

Exploring the Effect of Administering Three Different Doses of Dexmedetomidine as an Adjuvant to Lidocaine in Regional Intravenous Anesthesia for Patients

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ABSTRACT

Background: This study aimed to determine the effect of adding low doses of dexmedetomidine as an adjuvant to lidocaine in regional intravenous anesthesia in patients receiving surgery.

Methods: In the present clinical trial, 120 patients' candidates for upper extremity orthopedic surgery with regional venous anesthesia in 4 groups of 30 people distributed in groups respectively 0.6, 0.5 and 0.4 micrograms/kg of dexmedetomidine plus 0.5 lidocaine were injected and in the fourth group, an equal volume of normal saline was administrated. Patients were examined and compared before drug injection and 1, 5, 10, 15, 30, 45 and 60 minutes after drug injection in terms of time of onset and recovery of sensory and motor block, hemodynamic parameters, postoperative pain intensity and analgesic consumption.

Results: The average pain intensity during the research in the four dexmedetomidine groups was 0.6, 0.5, 0.4 and the control group, respectively, 2.12 ± 1.33 , 2.82 ± 0.76 , 2.26 ± 2.3 , and 4.4 ± 1.5 , and the difference between the groups was significant (>0.001). P). In the two-by-two analysis of the groups, the average pain intensity was significant between the two groups: dexmedetomidine 0.6 and control ($P<0.001$), dexmedetomidine 0.5 and control ($P=0.003$), and dexmedetomidine 0.4 and control ($P<0.001$).

Conclusion: Using a dose of 0.6 micrograms/kg of dexmethomidine along with lidocaine leads to a decrease in the severity of the postoperative period, a decrease in the need for painkillers, and also an increase in the time of postoperative pain relief in patients.

Introduction

Intravenous regional anesthesia (IVRA) introduced by Bier in 1908 is a method for administering anesthesia during hand and forearm surgeries (1). The IVRA method, also known as Bier's block, is a technique that involves the intravenous administration of a local anesthetic into an organ after the blood flow to the organ has been occluded by a tourniquet. The local anesthetic then diffuses from the vascular bed to non-vascular tissues, such as axons and nerve endings. This technique

is favored for its simplicity, efficiency in emergency and outpatient surgeries, regional anesthesia, and cost-effectiveness [2].

Potential complications of IVRA include local anesthetic toxicity, delayed onset of the anesthetic effect, inadequate muscle relaxation, discomfort due to the tourniquet, and the emergence of postoperative pain following the release of the tourniquet cuff [3]. Meanwhile, it has been discovered that group A nerve fibers and unmyelinated C fibers play a significant role in tourniquet-induced pain, because the ischemia resulting from tourniquet application increases the compression of peripheral nerves. Additionally, serotonin is released

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from the platelets of ischemic and damaged tissues, which can contribute to pain transmission through peripheral pain receptors, including 5HT₃ [4].

The optimal drug for IVRA should exhibit a rapid onset of action, require a low dose of local anesthetic, cause minimal tourniquet discomfort, and provide prolonged analgesia following the release of the tourniquet cuff [5]. Additionally, the drug should be a strong analgesic with a rapid action onset. Various additives, including opiates, non-steroidal anti-inflammatory drugs, dexmedetomidine, magnesium sulfate, neostigmine, ondansetron, and ketamine, have been combined with local anesthetics to mitigate these issues during intravenous local anesthesia, each with varying degrees of effectiveness [6-9].

Lidocaine is recognized as a crucial drug in regional anesthesia. It competes with calcium for receptor sites on the nerve membrane, thereby controlling the flow of sodium through the cell membrane and diminishing the depolarization phase of the action potential. These effects halt the initiation and propagation of nerve impulses by stabilizing the nerve cell membrane, which results from a decrease in the membrane permeability to sodium ions [10]. When a substantial quantity of lidocaine is absorbed, it can initially exert a stimulatory effect, followed by a depressant effect on the central nervous system (CNS). Presently, lidocaine is considered one of the most significant drugs in the realm of regional anesthesia [11].

Adjuvant medications are employed to mitigate complications following local anesthesia. Dexmedetomidine, an injectable drug, is utilized in certain procedures that necessitate injectable anesthesia, such as the intubation of patients hospitalized in the intensive care unit [12]. This drug is utilized in situations that demand a swift induction of anesthesia. However, it is important to note that dexmedetomidine alone does not produce a full anesthetic effect. Therefore, the co-administration of other medications may be necessary if a complete anesthetic effect is required [13]. Generally, dexmedetomidine is a selective alpha-2 receptor agonist. By interacting with these receptors in the CNS, it suppresses the release of norepinephrine via the G proteins. This results in the induction of analgesic and hypnotic effects dose-dependently [14].

Numerous studies have demonstrated the benefits of adding an adjuvant to the local anesthetic, as it can reduce procedural complications. Dexmedetomidine has been used as an adjuvant with lidocaine in some previous studies, but they have primarily involved single doses. More studies are required to better understand the efficacy of dexmedetomidine and to identify the most effective dose that minimizes side effects [15]. Therefore, we assessed the impact of incorporating low doses of dexmedetomidine as an adjuvant to lidocaine in IVRA for patients receiving surgical procedures.

Methods

The present double-blind randomized clinical trial with the approval from the Ethics Committee of Isfahan University of Medical Sciences (IR.MUI.MED.REC.1398.409), was carried out in 2022 at Al-Zahra Hospital in Isfahan, Iran. The study population consisted of patients who were candidates for surgery under IVRA.

The inclusion criteria were age range of 18-60 years; candidates for upper limb orthopedic surgery under IVRA using lidocaine; ASA class I or II; lack of conditions, such as Raynaud's disease, sickle cell anemia, and peripheral arterial disease; and willingness to provide consent to take part in the research. The exclusion criteria were the patient's death during surgery, any change in the surgical technique for any reason, and the occurrence of an allergic reaction to the administered drugs.

The sample size was determined using the sample size estimation formula for comparing means, considering a test power of 80% and a confidence level of 95%. Given a minimum significant difference of 0.8 between groups and a standard deviation of 1.17 for postoperative pain intensity, it was estimated that each group should consist of 30 individuals. For selecting the participants, the convenience non-probability sampling method was employed, and patients were randomly allocated to groups using the random allocation software.

The blinding method was implemented in such a way that both the patients and the data collector remained unaware of the specific drug being administered. The study procedure was as follows: After making the necessary preparations and upon the researcher's visit to the operating room, eligible patients for the study were identified. Following initial examinations and the acquisition of written consent to take part in the research, the patients were assigned to groups according to the aforementioned method and the output list of the software:

- Group 1: The control group received 40 mL of a 0.5% lidocaine solution.
- Group 2: This group received a solution of 0.4 µg/kg dexmedetomidine mixed with 0.5% lidocaine, with the total volume equating to 40 mL.
- Group 3: This group received a solution of 0.5 µg/kg dexmedetomidine mixed with 0.5% lidocaine, with the total volume equating to 40 mL.
- Group 4: This group received a solution of 0.6 µg/kg dexmedetomidine mixed with 0.5% lidocaine, with the total volume equating to 40 mL.

A 0.5% lidocaine solution was prepared by combining 30 mL of a 0.9% normal saline solution with 10 mL of a 2% lidocaine solution.

Initially, the patients' demographic information, medical records, and basic details were gathered through interviews and examinations and then recorded in each

patient's information form. Subsequently, the patients underwent orthopedic surgery under regional anesthesia. Throughout the study, all patients were monitored using pulse oximetry, and their systolic, arterial and diastolic blood pressure, blood oxygen saturation percentage, heart rate, and respiratory rate per minute were recorded. These parameters were measured before the start of anesthesia and at 1, 5, 10, 15, 30, 45, and 60 minutes thereafter.

Several parameters were measured and compared across the four groups, including the duration of the surgery, the duration of the block and anesthesia, the duration of the anesthesia effects, the onset and length of the motor block, the postoperative anesthesia amount, and the occurrence of tourniquet-induced pain (using the Visual Analog Scale [VAS]). These measurements were taken immediately after the removal of anesthesia and at intervals of 5, 10, 15, 30, 45, 60, 90, 120, and 150 minutes thereafter. Additionally, the frequency and initial time of painkiller administration were recorded for all patients.

Ultimately, the collected data were inputted into SPSS 26 for analysis. Statistical tests,

First, the descriptive results with qualitative variables with normal were performed with Chi-square. Quantitative variables with normal distribution were performed with Mean and standard deviation, one-way analysis of variance (ANOVA), and t-test. Quantitative variables with non-normal distribution were performed with Wilcoxon. were performed at a significance level of $P>0.05$.

Results

We examined 120 patients who were undergoing upper limb orthopedic surgeries. They were divided into four groups of 30 individuals each. The groups received either normal saline or dexmedetomidine at doses of 0.4, 0.5, or 0.6 $\mu\text{g/kg}$. Upon comparison, the four groups showed no significant differences in terms of demographic and basic variables (Table 1).

The average time for sensory block in the 0.6, 0.5, and 0.4 $\mu\text{g/kg}$ dexmedetomidine groups and the controls was 4.03 ± 0.89 , 4.05 ± 1.05 , 3.8 ± 1 , and 4.1 ± 1.09 minutes, respectively. The variations among these groups were not significant ($P=0.69$). Similarly, the average time for motor block in the four groups was 7.93 ± 1.01 , 7.87 ± 1.33 , 7.47 ± 1.20 , and 7.9 ± 1.06 minutes, respectively, with no significant variations detected among the groups ($P=0.37$).

The average recovery time from anesthesia in the dexmedetomidine groups (0.6, 0.5, and 0.4 $\mu\text{g/kg}$) and the controls was 51.5 ± 7.56 , 51.17 ± 8.68 , 50.77 ± 8.20 , and 49.77 ± 9.70 minutes, respectively. The variations among these groups were not significant ($P=0.88$). Similarly, the average duration of motor block recovery in the four groups was 65.67 ± 7.16 , 68 ± 7.08 , 66.87 ± 6.80 , and

67 ± 7.31 minutes, respectively, with no significant variations detected among the groups ($P=0.65$) (Table 2).

Figures 1-6 illustrate the changes in the patients' hemodynamic and respiratory variables from the time before the drug injection up to the 60th minute across the four groups. Intra-group analyses revealed significant changes in heart rate, diastolic, systolic, and mean arterial blood pressure, and respiratory rate throughout the study period in all four groups. However, inter-group analyses found no significant differences in these parameters among the four groups.

The assessment of patients' pain intensity at various intervals post-operation (1, 2, 4, 6, 8, 12, 16, 20, and 24 hours) revealed no significant differences among the three groups. Similarly, the fluctuations in pain intensity were not significantly different across the groups under study. (Table 3) presents the mean pain intensity at the specified times.

Throughout the study period, the average pain intensity in the dexmedetomidine groups (0.6, 0.5, and 0.4 $\mu\text{g/kg}$) and the controls was respectively 2.12 ± 1.33 , 2.82 ± 0.76 , 2.26 ± 2.3 , and 4.4 ± 1.5 . The variation between the groups was significant ($P=0.001$). In a pairwise comparison of the groups, the average pain intensity was significantly different between the control and 0.6 $\mu\text{g/kg}$ dexmedetomidine groups ($P=0.001$), between the 0.5 $\mu\text{g/kg}$ dexmedetomidine and control groups ($P=0.003$), and between the 0.4 $\mu\text{g/kg}$ dexmedetomidine and control groups ($P<0.001$). However, the dexmedetomidine groups showed no significant difference. Table 3 displays the mean pain intensity from the immediate recovery of regional anesthesia to the 150th minute for the four groups under study.

In a detailed analysis, the average pain intensity at all times exhibited significant differences among the four groups. The inter-group analysis revealed significant variations in pain intensity up to the 150th minute across all four groups. Specifically, the intensity escalated following the cessation of anesthesia and began to decline around the 30th minute. The intergroup analysis demonstrated a significant difference in the changes in pain intensity among the four groups ($P<0.001$). In a pairwise comparison, significant differences were observed in the changes in pain intensity between the 0.7 $\mu\text{g/kg}$ dexmedetomidine group and the control group ($P<0.001$), between the control and 0.5 $\mu\text{g/kg}$ dexmedetomidine groups ($P=0.012$), and between the control and 0.4 $\mu\text{g/kg}$ dexmedetomidine groups ($P=0.001$). Nonetheless, no significant variations were detected between the 0.6 and 0.5 $\mu\text{g/kg}$ dexmedetomidine groups ($P=0.51$), between the 0.6 and 0.4 $\mu\text{g/kg}$ dexmedetomidine groups ($P=0.99$), and between the 0.6 and 0.4 $\mu\text{g/kg}$ dexmedetomidine groups ($P=0.67$). Figure 7 illustrates the trend of changes in pain intensity up to the 150th minute among the four groups.

To manage postoperative pain, out of 120 patients studied, 52 (43.3%) received painkillers, including 9 patients (30%) from the 0.6 µg/kg dexmedetomidine group, 9 patients (30%) from the 0.5 µg/kg dexmedetomidine group, 11 patients (36.7%) from the 0.4 µg/kg dexmedetomidine group, and 23 patients (76.7%) from the control group. The frequency of painkiller usage significantly differed among the four groups ($P<0.001$). The average time to first painkiller administration in the 0.6, 0.5, and 0.4 µg/kg dexmedetomidine groups and the controls was 13.6 ± 12.5 , 12.3 ± 6.6 , 11.4 ± 5.1 , and 10.8 ± 2.2 minutes,

respectively, and the difference was significant ($P=0.025$). In a pairwise comparison, the average time to painkiller administration was significantly different between the 0.6 µg/kg dexmedetomidine group and the control group ($P=0.045$). Nonetheless, the other groups showed no significant difference.

Complications, including decreased hemoglobin oxygen saturation, hypotension, hypertension, tachycardia, and bradycardia, were observed during the study. However, the four study groups did not show statistically significant differences concerning these complications (Table 4).

Table 1- Comparison of variables and demographic characteristics of patients in the groups

Variables	Dexmedetomidine 0.6	Dexmedetomidine 0.5	Dexmedetomidine 0.4	Control	P value
Age Yrs.	39.14 ± 12.53	40.58 ± 15.80	40.10 ± 16.40	40.8 ± 12.53	0.560
Weight Kg	75.27 ± 1.73	71.05 ± 1.73	73 ± 1.43	72.15 ± 1.53	0.120
Height cm	169.05 ± 1.33	168.91 ± 1.11	170.41 ± 1.02	168.41 ± 1.02	0.540
Duration of surgery min	31.43 ± 5.41	31.2 ± 6.16	30.9 ± 6.63	5.89 ± 29.47	0.590
Gender n (%)	F 4(13.3) M 26(86.7)	F 5(16.7) M 25(83.3)	F 4(13.3) M 26(86.7)	F 4(13.3) M 26(86.7)	0.900
ASA I	23(76.7)	21(70.0)	22(73.3)	23(76.7)	0.930
ASA II	7(23.3)	9(30.0)	8(26.7)	7(23.3)	

Table 2- Time to initiation and duration of motor and sensory block in study groups.

Variables	Dexm0.6	Dexm0.5	Dexm0.4	Control	P value
Initiation Sensory block	4.0 ± 0.89	4.0 ± 1.05	3.8 ± 1.00	4.0 ± 0.89	0.691
Initiation Motor block	7.93 ± 1.01	7.87 ± 1.33	7.87 ± 1.33	7.9 ± 1.06	0.373
Duration Sensory block	3.8 ± 1.00	7.87 ± 1.33	50.77 ± 8.30	49.77 ± 9.70	0.882
Duration Motor block	65.97 ± 7.16	68.0 ± 7.08	7.47 ± 1.20	7.9 ± 1.06	0.655

Table3- Time to initiation and duration of motor and sensory block in study groups.

Recovery time from	Group	Group	Group	Group	P value*
regional anesthesia	Dexmedetomidine 0.6	Dexmedetomidine 0.5	Dexmedetomidine 0.4	Dexmedetomidine 0.4	
0 min	0	0.67 ± 0.44	0	1.60 ± 1.28	0.001
5 th min	0	0.4 ± 0.12	1.67 ± 0.53	3.10 ± 1.79	0.001
10 th min	2.30 ± 0.53	4.93 ± 1.20	2.47 ± 0.70	0.58 ± 2.25	0.001
15 th min	3.13 ± 2.64	4.60 ± 1.00	3.93 ± 0.77	6.20 ± 2.40	0.001
30 th min	3.90 ± 2.11	3.83 ± 0.39	4.40 ± 3.80	6.23 ± 2.42	0.001
45 th min	3.50 ± 0.98	3.17 ± 1.37	4.00 ± 3.44	6.07 ± 2.23	0.001
60 th min	2.97 ± 2.10	2.77 ± 1.41	2.93 ± 0.62	5.23 ± 2.57	0.001
90 th min	2.43 ± 1.77	2.56 ± 1.28	1.73 ± 0.55	4.83 ± 2.48	0.001
120 th min	1.83 ± 1.76	2.75 ± 1.36	1.37 ± 2.78	3.40 ± 2.21	0.003
150 th min	1.17 ± 1.51	2.76 ± 1.24	1.47 ± 2.78	2.60 ± 2.13	0.004
P value**	0.001	0.001	0.001	0.81	

Table 4- distribution of complications in study groups

Variables	Tachycardia	Bradycardia	Hypotension	Hypertension	Desaturation
Dexmedetomidine0.6	3	2	3	2	3
Dexmedetomidine0.5	4	1	2	6	2
Dexmedetomidine0.4	3	1	4	4	4

Control	8	0	1	6	1
P value	0.33	0.56	0.33	0.24	0.36

Discussion

Management of postoperative pain, particularly following upper limb orthopedic surgeries, remains a significant challenge for anesthesiologists. Numerous pharmacological and non-pharmacological approaches have been devised to manage and mitigate this pain. Yet, a universally agreed-upon ideal method remains elusive. The use of dexmedetomidine to control side effects, particularly postoperative pain, has attracted significant attention from anesthesiology specialists and researchers in recent years. Dexmedetomidine, a medication that has been recently introduced to the Iranian pharmaceutical market, is currently being examined for its positive and negative effects when administered in various doses and using different methods. Consequently, this study was conducted to investigate the effects of adding different doses of dexmedetomidine as an adjuvant to lidocaine in IVRA.

In our study, an examination of the patients' demographic characteristics revealed no significant differences among the four groups in terms of age, gender distribution, ASA class, body mass index, and operation duration. No confounding effects of these factors were observed on the hemodynamic parameters and other research variables. Therefore, the differences observed among the groups were most likely attributable to the varying doses of dexmedetomidine used.

The average duration of sensory and motor block, as well as the recovery time for both, did not significantly differ among the groups. In a 2013 study by Marhofer et al., three groups of 36 patients undergoing ulnar nerve block received injections of 3 mL of 75% ropivacaine, 3 mL of 75% ropivacaine plus 20 µg/kg of dexmedetomidine, and 3 mL of 75% ropivacaine plus 20 µg/kg of systemic dexmedetomidine, respectively. The sensory and motor scores were then compared across the three groups. According to the findings of this study, while the duration of sensory onset did not vary among the groups, the duration of motor onset was significantly shorter in the group that received the injection of ropivacaine plus dexmedetomidine [12].

The examination of hemodynamic parameters during surgery and recovery revealed no significant differences among the four groups. This suggests that dexmedetomidine doses of 0.6, 0.5, and 0.4 µg/kg are safe and associated with few complications in regional anesthesia. In a study conducted by Fritsch et al., 62 patients underwent shoulder joint surgery under general anesthesia. The patients were divided into two groups: one received 12 mL of 5% ropivacaine, and the other received 12 mL of 5% ropivacaine plus 150 µg of

dexmedetomidine. The results indicated that the average duration of the sensory block was longer in the group that received the ropivacaine-dexmedetomidine combination. However, no significant differences were found in the hemodynamic parameters during surgery and recovery between the two groups [16].

An examination of the patients' pain intensity up to 15 minutes post-operation revealed a significant difference among the four groups, and the trend of pain intensity changes varied significantly across these groups. In a study conducted by Jarineshin et al., the effect of adding dexmedetomidine to bupivacaine on the quality of iliac fascia compartment block under ultrasound guidance was investigated in adults undergoing femoral fracture surgery. The pain intensity at 1, 2, 6, and 24 hours post-operation was lower in the dexmedetomidine group compared to the control group. Furthermore, the consumption of painkillers at 6 and 24 hours post-operation was lower in the dexmedetomidine group. These findings align with the results of our study.

The initial administration of painkillers was delayed in the 0.6 µg/kg dexmedetomidine group compared to the other groups. While the 0.5 and 0.4 µg/kg dexmedetomidine groups received painkillers earlier than the control group, the difference was only significant between the 0.6 µg/kg dexmedetomidine group and the control group. In the study conducted by Jarineshin et al., a significant difference was observed in pain intensity between the dexmedetomidine and control groups. However, the timing of painkiller administration did not significantly differ between these two groups [17].

In a study conducted by Farouk et al., it was found that the addition of a 5HT3 antagonist to lidocaine for IVRA significantly enhanced the quality of anesthesia. This combination not only shortened the onset time but also extended the duration of sensory and motor block. Furthermore, it reduced tourniquet pain and alleviated pain during and after surgery [18]. In another study conducted by Gupta et al., it was found that dexmedetomidine, when added to lidocaine, had a more beneficial impact in reducing postoperative pain over a 24-hour period compared to midazolam [19].

Conclusion

In conclusion, our findings suggest that a 0.6 µg/kg dose of dexmedetomidine could reduce postoperative pain, shorten the time to sedation, and decrease the need for painkillers. Importantly, it had no adverse impact on hemodynamic parameters, sensory and motor block duration, or recovery time. However, our study had certain limitations, such as a small sample size and a brief patient follow-up period. Therefore, we recommend

further research in this area. Overall, the use of 0.6 µg/kg of dexmedetomidine, as an adjuvant to lidocaine in IVRA injections, appears to reduce postoperative pain severity, decrease the requirement for painkillers, and extend the duration of postoperative analgesia in patients.

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