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Research Article

COMPARISON OF POST OPERATIVE ANALGESIC EFFECTS OF KETAMINE VERSUS MIDAZOLAM WITH 0.5% LIGNOCAINE FOR INTRAVENOUS REGIONAL ANAESTHESIA

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A B S T R A C T

Background: Intravenous Regional Anaesthesia (IVRA) is a technically simple and reliable method of providing analgesia to the distal part of limbs. Major limitations of this technique is slow onset of sensory and motor block, tourniquet pain and short duration of post-operative analgesia. Numerous studies have been conducted to find the ideal adjuvant which can modify these limitations. In this study we observed, compared and evaluated the effect of ketamine and midazolam when used as adjuvants to 0.5% lignocaine for IVRA on sensory block onset time, tourniquet pain and postoperative analgesia.

Materials and Methods: A total of 40 patients undergoing implant removal from hand and forearm surgery under IVRA were divided in two groups of 20 each, with 0.5 mg/kg ketamine or 50 microgm/kg midazolam added to 0.5% lignocaine made to 40ml. Time of onset of sensory blockade and tourniquet pain was monitored. Duration of postoperative analgesia and side effects were also noted. Data analyzed using IBM SPSS Statistics 16.0 software and $P < 0.05$ was considered as statistically significant.

Results: The mean time to onset of sensory block was 3.41 ± 0.54 minutes in the lignocaine - ketamine group and 4.02 ± 0.298 minutes in the lignocaine - midazolam group. The difference was statistically significant with p value 0.017. Even though tourniquet pain onset time and postoperative analgesia was prolonged in lignocaine – ketamine group compared to lignocaine –midazolam, it was not statistically significant. No side effects were observed during the study.

Conclusion: We conclude that adding 0.5 mg/kg ketamine to 0.5 % lignocaine will provide significantly earlier sensory onset of IVRA compared to 50 microgm/ kg midazolam

INTRODUCTION

Intravenous regional anaesthesia (IVRA) was first described in 1908 by August Karl Gustav Bier[1], a German surgeon in Berlin. It was initially described as "vein anaesthesia"[2]. His method included exsanguination and occlusion of circulation in a limb using twotourniquets, introduction of a venous cannula after dissection and injecting 0.5 % prilocaine [3]. He observed a rapid onset of anaesthesia in the area between the two tourniquets. Bier first presented his new method of intravenous regional anaesthesia (IVRA) at the 37th Congress of the German Surgical Society on 22 April, 1908, 10 years after his significant communication on spinal anaesthesia.

The first reports by Bier proposed several technical, pathophysiological, and clinical concepts. He recognized that, injection of the anesthetic solution in the central or distal direction did not change the characteristics of the anesthesia and the importance of limb exsanguination for the rate of installation and effectivity of anesthesia was stressed. It was verified that thermal, painful, and tactile sensitivity disappeared in this order and returned in the opposite order.

The occurrence of anesthetic failure and temporary muscular paralysis was discussed and the mechanism of action of IVRA was described in two phases: an immediate phase of usually 2 minutes, between the two tourniquets, which he called direct anesthesia, and another slow of up to 20 minutes, beyond the distal tourniquet, which he called indirect anesthesia[1]. It is a technically simple and reliable procedure, with success rates between 94% and 98%. Holmes popularized this technique in the 1960s by using lidocaine and getting betterresults than those who preceded him. As a consequence more number of studies were undertaken and newer advancements were made in this field.[4] 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 the circulation is occluded by the application of tourniquet. Local anaesthetic diffuses into small veins surrounding the nerves and then into vasa nervosum and capillary plexus of veins,

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leading to conduction block in nerves involved. The mechanisms of action in intravenous regional [5] neural blockade are multiple and depend primarily on ischemia and on the transport of local anesthetic solution through a venous network into veins inside nerve trunks.[5] Some disadvantages related to IVRA include toxicity of local anesthetic (LA), slow onset of sensory and motor block, poor muscle relaxation, tourniquet pain and short duration of postoperative analgesia.

An ideal solution of intravenous regional anaesthesia should be rapid in onset, with minimal tourniquet pain and prolonged postoperative analgesia. In recent years, clinical research has focused on pharmacokinetics, toxicity, and benefits of additives in the local anesthetic solutions used.

Therefore this study compares the postoperative analgesia when two common drugs, used in intravenous anaesthesia are used as adjuvants to lignocaine.

Ketamine is a phenyl piperidine derivative used as an intravenous anaesthetic agent. It has been found to be an effective anesthetic agent for IVRA at concentrations between 0.3% and 0.5%. At sub anaesthetic doses ketamine exerts a noncompetitive blockade of NMDA receptors(N-Methyl-D-Aspartate receptors). These NMDA receptors are specifically implicated in Central nervous system facilitation of pain processing. They have also been identified on peripheral unmyelinated sensory axons.[6] Midazolam, is a short acting benzodiazepine, a central nervous system depressant with significant beneficial amnesia and anxiolytic effects. It has been found to have analgesic properties when administered intrathecally because of the agonism at benzodiazepine binding site on a subunit of pentameric $GABA_A$ receptors (Gamma Amino Butyric Acid receptor). Spinal midazolam is found to stimulate opioid system through delta and kappa receptors. $GABA_A$ receptors and opioid receptors in peripheral nerves can be responsible for IVRA analgesia.[7- 10] The primary objective of this study is to compare and evaluate the effect of ketamine and midazolam when used as adjuvants to 0.5% lignocaine for IVRA on sensory block onset time, tourniquet pain and post operative analgesia.

MATERIALS AND METHODS

After obtaining ethical committee clearance as well as informed consent from all patients this observational study entitled "a comparison of post-operative analgesic effects of ketamine versus midazolam with 0.5% lignocaine for intravenous regional anaesthesia" was under taken in Government Medical College, Thrissur during the period of January 2016 to December 2016. A total of 40 patients belonging to American Society of Anaesthesiologists Physical Status (ASA- PS) class I&II, of either sex, in the age group of 18-60years, scheduled to undergo implant removal from hand and forearm under IVRA.Those who refused the procedure , patients belonging to ASA 3 and 4, pregnant and lactating females, those with known hypersensitivity to ketamine, midazolam, lignocaine, patients with severe Raynaud's disease, Sickle cell disease, Scleroderma, those with infection or cellulitis over operative area were excluded from the study. During the pre anaesthetic examination, the procedure and verbal numerical pain rating scale was explained to patient. Patient was kept nil per orally for minimum 6 hours. Mean arterial blood pressure (MAP), peripheral oxygen saturation (SpO2) and heart rate (HR) was monitored. Two intravenous cannulae placed. One 22G cannula in a vein on the dorsum of the operative hand and the other 18G cannula in the opposite hand for crystalloid infusion. The operative arm was elevated for 3 minutes, then exanguinated with an esmarch bandage and a double cuffed pneumatic tourniquet was placed around the upper arm and the proximal cuff was inflated to 100mmHg more than systolic blood pressure. Circulatory isolation of the arm was verified by inspection, absence of radial pulse, and loss of pulse oximetry tracing of the ipsilateral index finger. Adjuvant to be given was decided by the senior anaesthesia care provider.

Group A included those who received 0.5% lignocaine made to 40ml with normal saline and 0.5 mg/kg ketamine. Group B included those who received 0.5% lignocaine made to 40ml with normal saline and 50 microgm/kg midazolam. Intraoperative pulse rate, blood pressure, ECG, oxygen saturation was monitored every 10minutes. Time of onset of sensory block and time of recovery from sensory block was monitored. Side effects such as dizziness, nausea, vomiting, tinnitus, perioral tingling, muscle twitching, loss of consciousness, convulsions were also monitored.

Onset of sensory blockade is defined as time taken from the completion of the injection of study drug till the subject does not feel the pin prick in any of the dermatomes.

Assessment of tourniquet pain was done using verbal numerical pain rating scale (0= no pain, 1-3 =mild pain, 4-6=moderate pain, 7-10=severe pain). Pain was monitored at 5, 10, 20, 30, 40, 60 min after tourniquet application.

Injection butorphanol 1-2mg (0.02-0.05mg/kg) was administered for tourniquet pain treatment for numerical rating more than 3. These subjects were excluded from study. The tourniquet was not deflated within 40 minutes and was not inflated more than 1.5 hours.

At the end of surgery, the tourniquet deflation was performed by the cyclic deflation technique that is, the tourniquet was deflated three times in a cyclic manner with 10 second period of deflation separated by 1 minute period of reinflation.

Postoperatively subjects were monitored at 30 minutes interval for 4 hours by qualified nursing personnel. Injection diclofenac 75mg intramuscularly was given when verbal numerical pain scale more than 5 and the time recorded. Duration of postoperative analgesia was defined from the time of deflation of tourniquet to the first intake of diclofenac.

RESULTS

The results obtained from both the groups of patients (A and B) were coded and entered in Excel. Normally distributed data were analyzed using t test and categorical data were analyzed using the Chi square test. Continuous data are presented as mean and standard deviation, whereas categorical data are presented as number of patients. Data were analyzed using IBM SPSS statistics 20.0 software. P value less than 0.05 was considered statistically significant.

Demographic data including age, height, weight were comparable between the two groups. No statistically significant difference noted.(Table 1)

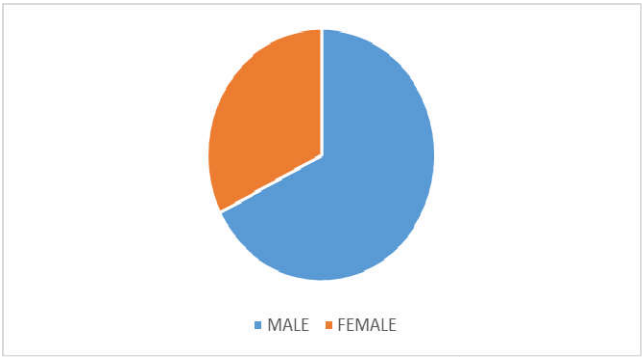
Table 1 Demographic Variables

Parameters	Mean ±SD
Age (yrs)	30.4 ±9.28
Weight (kg)	56.48 ± 6.46
Height (cms)	169 ± 8.83
Duration of operation (mts)	51.2 ± 5.56
Tourniquet application time (mts)	63.35 ± 5.58
Sensory block onset time (mts)	3.715 ±
Tourniquet pain onset time (mts)	62.65 ± 4.8

Table 2

Parameter	Group a (mean ±sd)	Group b (mean ±sd)	P value
Age (yrs)	30.6±10.91	30.20±7.58	0.13
Weight (kg)	54.35± 6.41	58.6± 5.93	0.75
Height (cm)	166.7±8.2	172.35± 8.72	0.99

Gender Distribution



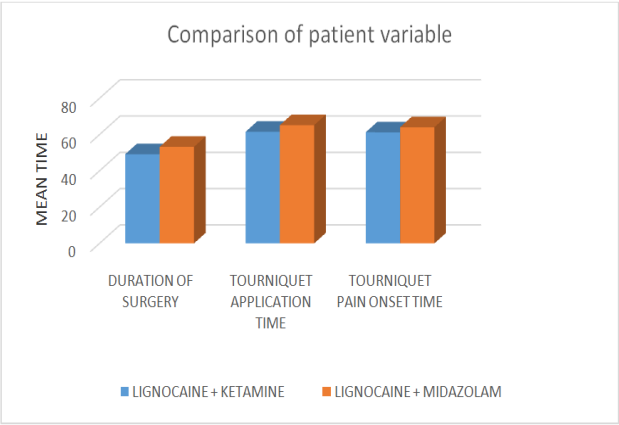
In the study group 67.5 % were males and 32.5 % were females.

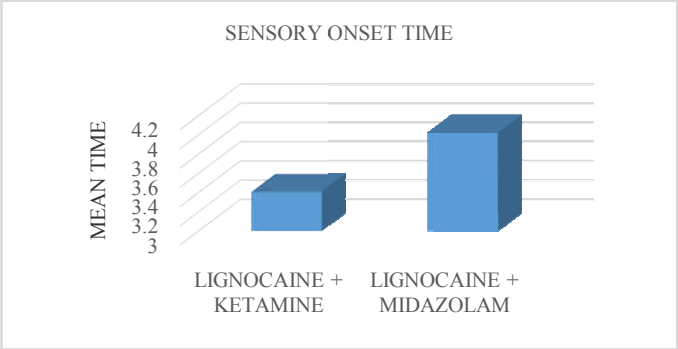
Table 3 Asa Ps

		Group	
		Group 1	Group 2
ASAclass	ASA PS 1	15	16
	ASA PS 2	5	4

Table 4 Comparison of Patient Variable

Variables	Group A	Group B	P value
Duration of surgery (mts)	49.2 ± 5.64	53.2 ± 4.83	0.37
Tourniquet application time (mts)	61.5 ± 5.69	65.2 ± 4.93	0.56
Sensory block onset time (mts)	3.41 ± 0.54	4.02 ± 0.29	0.017
Touniquet pain onset time (mts)	61.25 ± 5.4	64.05 ± 3.79	0.117

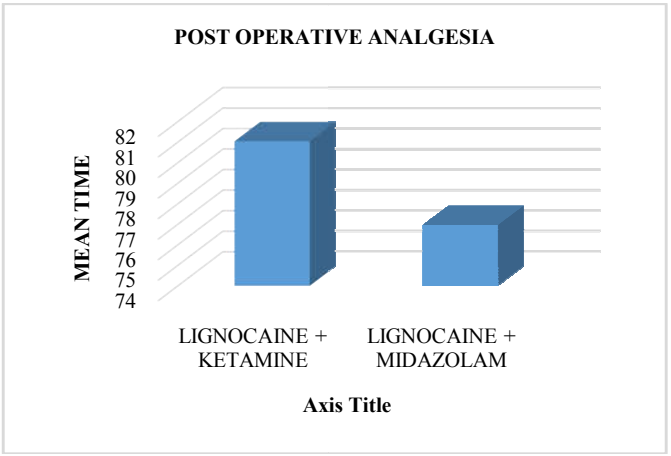




Comparison of post operative analgesia

Table 5 Post Operative Analgesia

	Group A	Group B	P value
Post-operative analgesia (mts)	81.05 ± 6.26	76.94 ± 4.42	0.113



DISCUSSION

40 patients undergoing forearm and hand surgeries under intravenous regional anesthesia were observed in Government Medical College, Thrissur. Those who received 0.5% lignocaine with 0.5 mg/kg Ketamine were included in group A while those who received 0.5% lignocaine with 50 microgm/kg Midazolam were included in group B.

The baseline demographic data of study population is as given in table 1. The mean age of study population was 30.4 ± 9.28 years. Mean weight was 56.48 ±6.46 kg. Mean height was 169 ± 8.83 cm. Mean duration of surgery was 51.2±5.56 minutes. Mean tourniquet application time was 63.35 ± 5.58 minutes. Mean sensory block onset time was 3.71 minutes. Mean tourniquet pain onset time was 62.65±4.82 minutes.

Demographic data of Group A and Group B were comparable. (Table 2). The mean age for Group A was 30.6±10.91years and that of Group B was 30.2±7.58 years. The p value was 0.135 and found not to be of statistical significance. The mean weight for Group A was 54.35± 6.41kg and that of Group B was 58.6± 5.93 kg. The p value calculated was 0.75 which was not statistically significant. The mean height for Group A was 166.7± 8.2 cm and that of Group B was 172± 8.72cm. The p value calculated was 0.99 and was not statistically significant. Chance of confounding in terms of age, weight and height was thus excluded.In the study group 67.5 % were males and 32.5 % were females. Gender distribution among Group A and B were tested using chi square test and p value calculated as 1 which was found to be statistically insignificant. Distribution

of ASA PS class 1 & 2 between Group A and B were tested using chi square test and p value calculated as 0.802 which was not statistically significant. (Table 3)

Duration of surgery was compared between Group A and Group B. The mean duration of surgery in Group A was 49.2± 5.64 minutes and that in Group B was 53.2±27.6 minutes. The p value was calculated as 0.37 was not found to be of statistical significance. Time taken for onset of sensory block was compared between the two groups. The time of onset was taken as the earliest time when all the four nerve territories showed complete sensory block. The mean time of onset of sensory block in Group A was 3.41± 0.54 minutes and that in Group B was 4.02± 0.29 minutes. P value was 0.017. There was significantly earlier onset of sensory block in Group A. (Table 4). This result was comparable to study conducted by Elmetwaly *et al* in 2010 [11] where sensory onset in lignocaine ketamine group was 4.4 ± 1.2 minutes and the study by Gupta *et al* where mean sensory onset time after adding 50microgm midazolam was 6.49 ± 4.26 minutes.[12]

Duration of tourniquet application was compared between the two groups. During operation if there was no tourniquet pain more than numerical rating 3, tourniquet pain onset time was accepted as the duration of tourniquet application time. The mean duration of tourniquet application in Group A was 61.5± 5.69 minutes and that in Group B was 65.2± 4.93 minutes. P value was 0.5 and the comparison was not statistically significant. (Table 4)

Assessment of tourniquet pain was done using verbal numerical pain rating scale (0= no pain, 1-3 =mild pain, 4-6=moderate pain, 7-10=severe pain). Pain was monitored at 5, 10, 20, 30, 40, 60 minutes after tourniquet application. The onset of tourniquet pain was compared between the two groups. The mean time of onset of sensory block in Group A was 61.25± 5.4 minutes and that in Group B was 64.05± 3.79 minutes. P value was 0.117 and it was not statistically significant.

No incidence of LA toxicity or any side effects was reported in both the groups. All the patients were hemodynamically stable throughout the procedure.

Postoperatively subjects were monitored at 30 minutes interval and injection diclofenac 75mg intramuscularly was given when verbal numerical pain scale more than 5. Duration of postoperative analgesia was defined from the time of deflation of tourniquet to the first intake of diclofenac. The mean duration of post-operative analgesia in Group A was 81.05±6.26 minutes and that in Group B was 76.94± 4.42 minutes. P value was 0.113 and it was not statistically significant. (Table 5). The result was consistent with the study by Gupta *et al* comparing analgesic efficacy of dexmedetomidine and midazolam as adjuvants to lignocaine for Intravenous Regional Anesthesia. This study was conducted on sixty patients scheduled for upper limb orthopedic surgery. Group M-received 40 ml of 0.5% lignocaine with midazolam 50 microgm/kg and Group D-received 40 ml of 0.5% lignocaine with dexmedetomidine 1 microgm/kg. Mean duration of analgesia was 93 ± 28 minutes in dexmedetomidine group and 84 ± 28 minutes in midazolam group, and onset of sensory block was comparable in both groups. [13] However the result could not be correlated with the study by Abdel-Ghaffar *et al* which had reported 20.4 ± 3.7 hours post-operative analgesia in those who received 50mg ketamine as additive with 3mg/kg lignocaine IVRA. [14] At the end of surgery as the tourniquet deflation was performed by the cyclic deflation technique, chance of sudden release of large quantities of local anaesthetic into the circulation is minimal. Therefore no side effects or signs of local anaesthetic systemic toxicity was reported.

However some drawbacks of this study are inability to assess motor block because of inconsistent findings, false interpretation of early onset of tourniquet pain during very short duration procedures. Also postoperatively subjects were to be monitored at 30 minutes interval for 4 hours. But as majority of patients complained pain by less than 2 hours, all patients could not be monitored for 4 hours postoperatively. Difference in type of surgical procedure, surgical skill and presence of infection provided with inconsistent results.

CONCLUSION

In our study we compared the onset of sensory block, onset of tourniquet pain, duration of post-operative analgesia between ketamine and midazolam when used as additives with 0.5 % lignocaine in intravenous regional anaesthesia.

We conclude that the addition of ketamine 0.5mg/kg with lignocaine in IVRA significantly shortens the onset time of sensory block, than adding midazolam 50 microgm/ kg with lignocaine. There may not be any significant difference between both drug combinations in case of tourniquet pain and postoperative analgesia

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