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ORIGINAL RESEARCH

Comparison of anesthetic and analgesic efficacy of ketamine and dexmedetomidine as adjuncts to lignocaine for intravenous regional anesthesia: A randomized controlled study

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ABSTRACT

Context: Ketamine and dexmedetomidine decrease anesthetic requirement and provide analgesia to patients.

Aims: We designed this study to compare the effect of dexmedetomidine and ketamine when added to lignocaine in intravenous regional anesthesia (IVRA).

Methods and Material: Sixty patients undergoing hand surgery were randomly assigned to three group (each n=20) to receive IVRA. Group (I) control group received 3 mg/kg lidocaine 2% with maximum dose of 200 mg diluted to 40 ml with 0.9% saline. Group (II) ketamine group received 3 mg/kg lidocaine 2% with maximum dose of 200 mg plus 0.1 mg/kg ketamine diluted to 40 ml with 0.9% saline. Group (III) dexmedetomidine group received 3 mg/kg lidocaine 2% with maximum dose of 200 mg plus 0.5mcg/kg dexmedetomidine diluted to 40 ml with 0.9% saline. Sensory and motor block onset and recovery time were noted. After the tourniquet deflation, pain and sedation values, time to first analgesic requirement and any side effects were noted.

Results: Shortened sensory and motor block onset times (2.3 min and 3.1 min respectively, $P < 0.0001$ for group II, 2.2 min and 3.0 min respectively, $P < 0.0001$ for group III) and improved quality of anesthesia (satisfaction score = 2.8 and 2.9, $P < 0.05$) were found in group II & III. Visual analog scale scores (3.15 & 3.13, P<0.0001) were comparable while time to first analgesic requirement (168.15min & 212.30 min, $P < 0.0001$) was significantly longer in group II & III after tourniquet release.

Conclusions: We conclude that the addition of 0.5 mcg/kg of body weight dexmedetomidine or 0.1 mg/kg of body weight ketamine to lignocaine for IVRA improves quality of anesthesia and perioperative analgesia without causing side effects. We considered adjuvants like ketamine and dexmedetomidine reduced the time for

onset of block, delayed the onset of tourniquet pain, and reduced postoperative analgesic requirement and had a better patient satisfaction than only lidocaine.
Keywords: Biers block; dexmedetomidine; intravenous regional anesthesia; ketamine; lignocaine; regional anesthesia

INTRODUCTION

Intravenous regional anesthesia (IVRA), first described by August Bier in 1902, is technically simple and reliable, with success rates between 94% and 98%.[1] IVRA is a method of producing analgesia in the distal part of a limb by intravenous (IV) injection of a local anesthetic solution into the vein of the same limb, while circulation to the limb is occluded by the application of tourniquet. Different agents have been used as additive to local anesthetic for IVRA including phencyclidines, non-steroidal anti-inflammatory drugs, opioids, and muscle relaxants.[2] Ketamine is an effective anesthetic agent for IVRA at lower concentrations.[3] Dexmedetomidine, a potent alpha (α) 2-adrenoceptor agonist, has been shown to decrease anesthetic requirements by up to 90% and to induce analgesia.[4,5] Addition of dexmedetomidine to lignocaine in IVRA also improves the quality of anesthesia but has no effect on the sensory and motor block onset and regression time.[6] We compared the onset of anesthesia and onset of tourniquet pain during IVRA using lignocaine alone, lignocaine with ketamine, and lignocaine with dexmedetomidine and assessed postoperative analgesic requirement and satisfaction score of the patients.

SUBJECTS AND METHODS

This prospective randomized double-blind study was conducted after obtaining clearance from Institutional Ethical Committee of the institute and written informed consent from all patients. Patients of American Society of Anesthesiologists physical status I/II aged between 20 to 50 years scheduled for surgery in distal region of upper limb under IVRA were included. Those with history of allergic reaction to lignocaine, significant cardiovascular disease, sickle cell disease, history of chronic pain or regular medication with analgesics, history of opioid dependence, drug or alcohol abuse, psychiatric disorder, peripheral vascular disease, and neurological diseases were excluded from the study. At the pre-operative visit, on the evening before surgery, the visual analog scale (VAS) scoring system was explained to all the patients. Patients were assigned randomly to one of three groups depending on the drug solution used for IVRA (n = 20 in each group). Group (I) control group received 3 mg/kg lidocaine 2% with maximum dose of 200 mg diluted to 40 ml with 0.9% saline. Group (II) ketamine group received 3 mg/kg lidocaine 2% with maximum dose of 200 mg plus 0.1 mg/kg ketamine diluted to 40 ml with 0.9% saline. Group (III) dexmedetomidine group received 3 mg/kg lidocaine 2% with maximum dose of 200 mg plus 0.5mcg/kg dexmedetomidine diluted to 40 ml with 0.9% saline No premedication was given to any of the patients. Standard monitoring was used in all patients, which included noninvasive arterial blood pressure, heart rate, electrocardiogram and pulse oximetry. Prior to administration of IVRA, an infusion of 0.9 % normal saline was started in the normal limb. A 22G IV cannula was inserted into distal vein of the extremity that was to be studied; cotton pad was applied to the arm to protect the skin. Two tourniquets (double cuffed) were placed over the cotton pad. The arm was exsanguinated by using an Esmarch bandage. The proximal tourniquet was inflated to 100 mm Hg above the systolic pressure of the patient. The absence of radial artery pulsations and failure of pulse oximetry tracing in the ipsilateral index finger was confirmed. 40 ml of test solution was injected over 1 min by an anesthesiologist who was blinded to the drug being administered. After the injection of different study solutions, the onset of sensory block (defined as loss of pain sensation) was determined by the pin prick method, with a 22G hypodermic needle, distal to the tourniquet at 20 sec intervals. The motor

block was assessed at one min interval till the patient was not able to produce movement of any fingers. On complaint of the tourniquet pain by patient intraoperatively, the distal cuff was inflated, and the proximal cuff was deflated. Need for intraoperative analgesia was also recorded. At the end of the operation, a blinded anesthesiologist recorded the satisfaction score of the patient for the anesthetic technique according to the following numeric scale: 3 = good (no complaint from patient), 2 = moderate (minor complaint with no need for supplemental analgesics), 1 = poor (complaint which required supplemental analgesics). Recovery room pain score, time to first analgesic demand, and sedation score (Ramsay Sedation Score) were compared. We also recorded the occurrence of any unpleasant psychologic effects postoperatively. Postoperatively patients received diclofenac 75 mg intramuscular if VAS was >4. All values were calculated with a 95% Confidence Interval (CI). The parameters were expressed as mean ± SD and t-test was used for comparing demographic and clinical data. Analysis of variance (ANOVA) technique was used for comparison between the three groups for parametric data. Chi-square test was used for non-parametric data. For the comparisons, $p< 0.05$ was statistically significant. The statistical evaluation was performed using SPSS version 11.0.

RESULTS

A total of 60 patients were enrolled in the study (n = 20 in each group). There was no significant difference between the four groups as regards demographic data, ASA classification, duration of surgery, site of the surgery, and duration of the surgery (Table 1).Types of surgery performed are depicted in (Figure 1). Regarding heart rate (Table 2) and mean arterial pressure (Table 3), there were no statistically significant differences between the three groups.As regards the characteristics of the block, it was found that the onset of sensory block was more rapid in the group III (2.2 +/- 0.4 min) followed by group II (2.3 +/- 0.6 min), and finally the control group (4.45 +/- 1.1 min). This difference was significant to the control group but there was no significant difference between the other two groups. Onset of motor block was significantly faster in group III (3.0 +/- 0.3 min), and group II (3.1 +/- 0.4 min) in comparison to the control group (9.25 +/- 3.25 min). Sensory recovery time after tourniquet deflation was significantly earlier in the control group (12.25 +/- 5.5 min) when compared to the other groups as group II (29.65 +/- 10.25 min), and group III (34.80 +/- 11.2min) without significant difference between them. Motor recovery time was significantly more rapid in the control group (19.50 +/- 6.5min) in comparison to the other two groups where it was (38.25 +/- 12.30 min) in group II, and (40.50 +/- 14.50 min) in group III, without significant difference between the two test groups (Table 1).As regards the tourniquet pain which assessed by the VAS it was significantly higher in the control group more than the adjuvant groups at all study times. There was no significant difference between the two adjuvant groups (Table 1). Intraoperative fentanyl doses required to overcome tourniquet pain was significantly higher in the control group (75.5 +/- 20.5 µg) when compared to the adjuvant groups as it was (30.5 +/- 11.0 µg) in group II, and (29.0 +/- 9.0 µg) in group III. There was no significant difference between the two adjuvant groups (Table 1).As regards postoperative pain which was assessed by VAS it was significantly higher in the control group more than the adjuvant groups at all the study times (Figure 2), and the time to 1st analgesic request was more prolonged in group II (168.15 +/- 33.20), followed by group III (212.30 +/- 25.10), and control group (12.23 +/- 2.41). There was significant difference between the two adjuvant groups and the control group without significant difference between them (Table 1).As regards the satisfaction score / quality of anaesthesia evaluated by the anaesthesiologist it was noticed that more patients in the group II (2.8+/- 0.75) and group III (2.9 +/- 0.62) experienced excellent quality of anaesthesia, compared to

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control group (2.25 +/- 0.55). As regards the side effects, no one of the patients complained from, hypotension, bradycardia, excessive sedation or hallucinations (Table 1).

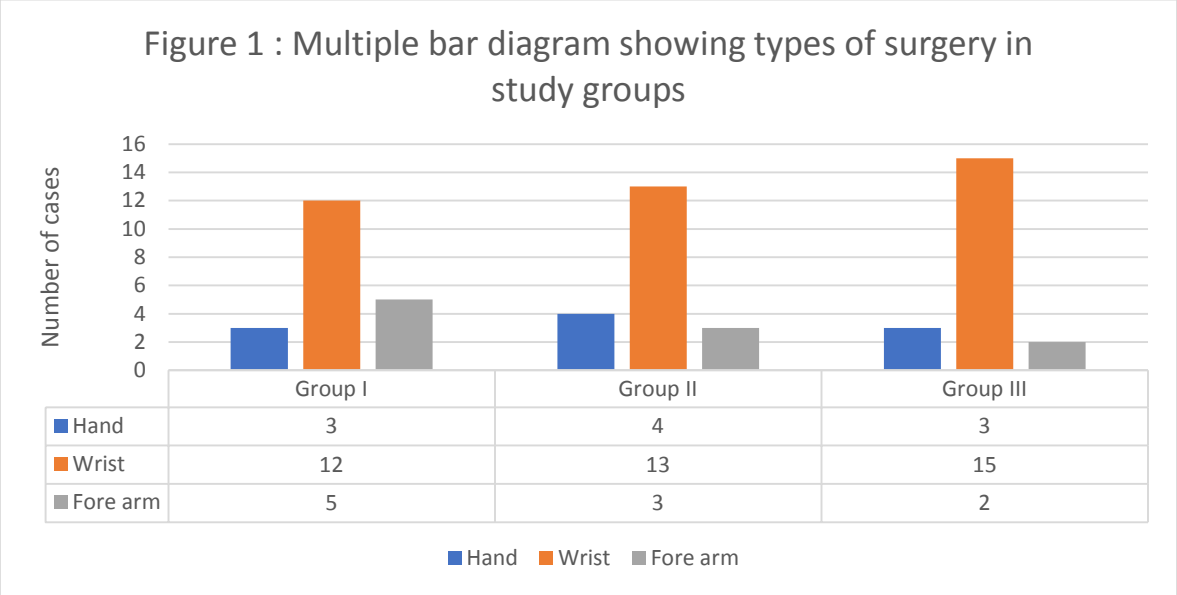

Table 1: Patient characteristics and outcome measures

Parameters	Group I	Group II	Group III	*P* value
Age (years)	31.2 +/- 9.2	29.5 +/- 8.3	33.6 +/- 8.0	>0.05
Weight (kg)	70.3 +/- 8.8	71.5 +/- 7.9	69.8 +/- 9.1	<0.001
Gender (M: F)	11/9	12/8	10/10	>0.05
ASA (I/II)	16/4	17/3	18/2	>0.05
Surgical Site (Hand/Wrist/Forearm)	3/12/5	4/13/3	3/15/2	>0.05
Duration of surgery (min)	48 +/- 16.41	42.05 +/- 11.25	44.1+/- 12.12	>0.05
Onset of sensory block (min)	4.45 +/- 1.1	2.3 +/- 0.6	2.2 +/- 0.4	<0.001
Onset of motor block (min)	9.25 +/- 3.25	3.1+/- 0.4	3.0 +/- 0.3	<0.001
Sensory recovery time (min)	12.25+/- 5.5	29.65 +/-10.25	34.80 +/- 11.2	<0.001
Motor recovery time (min)	19.50+/- 6.5	38.25±+/-12.30	40.50 +/- 14.50	<0.001
Intra op fentanyl consumption (mcgm)	75.5 +/- 20.5	30.5+/- 11.0	29.0 +/-9.0	<0.001
First analgesia time (min)	12.23 +/- 2.41	168.15+/-33.20	212.30 +/- 25.10	<0.0001
Post recovery pain score (VAS)	4.8 +/- 0.35	3.15 +/- 22.0	3.13 +/- 19.15	<0.0001
Satisfaction score	2.25 +/- 0.55	2.8 +/- 0.75	2.9 +/- 0.62	<0.05
Sedation score	1.55 +/- 0.88	2.35 +/- 0.75	2.88+/- 3.22	<0.0001
Side effects:				
Hypotension/bradycardia	0	0	0	-
Excessive sedation	0	0	0	-
Hallucination	0	0	0	-

Numerical data expressed as mean ± SD. Categorical data are expressed as number.
One way ANOVA test for quantitative data and chi square for qualitative data between the groups.
P value <0.05 is considered significant.

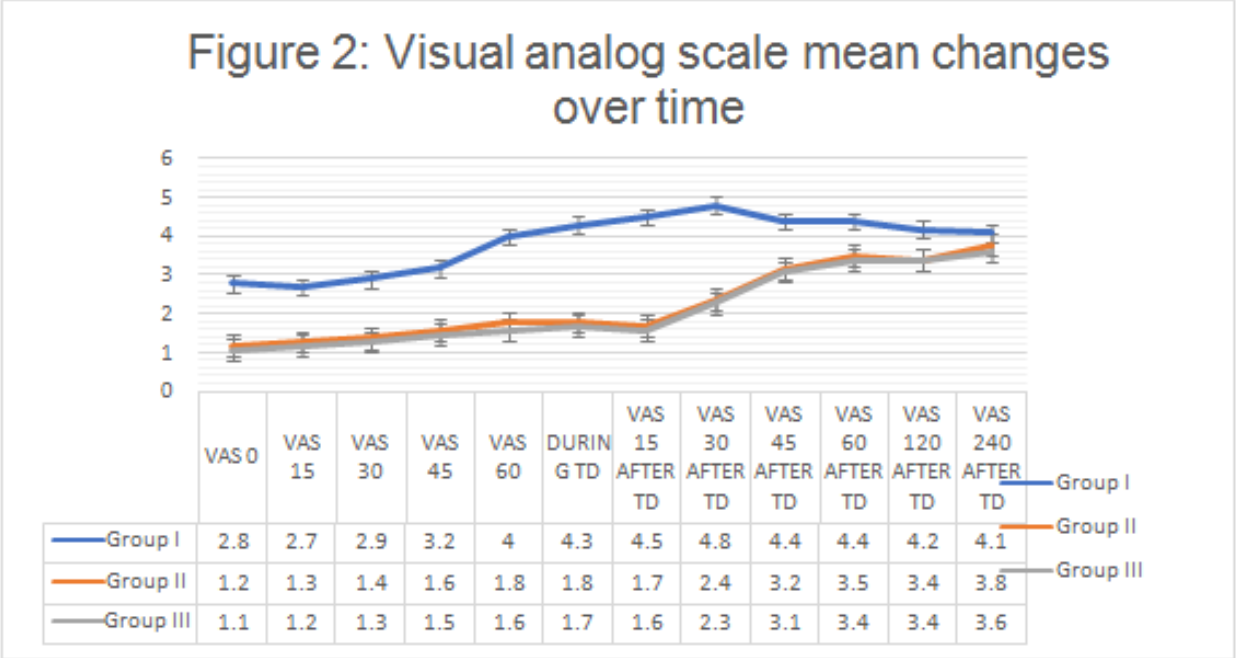

Table 2: Comparison of heart rate

Time Interval	Group I	Group II	Group III	P Value
Baseline	84.1 +/- 9.2	88.1+/- 9.7	86.5 +/- 8.5	>0.05
5 min	83.8 +/- 10.1	86.5 +/-11.4	84.2 +/- 9.5	>0.05
10 min	82.6+/- 10.5	85.5 +/- 9.9	83.8 +/- 7.3	>0.05
15 min	82.9 +/-9.9	85.2+/- 7.5	83.0 +/- 9.9	>0.05
20 min	82.7 +/-11.2	84.5 +/-10.0	82.8+/- 8.8	>0.05
40 min	80.4 +/-10.4	85.1 +/-9.8	82.5 +/- 7.5	>0.05
60 min	78.8+/-12.5	87.8+/-8.8	82.0 +/- 6.8	>0.05
90 min	77.5 +/- 11.5	86.2+/- 8,5	83.5 +/- 9.1	>0.05

Table 3: Comparison of MAP

Time Interval	Group I	Group II	Group III	P Value
Baseline	109.5 +/- 9.2	108.9 +/-8.9	99.3+/- 8.5	>0.05
5 min	107.8 +/-9.9	108.7 +/-7.8	98.0 +/-8.9	>0.05
10 min	108.4 +/-8.9	108.1 +/- 8.8	96.5+/-8.2	>0.05
15 min	108.5 +/-8.7	108.2+/- 6.9	97.3+/-8.2	>0.05
20 min	106.3 +/- 8.1	109.1 +/- 7.8	98.5 +/- 8.9	>0.05
40 min	104.9 +/-9.0	108.5 +/-8.8	94.2 +/-6.8	>0.05
60 min	103.0 +/- 8.0	106.4 +/- 8.4	93.2 +/-8.3	>0.05
90 min	106.8+/- 8.8	107.1 +/-7.5	93.2 +/-5.9	>0.05

DISCUSSION

IVRA technique is widely used for surgery on arms. IVRA is safe and problems are few. The advantages of IVRA are high indices of reliability, rapid onset of analgesia within 5-10 minutes and good muscular relaxation. The disadvantage of IVRA is the application of a tourniquet, which must remain inflated continuously throughout the procedure. The duration of surgery is limited by the time during which the arterial tourniquet could be kept safely inflated. Tourniquet pain, which is described as a dull and aching pain sensation, is a well-known limitation of IVRA. Skin compression, tourniquet size, and inflation pressure have

been implicated as factors involved in tourniquet pain. Another drawback with this technique is the absence of postoperative analgesia. 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. Non-steroidal anti-inflammatory drugs, opioids, and combination of opioid and muscle relaxant have been used without demonstrating clear advantage.[2] Ketamine, a phenyl-piperidine derivative, was first synthesized in the early 1960s as an IV anesthetic agent. At subanesthetic doses, ketamine exerts a noncompetitive blockade of *N*-methyl-aspartate (NMDA) receptors. NMDA receptors play a major role in synaptic plasticity and are specifically implicated in central nervous system facilitation of pain processing. NMDA receptor antagonists have been implicated in perioperative pain management. Ketamine also has local anesthetic qualities, which have been studied as a sole agent for IVRA.[7] In addition to spinal cord NMDA receptors, NMDA receptors have also been identified on peripheral unmyelinated sensory axons. This can explain why ketamine as an NMDA receptor antagonist was able to attenuate the tourniquet pain. Although 0.3% concentration provides complete sympathetic, sensory, and motor blockade when injected into the isolated extremity. Unpleasant psychotomimetic effects after the release of the tourniquet limit the usefulness of this use of ketamine. [8,9] When ketamine is used with lignocaine (0.5%) in a dose of 3 mg/kg of body weight, duration of analgesia after release of tourniquet is longer, and the quality of analgesia is superior. The onset of analgesia and motor blockade remains similar and all patients suffered from disorientation and hallucinations.[8] In comparison to systemic administration, there is no selective benefit to adding ketamine to the IVRA injectate.[10] Ketamine cannot be recommended as a sole agent for IVRA unless these unpleasant side effects are abolished or controlled by means of pharmacologic adjuvant.[11] When used in the doses of 0.1 to 0.5 mg/kg of body weight in IVRA no central nervous system symptoms have been observed.[12] Our study clearly demonstrated benefit of ketamine in IVRA when compared to a placebo. There was an early onset of sensory and motor block and good postoperative analgesia, although postoperative analgesia was longer in the dexmedetomidine group. No second cuff inflation was required in any patient denoting delay in onset of the tourniquet pain. Ketamine has well known hemodynamic effects (hypertension and tachycardia) but it failed to show any of these effects when given as an adjuvant in IVRA in our study. This could be due to fact that the tourniquet was not deflated before 30 min. Clonidine has been shown to decrease tourniquet pain and intraoperative analgesic requirement in IVRA.[13] Dexmedetomidine is approximately eight times more selective toward the α2 -adrenoceptors than clonidine.[5] Centrally active α -adrenergic agonists exert powerful analgesic action that probably is transduced at several levels. Dexmedetomidine has been shown to enhance the local anesthetic action of lignocaine via α 2A adrenoceptor.[14] Perioperative dexmedetomidine administration decreases the requirements for opioid or non-opioid analgesics both intra and postoperatively.[15] IV dexmedetomidine as a premedication has been effective before IVRA because it reduces patient anxiety, sympathoadrenal responses, and opioid analgesic requirements but it did not reduce tourniquet pain.[16,17] Addition of dexmedetomidine to prilocaine in IVRA decreases pain scores, improves anesthesia quality, decreases analgesic requirement, shortens sensory block onset time, and prolongs sensory block recovery time.[18] Addition of dexmedetomidine to lignocaine in IVRA also improves the quality of anesthesia and decreases the analgesic requirements but has no effect on the sensory and motor block onset and regression time.[6] Our study demonstrated that the addition of dexmedetomidine, in dose of 0.5 mcg/kg of body weight, to lignocaine for IVRA not only improved quality of anesthesia and postoperative analgesia without causing significant side effects but also shortened the onset of sensory and motor block as compared to placebo. Dexmedetomidine administration produces abrupt hypertension and bradycardia until the central sympatholytic effect dominates, resulting in moderate decrease in both mean

arterial pressure and heart rate from baseline.[19] In our study, no such hemodynamic changes were observed with low dose use of dexmedetomidine in IVRA. IV dexmedetomidine is also known to exert a sedative effect, which was significantly higher than other groups in our study.

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