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RESEARCH ARTICLE

Effect of Dexmedetomidine on Postoperative Pain in Knee Arthroscopic Surgery; a Randomized Controlled Clinical Trial

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Abstract

Background: Various drugs are administered intra-articularly to provide postoperative analgesia after arthroscopic knee surgery. The purpose of this study was to assess the analgesic effects of intra-articular injection of a dexmedetomidine following knee arthroscopy.

Methods: Forty six patients scheduled for arthroscopic knee surgery under general anaesthesia, were randomly devided into two groups. Intervention group received 1μg/kg dexmedetomidine (D) and isotonic saline. Control group received 25ml isotonic saline (P). Analgesic effects were evaluated by measuring pain intensity (VAS scores) and duration of analgesia.

Results: There was no significant difference between the two groups in terms of age, sex and weight. The mean of post-operation pain severity in 1, 3, 6,12, and 24 h was significantly lower in the intervention group (D) in comparison with the control group (P). the mean of the total dose of tramadol consumption was significantly lower in the intervention group in comparison with the control group (P<0.001).

Conclusions: Intra-articular injection of dexmedetomidine at the end of arthroscopic knee surgery, alleviates the patients' pain, reducing the postoperative need for narcotics as analgesics, and increase the first analgesic request after operation.

Key words: Analgesia, Dexmedetomidine, Intra-articular, Knee surgery, Postoperative pain

Introduction

Arthroscopic surgery is one of the most common orthopedic surgeries that usually do not require patients to be hospitalized before or after surgery. However, these surgeries can evoke different levels of pain, which at times can be unbearable (1-3). Therefore, various strategies have been used for analgesia after performing arthroscopic surgeries such as the administration of systemic drugs such as NSAIDS, central and peripheral nerve blocks, and intra-articular administration of different drugs (4, 5). Intra-articular injection of different drugs causes good analgesia during the postoperative period (2).

In previous studies, local anesthetics such as lidocaine and bupivacaine, opioids like morphine and fentanyl, and α2-agonists such as clonidine and even magnesium sulfate have been tested for intra-articular use, alone or in combination (6-11).

Dexmedetomidine is a highly selective α2-adrenergic receptor agonist, which in case of intravenous injection has sedative, anxiolytic, analgesic, anti-hypertensive and sympatholytic properties (12). This medication binds to α2-receptor, eight times greater than clonidine (5). Previous studies have shown the analgesic effect of systemic dexmedetomidine in arthroscopic surgeries; though this method of drug administration has been associated with negative hemodynamic effects on patients (13, 14). In this study, the postoperative analgesic effect of intra-articular dexmedetomidine alone was evaluated in knee arthroscopy.

Materials and Methods

This study was a double-blind randomized controlled trial. The ethics committee of the Mashhad University of Medical Sciences approved the study and written consents were obtained from the patients.

Inclusion criteria were as follows:

- Patient's consent to participate in the study
- Candidate for knee arthroscopic meniscectomy
- Patient with ASA class I and II

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Table 1. Demographic characteristics of patients (data are indicated as mean or standard deviation)

	SD	Intervention group (D) (n=21)	SD	Control group (P) (n=23)	*P* value
Age (years)	10.4	30.8 (20-60)	9.3	29.43 (16-45)	0.64
weight (Kg)	9.9	75.04	12	73.52	0.65
sex (M/F)	-	15/6	-	17/6	0.85

Patients were excluded from the study if they met the following criteria:

Renal insufficiency, liver dysfunction, ischemic or valvular heart diseases (evaluated by examining the patient's history and physical status, and performing an ECG and echocardiography), hypertension, opioid use, NSAIDs or any narcotics 24 h before surgery, history of infection or malignancy, history of coagulation disorders, surgery taking more than one and a half hours, over manipulation of the knee (patients who required any type of procedure except knee arthroscopic meniscectomy), drug allergy, cases which required drain insertion, and if the injection of opioids were repeated during the surgery.

The sample size was calculated based on the study by Paul *et al*, in terms of type I error (or α=0.05). Also, to have 90% power for comparing the mean of groups at different times, we had the maximum sample size of 20 patients in each group (2).

In total, 46 patients (age range: 18-60), who met the inclusion criteria were randomly divided into two groups: the experimental (D), which received intra-articular dexmedetomidine (23 patients); and the control group (P), which received the same volume of intra-articular normal saline (23 patients). During the follow-up, it was revealed that two patients from the intervention group were addicted to drugs and therefore were excluded from the study.

The block randomization method (with a block size of four) was used, and a person unaware of the study objectives sealed the obtained codes in secure envelopes and then the envelopes were given to one of the researchers who had no role in the treatment or evaluation. Afterwards, the researcher provided a syringe containing the solution based on the confidential codes and gave it to the physician to inject. In the preoperative visit, the visual analogue scale (VAS) with a 10 cm length was fully explained to the patient; based on this scale, zero indicates "lack of pain", and ten signifies "unbearable pain".

The night before the surgery, all the patients received oral Alprazolam 0.5 mg as premedication, and were NPO 8 h before surgery.

Initially in the operating room, the patients underwent standard monitoring (e.g., noninvasive blood pressure amplifier (NIBP), SPO2, ECG, and heart rate (HR), and then general anesthesia was performed on all patients, following the same procedure:

10 cc/Kg Ringer's serum was given to all of the patients within 15 min, and midazolam 40 µg/kg was administered after three minutes of pre-oxygenation. Afterwards, fentanyl 2 µg/kg, thiopental sodium 5 mg/kg, and atracurium 0.6 mg/kg were injected, and then the intubation was performed.

General anesthesia was maintained by administering 40%/60% N2O/O2 and propofol 100-150 µg/kg/min. End-tidal CO2 (ETCO2) was kept between 35-40 mmHg during the operation. Additional narcotics were not injected while the patients were under general anesthesia. At the end of the operation, neostigmine 0.04 mg/kg plus atropine 0.02 mg/kg were used to remove the effect of relaxants. At the end of the surgery and before opening the tourniquet, a syringe containing 25 cc of solution was injected into the patient's knee joint by a surgeon who was unaware of the medication type used.

A group of patients received intra-articular dexmedetomidine 1 µg/kg (group D), in order to provide 25 cc of solution, normal saline was added. The control group (group P) received 25 cc of intra-articular normal saline.

The severity of postoperative pain at 1, 3, 6, 12, and 24 h was evaluated according to VAS, on a scale from 0 to 10; the evaluation was conducted by an anesthesiology resident who was unaware of which drug was injected into the patient (the patient was also unaware of the injected drug).

If the VAS score was greater than 4, tramadol 50 mg was injected intravenously, and this injection was repeated every 8 h as needed. Time of the first dose of analgesic administration was recorded for each patient, within the first 24 h after surgery.

Patients were evaluated and controlled during the repeated visits by the researchers, dexmedetomidine complications are hypotension, pruritus, bradycardia, nausea, vomiting and sedation.

Statistical analysis

Number, percentage, mean and standard deviation were used for data description. To compare the data in the two groups, the t-test and Mann-Whitney test were used for the normal and non-normal (and ranked) distribution of the data, respectively. We used SPSS software version 11.5 (SPSS Inc., Chicago, IL) for data analysis and a *P*-value less than 0.05 was considered as statistically significant.

Results

The groups were compared in terms of age, sex and weight. There was no significant difference in terms of these characteristics (Table 1).

The mean of post-operation pain severity in 1, 3, 6, 12, and 24 h was significantly lower in the intervention group (D) in comparison with the control group (P)

Table 2. Postoperative pain severity based on VAS (mean and standard deviation)

Time of follow up	Intervention group (D)			Control group (P)			*P* value
	SD	Range	Mean	SD	Range	Mean	
1 h	1.5	0-5	1.76	1.5	0-8	4.13	*P*<0.001
3 h	1.4	0-5	1.90	1.8	2-8	3.96	*P*<0.001
6 h	1.3	0-4	1.76	1.9	0-8	3.43	*P*=0.004
12 h	1.2	0-4	1.38	1.4	0-5	2.78	*P*=0.002
24 h	1.0	0-3	1.00	1.6	0-6	2.61	*P*<0.001

Table 3. Frequency of need or lack of need for postoperative analgesia

	Intervention group (D)		Control group (P)	
	Percent	Number	Percent	Number
Lack of need for postoperative analgesia	90.5	19	30.4*	7
Need for postoperative analgesia	9.5	2	69.6*	16

*P<0.001

(Table 2).

In the control group, 16 of 23 patients (69.6%) needed narcotics for postoperative analgesia; however, for the intervention group, it was only 2 of 21 (9.5%) and the difference between the groups was statistically significant (P<0.001) (Table 3).

The mean duration of analgesic effect in the patients and the total dose of tramadol consumption in the two groups are shown in Tables 4 and 5; the mean of the total dose of tramadol consumption was significantly lower in the intervention group in comparison with the control group (P<0.001).

During the first 24 h after surgery, no side effects such as nausea, vomiting, pruritus, hypotension, and reduced heart rate were observed.

Discussion

The main findings of this study show that the intra-articular injection of dexmedetomidine 1 µg/kg alone, at the end of knee arthroscopic meniscectomy, alleviates patients' pain; also intra-articular injection of this drug reduces the postoperative need for narcotics such as analgesia and increases the duration of analgesic effect.

Karaaslan *et al* evaluated the systemic analgesic effect of dexmedetomidine after arthroscopic knee surgery and concluded that buccal dexmedetomidine is more effective than the intramuscular injection of dexmedetomidine in terms of pain reduction (13).

Gomez *et al* reported that despite the moderate postoperative analgesic effect, the intravenous injection of dexmedetomidine before epidural anesthesia was

Table 4. Duration (hours) of analgesic effect in patients

Duration (h) of analgesic effect	Intervention group (D)		Control group (P)	
	SD	Mean	SD	Mean
	6.3	21.97*	10.1	9.26*

*P <0.001

Table 5. Total Dose of tramadol consumption in the first 24 h after the operation

Total dose of tramadol consumption (mg)	Intervention group (D)		Control group (P)	
	SD	Mean	SD	Mean
	15.0	4.76*	38.3	47.82*

*P <0.001

associated with hemodynamic effects, especially hypotension and bradycardia (14).

The analgesic effect of α2-agonists is produced through supraspinal, spinal and peripheral routes (15). The analgesic effect of intra-articular dexmedetomidine is mainly due to the direct local effect, although the central analgesic effect of the drug through systemic absorption cannot be denied (5). The analgesic mechanism of intra-articular dexmedetomidine is probably similar to the analgesic effect of intra-articular clonidine. The analgesic effect of clonidine is mainly in inhibiting the transmission of painful stimuli in the posterior horn of the spinal cord (9, 16).

Similar to clonidine, dexmedetomidine probably produces peripheral analgesic effects by inhibiting the transmission of nerve signals through the Aδ and C-fibers, and stimulating the release of enkephalin-like substances in the peripheral regions (17, 18). Analgesic effects of clonidine are due to their combination with the analgesic route of opioids (19).

It should be noted that intra-articular clonidine reduced pain-related behaviors in animal studies (20, 21).

The level of pain after arthroscopic surgery can vary considerably. The reasons for the pain can be the stimulation of free nerve endings in synovial tissue, anterior adipose tissue, and articular capsule, due to a surgical incision (22).

The study by Breu et al. showed that bupivacaine, ropivacaine and mepivacaine have toxic effects on the cartilage tissue, which are associated with the time, concentration and method of drug administration (23).

In this study, intra-articular dexmedetomidine alone as an analgesia was compared with a placebo after arthroscopic knee surgery. The duration of postoperative analgesia in the dexmedetomidine and control groups was 21.97 ± 6.3 h (1318 ± 378 m), and 9.26 ± 10.1 h (555 ± 606 m), respectively. The obtained results are statistically significant (P<0.001).

The mean total dose of tramadol consumption during the first 24 h was 4.76 mg in the intervention group and 47.82 mg in the control group and the difference is statistically significant (P<0.001).

The intra-articular administration of dexmedetomidine alone after knee arthroscopic meniscectomy can reduce postoperative pain and can be effective in reducing postoperative analgesic consumption.

Given the good analgesic effect of intra-articular dexmedetomidine 1 μg/kg alone in knee arthroscopic meniscectomy, this drug can reduce postoperative pain in extensive arthroscopic knee surgeries such as ACL reconstruction and meniscus surgery.

To date, only a limited number of studies have evaluated the analgesic effects of intra-articular dexmedetomidine alone in knee arthroscopic meniscectomy.

One limitation of our study was that we excluded those patients who required other procedures except knee arthroscopic meniscectomy.

It is highly recommended that the effects of dexmedetomidine alone be compared with other medications such as opioids. Also, further research should be conducted on the effects of different doses of dexmedetomidine to determine the appropriate dose of analgesia.

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