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The Effect of Ketamine as Adjuvant in Ultrasonic Guided Supraclavicular Brachial Plexus Block

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ABSTRACT

Background: many of the surgical procedures are done daily all over the world. Patients get benefit from the amazing advances in both surgical and anesthesia techniques. However, despite the progress in understanding the physiology of pain and the pharmaceutical properties of painkillers, many patients are still suffering from severe postoperative pain after surgery. **Objective:** The aim of the current study was to determine the effect of the addition of 25 µg/kg body weight ketamine to 0.5% bupivacaine supra-clavicular brachial plexus block on quality of block, the time of onset and postoperative analgesia time. **Patients and Methods:** it is a prospective double blinded controlled study that was carried out on 150 patients ASA I – II, aged 18-50 years with different upper limb surgeries of the forearm and the hand in Assiut and Al-Azhar University Hospitals.

Results: ketamine was more effective with a mean complete sensory block onset of 11.93±2.95 minute in the ketamine group compared to12.60±3.00 minutes in the control groups. The study also showed that ketamine hastened the onset of complete motor block, with a mean complete motor block onset of 17.33±3.79 minute in the ketamine group compared to 19.67±4.45 minutes in the control group. As regard analgesia duration, the present study showed that ketamine group prolonged the analgesia duration.

Conclusion: It could be concluded that addition of (25 µg/kg) ketamine to bupivacaine improves onset of the block, postoperative pain-free time (VAS) and reduces the consumption of postoperative analgesics in patients undergoing different upper limb surgeries of the forearm and the hand.

Keywords: Ketamine, Ultrasonic guided, Supraclavicular brachial, Plexus block

INTRODUCTION

Brachial plexus blocks are commonly achieved via an interscalene, supraclavicular, infraclavicular, or axillary approach. The supraclavicular level is an ideal site to achieve anesthesia of the entire upper extremity just distal to the shoulder as the plexus remains relatively tightly packed at this level, resulting in a rapid and high-quality block. For this reason, the supraclavicular block is often called the ‘‘spinal of the arm.’’**(1).**

Kulenkampf described the first percutaneous supraclavicular block of the brachial plexus in the early 1900s. However, the original technique was associated with a high incidence of pneumothorax. **(2).**

With the increased availability of ultrasound in clinical practice ,the ability to identify and avoid vascular and pleural structures as well as allow real-time visualization of the needle has come The evidence for the use of ultrasound in regional anesthesia is growing it shortens block performance time, improves sensory and motor block, and reduces the need for block supplementation **(3).**

Whilst there is evidence that the use of ultrasound decreases the incidence of pneumothorax and local anesthetic systemic toxicity, there is no evidence that it reduces the incidence of peripheral nerve injury **(4).**

Ketamine is a non-competitive NMDA receptor antagonist, which is used for premedication, analgesia, sedation, induction, and maintenance stage of general anesthesia. Ketamine has been also used as local, regional, and central analgesic **(5).**

The addition of ketamine to epidural lidocaine or bupivacaine increases the duration of regional anesthesia and postoperative analgesia. It has been seen that peri-incisional use of 0.3-0.5% ketamine combined with local anesthetic in surgical wounds enhances analgesia by a peripheral mechanism **(6).**

Ketamine is a well-known anesthetic agent with potent local effect on peripheral nerves. This local effect of ketamine is most probably by blocking the voltage-operated sodium channels**(7).**

The effect of ketamine on (NMDA) N-methyl-D-aspartate antagonism abolishes peripheral afferent noxious stimulation **(8).**

The use of 0.5 mg/kg body weight ketamine as an adjuvant to local anesthetic agent in caudal anesthesia can double or triple the analgesic period and reduces the need of analgesia **(9).**

The aim of the current study was to determine the effect of the addition of 25 µg/kg body weight ketamine to 0.5% bupivacaine supra-clavicular brachial plexus block on quality of block , the time of onset and postoperative analgesia time.

PATIENTS AND METHODS

This prospective double blinded controlled study included a total of 150 patients ASA I – II, aged 18-50 years with different upper limb surgeries of the forearm and the hand, attending at Assiut and Al-Azhar University Hospitals.

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Ethical considerations:

1. **Approval of the ethical committee was obtained.**
2. Written and informed consent was obtained from every study participant.
3. All collected data was confidential and had been used for the purpose of scientific research only.
4. Every research participant had the complete right and freedom to withdraw at any time from the study with no negative consequences on the medical service provided to him or her

The included subjects were randomly divided into two groups using computer generated random numbers; **Control group (C)** consisted of 75 patients who had received only pure 0.5% bupivacaine in 20 ml volume in supraclavicular block and **Ketamine group (K)** consisted of 75 patients who had received 25 µg/kg body weight ketamine added to 0.5% bupivacaine in 20 ml volume in supraclavicular block.

Preparation of the patient:

1. Written consent
2. Coagulation profile (PT, I.N.R)
3. Intravenous line
4. Emergency resuscitation equipment, including airway devices, advanced cardiac life support drugs for local anesthetic toxicity were available.

Technique:

Distribution of Blockade

The supraclavicular approach to the brachial plexus blockade results in anesthesia of the upper limb below the shoulder because all trunks and divisions can be anesthetized. The medial skin of the upper arm (intercostobrachial nerve, T2), however, is never anesthetized by any technique of the brachial plexus block and when needed can be blocked by an additional subcutaneous injection just distal to the axilla. For a more comprehensive review of the brachial plexus anatomy and distribution.

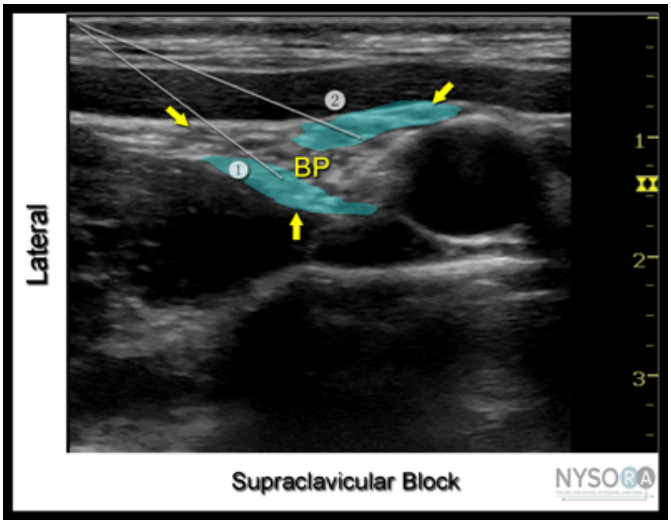

Fig. (1): Desired spread of the local anesthetic (areas shaded in blue) through two different needle positions (1 and 2), to accomplish brachial plexus (BP) block. Local anesthetic should freely spread within the tissue sheath resulting in separation of the BP cords.

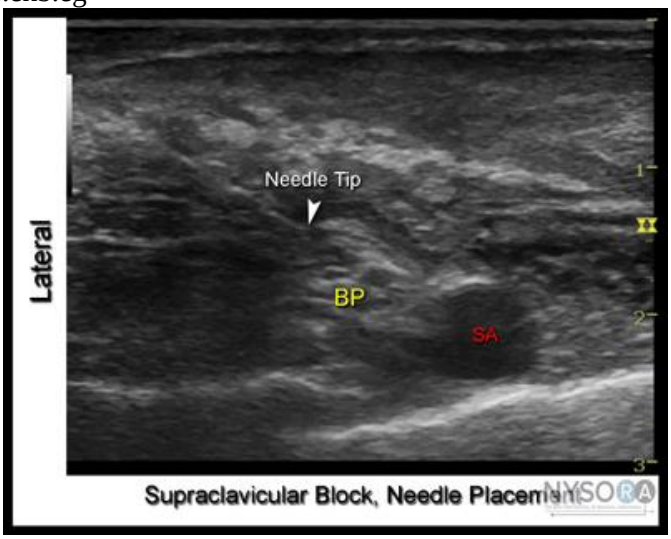

Fig. (2): Supraclavicular brachial plexus (BP) with an actual needle passing the tissue sheath surrounding brachial plexus. Needle is seen within the BP, although its tip is not visualized. Injection at this location often results in deterioration of the ultrasound image; reliance on additional monitoring (injection pressure, nerve stimulation) to avoid intrafascicular injection is essential.

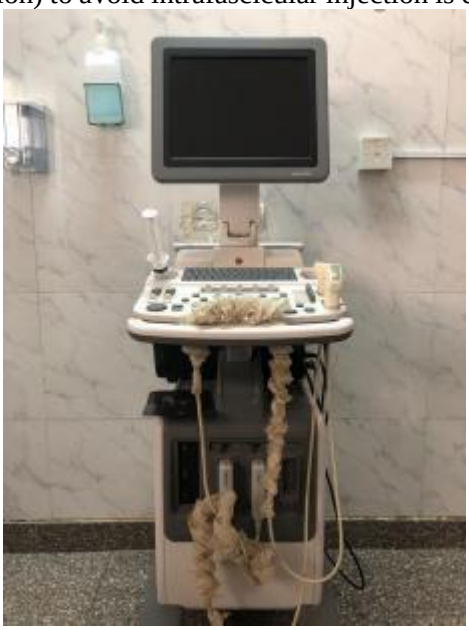

Fig. (3): SonoAce 6 ultrasound machine with high frequency linear probe used in our study

Preparation:

By i.v cannula in the contralateral upper limb

Montoring:

- ECG: five leads
- Pulse oximatry to detect oxygen saturation
- Non invase blood pressure to detect changes in blood pressure

This block was performed with the patient in the supine, semi-sitting (our favorite), or slight oblique position, with the patient's head turned away from the side to be blocked. When possible we asked the patient to reach for the ipsilateral knee will depress the clavicle slightly and allow better access to the structures of the anterolateral neck. Also, a slight elevation of the head of the bed was more comfortable for the patient and allowed for better drainage and less prominence of the neck vein.

The skin was disinfected and the transducer is positioned in the transverse plane immediately superior to the clavicle at approximately its midpoint. The transducer is tilted caudally to obtain a cross-sectional view of the subclavian artery. The brachial plexus was seen as a collection of hypoechoic oval structures lateral and superficial to the artery.

Using a 25- to 27-gauge needle, 1 to 2 mL of local anesthetic was injected into the skin 1 cm lateral to the transducer to decrease the discomfort during needle insertion The needle should never be inserted deeper than 1 cm to avoid inadvertent puncture of and injection into the brachial plexus.

We injected small amounts of the local anesthetic as the needle advances through tissue layers (hydro-localization) to observe the distribution of the local anesthetic during administration.

Then block needle was inserted in-plane toward the brachial plexus, in a lateral-to-medial direction In addition, a motor response of the arm, forearm, or hand was a confirmation of the proper needle placement. However, that motor response might be absent despite the adequate needle placement. After a careful aspiration, 1 to 2 mL of local anesthetic is injected to document the proper needle placement. When the injection displaces the brachial plexus away from the needle, an additional advancement of the needle 1 to 2 mm deeper may be required to accomplish adequate spread of the local anesthetic. When injection of the local anesthetic did not appear to result in a spread in and around the brachial plexus, additional needle repositioning and injections might be necessary.

Data collection:

1- Patient data: include patient gender, age, weight, height, BMI and ASA classification

2- Surgical data: include both type and duration of surgery.

3- Preoperative data:

a- Hemodynamics.

b- Preoperative investigations.

c- Basal assessment of motor power and sensation of the limb.

4- Intraoperative data:

a- Onset of sensory block.

b- Onset of motor block.

c- The degree of sensory and, motor block.

d- Hemodynamics.

e- Duration of surgery.

f- Surgeon satisfaction.

5- Postoperative data:

a- Duration of sensory and motor block.

b- Duration of analgesia.

c- Analgesia assessment:

d- Haemodynamic.

e-Analgesia time.

f-Time of the 1st analgesic requirement.

g- Total analgesic requirement & rescue analgesia.

h- Patient satisfaction.

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (x^2) test of significance was used in order to compare proportions between two qualitative parameters.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. The p-value was considered significant as the following:
- Probability (P-value)
- P-value <0.05 was considered significant.
- P-value <0.001 was considered as highly significant.
- P-value >0.05 was considered insignificant.

RESULTS

Table (1): Demographic data in study & control groups.

Item	Group "1" control group "n=75"	Group "2" study group "n=75"	p-value
1-Age "years"	33.30±11.15	35.56±10.41	P=0.203n.s
2- Sex:	56(74.7%)	49(65.33%)	
Male	19(25.3%)	26(34.67%)	P=0.275n.s
Female	74.00±6.52	72.90±5.70	
3- Weight	171.06±4.17	171.28±3.21	P=0.375n.a
4-Height			P=0.447n.s
5-BMI(kg/m^2)	25.30±2.19	25.50±1.76	P=0.536n.s
6-ASA			
• I	58(77.3%)	65(86.7%)	P=0.101n.s
• II	17(22.7%)	10(13.3%)	

Table (1) shows demographic data in study & control groups. There were no significance difference between study & control groups with each of age, sex, weight, height, BMI and ASA (P>0.05).

Table (2): Heart Rate in study & control groups.

Item	Group "1" control group "n=75"	Group "2" study group "n=75"	p-value
1-Baseline	70.83±5.01	72.41±4.40	P<0.04*
2-At skin	75.04±5.85***	71.97±3.25	P<0.000***
3-At 3min.	73.10±5.14***	72.26±3.17	P=0.231n.s
4-At 15min.	71.61±4.89*	72.10±3.76	P=0.490n.s
5-At 30min.	71.08±5.09	70.92±3.94*	P=0.830n.s
6-At 45min.	70.46±5.11	70.88±3.35*	P=0.559n.s
7-At the end	70.46±4.85	70.88±2.49**	P=0.512n.s

Table (2) shows heart rate in study & control groups. There were no significance difference (P>0.05) between study & control groups (P>0.05) at times from 30mins to at the end. There were significance difference (P<0.05) at baseline, also there were highly significance

difference (P<0.000) between study & control groups at skin.

When compare baseline between different times. In control group there were highly significance difference (P<0.000) between baseline and at skin & at 3 minutes, and there were significance difference (P<0.05) between baseline and at 15minutes. In study group there were significance difference (P<0.05) between baseline and at 30 & at 45 minutes, and there were moderate significance difference (P<0.001) between baseline and at 30mins, 45mins. & at the end.

Table (3): Respiratory Rate in study & control groups.

Item	Group "1" control group "n=75"	Group "2" study group "n=75"	p-value
1-Baseline	17.61±0.82	17.96±0.47	P<0.002**
2-At skin	17.69±0.69	18.01±0.62	P<0.004**
3-At 3min.	17.69±0.73	17.38±0.78***	P<0.01*
4-At 15min.	17.64±0.70	17.98±0.67	P<0.002**
5-At 30min.	17.61±0.71	17.78±0.41**	P<0.04*
6-At 45min.	17.58±0.63	17.93±0.77	P<0.003**
7-At the end	17.67±0.66	17.84±0.36	P<0.04*

Table (3) shows respiratory rate in study & control groups. There were moderate significance difference (P<0.001) at baseline, at skin, at 15mins and at 45mins. also there were significance difference (P<0.05) between study & control groups at times from 3mins, 30 mins and at the end.

When compare baseline between different times. In control group there were there were non significance difference (P>0.05) between baseline and different times. In study group there were moderate significance difference (P<0.001) between baseline and at 30mins. and there were highly significance differences (P<0.000) between baseline and at time 3mins.

Table (4): Spo2 in study & control groups.

Item	Group "1" control group "n=75"	Group "2" study group "n=75"	p-value
1-Baseline	99.46±0.55	99.58±0.49	P=0.164n.s
2-At skin	95.74±9.81**	99.40±0.59*	P<0.002**
3-At 3min.	99.58±0.54	99.16±0.59***	P<0.000***
4-At 15min.	99.65±0.47**	99.05±0.78***	P<0.000***
5-At 30min.	99.62±0.48*	99.13±0.75***	P<0.000***
6-At 45min.	99.68±0.46**	99.21±0.72***	P<0.000***
7-At the end	99.62±0.53*	99.06±0.62***	P<0.000***

Table (4) shows Spo2 in study & control groups There were no significance difference (P>0.05) between study & control groups (P>0.05) at baseline. There were moderate significance difference (P<0.001) at skin, also there were highly significance difference (P<0.000) between study & control groups at times from 3mins to at the end.

When compare baseline between different times. In control group there were there were significance difference (P<0.05) between baseline and at skin, at 30min. there were moderate significance difference (P<0.001) between study & control group baseline with at 15 mins. And at 45mins. In study group there were significance difference (P<0.05) between baseline and at skin and there were highly significance difference (P<0.000) between baseline and at time 3mins, & at the end.

Table (5): Onset of complete sensory block, onset of motor block in study & control groups.

Item	Group "1" control group "n=75"	Group "2" study group "n=75"	p-value
1- Onset of complete sensory block	12.60±3.00	11.93±2.95	P=0.173n.s
2- onset of motor block	19.67±4.45	17.33±3.79	P<0.001**

Table (5) shows Onset of complete sensory block, onset of motor block in study & control groups. There were non significance differences (P>0.05) between study & control group. But there was moderate significance difference (P<0.001) between study & control groups with onset of motor block.

Table (6): Scale & pain score in study & control groups.

Item	Group "1" control group "n=75"	Group "2" study group "n=75"	p-value
1-Scale	1.98±0.76	1.46±0.82	P<0.000***
2-Pain score	4.84±2.12	2.93±2.15	P<0.000***

Table (6) shows Scale & pain score in study & control groups. There were highly significance difference (P<0.000) between study & control groups in both of scale and pain score

Table (7): Analgesic in study & control groups.

Item	Group "1" control group "n=75"	Group "2" study group "n=75"	p-value
1-Post op. duration of sensory block	1.84±0.32	2.18±0.43	P<0.000***
2-Post op. duration of motor block	3.62±0.59	4.26±0.58	P<0.000***
3-1st analgesic request	3.69±0.51	18.70±2.88	P<0.000***
4-Total dose of analgesia	1.88±0.40	1.00±0.00	P<0.000***
5-Opioid consumption:	48(64.0%)	23(30.7%)	P<0.000***
• **Yes**	27(36.0%)	52(69.4%)	
no			

Table (7) shows Analgesic in study & control groups. There were highly significance difference (P<0.000) between study & control groups in post operative duration of sensory block, post operative duration of motor block, first analgesic request, total dose of analgesia and opioid consumption.

Table (8): Post-operative duration block in study & control groups.

Item	Group "1" control group "n=75"	Group "2" study group "n=75"	p-value
1- Post op.	1.84±0.32	2.18±0.43	P<0.000***
2- duration of sensory block	3.62±0.59	4.26±0.58	P<0.000***
3- Post op. duration of motor block			

Table (8): Post operative duration block in study & control groups. There were highly significance difference (P<0.000) between study & control groups in post operative duration of sensory block, post operative duration of motor block.

DISCUSSION

IN agreement with our study Local anesthetic properties of ketamine were demonstrated by **Dale *et al.*** [10] who reported that ketamine could produce reversible inhibition of the compound action potential in the stimulated frog sciatic nerve. Also, dogs injected with ketamine rapidly developed reversible segmental paralysis (with no alteration of the state of consciousness).

The effect of ketamine on nerve conduction was confirmed by **Argiriadou *et al.*** [11] who reported that the subcutaneous infiltration of ketamine caused a loss of thermal and pain sensations for eight to ten minutes.

Ketamine has other effects that may contribute to its systemic analgesic behavior include, enhancement of the descending inhibition, interaction with other receptors, including the μ-opioid receptor, anti-inflammatory effects, and effect on the NMDAR at presynaptic sites [12].

As regard hemodynamic in present study there were no significance difference (P>0.05) between study and control groups. This agrees with **El Mourad and Amer** [13] who studied the effect of adding ketamine as adjunct to bupivacaine in TPVB on the quality of postoperative analgesia in participants undergoing modified radical mastectomy.

These Patients had a stable hemodynamic profile at all times of measurements with no significant difference between the different groups.

Loix *et al.* [14] had shown that the local effect of ketamine as an adjuvant to bupivacaine may persist for longer time. The analgesia may persist for 7 days**.** While in our study analgesia remained for 24-48 hours

In some studies and in contrast to this study, the addition of ketamine to local anesthetics has not improved the peripheral, regional, or local analgesia compared the analgesic effects of peri femoral nerve infusion of ketamine plus ropivacaine versus ropivacaine, after operation, in patients who underwent elective knee surgery for repairing the anterior cruciate ligament, under spinal anesthesia. They reported that the addition of ketamine 1 mg/kg to 0.1% ropivacaine could not improve postoperative pain relief in the first 48 hours after the operation [15]**.** And they explained that results as by **Zohar *et al.*** [16] reported that ketamine added to local bupivacaine did not enhance analgesia after wound infiltration following Cesarean section.

The addition of ketamine to local anesthetics failed to improve analgesia after intra-articular injection for knee arthroscopy and its addition to bupivacaine for nerve block and wound infiltration after inguinal hernia repair did not improve postoperative pain relief significantly [17]**.**

Tverskoy *et al.* [18] showed that in patients whose wound were infiltrated with a solution of bupivacaine 0.5% and ketamine 0.3%, the enhanced local anesthetic and analgesic effects of bupivacaine could not be explained by a central action of ketamine, and therefore, this effect was most likely peripheral. As **Tverskoy and colleagues** [18] showed, the effect of ketamine on the inhibition of central sensitization explained the long-lasting analgesic effect of ketamine on postoperative pain, they demonstrated that the analgesic efficacy of ketamine when added to bupivacaine infiltration before inguinal hernia repair, by the same mechanism, lasted for one week after infiltration.

The variable effect of ketamine in various studies probably came from the different ketamine concentrations and sites of injection. They administered 100-200 mg ketamine and it was more than what the previously mentioned studies had used and the complications and alterations in the level of consciousness were minor and transient [12]**.**

In present study there were highly significance differences (P<0.000) between study & control groups in both of scale and pain score with lower in mean of pain score in study group than control groups. This agrees with **Lewis *et al.*** [3] who studied and reported that ketamine decreased the severity of postoperative pain till 24 hours after surgery.

Gamil and Fathy [19] studied the effect of ketamine as an adjuvant to bupivacaine in spermatic cord block for testicular sperm extraction surgery under general anesthesia. At the end of surgery, patients were allocated to receive either bupivacaine 0.5% plus ketamine 20 mg or bupivacaine 0.5% alone for spermatic cord block. They concluded that the addition of ketamine as an adjuvant to bupivacaine for spermatic cord block is a good option for postoperative pain control as it prolongs the duration of pain-free time and lowers the VAS score. The observed analgesic effect of ketamine in this study is not likely from central action, and it is most likely peripheral in origin.

Previous studies by **Tverskoy *et al.*** [18]**, Lashgarinia *et al.*** [20] **and Tan *et al.*** [21] assessed the effect of ketamine as adjuvant to peripheral nerve block concluded that addition of ketamine in peripheral nerve block results in decreasing the VAS postoperative pain and need for rescue analgesics. The results indicate that

ketamine acting by a peripheral mechanism can profoundly enhance anesthetic and analgesic actions of a local anesthetic administered for infiltration anesthesia.

Noyan [22] concluded that ketamine enhances the activity of local anesthetic, so it shortens the onset and prolongs the duration of action. It was explained by the following reasons. Ketamine might increase the binding capacity of local anesthetic to albumin α-1 acid glycoprotein and change ionic balance.

Previously published studies suggest that the effect of ketamine is more likely to occur locally in an inflamed tissue, but not at the level of a nerve plexus distant from the surgical site. Ketamine has demonstrated a significant anti-inflammatory effect that significantly inhibits the early postoperative inflammatory response. It can act at different levels of inflammation, interacting with inflammatory cell recruitment, cytokine production, and inflammatory mediator regulation [10, 12].

CONCLUSION

It could be concluded that addition of (25 µg/kg) ketamine to bupivacaine improves onset of the block, postoperative pain-free time (VAS) and reduces the consumption of postoperative analgesics in patients undergoing different upper limb surgeries of the forearm and the hand.

RECOMMENDATION

The addition of ketamine could be considered as an option to enhance the analgesic effects of the supraclavicular brachial plexus block. And it's better to reduce the dose of ketamine to avoid it's neurotoxic effect and add another adjuvant to achieve this like fentanyl or magnesium

REFERENCES

1. **Argiriadou KS, McEwen A, Matthew G (2018):** Ultrasound-Guided Supraclavicular Brachial Plexus Block. https://www.wfsahq.org/components/com_virtual_library/media/2ffc0a053d75e1cae94f93f57cddb8ff-atow-384-00-01.pdf.
2. **Kulenkampff D (1928):** Brachial plexus anesthesia: its indications, technique and dangers. Ann Surg., 87(6):883-891.
3. **Lewis SR, Price A, Walker KJ *et al.* (2015):** Ultrasound guidance for upper and lower limb blocks. https://www.ncbi.nlm.nih.gov/pubmed/26361135
4. **Neal JM (2016):** Ultrasound-guided regional anesthesia and patient safety: update of an evidence-based analysis. Reg Anesth Pain Med., 41(2):195-204.
5. **Zaman B, Ashrafi SH, Siamdoust SS *et al.* (2017):** The Effect of Ketamine and Dexamethasone in Combination with Lidocaine on the Onset and Duration of Axillary Block in Hand and Forearm Soft Tissue Surgery. http://anesthpain.com/en/articles/15570.html
6. **Sethi M, Sethi N, Jain P *et al.* (2011):** Role of epidural ketamine for postoperative analgesia after upper abdominal surgery. Indian J Anaesth., 55:141-5.
7. **Ismael AH, Latef AH, Al-Shamari AL (2012):** Non-opioid analgesia with Regional block: The effect of ketamine as adjuvant with 0.5% bupivacaine in infraclavicular brachial plexus block. Mustansiriya Medical Journal, 11(1):78-84.
8. **Trehan V, Srivastava U, Kumar A *et al.* (2010):** Comparison of two approaches of infraclavicular brachial plexus block for orthopedic surgery below mid -humerus. Indian J Anaesth., 54:210-4.
9. **Reves JG, Glass PS, Lubarsky DA *et al.* (2009):** Intravenous Anesthetics. In: Miller R, editor. Miller's Anesthesia. 7th ed. Orlando: Churchill Livingstone/ https://anesthesiology.pubs.asahq.org/article.aspx?articleid=1932719
10. **Dale O, Somogyi AA, Li Y *et al.* (2012):** Does intraoperative ketamine attenuate inflammatory reactivity following surgery? A systematic review and meta-analysis. Anesth Analg. ,115:934–43.
11. **Argiriadou H, Papagiannopoulou P, Foroulis CN *et al.* (2011):** Intraoperative infusion of S(+)-ketamine enhances post-thoracotomy pain control compared with perioperative parecoxib when used in conjunction with thoracic paravertebral ropivacaine infusion. J Cardiothorac Vasc Anesth., 25:455–61.
12. **Niesters M, Martini C, Dahan A (2014):** Ketamine for chronic pain: Risks and benefits. Br J Clin Pharmacol., 77:357–67.
13. **El Mourad MB, Amer AF (2018):** Effects of adding dexamethasone or ketamine to bupivacaine for ultrasound-guided thoracic paravertebral block in patients undergoing modified radical mastectomy: A prospective randomized controlled study. Indian Journal of Anesthesia, 62(4):285-93.
14. **Loix S, De Kock M, Henin P (2011):** The anti-inflammatory effects of ketamine: state of the art. Acta Anaesthesiol Belg., 62(1):47-58.
15. **Rahimzadeh P, Faiz SH, Ziyaeifard M *et al.* (2013):** Effectiveness of adding ketamine to ropivacaine infusion via femoral nerve catheter after knee anterior cruciate ligament repair. Journal of research in medical sciences. The Official Journal of Isfahan University of Medical Sciences, 18(8):632-36.
16. **Zohar E, Luban I, Zunser I *et al.* (2002):** Patient-controlled bupivacaine wound instillation following cesarean section: The lack of efficacy of adjuvant ketamine. J Clin Anesth., 14:505–11.
17. **Clerc S, Vuilleumier H, Frascarolo P *et al.* (2005):** Is the effect of inguinal field block with 0.5% bupivacaine on postoperative pain after hernia repair enhanced by addition of ketorolac or S(+) ketamine? Clin J Pain, 21:101–5.
18. **Tverskoy M, Oren M, Vaskovich M *et al.* (2016):** Ketamine enhances local anesthetic and analgesic effects of bupivacaine by peripheral mechanism: A study in postoperative patients. Neurosci Lett., 215: 5–8.
19. **Gamil K, Fathy A (2013):** Spermatic cord block with ketamine as an adjuvant to bupivacaine improves postoperative analgesia for testicular sperm extraction surgery. Ain-Shams Journal of Anaesthesiology, 6(2):153-158.
20. **Lashgarinia M, Naghibi K, Honarmand A *et al.* (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.
21. **Tan PH, Cheng JT, Kuo CH *et al.* (2007):** Pre-incisional subcutaneous infiltration of ketamine suppresses postoperative pain after circumcision surgery. Clin J Pain, 23:214–218.

Noyan A (2002): On effects of ketamine to axillary block in hand surgery. J Reconstr Microsurg., 18:197–198.