	HS
Mean HR (bpm)	69.4 ± 9.8	75.3 ± 9.5	76.5 ± 8.8	0.045	S

Hypotension was more frequent in the DB group representing 30% as compared to 20% in the other 2 groups, but there was no significant difference with a p value of 0.689. Bradycardia was also more frequent in the DB group representing 40% and least in the KB group 10% while representing 30% in the FB group with no significant difference between the three groups with a p value of 0.092. The incidence of nausea and vomiting between the groups also showed no significant difference (p value of 0.287) (Fig. 3).

Post-operative analgesia was evaluated by measurement of (Abdallah and Brull 2013) the time to first analgesic request, (Hanumanthaiah et al. 2013) the total amount of rescue analgesia in 24 h, and (Swami et al. 2012) VAS in 1 and 6 h post-operative measured at rest and at the movement of the limb. As regards the time to first analgesic request, the differences between the three groups were highly significant with a p value of 0. The duration to the request was significantly longer in the group DB than the group KB, followed by the group FB. Concerning rescue analgesia, there was a statistically significant difference between the 3 groups with least total analgesic given in the DB group, followed by the KB group, and the group which required the most analgesic was the FB group (Table 3).

The VAS was measured in the first hour post-operative at rest and on limb movement. Results indicated a significant difference between the three groups with a p value of 0 at both measurements. It was significantly lower in groups DB and KB when compared to group FB, but there was no significant difference between groups DB and KB with a p value of 0.661 at rest and a p value of 0.403 at limb movement. At 6 h, results were also statistically significant between the three groups at rest and at limb movement with a p value of 0.00 at rest and 0 at limb movement. The difference was between the DB and KB groups when compared to the FB group, but there was no difference between the DB and KB groups (p value of 0.482 at rest and 0.464 at limb movement). These results were indicators that dexmedetomidine and ketamine provided more adequate post-operative analgesia as compared to fentanyl (Table 4).

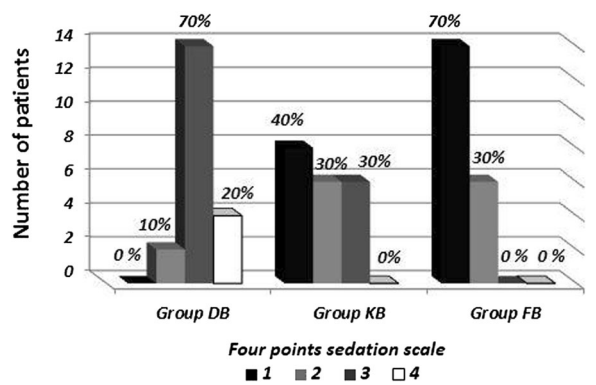

Fig. 2 Sedation level using 4-point scale

Discussion

In our study, we aimed to evaluate the efficacy and safety of different adjuvants such as dexmedetomidine, ketamine, or fentanyl when added to bupivacaine in ultrasound-guided supraclavicular block. We found that the dexmedetomidine group was more effective in prolongation of sensory and motor block when compared to ketamine and fentanyl. It also provided better intra-operative analgesia. Post-operative analgesia was adequate in dexmedetomidine and ketamine groups when compared to fentanyl group.

Recently, surgeries of the upper limb are commonly done under regional anesthetic techniques. Peripheral nerve blocks allow adequate intra-operative anesthesia and provide analgesia in the post-operative period (Murphy et al. 2000).

Dexmedetomidine is a potent α2 agonist which exerts its primary analgesic effect through the activation of the α2 receptors on the dorsal horn of the spinal cord and by the inhibition of substance P (Tobias 2007). Ketamine is a phencyclidine derivative that has various central effects through the *N*-methyl-D-aspartate (NMDA) receptor. Ketamine is gaining increasing interest in pain management due to its anti-hyperalgesic or antiallodynic properties (Visser and Schug 2006). Fentanyl mediates its effect by acting directly on primary afferent tissues (dorsal horns) which have been found to contain opioid binding sites and accounts for the analgesic effect of fentanyl. It has been added to local anesthetics for some time, with different results (Karakaya et al. 2001).

As regards the sensory and motor block onset, there were no statistically significant differences between the three groups. This result is consistent with the study done by Gandhi et al. (Gandhi et al. 2012) who studied the use of dexmedetomidine along with bupivacaine for brachial plexus block in which the onset of sensory and motor block was not shortened in the group with dexmedetomidine as compared to the control group. On the contrary, it is not consistent with Esmaoglu et al. (Esmaoglu et al. 2010) whose study

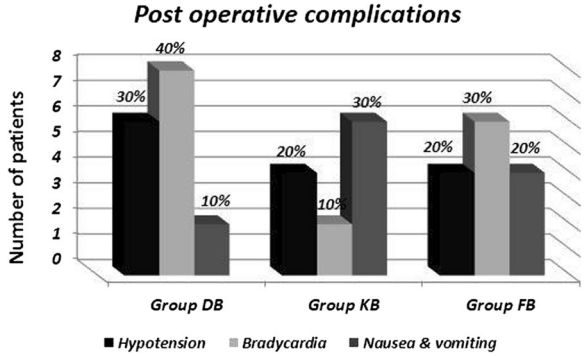

Fig. 3 Postoperative complications

was on the effect of dexmedetomidine added to levobupivacaine in axillary brachial plexus block in which there was shortened sensory and motor block onset. This difference could be due to the use of levobupivacaine instead of bupivacaine. Lashgarinia et al. (Lashgarinia et al. 2014) added 2 mg/kg ketamine with lidocaine 1.5% 5 mg/kg and concluded that no shortening of onset of sensory or motor block and no increase in their duration had occurred.

Concerning the duration, there was a statistically significant difference between the 3 groups in the sensory and motor block duration. This difference was higher in the dexmedetomidine group with prolonged duration of action in comparison with the other two groups. The duration was also significantly longer in the ketamine group than the fentanyl group. Swami et al. (Swami et al. 2012) in their study comparing the addition of dexmedetomidine and clonidine to bupivacaine in supraclavicular plexus block also concluded that the sensory and motor block were significantly prolonged in patients receiving dexmedetomidine.

The inhibitory action of α2 receptor agonist could explain this prolongation via the hyper-polarization effect leading to decrease firing of the central nervous system excitable cells. Another mechanism could be the reduction of calcium conductance into the cells which leads to inhibition of neurotransmitter release and prevention of nerve firing and propagation of signals to the neighbor's cells (Kaygusuz et al. 2012).

Sensory and motor block durations were also significantly prolonged in the study done by Biswas et al. (Biswas et al. 2014) who studied the effect of adding 1 ml (100 μg) dexmedetomidine to 35 ml of levobupivacaine 0.5%. Agarwal et al. (Agarwal et al. 2014) added 30 ml of 0.325% bupivacaine to 1 ml (100 μg) of dexmedetomidine and concluded that sensory and motor block were significantly prolonged than the control group. In the study done by Lee et al. (Lee et al. 2002) in the form of the addition of 30 mg of ketamine to 30 ml of 0.5% ropivacaine in brachial plexus block, there was no improvement in the onset or duration of sensory or motor block which was consistent with our study.

In a study done by Chavan et al. (Chavan et al. 2011), the authors concluded that the addition of fentanyl to bupivacaine in brachial plexus block caused a statistically significant increase in the duration of the sensory block than the control group. This result could not be so different from our results, as our study was aiming mainly to compare between fentanyl, ketamine, and dexmedetomidine, in which, in comparison with the other drugs, fentanyl was the least in the duration of the sensory block. Also, there was no difference in the time required for the onset of complete motor block and this was the same as our results.

On measuring the mean blood pressure throughout the procedure, the results showed a significant difference between the three groups. This difference was significantly lower in the dexmedetomidine group than the ketamine group and fentanyl group. Meanwhile, it showed no significant difference between ketamine and fentanyl group. Also, the mean heart rate throughout was lower in the dexmedetomidine group when compared to the other two groups. This decrease in heart rate in the dexmedetomidine group is due to baroreceptor reflex and increased vagal activity which results in the stimulation of parasympathetic and inhibition of sympathetic outflow (Talke et al. 2000). Esmaoglu et al. (Esmaoglu et al. 2010) also recorded lower blood pressure and heart rate in patients given dexmedetomidine with levobupivacaine in axillary brachial plexus block. Lashgarinia et al. (Lashgarinia et al. 2014) concluded that there were no differences between the ketamine group and the control group in heart rate and mean blood pressure throughout the procedure.

We also intra-operatively measured the sedation level using a 4-point scale where 1 is awake and 4 unresponsive to verbal or physical stimulus. Seventy percent of patients in the dexmedetomidine group experienced level 3 sedation in comparison with 30% in the ketamine group and 0% in the fentanyl group. The results indicate optimum sedation

Table 3 Time for the first request of analgesia (min) and the total amount of rescue analgesia (pethidine/mg) over 24 h

Variable	Group DB (n = 20)	Group KB (n = 20)	Group FB (n = 20)	P value	Sig.
	Mean ± SD	Mean ± SD	Mean ± SD		
Time to first analgesic request (min)	646.3 ± 121.2	458.7 ± 57.1	256.6 ± 35.1	0	HS
Rescue analgesia (mg)	84.1 ± 8.5	110.5 ± 23.8	170 ± 34.0	0.00	HS

Table 4 VAS at 1 h and 6 h (cm)

Time	Variable	Group DB (n = 20)	Group KB (n = 20)	Group FB (n = 20)	P value	Sig.
		Median (IQR)	Median (IQR)	Median (IQR)		
Hour 1	VAS rest	0 (0–1)	0.5 (0–1)	3 (2.75–4)	0.00	HS
	VAS movement	1 (0.75–1.25)	1 (1–2)	3.5 (3–5)	0.00	HS
Hour 6	VAS rest	1.5 (0.75–2.25)	2 (1–3)	4 (3–5)	0.001	HS
	VAS movement	2 (1.75–3)	2 (2–3.25)	5 (4.75–6)	0.00	HS

level in dexmedetomidine group as compared to the other two groups.

Dexmedetomidine acts on the α2 receptors located in the locus coerulus and the spinal cord dorsal horn by reducing the central sympatholytic output and subsequently increasing the firing of the inhibitory neurons which produces analgesia (Das et al. 2014).

Swami et al. (Swami et al. 2012) on measuring sedation level concluded that 80% of patients experienced level 4 sedation in the dexmedetomidine group in comparison with 40% in the clonidine group. This difference could be attributed to the different doses of bupivacaine as we used 0.5% and they used 0.25%. Memis et al. (Memis et al. 2004) in their study showed that adding dexmedetomidine to lidocaine for intravenous regional anesthesia improves both the quality of anesthesia and intra- and post-operative analgesia.

The current study evaluated postoperatively the time for the first request of analgesia in which there was a significant difference with increased duration of analgesia in the dexmedetomidine group followed by ketamine group, and the least duration of analgesia was in the fentanyl group. The total amount of rescue analgesia given over the first 24 h was least in the dexmedetomidine group, followed by the ketamine group and lastly the fentanyl group, indicating prolonged postoperative analgesia in the dexmedetomidine group and ketamine group more than the fentanyl group. Also, on the assessment of VAS in all patients at 1 h at rest and at movement, dexmedetomidine and ketamine groups showed significantly lower values than the fentanyl group. At 6 h post-operative, the results were also significantly lower in the dexmedetomidine and ketamine group when compared to the fentanyl group. These results indicate that dexmedetomidine and ketamine show almost the same level of post-operative analgesia, whereas fentanyl did not provide enough post-operative analgesia. NMDAR, an excitatory glutamatergic receptor in the supraspinal and spinal sites involved in the afferent transmission of nociceptive signals, could explain the analgesic properties of ketamine. Also, other effects include enhancement of descending inhibition and interaction with other receptors such as μ-opioid receptor and anti-inflammatory effects at presynaptic sites (Niesters et al. 2014).

In the study done by Swaro et al. (Swaro et al. 2016), who compared the addition of dexmedetomidine and fentanyl in a bupivacaine supraclavicular plexus block, they showed a significant prolongation of the duration of analgesia in the dexmedetomidine group when compared to the fentanyl group. There was also an increase in the quality of anesthesia in the same group indicating better analgesia and anesthesia with the addition of dexmedetomidine in comparison with fentanyl.

In another study done by Lashgarinia et al. (Lashgarinia et al. 2014), they concluded that ketamine decreased the severity of postoperative pain till 24 h after surgery. They also concluded that these patients had the least pain scores compared to the control group at all time points. Tverskoy and colleagues (Tverskoy et al. 1996) in their study showed the effect of ketamine on the inhibition of central sensitization which explained the long-lasting analgesic effect of ketamine on post-operative pain. In the Tverskoy et al. (Tverskoy et al. 1996) study, the analgesic efficacy of ketamine when added to bupivacaine infiltration before inguinal hernia repair, by the same mechanism, lasted for 1 week after infiltration.

Swami et al. (Swami et al. 2012) showed a significant increase in analgesia duration when adding dexmedetomidine to bupivacaine 0.25% in brachial plexus block with a subsequent decreased need for rescue analgesia. In the study done by Biswas et al. (Biswas et al. 2014), none of the patients in the group receiving dexmedetomidine required any other sedation, which can be explained on the basis of some amount of systemic absorption of the drug.

Conclusion

To conclude, the addition of 100 μg dexmedetomidine to bupivacaine 0.5% in supraclavicular brachial plexus block was more effective in prolongation of the sensory and motor duration of the block, as well as providing adequate intra-operative analgesia when compared to ketamine and fentanyl. We also concluded that dexmedetomidine and ketamine both effectively produced post-operative analgesia.

Abbreviations
ANOVA: Analysis of variance; ASA: American Society of Anesthesiologist; HS: Highly significant; IV: Intravenous; *n*: Number; NMDAR: *N*-Methyl-D-aspartate receptor; S: Significant; SD: Standard deviation; VAS: Visual analogue scale

Acknowledgements
Not applicable.

Authors' contributions
ReMH put the study design, collected the material, data, and drafted the research article. RaMH participated in the study design and material collection, did the statistical analysis, and revised the article. Both authors read and approved the final manuscript.

Funding
The authors declare that they have no funding.

Availability of data and materials
All data generated or analyzed during this study are included in this published article.

Ethics approval and consent to participate
This is a prospective, randomized, double-blinded study which was done after obtaining the approval of the Ain Shams University ethical committee. A written informed consent was taken from 60 patients undergoing elective upper limb surgery.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no competing interests.

Received: 26 March 2019 Accepted: 25 June 2019
Published online: 16 July 2019

References

Abdallah F, Brull R (2013) Facilitatory effects of perineural dexmedetomidine on neuraxial and peripheral nerve block: a systematic review and meta-analysis. Br J Anaesth 110(6):915–925
Agarwal S, Aggarwal R, Gupta P (2014) Dexmedetomidine prolongs the effect of bupivacaine in supraclavicular brachial plexus block. J Anaesthesiol Clin Pharmacol. 30(1):36–40
Biswas S, Kumar D, Mukherjee G, Ghose T (2014) Dexmedetomidine an adjuvant to levobupivacaine in supraclavicular brachial plexus block: a randomized double blind prospective study. Ethiop J Health Sci. 24(3):203–208
Chavan S, Koshire A, Panbude P (2011) Effect of addition of fentanyl to local anesthetic in brachial plexus block on duration of analgesia. Anesth Essays Res. 5(1):39–42
Das A, Majumdar S, Halder S, Chattopadhyay S, Pal S, Kundu R et al (2014) Effect of dexmedetomidine as adjuvant in ropivacaine-induced supraclavicular brachial plexus block: a prospective, double-blinded and randomized controlled study. Saudi J Anaesth 8(1):72
Esmaoglu A, Yegenoglu F, Akin A, Yildirim TC (2010) Dexmedetomidine added to levobupivacaine prolongs axillary brachial plexus block. Anesth Analg 111: 1548–1551
Gandhi R, Shah A, Patel I (2012) Use of dexmedetomidine along with bupivacaine for brachial plexus block. Natl J Med Res 2(1):67
Hanumanthaiah D, Vaidiyanathan S, Garstka M, Szucs S, Iohom G (2013) Ultrasound guided supraclavicular block. Med Ultrason 15(3):224–229
Karakaya D, Büyükgöz F, Bariş S et al (2001) Addition of fentanyl to bupivacaine prolongs anaesthesia and analgesia in axillary brachial plexus block. Reg Anesth Pain Med 26:434–438
Kaygusuz K, Kol I, Duger C, Gursoy S, Ozturk H, Kayacan U et al (2012) Effects of adding dexmedetomidine to levobupivacaine in axillary brachial plexus block. Curr Ther Res Clin Exp 73(3):103–111
Lashgarinia M, Naghibi K, Honarmand A, Safavi M, Khazaei M (2014) Effect of ketamine as an adjuvant in ultrasound-guided supraclavicular brachial plexus block: a double-blind randomized clinical trial study. Adv Biomed Res. 3:232
Lee I, Kim W, Kong M, Lee M, Kim N, Choi Y et al (2002) No enhancement of sensory and motor blockade by ketamine added to ropivacaine interscalene brachial plexus blockade. Acta Anaesthesiol Scand. 46:821–826
Memis D, Turan A, Karamanlioglu B, Pamukçu Z, Kurt I (2004) Adding dexmedetomidine to lignocaine for IVRA. Anesth Analg. 98:835–840
Murphy D, McCarteny C, Chan V (2000) Novel analgesic adjuvants for brachial plexus block: a systemic review. Anesth Analg. 90:1122–1128
Niesters M, Martini C, Dahan A (2014) Ketamine for chronic pain: risks and benefits. Br J Clin Pharmacol. 77:357–367
Nishikawa K, Kanaya N, Nakayama M, Igarashi M, Tsunoda K, Namiki A (2000) Fentanyl improves analgesia but prolongs the onset of axillary brachial plexus block by peripheral mechanism. Anesthesia and Analgesia 91(2): 384–387
Rajkhowa T, Das N, Parua S, Kundu R (2016) Fentanyl as an adjuvant for brachial plexus block: a randomized comparative study. Int J Clin Trials 3(2):64–67
Sethi M, Sethi N, Jain P, Sood J (2011) Role of epidural ketamine for postoperative analgesia after upper abdominal surgery. Indian J Anaesth. 55: 141–145
Swami S, Keniya V, Ladi S, Rao R (2012) Comparison of dexmedetomidine and clonidine (α2 agonist drugs) as an adjuvant to local anaesthesia in supraclavicular brachial plexus block: a randomised double-blind prospective study. Indian J Anaesth. 56(3):243–249
Swaro S, Karan D, Banerjee S (2016) Comparison of fentanyl and dexmedetomidine as an adjuvant to bupivacaine in supraclavicular brachial plexus block: a randomized-double blind prospective study. Asian J Pharm Clin Res. 9(5):74–77
Talke P, Chen R, Thomas B, Aggarwall A, Gottlieb A, Thorborg P et al (2000) The hemodynamic and adrenergic effects of perioperative dexmedetomidine infusion after vascular surgery. Anesth Analg 90:834–839
Tobias JD (2007) Dexmedetomidine: applications in pediatric critical care and pediatric anesthesiology. Pediatr Crit Care Med 8:115–131
Tverskoy M, Oren M, Vaskovich M, Dashkovsky I, Kissin I (1996) Ketamine enhances local anesthetic and analgesic effects of bupivacaine by peripheral mechanism: a study in postoperative patients. Neurosci Lett. 215:5–8
Visser E, Schug S (2006) The role of ketamine in pain management. Biomed Pharmacother. 60:341–348

Publisher's Note