Original Research Article

The impact of Verapamil addition to Ketamine and Lidocaine Intravenous regional Anesthesia: A Randomized controlled study

Sarat Babu Chevuri[1*], Vijay Rekha[1]

[1]Associate Professor
Department of Anesthesia, Deccan College of Medical Sciences, Hyderabad, Telangana State, India
[*]Corresponding author email: **sarat52@gmail.com**

International Archives of Integrated Medicine, Vol. 4, Issue 4, April, 2017.

Available online at http://iaimjournal.com/
ISSN: 2394-0026 (P) **ISSN: 2394-0034 (O)**
Received on: 21-03-2017 **Accepted on:** 31-03-2017
Source of support: Nil **Conflict of interest:** None declared.
How to cite this article: Sarat Babu Chevuri, Vijay Rekha. The impact of Verapamil addition to Ketamine and Lidocaine Intravenous regional Anesthesia: A Randomized controlled study. IAIM, 2017; 4(4): 27-34.

Abstract

Background: The use of adjuncts along with Lidocaine during intravenous regional anesthesia (IVRA) decreases tourniquet pain and prolongs post-operative analgesia. Addition of ketamine reduces the time for onset of block, delays the onset of tourniquet pain and reduces postoperative analgesic requirement. Verapamil potentiates the effect of neuromuscular blocking agents. This study was designed to evaluate the effect of adding Verapamil (2.5 mg) to Lidocaine plus Ketamine (0.5 mg/kg) in comparison with lidocaine plus ketamine IVRA.

Materials and methods: Hundred and twenty patients, aged 18–50 years, ASA physical status I and II undergoing elective hand or forearm surgery under Bier's Block lasting one to one and half hours were included in this double-blinded, randomized and controlled study. Patients were divided into two groups of 60 patients each. Group- I (control group) received 40 ml of 0.5% Lidocaine plus ketamine (0.5 mg/kg) and Group- II received an addition of 2.5 mg of verapamil IVRA. Sensory and motor block onset and recovery time were noted. After the tourniquet deflation: pain, sedation values, time to first analgesic requirement and side effects were evaluated over a period of 12 hours.

Results: Significant postoperative hemodynamic changes, sedation score, pain score and delayed first request for analgesia was observed in-group II when compared to group I. Sensory and motor block characteristics were significant in-group II as against group I. The side effect profile of verapamil (2.5mg) was minimal with a few episodes of hypotension and bradycardia, which were clinically managed by ephedrine and atropine respectively.

Conclusions: Adding verapamil 2.5 mg to Lidocaine plus ketamine (0.5 mg/kg) for IVRA proved to be an effective and safe adjuvant for acute pain after surgery..

Key words

Verapamil, Lidocaine, Ketamine, Bier's block.

Introduction

IVRA is a simple and safe technique of producing analgesia in the distal part of a limb by intravenous (IV) injection of a local anesthetic with simultaneous occlusion of the circulation to the limb by application of tourniquet [1]. IVRA is effective for short operative procedures on the extremities performed on an ambulatory, daycare basis with a success rate of 94%-98% [2]. Bier's block regional anesthesia isolates the limb from the systemic circulation using pneumatic tourniquet pressure to the proximal extremity [1].

Lidocaine IVRA reduces operating room time and overcomes the unnecessary complications of general anesthesia however, it has its own set of disadvantages such as local anesthetic toxicity, poor muscle relaxation, early tourniquet pain, short duration of analgesia and possibility of nerve damage [3]. Therefore various adjuncts have been used in the recent years to improve the quality of the block, maintain adequate muscle relaxation, decrease tourniquet pain and increase the efficacy and duration of postoperative analgesia [4].

Opioids when added to local anesthetics for treating acute post-operative pain has been associated with nausea, vomiting, mood alteration, respiratory depression and pruritus. Non-opioid analgesics (NSAIDs) have a morphine sparing effect and reduce these side effects. However, NSAIDs are associated with other adverse event profiles such as renal impairment and gastrointestinal hemorrhage [5]. Various other adjuncts such as bicarbonate, epinephrine, clonidine, dexamethasone, muscle relaxants, magnesium, neostigmine and dexmedetomidine have been used concomitantly for IVRA with varied effects [6].

Ketamine, a phenyl-piperidine derivative is an effective anesthetic agent for IVRA at concentrations between 0.3% and 0.5%. It has effective local anesthetic properties and provides sympathetic, sensory and motor block [7]. At sub anesthetic doses, ketamine exerts a non-competitive blockade of N-methyl-D-aspartate (NMDA) receptors [8]. Verapamil is a dihydropiridine L-type voltage-gated calcium channel antagonist [9].

There is growing evidence suggesting that calcium ions play a vital role in analgesia mediated by local anesthetics and are involved in endogenous regulation of pain sensitivity [10]. Increases in intracellular calcium are associated with central sensitization after noxious stimuli, suggesting that voltage-gated calcium channels have an important role and affect the transmission of nociceptive impulses [11]. This study was designed to compare the effectiveness of using Verapamil as an additional adjunct to Ketamine in Lidocaine IVRA.

Materials and methods

A prospective, double blinded, randomized controlled study was carried out in a tertiary care hospital during January 2016 to February 2017. Hundred and twenty patients aged between 18 to 50 years of both sexes with American Society of Anesthesiologists (ASA) physical status I and II, body weight ≥ 60 kg to 100 kg undergoing elective upper limb surgery (hand or forearm) under Bier's Block were included in the study. Written informed consent was obtained from all the patients. Patients with weight <60 or >100, infection at the site of injection, history of allergy to local anesthetic solution and verapamil, history of significant cardiac, renal, hepatic or psychiatric disease, peripheral vascular or neurological disease, a positive history of

coagulopathy, sickle cell anemia, patients receiving chronic analgesic therapy, those using antihypertensives, antiarrhythmics and patients with significant bradycardia or hypotension were excluded from the study.

During the Pre-anaesthetic evaluation 120 patients meeting the inclusion criteria were divided into two equal groups) by computer-generated double blinding randomization [12]. Group – I (control group, n=60) received 40 ml of 0.5% Lidocaine plus ketamine (0.5 mg/kg) and Group – II (n=60) received 40 ml of 0.5% Lidocaine plus verapamil 2.5 mg plus ketamine (0.5 mg/kg).

After shifting the patient to the Operation theatre, standard monitoring was done using 5 lead ECG, noninvasive arterial blood pressure monitor and pulse oximetry. An intravenous catheter (20 G) was inserted into a distal vein on the dorsum of the hand of the operative extremity for injection of the local anesthetic and the non-operating upper limb was cannulated with 18 gauge intravenous cannula for intravenous fluid infusion (Ringer's solution). All patients received 2 mg midazolam for sedation.

A double-cuffed pneumatic tourniquet was placed around the upper operative arm, and the arm was elevated for 3–5 minutes and then exsanguinated with Esmarch bandage, and the proximal cuff was inflated to 250 mmHg, complete exsanguination of blood was confirmed by inspection and absence of radial pulse. An intravenous solution of either lidocaine 2 mg/kg 0.5% plus ketamine (0.5 mg/kg) diluted with 0.9% normal saline to a volume of 40 ml (Group I) and lidocaine 2 mg/kg 0.5% plus verapamil 2.5 mg plus ketamine (0.5 mg/kg) diluted with normal saline to a volume of 40 ml (Group II) for IVRA was injected over 1 min in the operating limb.

Surgery was allowed to proceed with the single tourniquet until the patient became pain free. The second tourniquet was inflated and the first deflated only when the patient felt pain before surgery was complete or when the first tourniquet inflation time exceeded 30 min. The second tourniquet was deflated when the surgery was complete, with total duration not exceeding one and half-hours.

The following parameters were recorded: time for onset of sensory blockade (evaluated once in every 5 minutes using pinprick response) and time for onset of motor blockade (evaluated at 1-min interval by asking the patient to flex and extend his/her wrist and fingers). All observations were made in the four major nerve distribution areas (radial, median, ulnar and musculocutaeneous nerve).

After sensory and motor block, the distal cuff was then inflated to 250 mmHg and the proximal cuff was released. Time to the onset of pain after tourniquet inflation (First tourniquet pain time) was recorded in each patient. The tourniquet cuff was deflated only after 40 min, with total duration not exceeding 90 min by repeated inflation–deflation technique (deflating the tourniquet for 10 s followed by 1 min of re-inflation for three times).

Sensory and motor recovery time after deflation of the tourniquet was assessed by the time taken for the return of pinprick sensation and recovery of voluntary movement respectively in area of distribution of the radial, ulnar, median and musculocutaneous nerve. (Assessed at 1 min interval for first 10 min and then every 30 min once in the post anesthesia recovery room.)

Hemodynamic parameters (HR and MAP) were monitored and recorded before and after inflation of the tourniquet at 10 min, 20 min, 40 min, 60 min, 2 h, 6 h and 12 h after the injection of anesthetic by an independent anesthesiologist not involved in the study. Hypotension (20% decrease from baseline reading) was treated with bolus 3–9 mg ephedrine intravenously, and bradycardia (20% decrease from baseline reading) was treated with 0.5 mg atropine intravenously.

Pain (tourniquet or postoperative) was assessed using 10 cm marked visual analog scale (VAS) where zero = no pain and ten = most severe pain. Pain was assessed at 30 min, 1, 2, 6 and 12 hour (h) after operation. The rescue analgesia used was intravenous injection of pethidine 0.5 mg/kg whenever demanded intraoperatively (for relieving tourniquet pain) or intramuscular injection postoperatively if VAS was greater than 3. The total pethidine consumption was recorded. Time to the first request for analgesic was used as an indicator of the duration of postoperative analgesia from the time of local anesthetic injection.

Postoperative assessment of sedation was done according to sedation score (where 0 =alert, 1 =sleepy but, arousable by verbal command, 2 =sleepy but, arousable by tactile stimulation and 3 =sleepy but, arousable by painful stimulation). The satisfaction score of the patient for the anesthetic technique was assessed postoperatively according to a numeric scale as follows: 3= good (no complaint from patient), 2= moderate (minor complaint with no need for supplemental analgesics), and 1 = poor (complaint which required supplemental analgesics).

Data was analyzed by using SPSS software (version 22) and statistical significance was calculated by p-value interpretation.

Results

Present study was designed to study the impact of using verapamil in addition to ketamine and lidocaine during IVRA. There were no dropouts during the study and the final data analysis included all 120 patients. There was no significant difference in the demographic data among the two groups with regards to age, sex (male to female ratio), weight, height, ASA physical status and the duration of surgery in minutes. (**Table – 1**)

Onset of sensory and motor block was significantly faster among group II subjects in comparison to group I subjects. Group II showed better Tourniquet pain tolerance and faster recovery from sensory & motor block. The time taken for first rescue analgesia (minutes), requirement of intraoperative pethidine, total pethidine requirement (mg) in 12 hours duration, satisfaction score and sedation score ($p < 0.05$) were significantly superior among group II in comparison to group I subjects. (**Table – 2**)

Visual analog score was significantly lower in-group II in comparison with group I at 30 min, 1, 2, 6 and 12 h postoperatively (**Table – 3**). Pain score was lower in-group II compared to group I at 6 and 12 h postoperatively.

Intra-operatively there was no significant difference in the HR and the MAP. However, post operatively a significant decrease in the HR and MAP was seen among group II patients. No significant changes were noted with regards to the SpO_2 measurement both intra-operatively and postoperatively. Restlessness and hallucinations were the main side-effects seen among group I patients which were not seen among group II patients (**Table – 4**).

Discussion

Peripheral nerve blocks offer the potential benefits of prolonged analgesia, with fewer side effects, greater patient satisfaction, and faster functional recovery after surgery [13]. Lignocaine IVRA technique is widely used for surgery on the upper limbs and is the mainstay to control perioperative pain but it is of little or no benefit postoperatively [14]. IVRA has high indices of reliability, rapid onset of analgesia within 5-10 minutes and good muscular relaxation. However the disadvantage is the application of an arterial tourniquet, which must remain inflated continuously throughout the procedure thereby limiting the time duration available for surgery [15].

Ketamine inhibits NMDA receptors on the peripheral un-myelinated sensory axons as well as the spinal cord and thereby attenuate

tourniquet pain. Studies by Viscomi, et al. [16], Kumar, et al. [17] and Kaul, et al. [18] have proved that ketamine when used with lignocaine (0.5%) in a dose of 3 mg/kg of body weight, can increase the duration of analgesia after release of tourniquet and the quality of analgesia is superior. However the onset of analgesia and motor blockade remains unaltered [17]. Ketamine therefore cannot be recommended as a sole agent for IVRA unless the unpleasant side effects are abolished or controlled by means of pharmacologic adjuvant [18].

Table - 1: Demographics.

Variables	Group-I (n=60)	Group-II (n=60)	P - value
Age (years)	29.65 ± 4.6	30.02 ± 4.18	0.64
Sex (M:F)	28/32	31/29	1
Weight (kg)	69.5 ± 4.5	70 ± 4.32	0.53
Height (cm)	165.8 ± 4.5	166.2 ± 4.12	0.61
ASA(I/II)	43/17	46/14	1
Duration of surgery	52 ± 5.7	53 ± 4.9	0.3

Data in the form of mean ± Standard deviation or median
P value > 0.05 is statistically insignificant.

Table - 2: Block characteristics.

Block characteristics	Group I	Group II	P value
Onset of sensory block (min)	4.6 ± 1.2	2.8 ±1.6	< 0.001
Onset of motor block (min)	13.1 ± 1.4	10.24 ± 0.5	< 0.001
First tourniquet pain (min)	27.3 ± 2.1	43.6 ± 1.8	< 0.001
Recovery from sensory block (min)	12.01 ± 1.3	33.04 ± 1.7	< 0.001
Recovery from motor block (min)	7.4 ± 1.52	15.2 ± 1.2	< 0.001
Time for first rescue analgesia (min)	32 ± 2.6	246 ± 4.5	< 0.001
Patients requiring intraoperative pethidine	41	13	< 0.001
Total pethidine requirement in 12h (mg)	118 ± 5.8	64.1 ± 6.4	< 0.001
Satisfaction score	2 (1-3)	4 (3-4)	< 0.001
Sedation score	1 (0-1)	3 (2-3)	< 0.001

Data in the form of mean ± Standard deviation or median (IQR)
P value <0.001 is statistically highly significant.

L-type calcium channel blockers like verapamil and diltiazem produce both somatic and visceral pain relief in a dose-dependent manner. A Study by Hara, et al. [19] has proved that verapamil potentiates the actions of local anesthetics and opioids, and can be used as an adjunct for plexus blockade.

In the present study, addition of verapamil 2.5 mg to lidocaine plus ketamine reduced the tourniquet pain, lowered the VAS scores at the site of tourniquet application, delayed the first request for tourniquet pain relief, resulted in rapid onset and delayed offset of sensory and motor block, delayed the onset of postoperative pain and reduced the consumption of postoperative (12 hours) supplementary analgesia (pethidine). Addition of verapamil further resulted in higher sedation and satisfaction scores. The findings of the present study were in agreement with studies by Esmat, et al. [20] and Tabdar, et al. [21].

Table - 3: Visual Analog Score.

Time of assessment postoperatively	Group I	Group II	P value
30 min	6 (5-6)	1 (0-1)	< 0.001
1 h	4 (4-5)	1 (0.5-1)	< 0.001
2 h	4 (4-5)	2 (1-2)	< 0.001
6 h	5 (5-6)	3 (2-3)	< 0.001
12 h	5 (4-5)	3 (2-3)	< 0.001

Data in the form of median and IQR
P value<0.001 is statistically highly significant.

Table - 4: Side effect profile.

Side effects during intra and post-operative period	Group I	Group II	P value
Restlessness	4	0	< 0.001
Hallucinations	3	0	< 0.001
Paresthesia	1	1	> 0.05
Tachycardia	0	0	> 0.05
Bradycardia	0	1	> 0.05
Hypertension	1	0	> 0.05
Hypotension	0	3	< 0.001
Nausea	3	3	> 0.05
Vomiting	1	2	> 0.05

Data represented as number of patients presenting with the side effect in the particular group.
P value<0.001 is statistically highly significant.
P value >0.05 is statistically not significant.

Hallucinations and restlessness were the predominant side effects seen among group I patients. However, upon the addition of verapamil 2.5 mg (group II) hypotension was the only notable side effect. Findings of the present study were in correlation with studies by Gorgias, et al. [22], Kumar, et al. [17] and Haider, et al. [23], which reported the presence of hallucinations, paresthesia, dizziness and nausea upon the use of ketamine along with lidocaine for IVRA.

Conclusion

The present study demonstrated that the addition of verapamil 2.5 mg to ketamine and lidocaine IVRA of upper limb improved the quality of anesthesia, resulting in faster onset of sensory and motor block, lengthened recovery of sensory and motor blockade, and improved postoperative analgesia without significant side effects, in comparison with keatamine + lidocaine IVRA. Therefore verapamil proved to be a safe adjuvant when used along with katamine and lidocaine at the dose of 2.5mg for management of pain in the intra and post-operative period.

References

1. Holmes CM. Intravenous regional anesthesia. A useful method of producing analgesia of the limbs. Lancet, 1963; 1: 245–7.
2. Choyce A, Peng P. A systematic review of adjuncts for intravenous regional anaesthesia for surgical procedure. Can J Anesth., 2002; 49: 32–45.
3. Johnson CN. Intravenous regional anesthesia: new approaches to an old technique. CRNA, 2000; 11: 57–61.
4. Kirksey MA, Haskins SC, Cheng J, Liu SS. Local anesthetic peripheral nerve block adjuvants for prolongation of analgesia: a systematic qualitative

review. PLoS One, 2015; 10(9): e0137312.

5. Ng A, Parker J, Toogood L, Cotton BR, Smith G. Does the opioid-sparing effect of rectal diclofenac following total abdominal hysterectomybenefit the patient? Br J Anaesth., 2002; 88: 714–716.
6. Culebras X, van Gessel E, Hoffmeyer P, Gamulin Z. Clonidine combined with a long acting local anesthetic does not prolong postoperative analgesia after brachial plexus block but does induce hemodynamic changes. Anesth Analg., 2001; 92: 199–204.
7. Durrani Z, Winnie AP, Zsigmond EK, Burnett ML. Ketamine for intravenous regional anesthesia. Anesth Analg., 1989; 68: 628–32.
8. De Kock MF, Lavand'homme PM. The clinical role of NMDA receptor antagonists for the treatment of postoperative pain. Best Pract Res Clin Anaesthesiol., 2007; 21: 85–98.
9. Gerancher JC. Upper extremity nerve blocks. Anesthesiol Clin North America, 2000; 18: 297–317.
10. Fassoulaki A, Sarantopoulos C, Zotou M. Nitrous oxide enhances the level of sensory block produced by intrathecal lidocaine. Anesth Analg., 1997; 85: 1108–1111.
11. Coderre TJ, Katz J, Vaccarino AL, Melzack R. Contribution of central neuroplasticity to pathological pain: review of clinical and experimental evidence. Pain, 1993; 52: 259–285.
12. Gerard E. Dallal, Ph.D. Randomization generator, 2013. Available from: ⟨http://www.randomization.com⟩
13. Liu SS, Salinas FV. Continuous plexus and peripheral nerve blocks for postoperative analgesia. Anesth Analg., 2003; 96: 263–272.
14. Morgan Jr GE, Mikhail MS,Murray MJ, Larson Jr CP. Clinical anesthesiology. 3rd edition. New York (NY): Lange Medical Books/ McGraw-Hill Medical Publishing Division; 2002.
15. Choyce A, Peng P. A systematic review of adjuncts for intravenous regional anesthesia for surgical procedures. Can J Anaesth., 2002; 49: 32-45.
16. Viscomi CM, Friend A, Parker C, Murphy T, Yarnell M. Ketamine as an Adjuvant in Lignocaine Intravenous Regional Anesthesia: A Randomized, Double-blind, Systemic Control Trial. Reg Anesth Pain Med., 2009; 34: 130-3.
17. Kumar A, Sharma D K, Datta B. Addition of ketamine or dexmedetomidine to lignocaine in intravenous regional anesthesia: A randomized controlled study. J Anaesthesiol Clin Pharmacol [serial online], 2012 [cited 2017 Feb 23]; 28: 501-504
18. Kaul TK, Mittal BR, Gupta S. Comparison of lignocaine and ketamine as intravenous regional anesthetics. Ind J Anaesth., 1993; 41: 234-9
19. Hara K, Saito Y, Krihara Y, Sakura S, Kosaka Y. Antinociceptive effects of intrathecal L-type calcium channel blockers on visceral and somatic stimuli in the rat. Anesth Analg., 1998; 87: 382–387.
20. Ibrahim M. Esmat, Dina Yehia Kassim. A double-blind trial of the combination effect of lidocaine, ketamine and verapamil in intravenous regional anesthesia. Egyptian Journal of Anaesthesia, 2016; 32: 207–212.
21. Tabdar S, Lama S, Kadariya ER. Comparison of Bier's block with Lidocaine versus Lidocaine plus Verapamil. J Kathmandu Med College, 2013; 2(3), No. 1.
22. Gorgias NK, Maidatsi PG, Kyriakidis AM, et al. Clonidine versus ketamine to prevent tourniquet pain during intravenous regional anesthesia with lidocaine. Reg Anesth Pain Med., 2001; 26(6): 512–7.
23. Haider HS, Mahdi FA. The combination effect of lidocaine, ketamine and

atracurium in intravenous regional anesthesia. Al Kindy Collegue Med J (KCMJ), 2013; 9(2): 61-3.