Original Article

Epidural Anesthesia with Lidocaine and Dexmedetomidine, Versus Lidocaine Alone on Plasma Levels of IL-6 in Patients with Proximal Femoral Fracture

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Abstract

Background: Interleukin-6 (IL-6) plays an important role in inflammatory. Epidural anesthesia is an appropriate method for controlling pain in lower limb surgeries. The aim of this study was to evaluate the effect of Dexmedetomidine and Lidocaine in the epidural injection by measuring IL-6 plasma levels.

Materials and Methods*:* Fifty-two patients with lower limb fractures in two groups receiving Dexmedetomidine doses and controls for the quality of epidural anesthesia and IL-6 index. After explaining the design and obtaining informed written consent, patients were randomly divided into two groups. After 4–6 minutes of administering the test dose, patients in group RC received 5 ml of 1.5% Lidocaine solution via epidural catheter. Patients in group RD were administered 15 ml solution of 1.5% ropivacaine and 0.6 µg/kg of Dexmedetomidine. The levels of IL-6 were evaluated before surgery and 6 hours after surgery.

Results: The two groups did not show ~~a~~ significant difference in age and level of interleukin prior to the operation. There was a significant difference in the second injection time and total drug volume between the control and intervention groups. Dexmedetomidine reduced the volume of total drug needed and increased the time interval from the first injection to the second one ($p < 0.001$).There was also lower levels of interleukin 6 in the Dexmedetomidine group at the 6th hour-after the operation.

Conclusion: Dexmedetomidine does not only reduce the need for patients on the amount and frequency of analgesic drugs, but also reduces stress and cellular damage.

Keywords: Interleukin-6, Dexmedetomidine, Lidocaine, Anesthesia

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Introduction

The increasing use of topical anesthetic, major and minor neural blocks has led to the selective use of general anesthesia. This is because avoiding general anesthesia risks, better postoperative pain control, and some other factors in long-term surgery and long-term postoperative pain control, local anesthetic drugs with a long-lasting effect are common. Meanwhile, auxiliary drugs are also used to maximize the length of the base drug (1).

Considering the history of local anesthesia and

many studies in this field, today, the tendency of anesthesiologists to perform local block has increased and this may reduce the need for general anesthesia (1). This method is used to carry out surgical procedures or control postoperative pain in order to remove pain and to create anesthesia (2), creating favorable conditions during surgery and faster postoperative patient mobility, and decreasing the risks of general anesthesia and hospital costs (3).

Lidocaine reduces inflammatory processes. The substance acts by lowers the release of cytokines from epithelial cells and neutrophils and reducing the production of cytokines caused by damage to endothelial cells (4). These cytokines are of the pro-inflammatory type (5).

Dexmedetomidine is an α-agonist (11). Some studies have shown that the use of this drug (due to its low toxicity) can reduce cell death. (6). This drug lowers the concentration of tumor necrosis alpha (TNF-α) (7,8). On the other hand, in various studies on apoptosis of the epithelial cells of the intestine, it has reduced the inflammatory response and accelerated the intestinal improvement after trauma (9,10). In several studies, the positive effect of intravenous Dexmedetomidine on the control of inflammatory responses and the reduction of levels of inflammatory mediators such as IL-6 has been confirmed (12-15).

The purpose of this study was to learn whether the use of this drug as an adjuvant in epidural injection has meaningful effects. Confirmation of this positive effect can provide a low cost and easy method to reduce the complications of inflammatory response after lower limb surgery.

Methods

In this study, all patients were referred to Taleghani Hospital (affiliated to Shahid Beheshti University of Medical Sciences, Tehran, Iran) in 2017, who suffered from lower limb fractures and who needed surgery were evaluated. The inclusion criteria were: 18-75 years old, lower limb fractures, ASA Class I & II, and no history of allergy. However, the following patients were not included in the study: absolute contraindication for using local anesthetics, and the presence of these comorbidities: diabetes mellitus, myocardial infarction, major cardiovascular events, cerebrovascular accidents, hypertension, malignancy, renal failure, liver dysfunction and coagulation disorders.

After explaining the design and obtaining informed written consent, patients were randomly divided into two groups. Patients were administered epidural block with 18-gauge Tuohy needle and catheter was secured 3–4 cm into epidural space and a test dose of 3 ml of 2% Lidocaine solution containing adrenaline 1:200,000 was injected. After 4–6 minutes of administering the test dose, patients in group RC received 5 ml of 1.5% Lidocaine solution. Patients in group RD were administered 15 ml solution of 1.5% ropivacaine and 0.6 μg/kg of Dexmedetomidine. The bilateral pin-prick method was used to evaluate and check the sensory level while a modified Bromage scale (0 = no block, 1 = inability to raise extended leg, 2 = inability to flex knee and 3 = inability to flex ankle and foot) was used to measure the motor blockade effect at 5, 10, 15, 20, 25 and 30 minutes intervals after the epidural administration of the drugs.

The second dose was injected every 45-60 minutes based on need (VAS> 3; Visual Analog Scale: VAS), then 8 mL of 1.5%, Lidocaine and the final dose of the received drug was recorded at the end of the operation. Blood samples were taken from all patients before entering the operating room to determine the level of the interleukin-6. During surgery, the onset of anesthesia, time to second injection, duration of operation and volume of blood loss, the volume of intake and output, and the amount of injected drug by the epidural catheter were recorded. In order to control the pain in all patients, intravenous morphine infusion pump was given at a dose of 3 to 5 mg/hr. Additional drug doses were prescribed if necessary to maintain VAS <3 in the first 24 hours. Blood samples were taken at 6 hours after surgery to measure the level of interleukin-6 in all patients.

IL-6 detection method

5 cc blood samples were taken from the patient and placed in a simple test tube. After blood clotting at room temperature (15-30 minutes), it was centrifuged (3000 to 3500) at room temperature for 15 minutes. The yielding plasma was poured into the microtube and stored in -70˚C. Collected samples evaluated by Bio-Science ELISA Kits.

The obtained data was collected and using descriptive statistics, the results of IL-6 were reported according to the variables in question. In addition, to compare the IL-6 level among the patients in both groups, independent t-test was used.

Results

Table 1: Descriptive statistics of variables

	N	Minimum	Maximum	Mean	Std. Deviation
Age (years)	52	24.00	75.00	53.4038	15.8439
Onset time (min)	52	10.00	22.00	15.8846	3.12268
Second injection(min)	51	35.00	165.00	60.7647	21.71690
LA Final Vol (ml)	52	20.00	65.00	42.0385	9.48469
Received fluid (L)	52	1.50	28.00	3.0808	3.55500
Blooding volume (ml)	52	50.00	600.00	257.3077	122.60434
Urine volume (ml)	52	50.00	1000.00	595.1923	173.56120
Base Serum IL (pg/ml)	52	0.20	23.50	4.1892	5.70042
Six hours IL_6 (pg/ml)	52	1.1	120	20.07	19.93
Surgery time (min)	52	75.00	300.00	177.2115	43.81796
Valid Number of cases	51				

In this study, 52 patients, 19 women (36.5%) and 33 men (63.5%), were divided into two groups of 26 patients. The mean age of the patients was 15.8±53.4 years (Table 1).

Based on the results, the mean of the second injection requirement (51 out of 52) was 60.7 ± 21.7. Duration of surgery was same between the two groups. Also no significant difference in volume of received fluid during surgery and the level of baseline interleukin was seen. On the other hand, based on independent t-test, there was a significant difference between the two groups regarding the bleeding and urine volumes ($p < 0.05$) (Table 2).According to the U Mann Whitney test, the second injection and drug levels were significantly different between the control and intervention groups. Dexmedetomidine reduced the need for a second injection ($p < 0.001$) (Table 3).

There was a significant difference between the two groups in terms of IL-6 after 6 hours of operation, and this was lower in the Dexmedetomidine group (Table 4).

Discussion

Today, use of regional anesthesia is superior to general anesthesia in many procedures, because it has fewer side effects and makes it easier for the patient to have mobility and daily activities. In recent years, however, stress and cellular damage have become a problem that attracts the attention of experts and researchers and has attracted efforts to reduce it. This study also considers the importance of the present method using two different drugs.

Lidocaine and relevant drugs, which are used primarily as positional anesthetics and antiarrhythmic factors. Lidocaine exerts immunoregulatory effects on a variety of cell types. For example, lidocaine-related local anesthetics were shown to inhibit lymphocyte maturation and proliferation, the migration of macrophages into tissues (16), the expression of CD11b/CD18 by polymorphonuclear cells (19), the adhesion of leucocytes to injured venules (17–19) and the LPS-stimulated secretion of LTB4 and IL-1a from peripheral blood mononuclear cells (20). Moreover, the anti-inflammatory effects of lidocaine were shown by in vivo studies as well. Taniguchi *et al.*, have shown that lidocaine treatment of rabbits injected with endotoxin reduced the serum concentrations of IL-8 and IL-6 (21).

Previous studies have shown DEX has a low cytotoxic effect, which in some studies reduces cell death (6). On the other hand, this drug lowers the concentration of tumor necrosis alpha (TNF-α) (7,8). In various studies on apoptosis of the epithelial cells of the intestine, it reduces the inflammatory response and accelerates the intestinal improvement after trauma (9,10). In several studies, the positive effect of intravenous Dexmedetomidine on the control of inflammatory responses and the decrease, of levels of inflammatory mediators such as IL-6 has been confirmed (12-15).

Accordingly, based on these results, dexmedetomidine not only reduces the amount and frequency of analgesic drug administration, but also reduces stress and cellular damage. So, dexmedetomidine is suggested as a good option for

similar surgeries. Of course, further studies are needed in order to evaluate the best application and other effects of the drugs used in this study can lead to better anesthesia plans.

Conclusion

Not only does dexmedetomidine reduce the need for patients on the amount and frequency of analgesic drugs, but also it lowers stress and cellular damage.

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Conflicts of Interest

The authors declare that they have no conflict of interest.

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Table 2- Based on independent t-test, among the variables studied in this study, the mean volume of bleeding and volume of urine show a significant difference between the control and intervention groups.

		Leven's Test for Equality of Variances		t-test for Equality of Means						
		F	Sig.	t	d.f	Sig.(2-tailed)	Mean Difference	Std. Error Difference	95% Confidence interval of the Difference	
									Lower	Upper
Blooding volume	**Equal variances assumed**	0.205	0.653	3.315	50	0.02	103.07692	31.09539	40.62000	165.53385
	Equal variances not assumed			3.315	49.843	0.02	103.07692	31.09539	40.61514	165.53871
Urine volume	**Equal variances assumed**	2.370	0.130	2.472	50	0.017	113.46154	45.89188	21.28498	205.63810
	Equal variances not assumed			2.472	46.173	0.017	113.46154	45.89188	21.09528	205.82779
Surgery time	**Equal variances assumed**	1.405	0.241	0.424	50	0.674	5.19231	12.25186	-19.41627	29.80089
	Equal variances not assumed			0.424	46.215	0.674	5.19231	12.25186	-19.46630	29.85092

Table 3- According to the U Mann Whitney test, the second injection and drug levels had a significant difference between the control and intervention groups

	Group	N	Mean Rank	Sum of Ranks
Drug rate	Normal saline	26	14.00	364.00
	Dexmedetomidine	26	39.00	1014.00
	Total	52		
Second injection	Normal saline	26	18.58	483.00
	Dexmedetomidine	25	33.72	843.00
	Total	51		
Received fluid	Normal saline	26	27.71	720.50
	Dexmedetomidine	26	25.29	657.50
	Total	52		
Base serum IL-6 level	Normal saline	26	26.15	680.00
	Dexmedetomidine	26	26.85	698.00
	Total	52		

Table 4: The mean level of interleukin six hours after surgery, which was the main presumption in this study, is also p <0.05, which shows a significant difference between the two groups.

	Group	N	Mean	Std. Deviation	Std. Error Mean
Six hours IL-6 level	**Normal saline**	27	26.6333	24.44054	4.70358
	Dexmedetomidine	25	12.9800	9.81411	1.96282