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

HOSTED BY

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

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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.

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

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Peer review under responsibility of Egyptian Society of Anesthesiologists.

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.