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Ketamine Plus Nitroglycerin Versus Ketamine as Adjuncts to Lidocaine for Intravenous Regional Anesthesia in Adult Patients Undergoing Hand Surgery

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Abstract

Background: Different agents have been used as adjutants to lidocaine for intravenous regional anesthesia (IVRA) to improve the quality of analgesia.

Aim of the Study: The aim of this double blinded randomized controlled trial is to evaluate if adding nitroglycerin to ketamine is more effective than using ketamine alone as an adjuvant to lidocaine for IVRA.

Patients and Methods: Fifty adult ASA I-II patients undergoing hand surgery using IVRA were divided into two equal groups: ketamine/nitroglycerin (K/N) group received lidocaine 3mg/kg (maximum 200mg) with ketamine 0.1mg/kg (maximum 10mg) plus nitroglycerin 2mcg/kg (maximum 200mcg) and ketamine (K) group received lidocaine 3 mg/kg (maximum 200 mg) with ketamine 0.1mg/kg (maximum 10mg). Statistical analysis was done using Student's t test or Chi square analysis whenever appropriate.

Results: The two groups were similar in demographic data and patients characteristics. The onset times of sensory and motor blockades were significantly shorter in K/N group. Although the preoperative visual analogue scale for pain intensity (VAS) was comparable, the intra-operative and postoperative VAS, were significantly less in K/N group. The intra-operative fentanyl consumption as an intra-operative analgesia was significantly less in K/N group. Also, the time to call for the first postoperative analgesia was significantly longer in K/N group than K group. However the postoperative analgesics consumption showed no significant difference between the two groups.

Conclusion: In comparison to ketamine, adding a combination of ketamine and nitroglycerin to lidocaine for IVRA improved the quality of anesthesia without inducing significant clinical side effects.

Key Words: *Nitroglycerin – Ketamine – Intravenous – Regional – Anesthesia.*

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Introduction

KETAMINE hydrochloride acts as a non–competitive antagonist for N-methyl-D-aspartate (NMDA) receptors [1]. Therefore, ketamine found a place in the field of IVRA as an effective additive, [2] or even in higher doses as a sole agent with local anesthetic qualities [3]. Nitroglycerin as a nitric oxide generator has been proved in several studies to have analgesic enhancement effects in acute and chronic pain conditions [4,5]. Recently, it was investigated as an adjuvant to lidocaine for IVRA with promising results [6].

The present double blinded randomized controlled trial aimed to compare between a combination of ketamine plus nitroglycerin versus ketamine solely as adjuncts to lidocaine for IVRA.

Patients and Methods

After approval of local ethical committee and getting an informed written consent we carried out this study at Zagazig university hospitals from January 2014 to December 2016. Fifty, ASA I-II, adult patients, age from 21 to 60 years of both genders who were undergoing hand surgery which was expected to be less than one hour duration, were included in the study. Exclusion criteria were decompensated cardiovascular or respiratory disease, sickle cell anemia, Reynaud's disease, peripheral cyanosis or neuropathy, regular use of analgesics, drug abuse and known allergy to one of the examined drugs.

All patients were pre-medicated with 2mg midazolam and atropine 0.01mg/kg half an hour before operation. Non invasive monitoring of electrocardiography, blood pressure and oxygen saturation were established. Two cannulae were inserted

and secured: One in a vein on the dorsum of the operated hand for injection of the local anesthetic and the investigated additives and the second cannula in the other hand for intravenous fluids and other drugs administration. A double cuffed pneumatic tourniquet was applied to the limb to be operated upon after exsanguinations with an Esmarch bandage. The proximal cuff was inflated to 100mmHg above patient's systolic pressure and circulatory isolation of the arm was verified by absence of radial pulse and loss of the pulse oximeter trace in the ipsilateral index finger. Then, patients were randomly assigned into one of two groups with twenty five patients in each group: Ketamine/Nitroglycerin (K/N) group in which patients received lidocaine 3mg/kg (maximum 200mg) plus ketamine 0.1mg/kg (maximum 10mg) and nitroglycerine 2mcg/kg (maximum 200mcg) versus Ketamine (K) group whereas patients received lidocaine 3mg/kg (maximum 200mg) and ketamine 0.1mg/kg (maximum 10mg). The drugs used in either group were pre-prepared, mixed and diluted together up to 40ml with normal saline by an anesthesiologist who was not included in the anesthesia administration. On the other hand, the patient and the anesthesiologist who provided and monitored the local intravenous anesthesia intra and postoperatively didn't know to which group the patient was allocated. When complete sensory and motor block was achieved, the distal cuff was inflated to 250mmHg and the proximal cuff was deflated and surgeon was asked to proceed in the procedure to be done. At the end of operation, the tourniquet was released by cyclic deflation technique. It was not permitted the release of tourniquet before thirty minutes or keeping it inflated more than one hour and half.

Outcome measurements:

- Onset time of sensory block which was defined as the time elapsed from injection of the study drugs to the loss of sensation to pinprick in dermatomes of radial, median and ulnar nerves.
- Onset time of motor block which was defined as the time elapsed from injection of the study drugs to the inability of patient to flex the wrist or fingers.
- Visual analogue scale (VAS) for evaluation of pain intensity (zero value is the best and ten value is the worst) was measured one hour preoperatively, at thity minutes after tourniquet inflation and fifteen minutes postoperatively after complete deflation of the tourniquet and before administration of any postoperative analgesia.
- Heart rate and blood pressure were recorded at five minutes intervals and any increases or decreases by 25% of the baseline were reported.

  Intra-operative analgesic requirements were estimated, hence 1mcg/kg of fentanyl was given on patient request or with VAS > than 4 value.
- Time to the first call for analgesia which was defined as the time elapsed from the complete deflation of the tourniquet at the end of operation until the patients asked for postoperative analgesia.
- Postoperative consumption of analgesics whereas patients received ketorolac 30mg IM on patients request for analgesia with a minimum 6 hours interval and a maximum dose 120mg/24 hours.
- Side effects such as delirium, loss of consciousness and local anesthetic toxicity were noted.

Statistical analysis: The collected data from patients were verified prior to computerized data entry. The Statistical Package for Social Sciences (SPSS for Windows, Version 19) was used for statistical analysis. Simple randomization was done using random number generator in SPSS. All data are presented as mean ± standard deviation or number (percentage). Statistical analysis was done using Student's *t*-test or Chi square analysis whenever appropriate. All tests of significance were two-tailed with p-values <0.05 were considered statistically significant. Based on a priori sample size calculations that incorporated results from previous studies, [7] it was estimated that a twenty five patients per group (total fifty patients) would be required for a statistical power of 80 % at a two tailed level of significance of $p<0.05$.

Results

The two groups were similar in demographic data and patients characteristics including age, weight, height, gender, type of operation and duration of surgery (Table 1). The onset times of sensory and motor blockades were significantly shorter in the K/N group (Table 2). Although, the preoperative VAS was comparable, the intraoperative and postoperative VAS, were significantly less in K/N group than K group (Table 3). As been shown in (Table 4), the intra-operative fentanyl consumption as an intra-operative rescue analgesic was significantly less in the K/N group. Also, the time to call for the first postoperative analgesia was significantly longer in the K/N group than the K group. However, the postoperative analgesics consumption showed no significant difference between the two groups. No patient in the study developed hemodynamic increases or decreases by 25% of baseline blood pressure and heart rate or other clinical side effects were noted.

Table (1): Demographic data and patients characteristics.

	Ketamine/ Nitroglycerin (K/N) group (N = 25)	Ketamine (K) group (N = 25)	
Age (year)	41±8.4	38±10	0.26
Weight (kg)	81±6.7	83±7.3	0.36
Height (cm)	178±3.8	175±5.9	0.09
Sex:			
Male	14 (56)	17 (68)	0.38
Female	11 (44)	8 (32)	
Type of surgery:			
Carpal tunnel	12 (48)	9 (42)	0.85
Tendon repair	6 (24)	7 (28)	
Contracture release	4 (16)	5 (20)	
Trigger finger	3 (12)	4 (16)	
Duration of surgery (min)	59±10	57±9	0.41

- Data are presented as mean ± standard deviation or number (percentage).

Table (2): The onset times of sensory and motor blockades.

	Ketamine/ Nitroglycerin (K/N) group (N = 25)	Ketamine (K) group (N = 25)	
Onset time of sensory block (min)	3.7±0.57*	4.2±0.63	0.004
Onset time of motor block (min)	5.3±0.64*	6.1±0.87	0.001

- Data are presented as mean ± standard deviation.
- *Significant $p<0.05$.

Table (3): Preoperative, intra-operative and postoperative visual analogue scale (VAS) for pain intensity in the operated arm.

	Ketamine/ Nitroglycerin (K/N) group (N = 25)	Ketamine (K) group (N = 25)	
Preoperative VAS	0.8±0.81	0.6±0.74	0.59
Intra-operative VAS	1.8±1.1*	2.7±1.3	0.01
Postoperative VAS	2.1±1.06*	2.8±1.05	0.02

- Data are presented as mean ± standard deviation.
- VAS: Visual analogue scale for pain intensity with (0) value is the best and (10) value is the worst pain encountered.
- *Significant $p<0.05$.

Table (4): Intra-operative and postoperative analgesics consumption.

	Ketamine/ Nitroglycerin (K/N) group (N = 25)	Ketamine (K) group (N = 25)	
Intra-operative analgesia:			
- Patients required rescue fentanyl (number of patients)	3 (12)*	9 (36)	0.04
- Consumed amount of fentanyl (mcg)	10±27*	30±41	0.04
Time to call for first post-operative analgesia (min)	67±17*	50±18	0.002
Postoperative analgesia:			
- Consumed ketorolac (mg)	64±20	74±24	0.14

- Data are presented as mean ± standard deviation or number (percentage).
- *Significant $p<0.05$.

Discussion

The problematic issue with IVRA is the application of a tourniquet that should be kept inflated all the time of surgical procedure to maintain the regional anesthesia and avoid local anesthetic toxicity **[8]**. Also, one of its drawbacks is absence of postoperative analgesia after release of tourniquet **[9]**. Several trials were carried out to find an additive to lidocaine, **[10,11,12]** which promotes the relief of tourniquet pain, prolongs the duration of analgesia after tourniquet release and reduces the systemic analgesic drugs consumption **[13]**.

Ketamine acts as a non-competitive NMDA receptors antagonist. NMDA receptors antagonists have been widely used for control of peri-operative pain **[14]**. Hence the NMDA receptors have been found on peripheral unmyelinated sensory axons in addition to the spinal cord NMDA receptors, it can be explained why ketamine as an antagonist of NMDA receptors is capable to reduce tourniquet pain and improve the quality of anesthesia when added to lidocaine as an adjuvant in IVRA **[15]**. However, patients exhibited disorientation and hallucinations after the release of tourniquet which limited the usefulness of ketamine for this purpose. These unpleasant effects were associated with ketamine use in doses ≥0.5mg/kg of body weight. When it was used in doses <0.5mg/kg in IVRA no central nervous system effects have been noticed **[16]**. Therefore, in our study we used ketamine in a dose 0.1mg/kg to avoid these unpleasant side effects.

It is well known that nitroglycerin has a direct potent vasodilator effect that seems to enhance the

distribution of lidocaine to nerves [17]. This action of nitroglycerin is greatly dose dependent and can be increased by the increase in drug dose [18]. Also, nitroglycerin exhibits its analgesic action because it is metabolized to nitric oxide in the cells [19]. Nitric oxide elevates the intracellular concentration of cyclic guanosine monophosphate which modulates pain perception in the central and peripheral nervous systems [20]. Additionally, nitroglycerin as a nitric oxide generator by topical application produces an anti-inflammatory effect and analgesia through blocking hyperalgesia and the neurogenic component of inflammatory oedema [21].

Asadi and Mehri, [22] evaluated the analgesic effect of nitroglycerin when added to lidocaine on quality of intravenous regional anesthesia in patients undergoing elective forearm and hand surgery. Their study revealed that nitroglycerin as adjuvant drug to lidocaine is effective in improving the overall quality of anesthesia, shortening onset time of both sensory and motor blockades. Also, Elmetwaly et al., [23] compared and evaluated the effect of adding ketamine or nitroglycerin to lidocaine for IVRA on intra-operative and postoperative analgesia, onset of sensory and motor blockade and tourniquet pain. Their conclusion was that either ketamine or nitroglycerin when added to lidocaine improved the overall quality of anesthesia, reduced the tourniquet pain and improved the postoperative analgesia consumption. Moreover, ketamine as an adjuvant produced better tolerance to tourniquet while nitorglycerin as an adjuvant produced faster onset of sensory and motor blockades.

Our study evaluated if adding nitroglycerin to ketamine is more effective than using ketamine alone as an adjuvant to lidocaine for intravenous regional anesthesia. We found that the onset times of sensory and motor blockades were significantly shorter with adding nitroglycerin to ketamine. The tolerance of tourniquet pain was significantly better as reflected by lower intra-operative and postoperative VAS and less consumption of fentanyl as an intra-operative rescue analgesic. In addition, the time to call for the first postoperative analgesia was significantly longer with using the combination of nitroglycerin and ketamine. However, the postoperative analgesic consumption was similar in both groups.

Despite both ketamine and nitroglycerin are expected to cause tachycardia, our results did not show any significant hemodynamic changes or clinical side effects. This can be attributed to the small doses of both drugs which were used in the study (ketamine 0.1mg/kg with maximum dose 10mg, nitroglycerin 2mcg/kg with maximum dose 200mcg). Also, the presence of tourniquet, avoidance of tourniquet deflation before 30min and the use of cyclic deflation at the end of operation allowed gradual escape of both drugs to systemic circulation which limited their hemodynamic effects [24]. However, one of the limitations of the present study is the small number of patients which was enough to detect significant clinical differences between the two groups but is difficult to detect significant side effects. Because side effects are not common it necessitates a study of a huge number of patients to assure their statistical significance.

Conclusion:

Adding a combination of ketamine and nitroglycerin to lidocaine for intravenous regional anesthesia improved the quality of anesthesia, shortened the onset times of sensory and motor blockade and reduced the intra-operative analgesic consumption without inducing significant clinical side effects.

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الكيتامين بالإضافة إلى النيتروجليسيرين مقابل الكيتامين كمساعدات لليدوكايين فى التخدير الوريدى الموضعى لدى المرضى البالغين الخاضعين لعملية جراحية باليد

الهدف من هذه الدراسة هو تقييم إذا ما كان إضافة النيتروجليسرين إلى الكيتامين هو أكثر فعالية من استعمال الكيتامين وحده كمساعدات لليدوكايين فى التخدير الوريدى الموضعى، وعليه تم تقسم خمسين مريضاً يخضعون لعملية جراحية باليد إلى مجموعتين متساويتين حيث تلقت مجموعة الكيتامين/النيتروجليسرين ٣ ملى جرام لكل كيلو جرام (كحد أقصى ٢٠٠ ملى جرام) من الليدوكايين مع ٠.١ ملى جرام لكل كيلو جرام (بحد أقصى ١٠ ملى جرام) من الكيتامين بالإضافة إلى النيتروجليسرين ٢ميكروجرام لكل كيلو جرام (كحد أقصى ٢٠٠ ميكروجرام) بينما تلقت مجموعة الكيتامين ٣ ملى جرام لكل كيلو جرام (كحد أقصى ٢٠٠ ملى جرام) من الليدوكايين مع الكيتامين ٠.١ ملى جرام (كحد أقصى ١٠ ملى جرام)، وقد وجد أن فترة بداية الانحسار الحسى والحركى وكذلك شدة الألم أثناء وبعد العملية الجراحية أقل بدلالة إحصائية فى مجموعة الكيتامين/النيتروجليسرين، كما كان استهلاك عقار الفنتانيل أثناء العملية الجراحية أقل فى نفس المجموعة، وكذلك الوقت من إنتهاء الجراحة وحتى استدعاء المرضى للمسكنات. ومن ثم نستخلص أن إضافة مزيج من الكيتامين والنيروجليسرين إلى الليدوكايين يحسن من جودة التخدير مقارنة بأضافة الكيتامين وحده إلى الليدوكايين وذلك فى التخدير الوريدى الموضعى.