Comparison between Dexmedetomidine and Midazolam as an Adjuvant to Lidocaine in Intravenous Regional Anesthesia for below Elbow Surgeries.

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ABSTRACT

Background: Intravenous regional anesthesia (IVRA) is safe, technically simple but it has several disadvantages as limited duration, lack of postoperative analgesia and tourniquet pain.

Aim of the study: Comparing the effect of addition of dexmedetomidine and midazolam to lidocaine on the characters of the produced intravenous regional anesthesia for below elbow surgeries.

Patients and methods: Sixty patients of both sexes admitted for forearm and hand surgeries were randomly allocated into three equal groups: Lidocaine group (L group) received 40 ml of 0.5% lidocaine, Lidocaine/ Dexmedetomidine group (L/D group) received 40 ml of 0.5% lidocaine plus 0.5µg/kg dexmedetomidine and Lidocaine/Midazolam group (L/M group) received 40 ml of 0.5% lidocaine plus 5.5µg/kg dots be a standard be a standard be and the standard be added by the standard by the standard be added by the standard be added by the standard be added by the standard by the standard

Results: Both Dexmedetomidine and midazolam enhanced the onset of sensory block, only midazolam enhanced the onset of motor block, both lowered the mean of surgical pain scores, decreased the intraoperative fentanyl consumption, delayed the onset of tourniquet pain, and prolonged postoperative analgesia with minimal side effects.

Conclusion: Addition of each of dexmedetomidine and midazolam to lidocaine for IVRA, significantly improved the quality of the produced regional anesthesia.

INTRODUCTION

Intravenous regional anesthesia (IVRA) was first described by August Bier in 1908.⁽¹⁾ It has several advantages as being very simple, reliable and economic, very high success rate and rapid onset.⁽²⁾ On the other hand, it has several disadvantages as short duration, tourniquet pain, great liability to local anesthetic toxicity and very short postoperative analgesia after deflation of the tourniquet.⁽³⁾ In attempt to improve intra-operative and postoperative qualities of the IVRA, many adjuvant were added i.e. muscle relaxants ⁽⁴⁾, opioids ⁽⁵⁾, ketamine ⁽⁶⁾, non-steroidal anti-inflammatory drugs ⁽⁷⁾, neostigmine ⁽⁸⁾, dexmedetomidine⁽⁹⁾ and midazolam.⁽¹⁰⁾ Dexmedetomidine is highly selective $\alpha 2$ adrenoceptors. It decreases anesthetic requirements by up to 90% and

induces analgesia in patients.⁽¹⁰⁾ Midazolam is a short-acting benzodiazepine. It has sedative, anxiolytic, muscle relaxant, and anticonvulsant activity. The analgesic effect of midazolam is mediated by γ -amino butyric acid. It reduces A- δ and C-fiber evoked activity. γ -Amino butyric acid receptors have also been found in peripheral nerves. The role of A- δ fibers and unmyelinated C-fiber may be considered being involved in tourniquet pain.⁽¹⁰⁾ Nowadays, dexmedetomidine and midazolam are commonly used as adjuvant to local anesthetics to improve the quality of spinal, epidural, brachial plexus and intravenous regional block.^(9 &10)

Because there are few studies that compared the effect of adding each of dexmedetomidine and midazolam to lidocaine on the characters of the produced IVRA for below elbow surgeries so, the aim of this work is to do this comparison.

PATIENTS AND METHODS

This study was prospective comparative randomized controlled clinical study that had been carried out after obtaining approval of Institutional Review Board (IRB) Keywords: Dexmedetomidine, intravenous regional anesthesia, lidocaine, midazolam.

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and informed consent from the patients. This study was conducted in accordance with the Helsinki Declaration of 1975, as revised in 2013.

Sixty patients of both sexes were enrolled in this study. Inclusion criteria were patients of the American Society of Anesthesiologists (ASA) physical Status class I and II, aged between 18 and 50 years and their body weight between 75–95 kg, scheduled for unilateral minor operations on the forearm or hand (i.e., not need more than 60 min.). The exclusion criteria were patient refusal, uncooperative patients, difficult vein, crush injury, sickle cell disease, allergic reaction to the tested drugs, peripheral vascular and neurological diseases, muscle, hepatic and renal diseases beside cardiac conduction abnormalities.

All patients were visited for clinical evaluation to find out any exclusive criteria, to explain the technique of IVRA and to record the base line Heart rate, Mean arterial blood pressure, respiratory rate and peripheral arterial oxygen saturation (SpO₂). No premedication was prescribed.

In operating room, for safety, resuscitation equipments and emergency drugs were near to the patient. IV cannula and sphygmomanometer cuff were applied to the nonoperated limb for fluids and drug administration and continuous measurement of blood pressure respectively. Also, ECG leads, and pulse oximeter probe were applied to the chest and the big toe of one of the patient's lower limbs respectively for continuous monitoring of heart rate, rhythm and peripheral arterial oxygen saturation.

Another iv cannula was inserted into the most peripheral vein in the limb to be blocked. After that, the pre-checked double pneumatic tourniquet was applied to a well padded proximal third of the arm of the limb to be operated. Exsanguination of the limb was achieved by application of Esmarch bandage on the above heart raised limb. Immediately and after applying of Esmarch bandage, the proximal cuff of the pre-applied pneumatic tourniquet was inflated to a pressure of 100 mmHg above the initial systolic pressure. After securing pneumatic tourniquet, Esmarch bandage was removed and the upper limb was lowered and checked for colour (pale colour) and arterial occlusion (absence of radial pulse) to be sure of the efficacy of the tourniquet.

After that, the local anesthetic mixture was slowly injected. When sensory block reached to the level of middle third of the arm, the distal cuff of pneumatic tourniquet was inflated to a pressure of 100 mmHg above the initial systolic pressure. Then, the proximal one was deflated.

The study participants were randomized using a computer-generated random numbers table into three equal groups. These three groups were Lidocaine group (L group) which received 200 mg of preservative-free lidocaine (lidocaine Hcl; Hospira, Lake Forest, Illinois, USA) (supplied in 10-ml vial at concentration of 20mg/ml i.e. 2% concentration), Lidocaine/dexmedetomidine group (L/D group) which received 200 mg of preservative-free lidocaine plus $0.5 \mu g/kg$ dexmedetomidine (Precedex, Abbott Laboratories Inc., Abbott Park, IL) (supplied in 2-ml ampoule at concentration of 100 µg/ml) and Lidocaine/midazolam group (L/M group) which received 200 mg of preservative-free lidocaine plus 50 µg/kg midazolam (Midazolm hamlen, Hameln Pharmaceuticals GmbH, Hameln, Germany) (supplied in 2-ml ampoule at concentration of 1mg/ml).

The injected 200 mg of lidocaine (i.e., 10 ml of 2% lidocaine) with or without adjuvant were diluted up to 40ml by normal saline to make lidocaine concentration equal 0.5%.

After injection of each local anesthetic mixture, the following were detected and recorded:

I- **Onset of sensory and motor blocks:** It was the time (minutes) from the moment of local anesthetic mixture administration to the moment of loss of sensation to pin prick at the middle third of the arm for the first and to the moment at which the patient was unable to flex his fingers, wrist, and elbow joints for the later.

II- **The intraoperative analgesic potency:** It was evaluated by assessing intra-operative surgical pain intensity, the amount of supplemental systemic fentanyl which was needed intraoperatively to relief surgical pain and the duration of tolerance to tourniquet pain.

Intra-operative surgical pain intensity was evaluated by Visual Analogue Scale (VAS) and it was estimated at skin incision, every 5 minutes during the operation, and at skin closure. The mean of all these values were detected in each group. Duration of tolerance to tourniquet pain was the time from the moment of tourniquet inflation to the moment at which the patient was unable to tolerate more than the pain exerted by the inflated tourniquet on the applied area.

III- Offst of sensory and motor blocks:

These were the times from the moment of deflation of the tourniquet till the moment of return of pin prick sensation of the limb for the first and till the moment at which the patient can flex his fingers, wrist, and elbow joints for the later.

IV- **The time to ask for the 1**st **post operative analgesia** (time/min from the moment of tourniquet deflation to patient reporting pain intensity above 3 according to VAS) and the amount of systemic Diclofenac sodium which was needed to alleviate postoperative pain from the moment of deflation of tourniquet till the end of the first 24 hours postoperatively

Diclofenac sodium (75 mg im every 8 hours) was given to the patient if he was unable to tolerate postoperative pain i.e. VAS is more than 3.

V- The incidences of the various associated side effects:

The suspected associated side effects were local anesthetic toxicity, bradycardia (HR decrease by > 30% of basal reading), hypotension (MABP decrease by > 20% of basal reading) hypopnea (RR < 8 breaths/min), hypoxemia (SaO₂ < 92%) and sedation (i.e. sedation score more than 2 intra or postoperatively due to the tested drugs). The sedation level was assessed by means of six points Ramsay agitation/sedation scale (¹¹) that is presented in **Table (1)**. Bradycardia was treated with IV atropine (0.5 mg). Hypotension was treated with IV ephedrine (5 to 10-mg bolus). Hypoxemia was treated with O₂ supplementation via a face mask.

Sedation score	Response to stimuli
1	Patient anxious or agetated or both
2	Patient cooperative, oriented and tranquil.
3	Patient respond to commands.
4	A brisk response to light glabellar tap.
5	A sluggish response to light glabellar tap.
6	No response to stimulus.

 Table 1: Ramsay agitation/sedation scale(11)

At the end of surgery, the tourniquet was deflated by intermittent deflation and re-inflation technique. The tourniquet was not deflated within 30 minutes and was not inflated more than 1.5 hours.

One hour after tourniquet deflation postoperatively, all patients were discharged to ward.

Statistical analysis:

It was done on the basis of the Gergers study ⁽¹²⁾, power of the test was 80% and confidence level was 95%, so the sample size was calculated to be 48 subjects, 16 patients for each group. For compensation for any dropped cases, the group size increased from 16 to 20 in each group. The sample size was calculated using Open Epi program. The data were analyzed by using SPSS software program. The Values were presented as mean or median and standard deviation. Chi-square test and Mann-Whitney Utest were used for statistical analysis when appropriate. In all tests, P value below 0.05 was considered statistically significant.

RESULTS

The demographic data (age, sex, height, and weight and ASA ps classes), duration of surgery, tourniquet time and distribution of the various types of operations were comparable in the three studied groups **(Table 2).**

Onset of sensory block in each of L/D and L/M groups was highly significant faster than in L group (P <0.001) and in L/D group it was significantly faster than in L/M group (P =0.042). Onset of motor block in L/M group was highly significant faster than that in each of L group and L/D group (P <0.001), and in L/D group, it was comparable with that in L group (**Table 3**).

The mean of surgical pain scores in each of L/D and L/M groups was highly significant less than that in L group and in L/D group it was significantly less than that in L/M group.

Intraoperative fentanyl consumptions (μ g/patient) in each of L/D and L/M groups was highly significant less than that in L group and in L/D group it was significantly less than that in L/M group. Duration of tolerance to tourniquet pain in each of L/D and L/M groups was highly significant longer than that in L group and in L/D group it was highly significant longer than that in L/M group **(Table 4).**

Sensory block recovery time in each of L/D and L/M groups was highly significant longer than that in L group and in L/D group it was comparable with that in L/M group. Motor block recovery time power in each of L/D and L/M groups was highly significant longer than that in L group and in L/D group it was highly significant longer than that in L/M group (Table 5).

Duration of post-operative analgesia in each of L/D and L/M groups was highly significant longer than that in L group and in L/D group it was highly significant longer than that in L/M group **(Table 6)**.

The consumed amount of diclofenac to relief pain in the 1^{st} 24 hours postopertatively in each of L/D and L/M groups was significantly less than that in L group and in L/D group it was highly significant less than that in L/M group **(Table 5)**.

The associated side effects were bradycardia, hypotention and sedation that occurred after tourniquet deflation at the end of operations. Each side effect occurred in 4 patients in L/D group and in 3 patients in L/M group and did not occur in L group. Statistically, the incidences of the associated side effects in the three groups were comparable **(Table 7)**.

DISCUSSION

Intravenous regional anesthesia (IVRA) is safe, technically simple, and cost-effective technique compared to general anesthesia with success rates of 94–98% for upper and lower limb surgeries. ⁽²⁾ IVRA has several disadvantages as limited duration for surgery, lack of postoperative analgesia, and tourniquet pain.⁽³⁾ To overcome these disadvantages, various adjuvant to the used local anesthetic have been studied.

From the present study, it was found that addition of each of dexmedetomidine and midazolam to lidocaine, enhanced the onset of sensory block of IVRA with superiority of dexmedetomidine over midazolam. In contrast, midazolam but not dexmedetomidine enhanced the onset of motor block of IVRA.

These findings were in agreement with the reported findings of many workers. Gerges ⁽¹²⁾, Nasr and Waly ⁽¹³⁾, Elramely and Elmoutaz ⁽¹⁴⁾, Abdelkader *et al* ⁽¹⁵⁾ and Nilekani *et al* ⁽¹⁶⁾ reported that, addition of dexmedetomidine to lidocaine for IVRA enhanced the onset of sensory block but the onset of motor block did not affect. Honarmand *et al* ⁽¹⁷⁾ reported that, addition of midazolam to lidocaine for IVRA enhanced the onset of lidocaine for IVRA enhanced the onset of lidocaine for IVRA enhanced the onset of sensory and motor block. Mahmoud *et al* ⁽¹⁸⁾ reported that, addition of each of dexmedetomedine and midazolam to lidocaine for IVRA enhanced the onset of sensory block. Also, they found that midazolam but not dexmedetomidine enhanced the onset of its motor block.

On the other hand, these findings were against the reported findings of other workers. Farouk and Aly (19) reported that, addition of midazolam to lidocaine for IVRA did not affect the onset of sensory and motor blocks. Subramanya et al (20) Raghavendra et al (21) and Abo El-Enin *et al* ⁽²²⁾ reported that, addition of dexmedetomidine to lignocaine for IVRA led to earlier onset of both sensory and motor blocks. The controversy between the present study findings and Subramanya et al, Raghavendra et al and Abo El-Enin et al, findings was attributed to the premedication with 0.015 mg/kg midazolam intravenously that they gave to their patients.

In the present study, the detected rapid onset of sensory block of IVRA in dexmedetomidine added group means that, it has synergistic effect to sensory blockade of lidocaine in peripheral nerve blocks. The mechanism by which dexmedetomidine enhances the sensory blockade of local anesthetics in peripheral nerve blocks is unclear. It is postulated that, dexmedetomidine has a local anesthetic effect with rapid onset of sensory blockade.

In the present study, the detected rapid onset of sensory and motor block of IVRA in midazolam added group may be attributed to its vasodilatory effect that promotes distribution of lidocaine to nerves.⁽²³⁾

In the present study, it was found that addition of each of dexmedetomidine and midazolam to lidocaine for IVRA, increased its analgesic potency during surgery. The signs which indicated that were a decrease in the mean of surgical pain scores, an increase in the duration of tolerance to tourniquet pain and a decrease in the intraoperative fentanyle consumption. Dexmedetomidine was superior to midazolam in increasing the analgesic potency of lidocaine.

These findings were in agreement with some workers who reported that, addition of midazolam to lidocaine for IVRA increased the duration of tolerance to tourniquet pain and decreased the intra-operative fentanyle consumption.^(17&19) Nasr and Waly ⁽¹³⁾ reported that, addition of dexmedetomidine to lidocaine for IVRA increased the duration of tolerance to tourniquet pain intra-operative and decreased the fentanyle consumption. Mahmoud et al (18) reported that, addition of each of dexmedetomedine and midazolam to lidocaine for IVRA increased the duration of tolerance to tourniquet pain and decreased the intra-operative

fentanyle consumption with superiority to dexmedetomidine over midazolam.

The mechanism by which α 2-adrenergic receptor agonists produce analgesia and sedation is not fully understood but is likely to be multi-factorial. Peripherally, α 2 agonists produce analgesia by reducing release of norepinephrine and causing α 2 receptorindependent inhibitory effects on nerve fiber action potentials. ⁽²⁴⁾ Centrally, α 2 agonists produce analgesia and sedation by inhibition of substance P release in the nociceptive pathway at the level of the dorsal root neuron and by activation of α 2 adrenoceptors in the locus coeruleus.⁽⁹⁾

The analgesic effect of midazolam is mediated by γ -amino butyric acid. It reduces A- δ and C-fiber evoked activity. γ -Amino butyric acid receptors have also been found in peripheral nerves. The role of A- δ fibers and unmyelinated C-fiber may be considered being involved in tourniquet pain.⁽¹⁰⁾

In the present study, it was found that addition of each of dexmedetomidine and midazolam to lidocaine for IVRA led to prolongation of sensory and motor block recovery time after tourniquet deflation. The sensory block recovery times with these two adjuvants were comparable. These findings were in accordance with some workers who reported that addition of 50 μ g /kg of midazolam to 40 ml of 0.5% lidocaine for IVRA led to prolongation of the time to ask for postoperative anlagesia and lowers the post-operative pain scores.(17&19)

Mahmoud *et al* ⁽¹⁸⁾ reported that, addition of each of dexmedetomedine and midazolam to lidocaine for IVRA led to prolongation of the duration of post-operative analgesia with excellence of dexmedetomidine over midazolam. The detected prolonged sensory and motor power depression after release of tourniquet in dexmedetomidine and midazolam added groups may be attributed to the more stay of the combined lidocaine/dexmedetomidine and lidocaine/midazolam than lidocaine alone in the operating limb. ⁽²⁵⁾ The prolongation of motor blockade in lidocaine/midazolam group could also be described by benzodiazepine-induced attenuation of motor tonus at the ventral horn of the spinal cord after tourniquet release. ⁽²⁶⁾

In the present study, the associated side effects were bradycardia, hypotention and sedation. Each side effect occurred in 4 patients in dexmedetomidine added group and in 3 patients in midazolam added group. In the contrary side effects did not occur in lidocaine alone group. These results were in agreement with some workers who reported some bradycardia after deflation of the tourniquet in dexmedetomidine added group (13&14) and intraoperative and postoperative sedation score values were significantly higher in each of dexmedetomidine added group (13, 14 & 27) and midazolam added group (19) than in lidocaine alone group. On the contrary, other workers reported that, addition of each of dexmedetomedine to lidocaine for IVRA did not lead to any hemodynamic changes (15, 16, 20 & 28) and intraoperatively, there was no significant difference between sedation scores in dexmedetomidine added group and lidocaine alone group and postoperativly sedation score in dexmedetomidine added group was higher than that in lidocaine alone group.(15)

 α_2 -adrenergic receptors at the nerve endings are thought to play a role in the analgesic effect of the drug by preventing norepinephrine release.⁽²⁹⁾ The actions of dexmedetomidine as found to be mediated via postsynaptic α_2 -adrenoceptors activate G-proteins, thereby increasing conductance through potassium channels. Studies in mice have demonstrated that the α_{2A} adrenoceptor subtype is responsible for relaying the sedative and analgesic properties of dexmedetomidine.⁽³⁰⁾

Thus, α_2 -agonists are an attractive option as an adjuvant in pain management because of their potentiating effects at central and peripheral sites.⁽³¹⁾ Tourniquet deflation can lead to an abrupt introduction of dexmedetomidine into the systemic circulation. Acute intravenous administration of dexmedetomidine is known to produce hypotension, bradycardia and also sedation.^(32 & 33)

In the present study, bradycardia, hypotention and sedation occurred after tourniquet deflation in 20% of patients in dexmedetomidine added group, 15% of patients in midazolam added group and did not occur in lidocaine group with no statistically significant difference between them. The incidences of these detected side effects were nearly similar to some reported findings (16, 20 & 28) and markedly lower than others.(13,14, 19 & 27)

In the present study, the detected lower incidences of the side effects in comparison with those reported by other workers were attributed to the use of small dose of dexmeditomidine (0.5µg/kg versus 1µg/kg was used by the others) and in contrary with other studies, premedication and intraoperative sedation were not used in the present study. The occurrence of bradycardia and hypotension after tourniquet deflation in dexmedetomidine added group, was attributed to the postsynaptic activation of central α 2-adrenoceptors by dexmedetomidine, leading to decreased sympathetic activity that decrease the blood pressure and HR(34) but their occurrence in midazolam added group was attributed to the depressant effect midazolam on the sympathetic nervous system.(35&36)

The occurrence of sedation after tourniquet deflation in dexmedetomidine added group was attributed to the central sedative effect of dexmedetomidine by inhibition of substance P release in the nociceptive pathway at the level of the dorsal root neuron and by activation of $\alpha 2$ adrenoceptors in the locus coeruleus (9) but it's occurrence in midazolam added group was attributed to the effect midazolam on gamma-amino butyric acid receptors with subsequent release of the CNS inhibitory neurotransmitter gamma-aminobutyric acid (GABA).⁽³⁵ &36)

Limitations of this study were lack of patients and surgeon's assessment of intravenous regional block quality, lack of control groups received systemic dexmedetomidine and midazolam as adjuvant to lidocaine IVRA to compare their central versus peripheral sites of action and lack of postoperative analgesia and limited duration of anesthesia.

CONCLUSION

Addition of each of dexmedetomidine and midazolam to lidocaine for IVRA significantly improved the quality of the produced regional anesthesia with minimal associated side effects. The superiority of one over the other could not be established.

				T-tests		
	L Group (n=20)	L/D Group (n=20)	L/M Group (n=20)	X²/f	P-value	
	Mean±SD	Mean±SD	Mean±SD			
Age (years).	29.56±4.23	32.91±4.15	30.84±5.5	2.623	0.081	
Weight (kg).	86.43±5.12	84.62±6.28	86.21±5.07	0.641	0.531	
Height (cm).	170.4±5.67	168.23±6.4	168.12±5.33	0.977	0.383	
Sex ratio (Male/ Female ratio).	12/8	10/10	7/113	2.536	0.281	
ASA ps classes (Class I/II ratio).	17/3	18/2	15/5	1.680	0.817	
Duration of surgery (min.).	46.75± 5.2	48.35±5.1	47.2±6.3	0.440	0.646	
Tourniquet time (min.).	53.1±7.4	57.7± 5.6	56.3±7.9	2.246	0.115	
Distribution of the various types of oper	rations [N (%)]:					
- Carpal tunnel release.	8 (40%)	8 (40%)	9 (45%)	0.137	0.934	
- Ganglion excision.	4 (20%)	4 (20%)	5 (25%)	0.196	0.906	
- Fracture fixation.	2 (10%)	2 (10%)	1 (5%)	0.436	0.804	
- Tendon repair.	0 (0%)	1 (5%)	1 (5%)	1.034	0.596	
- Foreign body removal.	4 (20%)	3 (15%)	2 (10%)	0.784	0.676	
- Plate and screw removal.	1 (5%)	0 (0%)	1 (5%)	1.034	0.596	
- Tendon lengthening	0 (0%)	1 (5%)	1 (5%)	1.034	0.596	
- Nerve repair.	1 (5%)	1 (5%)	0 (0%)	1.034	0.596	

Table 2: Patients demographic data, duration of surgery, tourniquet time and distribution of the various types of operations in the three studied groups.

Data are expressed as Mean \pm Standard Deviation (SD) or numbers (%).

n = Group number. N = number of each operation type in each group.

L Group = Lidocaine (Control) group.

L/D group = Lidocaine/Dexmedetomidine group.

L/M Group = Lidocaine/Midazolam group.

ASA ps class = American Society of Anesthesiology physical status class.

f = one way ANOVA test.

P > 0.05 = nonsignificant difference.

 Table 3: Onset of sensory and motor block after establishment of IVRA in the three studied groups.

	L group (n=20)	L/D Group (n=20)	L/M Group (n=20)	ANOVA Test		Tukey's test			
	Mean±SD	Mean±SD	Mean±SD	f	P-value	L/D group vs L group	L/M group vs L group	L/D group vs L/M group	
Onset of sensory block (min.).	6.6±1.5	3.8±1.4	4.7±1.3	20.780	<0.001	<0.001	<0.001	<0.001	
Onset of motor block (min.).	10.5±3.7	9.3±3.2	4.9±1.4	20.147	<0.001	> 0.05	<0.001	<0.001	

Data are expressed as Mean \pm Standard Deviation (SD). n = Group number. vs = versus. L Group = Lidocaine (Control) group. L/D Group = Lidocaine/Dexmedetomidine group. L/M Group = Lidocaine/Midazolam group. f = one way ANOVA test. P< 0.05 = significant difference.

P< 0.001 = Highly significant different

Table 4: Intraoperative analgesic potency of intravenous regional block in the three studied groups.

	L Group (n=20)	L/D Group (n=20)	L/M Group (n=20)	ANOVA Test		Tukey's test			
	Range Mean±SD	Range Mean±SD	Range Mean±SD	f	P-value	L/D group vs L group	L/M group vs L group	L/D group vs L/M group	
Intraoperative surgical pain score (VAS values).	1–5 3.7 ±1.23	0-4 2.3 ±0.76	0-4 2.9.±0.95	9.89	<0.001	<0.001	<0.026	<0.03	
Total intraoperative fentanyl consumption (µg/patient).	50-100 75.5±10.7	50-75 53.8±8.76	50-75 63.7±11.03	22.63	<0.001	<0.001	<0.001	0.003	
Duration of tolerance to tourniquet pain (min.).	10-20 14.7±3.8	15-30 27.4±4.06	15-25 20.5±4.15	50.38	0.001	<0.001	<0.001	<0.001	

Data are expressed as Mean \pm Standard Deviation (SD).

n = Group number.

vs = versus.

L Group = Lidocaine (Control) group.

L/D Group=Lidocaine/Dexmedetomidine group.

L/M Group = Lidocaine/Midazolam group.

f = one way ANOVA test.

P < 0.05 = significant difference.

P< 0.001 = highly significant difference

Table 5: Offset of sensory and motor blocks after establishment of IVRA in the three studied groups.

	L Group (n=20)	L/D Group (n=20)	L/M Group (n=20)	ANOVA Test f P-value		Tukey's test			
	Mean±SD	Mean±SD	Mean±SD			L/Dgroup vs L group	L/M group vs L group	L/D group vs L/M group	
Sensory block recovery time (min.).	10.89±1.77	24.35±3.3 9	23.08±2.18	135.12 7	<0.001	<0.001	<0.001	0.167	
Motor block recovery time (min.).	13.35±2.39	32.8±2.29	26.42±3.4	264.50 4	<0.001	<0.001	<0.001	<0.001	

Data are expressed as Mean ± Standard Deviation (SD).

n = Group number.

vs = versus.

L Group = Lidocaine (Control) group.

L/D Group = Lidocaine/Dexmedetomidine group.

L/M Group = Lidocaine/Midazolam group.

P > 0.05 = nonsignificant difference.

P < 0.001 = Highly significant difference.

f = one way ANOVA test.

Table 6: The time to ask for the 1st post-operative analgesia and the consumed amount of diclofenac sodium to relief pain in
the 1st 24 hours postoperta-tively in the three studied groups.

	L Group (n=20)	L/D Group (n=20)	L/M Group (n=20)	ANOVA Test	Tukey's test			
	Mean±SD	Mean±SD	Mean±SD	f	P-value	L/D group vs L group	L/M group vs L group	L/D group vs L/M group
Time to ask for post operative analgesia (min).	52.5±18.7	127.8±22.6	97.5±24.7	58.572	<0.001	<0.001	<0.001	<0.001
The consumed amount of diclofenac sodium during the 1 st 24 hrs postoperativel y (mg/patients)	168.75±58.9 7	82.5 ± 23.08	116.25±38.28	20.700	<0.001	<0.001	<0.001	<0.001

Data are expressed as Mean \pm Standard Deviation (SD).

n = Group number. vs = versus.

L Group = Lidocaine (Control) group.

L/D Group = Lidocaine/Dexmedetomidine group.

L/M Group = Lidocaine/Midazolam group.

f = one way ANOVA test.

P < 0.001 = Highly significant difference.

Table 7: The incidences of the various associated side effects in the three studied groups.

	Grou	Groups								
	L Group (n= 20)		L/D Group (n= 20)		L/M Group (n= 20)		Chi-square test			
	N	%	N	%	N	%	X ²	P-value		
Haemodynamic changes:										
- Bradycardia	0	0	4	20	3	15	4.205	0.122		
- Hypotension	0	0	4	20	3	15	4.205	0.122		
Patient with sedation score more than 2 intra and postoperatively.	0	0	4	20	3	15	4.205	0.122		

Data are expressed as numbers (%).

n = Group number.

N = number of each associated side effect in each group.

L Group = Lidocaine (Control) group.

L /D Group = Lidocaine/Dexmedetomidine group.

L/M Group = Lidocaine/Midazolam group. P> 0.05 = non-significant difference.

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