Egyptian Journal of Anaesthesia (2016) 32, 207–212

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Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

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Research Article

A double-blind trial of the combination effect of lidocaine, ketamine and verapamil in intravenous regional anesthesia

Ibrahim M. Esmat [a,*], **Dina Yehia Kassim** [b]

[a] *Department of Anesthesia and Intensive Care Medicine, Ain Shams University Hospitals, 29-Ahmed Fuad St., Saint Fatima Square, Heliopolis, Cairo, Egypt*
[b] *Department of Anesthesia and Intensive Care Medicine, Beni Sweif University Hospitals, El Rehab City, Group 71, Building 15, New Cairo, Egypt*

Received 15 July 2015; revised 12 September 2015; accepted 30 September 2015
Available online 14 November 2015

KEYWORDS

Bier's block;
Lidocaine;
Ketamine;
Verapamil

Abstract *Background:* The aim of this study was to evaluate the effects of adding two different doses (2.5 mg or 5 mg) of verapamil to lidocaine ketamine (0.5 mg/kg) during Intravenous Regional Anesthesia (IVRA) compared with lidocaine with ketamine alone.
Methods: Seventy-five 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 randomized controlled double-blind study. Patients were divided into three groups, 25 each to receive either group (I, control group) received 40 ml of 0.5% Lidocaine plus ketamine (0.5 mg/kg), group (II) received as group I plus verapamil 2.5 mg or group (III) received as group I plus verapamil 5 mg for IVRA. Postoperative assessment of block characteristics, sedation, pain, first time for rescue analgesia, hemodynamic changes and side effects were evaluated over a period of 12 h.
Results: Block characteristics were significant in groups II and III compared with group I. There were significant hemodynamic changes, sedation score, pain score and delayed first request for analgesics postoperatively in groups (II) and (III) compared to group (I) postoperatively. There was no significant difference in group (III) compared to group (II) postoperatively. The incidence of postoperative side effects were more in group (III).
Conclusion: Adding verapamil 2.5 mg to Lidocaine plus ketamine (0.5 mg/kg) for IVRA was effective and safe adjuvant for acute pain after surgery.

* Corresponding author at: Department of Anesthesia and Intensive Care Medicine, Ain Shams University Hospitals, 29-Ahmed Fuad St., Saint Fatima Square, Heliopolis, Cairo, Egypt. Tel.: +20 0227748551, +20 01001241928.
E-mail addresses: himadouh@hotmail.com (I.M. Esmat), dinayk31@yahoo.com (D.Y. Kassim).
Peer review under responsibility of Egyptian Society of Anesthesiologists.

1. Introduction

Intravenous regional anesthesia (IVRA), first described by August Bier in 1902, proved to be successful for short operative procedures on the extremities performed on an

http://dx.doi.org/10.1016/j.egja.2015.09.011

ambulatory basis and is simple, reliable and cost-effective, with success rates between 94% and 98% [1,2]. Lidocaine 0.5% is the local anesthetic (LA) used but it has a short duration of action after tourniquet release [3]. Disadvantages of IVRA are LA toxicity, slow onset, poor muscle relaxation, tourniquet pain and minimal postoperative pain relief [2]. Different agents used as additive to local anesthetic for IVRA to avoid the disadvantages including phencyclidines, non-steroidal anti-inflammatory drugs, opioids and muscle relaxants [2].

Nociceptive stimulation, induced by the incision and tissue damage, causes neurotransmitter release, coupled with activation of voltage-dependent calcium conductance in synaptic terminal membranes of neurons. A disruption of calcium influx into the cells interferes with normal sensory processing and contributes to anti-nociception. Peripheral tissue injury provokes peripheral and central sensitization [4]. The actions of excitatory amino acids are mediated by the N-methyl-D-aspartate (NMDA) receptor and non-NMDA receptors. Activation of NMDA receptors leads to Ca^{2+} entry into the cell and initiates a series of central sensitization [5]. NMDA receptors are involved in decreasing postsynaptic depolarization of unmyelinated C-fibers [6]. This central sensitization could be prevented not only with NMDA antagonists such as ketamine and dextromethorphan, but also with calcium channel blockers that block Ca^{2+} entry into cells [7]. NMDA receptor antagonists are implicated in perioperative pain management as they modulate central sensitization [8].

Ketamine, a phenyl-piperidine derivative, was first synthesized in the early 1960s and marketed as an intravenous anesthetic at the beginning of the seventies. At subanesthetic (i.e., low) doses, ketamine exerts a non-competitive blockade of NMDA receptors [8]. Cardiovascular stimulating effects of ketamine are prevented by prior benzodiazepines, inhaled anesthetics, verapamil, etc. [9]. Ketamine is an effective anesthetic agent for IVRA at concentrations between 0.3% and 0.5%. Ketamine has effective local anesthetic properties and provides sympathetic, sensory and motor block [10].

Omote et al. showed that spinal verapamil with Lidocaine produced potent and prolonged pain relief with motor block [11]. Choe et al. demonstrated that addition of verapamil to Bupivacaine for epidural anesthesia resulted in less consumption of analgesic postoperatively [7]. Capt et al. showed that verapamil in addition to Lidocaine for brachial plexus block prolonged onset of sensory anesthesia without any effect on total analgesic duration [12]. Tabdar et al. demonstrated that verapamil 2.5 mg added to 40 ml of 0.5% Lidocaine for Bier's block is more effective than 0.5% Lidocaine alone [13].

The effects of ketamine (3, 10 and 30 mg/kg) alone and in combination with verapamil (10 mg/kg) on the acquisition, consolidation and retrieval of memory using a passive avoidance task in mice were studied. Ketamine significantly inhibited the acquisition and consolidation of memory at 10 and 30 mg/kg dose levels and these effects were not antagonized by verapamil 10 mg/kg. Studies of sleeping time demonstrated that pretreatment with verapamil 10 mg/kg increased the duration of sleeping time. The data also indicate that pretreatment of surgical patients with verapamil may reduce the dose of ketamine required for anesthesia [14].

In this study, our primary objective was to compare the effects of adding two different doses (2.5 mg or 5 mg) of verapamil to lidocaine ketamine (0.5 mg/kg) during IVRA to detect a mean difference of total analgesic (pethidine) consumption compared with lidocaine with ketamine alone. And our secondary goal was to compare the effects of adding two different doses (2.5 mg or 5 mg) of verapamil to lidocaine ketamine (0.5 mg/kg) during IVRA on sensory and motor block onset times, sensory and motor block recovery times, improvement of tourniquet pain, prolongation of first analgesic requirement time, pain score, sedation score and patient satisfactory score compared with lidocaine with ketamine alone.

2. Methods

This study was designed to be a randomized controlled double-blind parallel study. The study was conducted in Ain-Shams University Hospitals on 75 patients aged between 18 and 50 years of both sexes of ASA physical status I and II of 70–90 kg body weight and height 160–180 cm undergoing elective surgery of the hand or the forearm under Bier's Block lasting one to one and half hours. The study protocol was approved from the institutional ethical committee and written informed consent was obtained from all the patients.

The exclusion criteria were patients not meeting the above criteria, history of allergy to local anesthetic solution and verapamil, patients with a 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, patients using antihypertensives, antiarrhythmics, or patients with significant bradycardia or hypotension.

Totally 75 patients meeting the inclusion criteria during the preanesthetic evaluation were equally divided and were randomly assigned to one of the three groups of patients for administration of either; group (I, control group = 25 patients) received 40 ml of 0.5% Lidocaine plus ketamine (0.5 mg/kg), group (II = 25 patients) received 40 ml of 0.5% Lidocaine plus verapamil 2.5 mg plus ketamine (0.5 mg/kg) or group (III = 25 patients) received 40 ml of 0.5% Lidocaine plus verapamil 5 mg plus ketamine (0.5 mg/kg) for IVRA. Randomization was done using computer-generated number table of random numbers in a 1:1 ratio. The lignocaine used in the study was 2% preservative free (lidocaine injection 2%, ROTEXMEDICA, TRITTAU – GERMANY) and normal saline (0.9%, manufactured by Otsuka company) was added to make up the volume as required. The study drugs were prepared by the anesthesia resident not involved in any other part of the study.

On arrival in the operating room, standard monitoring was used for all patients, which included 5 lead ECG, noninvasive arterial blood pressure monitor, and pulse oximetry using Datascope monitors. 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 solution and the non-operating upper limb was cannulated with 18 gauge intravenous cannula for intravenous fluid infusion (Ringer's solution). Patients received 2 mg midazolam for sedation.

The operating limb was then lifted for 5 min to exsanguinate blood and then Esmarch bandage was applied for complete exsanguination of blood after which two tourniquets were applied on the arm one distal to the other. Circulatory isolation of the operative arm was confirmed by inspection of the hand and by the absence of radial pulse.

First, proximal tourniquet was inflated up to 250–300 mmHg. 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), 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), or lidocaine 2 mg/kg 0.5% plus verapamil 5 mg plus ketamine (0.5 mg/kg) diluted with normal saline to a volume of 40 ml (group III) for IVRA was injected over 1 min in the operating limb.

Surgery was allowed to proceed with the single tourniquet till 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 parameters recorded were time for onset of sensory blockade, sensory block and sensory recovery time after deflation of tourniquets (which were assessed at 1-min interval from the end of injection for the first 10 min and then every 30 min while in the postanesthesia care unit until the time of discharge using 25 guage short bevel needle prick for median nerve at thenar eminence, ulnar nerve at hypothenar eminence and first web space for radial nerve), onset of motor blockade and motor recovery time (which were evaluated at 1-min interval by asking the patient to flex and extend his/her wrist and fingers). Motor blockade was considered complete when the patient could not do any voluntary movement and incomplete when patient could perform supination and pronation of hand.

When sensory and motor block was completed, the distal cuff was then inflated to 250 mmHg followed by release of the proximal cuff. Time to complain from the tourniquet pain starting after tourniquet inflation for each patient (first tourniquet pain time) and second tourniquet pain time were recorded. Pain (tourniquet or postoperative) was assessed using 10 cm marked visual analog scale (VAS) where zero meant no pain and ten meant severe pain. Pain was assessed at 30 min, 1, 2, 6 and 12 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.

The tourniquet was not inflated for more than 90 min and was not deflated before 40 min of local anesthetic injection. At the end of surgery, the tourniquet was deflated by repeated inflation–deflation technique (deflating the tourniquet for 10 s followed by 1 min of reinflation for three times).

Postoperative assessment of sedation was according to sedation score where 0 = alert, 1 = sleepy and arousable by verbal command, 2 = sleepy and arousable by tactile stimulation and 3 = sleepy and arousable by painful stimulation.

Other parameters recorded were heart rate, mean arterial blood pressure and arterial SpO_2 intraoperatively every 15 min and 2, 6 and 12 h postoperatively. Side effects (such as dizziness, tinnitus, restlessness, hallucinations, hypotension and bradycardia) were also recorded. Hypotension was considered if there was 20% decrease below the baseline for mean arterial blood pressure, and it was treated with intravenous ephedrine (3–6 mg IV bolus). Bradycardia (heart rate < 55 beats/min) was treated with intravenous atropine (0.6–1 mg). If there was a decrease in arterial SpO_2 (< 90%), it was treated with oxygen through a transparent face mask.

The satisfaction score of the patient for the anesthetic technique was assessed postoperatively according to the following numeric scale: 3 = good (no complaint from patient), 2 = moderate (minor complaint with no need for supplemental analgesics), and 1 = poor (complaint which required supplemental analgesics).

2.1. Analysis of data

Using PASS 13 for sample size calculation, in a one-way ANOVA study it was calculated that a sample size of 22 patients per group will achieve 80% power to detect a mean difference of 50 mg in total Pethidine consumption with a SD of 25 between the three groups using an F test with a 0.05 significance level. 25 patients per group were intended to be included to replace any dropouts.

Data were analyzed using SPSS 18.0 for Windows (SPSS, Chicago, IL, USA). Analysis of variance was used to compare quantitative parametric data with Tukey's test as a post hoc test. Kruskal–Wallis test was used for quantitative nonparametric data. Chi square test was used for comparison of qualitative data. Continuous parametric data were presented as mean ± SD, non-parametric data as median (IQR) and categorical data as number of patients. *P*-values of < 0.05 were considered statistically significant.

3. Results

No patient was excluded after inclusion to study. All patients were able to complete the entire study and their data were included in the final analysis. The study was conducted since March 2013 till November 2013.

There was no significant difference in the demographic data of the three groups as regards age, sex (male to female ratio), weight, height, ASA physical status and the duration of surgery in minutes (Table 1).

There was significant difference in groups (II) and (III) as compared to group I in terms of tourniquet pain tolerance times, sensory and motor onset, sensory and motor recovery, time for first rescue analgesic(min), number of patients needed intraoperative pethidine, total pethidine requirements in 12 h (mg), satisfaction score and sedation score ($p < 0.05$) while there was no significant difference between groups (II) and (III) about these measured variables as shown in (Table 2).

There were significant lower recorded values in visual analog scale in group (II) and group (III) in comparison with group (I) 30 min,1, 2, 6 and 12 h postoperatively as shown in (Table 3). Pain score was lower in group (III) compared to group (II) 6 and 12 h postoperatively and this was not significant.

There was not a significant difference in the mean heart rate between the 3 groups intraoperatively. There was a significant decrease in the mean heart rate in group (II) and group (III) compared to group (I) 2, 6 and 12 h postoperatively as shown in (Fig. 1). Heart rate was lower in group (III) compared to group (II) 6 and 12 h postoperatively and this was not significant.

Table 1 Demographic data and duration of surgery.

Variables	Group (I) (n = 25)	Group (II) (n = 25)	Group (III) (n = 25)	P-value
Age (years)	31.56 ± 4.8	30.48 ± 4.14	30.76 ± 5.	0.56
Sex (M:F)	12/13	12/13	14/11	0.49
Weight (kg)	73.2 ± 6	71.6 ± 5.6	70.7 ± 5.32	0.14
Height (cm)	168.8 ± 7.1	170.2 ± 4.5	169.5 ± 5	0.68
ASA (I/II)	18/7	20/5	19/6	0.46
Duration of surgery (min)	57.84 ± 6.62	59.8 ± 5. 6	58.81 ± 6.2	0.6

Data are presented as mean ± SD. ASA: American Society of Anesthesiologists.
$P > 0.05$ is considered statistically non-significant between the 3 groups.

Table 2 Block characteristics of the studied groups.

Measured variables	Group (I) (n = 25)	Group (II) (n = 25)	Group(III) (n = 25)	P-value
First Tourniquet pain (min)	23.4 ± 2.9[†]	42.5 ± 2.66	46.3 ± 3	<0.001[*]
Second Tourniquet pain (min)	29.6 ± 4.4[†]	50.4 ± 2.7	51.9 ± 2.6	<0.001[*]
Onset of sensory block (min)	4.8 ± 1.23[†]	2.8 ± 0.7	2.39 ± 0.5	<0.001[*]
Onset of motor block (min)	12.6 ± 1.2[†]	9.53 ± 0.45	9 ± 0.5	<0.001[*]
Recovery of sensory block (min)	11.2 ± 3.3[†]	30. 6 ± 4.3	32.4 ± 3.5	<0.001[*]
Recovery of motor Block (min)	7.7 ± 1.34[†]	14.1 ± 1.5	14.5 ± 2. 9	<0.001[*]
Time for first rescue analgesic (min)	29 ± 2.7[†]	212.8 ± 4.3	230.4 ± 5.5	<0.001[*]
Number of patients needed intraoperative pethidine	17[†]	6	4	<0.001[*]
Total pethidine requirements in 12 h (mg)	122.8 ± 7.5[†]	61.3 ± 7.4	57.8 ± 5.8	<0.001[*]
Satisfaction score	2 (1–3) [†]	4 (3–4)	3 (3–4)	<0.001[*]
Sedation score	1 (0–1)[†]	3 (2–3)	3 (2.5–3.5)	<0.001[*]

Values were mean ± SD or median (IQR).
[*] $P < 0.001$ was considered statistically significant between the 3 groups.
[†] $P < 0.001$ was considered statistically significant between group (I) and groups (II) and (III).

Table 3 Visual analog scale (VAS).

Timing of assessment postoperatively	Group I (n = 25)	Group II (n = 25)	Group III (n = 25)	P-value
30 min	5 (4.5–6)[†]	1 (0–1)	0 (0–1)	<0.001[*]
1 h	4 (4–5)[†]	1 (0.5–1)	1 (0–1)	<0.001[*]
2 h	4 (4–5)[†]	1 (0.5–2)	2 (1–2)	<0.001[*]
6 h	5 (4.5–5)[†]	3 (2.5–3)	2 (2–3)	<0.001[*]
12th hour	5 (3.5–6)[†]	3 (3–4)	3 (3–4)	<0.001[*]

The pain score was expressed as median and IQR.
P value < 0.05 was considered significant. [*] denotes significant difference.
[*] $P < 0.001$ was considered statistically significant between the 3 groups.
[†] $P < 0.001$ was considered statistically significant between group I and groups II and III.

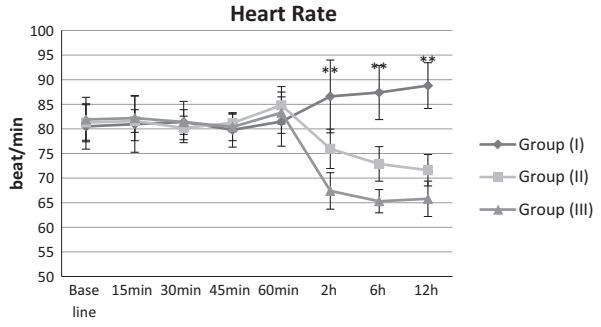

Figure 1 The heart rate changes (beats/min). ** denotes significant difference. Lines are mean values and error bars are SD.

There was not a significant difference in the mean arterial blood pressure between the 3 groups intraoperatively. There was a significant decrease in the mean arterial blood pressure in group (II) and group (III) compared to group (I) 2, 6 and 12 h postoperatively as shown in (Fig. 2). The mean arterial blood pressure was lower in group (III) compared to group (II) 6 and 12 h postoperatively and this was not significant.

No significant changes were noted in the SpO_2 between the studied groups throughout the study period (see Table 4).

4. Discussion

The use of lidocaine for IVRA block or Bier block has been the mainstay to control perioperative pain, but it provides little to

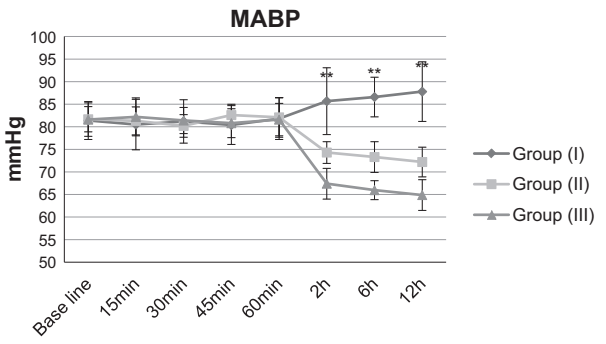

Figure 2 The mean arterial blood pressure (mmHg). ** denotes significant difference. Lines are mean values and error bars are SD.

Table 4 Incidence of adverse effects during and after the surgical operation among the study groups.

Adverse effects	Group I	Group II	Group III	*P*-value
	No.	No.	No.	
Restlessness	3	0	0	0.44
Hallucinations	3	0	0	0.44
Paresthesia	1	1	6	0.037*
Tachycardia	2	0	0	0.11
Bradycardia	0	2	6	0.009*
Hypertension	2	0	0	0.11
Hypotension	0	2	6	0.009*
Nausea	1	2	6	0.04*
Vomiting	0	1	6	0.015*
Drowsiness	1	1	6	0.037*

Data are presented as number of patients. * denotes significant difference.

* $P < 0.05$ is considered statistically significant between the 3 groups.

no benefit postoperatively [15]. Calcium is involved in the release of neurotransmitters at both adrenergic and cholinergic synapses [16]. In several studies it was tried to find a local anesthesia mixture that allows relief from tourniquet pain and prolonged duration of analgesia after tourniquet release.

The results of the present study demonstrated that addition of verapamil either 2.5 or 5 mg to lidocaine plus ketamine for IVRA was accompanied by reduced tourniquet pain (lower VAS scores) at the site of tourniquet application, delayed first request for tourniquet pain relief, more rapid onset and delayed offset of sensory and motor block, delayed onset of postoperative pain, and less postoperative consumption of supplementary analgesia (pethidine) in 12 h with higher sedation and satisfaction scores.

These results are in agreement with the findings of Tabdar et al. who reported that the administration of verapamil 2.5 mg added to 40 ml of 0.5% Lidocaine for Bier's block is more effective than 0.5% Lidocaine alone in prolonged first and second tourniquet pain tolerance time, faster onset of sensory block and motor block, delayed recovery of sensory and motor block with increased postoperative analgesia time and decreased total analgesic consumption of Tramadol in 24 h [13].

Kumar et al. also reported that the addition of 0.5 mg/kg of body weight ketamine to lignocaine for IVRA delayed the onset of tourniquet pain, reduced the time for onset of block, reduced postoperative analgesic requirement and had a better patient satisfaction [17].

Haider and Mahdi found that drug combination of ketamine, atracurium and lidocaine leads to rapid onset of sensory block, motor block and lower VAS score for pain [18].

In this study, Sedation score was significantly higher in group (II) and group (III) than in group (I) postoperatively. There was a significant decrease in the mean heart rate and the mean arterial blood pressure in group (II) and group (III) compared to group (I) 2, 6 and 12 h postoperatively. There were comparable differences between group (II) and group (III) in VAS, the mean heart rate and the mean arterial blood pressure 6 and 12 h postoperatively.

No significant changes were noted in the SpO_2 between the studied groups throughout the study period.

There were also comparable differences between the 3 groups as regards the side effects of IVRA. Ketamine failed to show significant tachycardia, hypertension, restlessness and hallucinations when given as an adjuvant in IVRA in our study due to the fact that tourniquet was not deflated before 20 min and verapamil was found to be effective in relief of the activation symptoms of anxiety, tension and excitement [19]. In spite of the tourniquet was not deflated before 20 min, ketamine has well known hemodynamic effects (hypertension and tachycardia) [17]. The occurrence of bradycardia, hypotension, nausea, vomiting, drowsiness and paresthesia were significant in group (III) compared to groups (I) and (II).

These results were partially consistent with the findings of Tabdar et al. who demonstrated that verapamil 2.5 mg added to 40 ml of 0.5% lidocaine for Bier's block is more effective than 0.5% lidocaine alone and stated that there was neither hemodynamic instability nor any side effects in the study group intraoperatively as well as postoperatively [13].

Gorgias et al. conducted a prospective randomized double-blinded study in 45 patients undergoing hand or forearm surgery under IVRA and also reported side effects of the addition of clonidine 1 μg/kg or ketamine 0.1 mg/kg to lidocaine 0.5% for IVRA in the form of hallucinations in 3 patients, paresthesia in 3 patients, dizziness in 2 patients, and nausea in 1 patient [20].

Kumar et al. compared the effect of dexmedetomidine and ketamine when added to lignocaine in IVRA in 72 patients undergoing hand surgery and mentioned that two patients had restlessness in group lidocaine ketamine [17].

Haider and Mahdi found that bradycardia, restlessness and muscle fasciculation had occurred and decreased by addition of ketamine or ketamine plus atracurium for IVRA [13].

4.1. Limitations of the study

We limited our study population to patients undergoing carpal tunnel release, excision of ganglion cysts, tenolysis and K wire fixation of radius or ulna excluding traumatic hand and wrist operations. In addition, we limited our study to surgical procedures scheduled for less than one and half hours, because patients typically experience discomfort when a tourniquet is required for greater than one and half hours.

4.2. Recommendations

A study evaluating the effectiveness of Addition of verapamil 2.5 mg or 5 mg to lidocaine plus ketamine for IVRA to decrease pain score 24 h after operation is planned as follow-up research to this study. Further studies are necessary to determine whether a lower IVRA dose of verapamil is more effective in decreasing postoperative pain related to surgical tissue disruption of the upper extremity with minimal side effects.

5. Conclusion

Addition of verapamil 2.5 mg or 5 mg to lidocaine plus ketamine for IVRA provided effective anesthesia, prolonged postoperative analgesia and decreased postoperative analgesic consumption. The postoperative undesirable side effects of verapamil 5 mg e.g. bradycardia, hypotension, nausea, vomiting, drowsiness and paresthesia were significantly common. Adding verapamil 2.5 mg to 40 ml of 0.5% Lidocaine plus ketamine (0.5 mg/kg) for Bier's block was effective and safe adjuvant for acute pain after surgery.

Conflict of interest

None.

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