Egyptian Journal of Anaesthesia (2016) 32, 213–217

HOSTED BY

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

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Research Article

A randomized controlled study of the effects of adding ultra-low dose naloxone to lidocaine for intravenous regional anesthesia

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Received 27 March 2015; revised 16 August 2015; accepted 30 September 2015
Available online 29 October 2015

KEYWORDS

Naloxone;
Low dose;
Lidocaine;
Bier block

Abstract *Objective:* This study was designed to evaluate the effect of adding ultra-low dose of naloxone as an adjuvant to lidocaine for intravenous regional anesthesia (IVRA).
Method: Forty patients undergoing elective short procedures in the upper limb were randomly and blindly divided into two groups of twenty patients each. Group L (n = 20) received 3 mg/kg of 2% lidocaine diluted with normal saline to 30 ml. Group LN (n = 20) received 3 mg/kg of 2% lidocaine and naloxone 100 ng (1 ml) diluted with normal saline to 30 ml. Onset and recovery time of sensory and motor block, intraoperative and post-operative pain were measured by visual analog score (VAS), and also intraoperative analgesic requirement, time of first requirement of diclofenac post-operatively, total amount of diclofenac needed in 24 h, patient's satisfaction and surgeon's satisfaction scores were measured.
Results: Recovery of sensory block was significantly longer in group LN (26.7 ± 2.8 min) compared to group L (16.3 ± 0.6 min); p value (0.000). Also the recovery of motor block was significantly longer in group LN (19.1 ± 1.0 min) compared to group L (17.9 ± 1.2 min), p value (0.002). Intraoperative fentanyl requirement was significantly less in group LN (15.8 ± 5.0 mcg) compared to group L (40.0 ± 10.5 mcg), p value (0.000). 1st fentanyl requirement time was significantly longer in group LN (22.4 ± 3.1 min) than in group L (14.5 ± 6.1 min), p value (0.000). Time of first analgesic requirement post-operative was longer in group LN (78.5 ± 6.8 min) compared to group L (40.5 ± 2.0 min), p value (0.000). Total amount of diclofenac needed in 24 h was significantly less in group LN (57 ± 50 mg) compared to group L (120 ± 45 mg), p value (0.000).
Conclusion: The addition of ultra-low-dose naloxone 100 ng to lidocaine for IVRA in upper limb surgery, prolonged the duration of sensory and motor block, and reduced tourniquet pain, as well as intraoperative and postoperative analgesic consumption.

1. Introduction

IVRA is simple, reliable, and cost-effective, with a success rate varying between 94% and 98% [1,2]. It is a favorable choice

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Peer review under responsibility of Egyptian Society of Anesthesiologists.

http://dx.doi.org/10.1016/j.egja.2015.09.010

among anesthesiologists for extremity operations lasting around one hour. However there are some concerns associated with IVRA such as tourniquet pain, inadequate muscle relaxation, insufficient postoperative analgesia and local anesthetic toxicity [2].

Naloxone has proved to have paradoxical effects as it antagonizes the opioid analgesia if given in high doses (microgram range) and produces anti-nociceptive effect if given in ultra-low doses (nanogram range) [3,4]. Different mechanisms have explained the effect of ultra-low dose naloxone including selective inhibition of the impulses from excitatory opioid receptors and release of enkephalin [5–8]. It has been used safely via the epidural and intrathecal routes for reducing opioids side effects or enhancing analgesia [9,10]. Also it was added to fentanyl and lidocaine for peri-bulbar anesthesia and prolonged the duration of postoperative analgesia without side effects [11].

We designed this study to evaluate the effect of adding ultra-low dose of naloxone to lidocaine for IVRA for elective short procedures in the upper limb. Our primary outcome was the time for first analgesic requirement (diclofenac). Secondary outcomes included the onset and recovery of sensory block, onset and recovery of motor block, intraoperative fentanyl requirement, time of first fentanyl requirement, intraoperative and post-operative VAS, total amount of diclofenac used in 24 h, and surgeon's and patient's satisfaction.

2. Methods

After obtaining ethical committee approval and written informed consent, forty patients with American Society of Anesthesiologists (ASA) I or II, between 20 and 60 years old; who were scheduled for short elective procedures for the hand and forearm; were included in our prospective, randomized, double blind study done at Saad Specialist Hospital, Saudi Arabia; between June 2014 and December 2014. Patients who have history of allergy to the study drugs, uncooperative patients, patients with open wounds and infection of the operative limb, patients with peripheral arterial disease, or sickle cell disease, patients received analgesia in the previous 24 h, and pregnant women were excluded from the study. Patients were randomly allocated into two groups of twenty patients each (Fig. 1). Group L (n = 20) received 3 mg/kg of 2% lidocaine diluted with normal saline to 30 ml. Group LN (n = 20) received 3 mg/kg of 2% lidocaine and naloxone 100 ng (1 ml) diluted with normal saline to 30 ml. Our patients were randomly allocated into two equal groups (20 patients each) according to a computer-generated table of random numbers (Excel, Microsoft, Inc., Redmond, Washington, USA). Study medications were prepared by a pharmacist who was not participating in the study; according to the table of randomization. The anesthesiologists were supplied with identical syringes with a code number given by the pharmacist. The anesthesiologist, investigator, surgeon and the patients were blinded to the study medications.

All patients were requested to be fasting for 8 h before operation, and the IVRA technique was explained to them preoperatively. On arrival to the operating room two intra-venous accesses were inserted, one in the non-operative side for intravenous fluid infusion and any needed medications and the second one in the operative side inserted in a distal vein in the dorsum of the hand for injection of the study medications for IVRA and was removed immediately after the block.

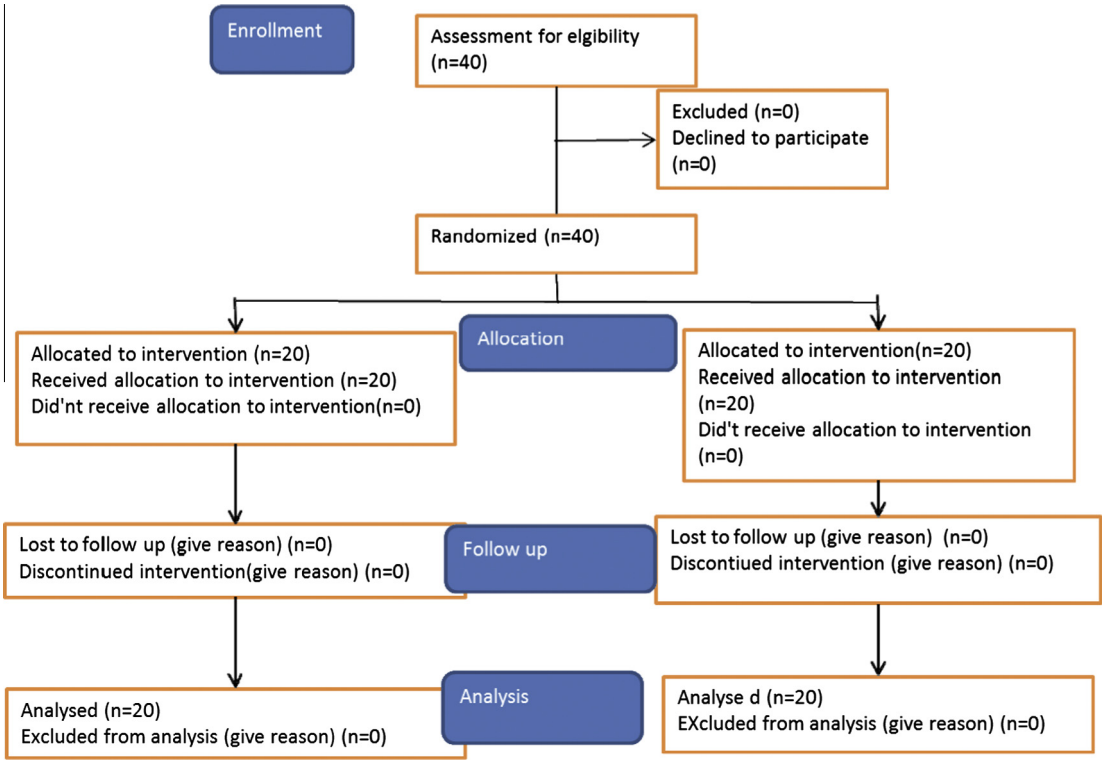

Figure 1 Participant flowchart.

Standard monitoring of electrocardiography, pulse oximetry, and noninvasive blood pressure were applied.

All patients were pre-medicated with intravenous midazolam (0.05 mg/kg) 10 min before the block. After exsanguination with an Esmarch bandage, double-cuff pneumatic tourniquet was applied at the upper arm and the proximal cuff was inflated to a pressure of at least 100 mmHg more than baseline systolic blood pressure or a minimum of 250 mmHg to occlude the circulation to the arm which was confirmed by the absence of radial pulse and failure of pulse oximetry tracing in the fingers of the same side, followed by injection of 30 ml of test solution over one minute. The distal tourniquet was inflated 10 min after the injection of the test medications and then the proximal tourniquet was deflated. After the injection of the test medications, the onset of sensory block was checked by the pin prick method, with a 22G hypodermic needle every 30 s in the sensory distribution of the median, ulnar, and radial nerves. Sensory block onset time was defined as the time from injection of the test drug until sensory block in all dermatomes distal to the tourniquet. The motor block was tested every one min until the patient was not able to flex or extend the wrist or move his fingers. Motor block onset time was considered as the time from injection of the test drug until the patient is unable to do any movement. Cyclic deflation technique was used for tourniquet deflation after at least 40 min and was not inflated for more than 1.5 h.

Intraoperatively; heart rate, blood pressure, and oxygen saturation were measured every 5 min. Intra-operative tourniquet pain was assessed every 15 min using VAS of (0–10); 0 means no pain and 10 means worst imaginable pain and if was recorded >3; fentanyl 25 mcg was given intravenously. The first fentanyl requirement time and the total amount of fentanyl given to the patient were recorded.

Post operatively, pain was measured using VAS at 0, 15, 30, 60, 120, 180, 240 and 360 min. For VAS >3, diclofenac 75 mg intramuscular was given every 12 h if needed. The time from the release of distal tourniquet till the sensation of a sharp pain at the surgical site was considered as the time of return of sensation. The time from the release of distal tourniquet to the time at which patients were able to move their wrist was considered as the time of return of motor power.

Time for first dose diclofenac given to the patient is the time of first analgesic requirement and total dose of diclofenac consumed in 24 h were recorded. Postoperative complications as tinnitus and convulsions were noted. Patient's satisfaction score for the anesthetic technique was also recorded according to the numeric score: 3 = good (no complaint from patient), 2 = moderate (minor complaint with no need for analgesics), and 1 = poor (complaint which required supplemental analgesics). The surgeon, who was blinded to the given medication, was asked to qualify the operative condition according to the following numeric scale: 1 = unsuccessful, 2 = poor, 3 = acceptable and 4 = perfect.

Sample size was calculated according to the time for first analgesic requirement (primary outcome); to reach a significant difference between both groups by accepting an alpha risk of 5% and a power of 99% $(1-\beta)$, twenty patients were needed in each group for a significant difference ($p < 0.05$). We considered clinical significant benefit of using ultra low-dose naloxone as an adjuvant to lidocaine for IVRA; if it leads to 15% prolongation in the time of first analgesic requirement needed if lidocaine was used alone [12].

2.1. Statistical analysis

Data were statistically described in terms of mean ± standard deviation (±SD), or frequencies (number of cases). Comparison of numerical variables between the study groups was done using Student's t test for independent samples in comparing normally distributed data and Mann Whitney U test for independent samples when data were not normally distributed. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. P values less than 0.05 were considered statistically significant. All statistical calculations were done using computer program Statistical Package for the Social Science (SPSS Inc., Chicago, IL, USA) release 15 for Microsoft Windows (2006).

3. Results

Demographic data and intraoperative data including age, weight, gender, duration of surgery, time of tourniquet application and type of surgery were comparable in both groups (Table 1).

The block characteristics are shown in Table 2. Time of onset of sensory and motor block was comparable in both groups, but the recovery of sensory block was significantly longer in group LN (26.7 ± 2.8 min) compared to group L (16.3 ± 0.6 min); p value (0.000). Also the recovery of motor block was significantly longer in group LN (19.1 ± 1.0 min) compared to group L (17.9 ± 1.2 min), p value (0.002). Intraoperative fentanyl requirement was significantly less in group LN (15.8 ± 5.0 mcg) compared to group L (40.0 ± 10.5 mcg), p value (0.000). First fentanyl requirement time was significantly longer in group LN (22.4 ± 3.1 min) than in group L (14.5 ± 6.1 min), p value (0.000). Time of first analgesic requirement post-operative was significantly longer in group LN (78.5 ± 6.8 min) compared to group L (40.5 ± 2.0 min), p value (0.000). Total amount of diclofenac needed in 24 h was significantly less in group LN (57 ± 50 mg) compared to group L (120 ± 45 mg), p value (0.000).

Table 3 demonstrates the intraoperative and postoperative VAS in both groups.

The complications, patients' satisfaction and surgeon's satisfaction score are shown in Table 4.

Table 1 Demographic and intraoperative data.

Data	Group L (n = 20)	Group LN (n = 20)	P value
Age (years)	37.8 ± 3.7	38.1 ± 2.4	0.763
Weight (kg)	67.4 ± 4.5	66.3 ± 6.4	0.534
Gender (m/f)	9/11	10/10	1.0
Duration of surgery (min)	36.0 ± 4.7	35.7 ± 7.5	0.880
Time of tourniquet application (min)	43.1 ± 3.2	42.3 ± 2.5	0.384
Type of surgery (carpal tunnel, ganglion excision, tendon release, trigger finger)	7/7/4/2	8/7/3/2	0.976

Values are expressed as mean ± SD and numbers.

Table 2 The block characteristics in both groups.

Data	Group L (n = 20)	Group LN (n = 20)	
Onset of sensory block (min)	6.3 ± 2.0	6.1 ± 1.5	0.732
Recovery of sensory block (min)	16.3 ± 0.6	26.7 ± 2.8	0.000*
Onset of motor block (min)	11.3 ± 1.0	10.8 ± 2.5	0.414
Recovery of motor block (min)	17.9 ± 1.2	19.1 ± 1.0	0.002*
Intraoperative fentanyl requirement (mcg)	40.0 ± 10.5	15.8 ± 5.0	0.000*
First fentanyl requirement time (min)	14.5 ± 6.1	22.4 ± 3.1	0.000*
Time of first analgesic requirement post op	40.5 ± 2.0	78.5 ± 6.8	0.000*
Total amount of diclofenac (mg)	120 ± 45	57 ± 50	0.000*

Values are expressed as mean ± SD.
* means p value < 0.05.

Table 3 Intraoperative and postoperative VAS.

Data	Group L (n = 20)	Group LN (n = 20)	
Before tourniquet inflation	0	0	
After 15 min	1.1 ± 0.2	0.9 ± 1.1	0.433
After 30 min	2.5 ± 0.7	1.2 ± 1.2	0.000*
After 45 min	2.7 ± 1.0	1.8 ± 1.0	0.007
Immediately after tourniquet release	2.7 ± 1.0	1.8 ± 1.0	0.007
15 min after release of tourniquet	3.2 ± 1.9	1.9 ± 1.7	0.028*
30 min after release of tourniquet	3.1 ± 1.8	2.3 ± 1.8	0.168
60 min after release of tourniquet	3.2 ± 1.0	2.9 ± 1.9	0.537
120 min after release of tourniquet	3.3 ± 1.2	3.0 ± 0.8	0.359
180 min after release of tourniquet	3.5 ± 1.3	3.1 ± 0.6	0.233
240 min after release of tourniquet	2.9 ± 1.2	2.0 ± 0.9	0.011*
360 min postop	2.9 ± 1.6	2.2 ± 2.0	0.230

Values are expressed as mean ± SD.
* means p value < 0.05.

Table 4 Complications, patients' satisfaction and surgeon's satisfaction score.

Data	Group L (N = 20)	Group LN (N = 20)	P value
Tinnitus	0	0	
Convulsions	0	0	
Patients' satisfaction (1/2/3)	(2/2/16)	(1/0/19)	0.274
Surgeon's satisfaction (1/2/3/4)	(0/1/2/17)	(0/0/2/18)	0.976

Values are expressed as numbers.

4. Discussion

The results of our study revealed that addition of ultra-low-dose naloxone to lidocaine for IVRA prolonged the duration of sensory and motor block, and reduced tourniquet pain, as well as intraoperative and postoperative analgesic consumption.

The antinociceptive effect of ultra-low dose naloxone was explained 20 years ago by Crain and Shen, who demonstrated that naloxone and naltrexone have selective antagonistic effects on the excitatory opioid receptor functions, unmasking the inhibitory effects of morphine and other opioids acting on mu (μ) delta (δ) and kappa (κ) receptors and cause prolongation of the Ca2 + dependent component of the action potential [5].

Naloxone interferes with the transient switch in G-protein coupling by μ-opioid receptor from Gi/o to Gs and reduces the opioid tolerance and dependence by the high-affinity interaction of naloxone to a penta-peptide area in c-terminal filamin A (FLNA) interacting with μ-opioid receptors [13].

Also, low dose naloxone has been shown to release endorphins, or displaces endorphins from receptor sites [14].

The release of enkephalin which is an endorphin is controlled by a presynaptic autoregulatory system. Large amount of enkephalins results in negative feedback, reducing further release. Naloxone, given as an ultra-low-dose infusion, blocks this negative feedback and enhances analgesia from enkephalins [4,15,16]; this could also explain its antipronociceptive effect.

Previous studies in both animal and human models suggested that naloxone produces a dose-dependent pain response. In rats, small doses of naloxone resulted in paradoxical analgesia, whereas larger doses caused hyperalgesia [4,16,17].

Movafegh et al. studied the effect of adding ultra-low-dose naloxone to lidocaine with or without fentanyl in axillary brachial plexus block and they revealed that ultra-low-dose naloxone prolongs the time to first post-operative pain, which is consistent with our results [18].

Also Gan et al. reported that an ultra-low dose naloxone infusion (0.25 ug/kg/h) enhanced morphine analgesia and reduced postoperative narcotic requirement after abdominal hysterectomies [14].

Similarly, Gordon et al. found that the use of low-dose naloxone and nalbuphine resulted in good pain control and no significant side effects after gynecological operations and even some patients did not require any rescue medication [19].

Hamann and Sloan reported a case of a patient with severe chronic low back pain post-laminectomy operation used intrathecal low dose 20 ηg naloxone added to intrathecal morphine 2 mg bolus and 5 mg morphine and 50 ηg naloxone intrathecally as infusion daily for 3 years and reported that the patient maintained pain reduction of 60–80% and returned to daily activities and no further hospitalization [20].

On the other hand, some studies failed to report the effect of ultra-low dose opioid antagonist in preventing opioid-induced side effects or to augment analgesia and this may be related to how the opioid antagonist was prepared and administered to the patients. In all these studies in which the antagonist was

ineffective, morphine and naloxone were mixed in saline and given through a PCA pump [21,22]. This might result in only small doses of naloxone intermittently given to the patients when the PCA pump was triggered. Also, naloxone and morphine may be incompatible when in a solution for a prolonged period.

The onset of sensory and motor block in our study was similar in both groups. On the contrary Movafegh et al. [18] reported prolongation of the onset time in the sensory and motor block in their naloxone group, but they stated that it was not clinically significant.

There was no difference in the patient's satisfaction score or surgeon's satisfaction score, and a larger sample size might be needed to detect a difference in the satisfaction of both patients and surgeons.

Limitation to our study is that we used only one concentration of naloxone (100 ng); other naloxone concentrations (smaller and larger doses) should be evaluated to determine the optimum dose of naloxone as adjuvant to lidocaine in IVRA.

In conclusion, the addition of ultra-low-dose naloxone 100 ng to lidocaine for IVRA in upper limb surgery prolonged the duration of sensory and motor block, and reduced tourniquet pain, as well as intraoperative and postoperative analgesic consumption.

Conflict of interest

The authors declare no conflict of interest about this study.

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