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Research Article

Effect of adding dexmedetomidine to intra-articular levobupivacaine on postoperative pain following arthroscopic meniscus surgery: A prospective, double-blind, randomized, placebo- controlled, clinical trial

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ABSTRACT

Objective: The aim of this study was to determine the effect of adding dexmedetomidine to intra-articular levobupivacaine on postoperative pain levels and analgesic requirements following arthroscopic meniscectomy.

Methods: A total of 60 American Society of Anesthesiologist physical status I-II patients, aged 20 to 62 years, and scheduled for arthroscopic partial meniscectomy under general anesthesia were included in this study. All the patients were randomly assigned to one of four groups (15 patients in each group): Group 1 (8 male, 7 female; mean age = 46.70 ± 13.13 years; 0.9% isotonic 20 ml), group 2 (7 male, 8 female; mean age = 42.60 ± 12.18 years; levobupivacaine 0.5 mg/kg plus 0.9% isotonic), group 3 (8 male, 7 female; mean age = 43.80 ± 12.63 years; 1μg/kg dexmedetomidine plus 0.9% isotonic), and group 4 (7 female, 8 male; mean age = 40.40 ± 11.79 years; levobupivacaine 0.5 mg/kg plus 1μg/kg dexmedetomidine and 0.9% isotonic). All medications were administered at the end of arthroscopic surgery. Pain levels were measured using a Visual Analogous Scale (VAS) and Verbal Rating Scale (VRS) at postoperative 1, 2, 4, 6, 12, and 24 hours.

Results: VAS scores at rest were significantly lower in Group 4 at postoperative 1th, 2nd, 4th, 6th,12th, and 24th hours than in other groups. The time to take the first analgesic was significantly higher in Group4 (964 ± 288 min), and total analgesic consumption was significantly lower in Group 4 compared to those of other groups.

Conclusion: Although administration of intra-articular dexmedetomidine alone may have a weaker effect than intra-articular levobupivacaine on postoperative pain relief after arthroscopic partial meniscectomy, adding dexmedetomidine to intra-articular levobupivacaine may increase the durationand quality of postoperative analgesia without any side effect.

Level of Evidence: Level I, Therapeutic Study

Introduction

Arthroscopic knee meniscectomy surgery is a minimally invasive orthopedic procedure that is used to diagnose and treat problems in joints. It shortens the duration of the healing process and increases the success rate of surgery because it causes less damage to connective tissue. However, unsuccessful management of postoperative pain after arthroscopic knee meniscectomy surgery is an important obstacle for early discharge and rehabilitation.[1] Intra-articular drug administration can be a therapeutic approach for the management of postoperative pain without any systemic side effects after arthroscopic knee meniscectomy surgery.[2] To reduce pain after arthroscopy, several different intra-articular drugs were used.[3-5] The optimal combination of the various components of analgesics and local anesthetics was not well established.[6] Lidocaine, prilocaine, bupivacaine, and levobupivacaine were all administered intra-articularly to provide postoperative analgesia.[7-10] In clinical practice, bupivacaine is often preferred because of its longer duration of effect intra-articularly for maintaining intraoperative local anesthesia and postoperative analgesia.[9] Levobupivacaine is the levoisomer of bupivacaine with a similar effect profile and also has a lower cardiac toxicity than conventional racemate bupivacaine, and therefore, it has a higher safety margin.[11] Dexmedetomidine is approximately 8 times more selective than clonidine toward α-2 adrenoceptors. Because of its sedative, analgesic, and sympatholytic effects with reduced anesthetic requirement, there is an increased interest in this drug.[12]

The main objective of this study was to assess the effect of intra-articular levobupivacaine, dexmedetomidine, or levobupivacaine plus dexmedetomidine on the postoperative pain management and analgesic requirements after arthroscopic knee meniscectomy surgeries.

Materials and Methods

After obtaining the approval of the local ethics committee, 60 patients of American Society of Anesthesiologists (ASA) physical status I and II, with age ranging from 20 to 62 years, who were scheduled for elective knee partial meniscectomy surgeries, were included in this study randomly. The patients with

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Anterior Cruciate Ligament (ACL) or other concommittant procedures together with meniscectomy and the patients with intra-articular cartilage problems were excluded. The written consent of the participants was obtained. Before surgery, the patients were instructed on the use of the Visual Analog Scale (VAS) for pain assessment. Patients with a history of sensitivity to local anesthetics and receiving analgesics preoperatively were excluded from the study. Surgical operations were operational knee meniscectomy arthroscopies not requiring intra-articular drainage postoperatively. Forty-two of 60 patients had partial meniscectomy through their medial meniscus.

The patients in the research were not premedicated. In all patients, propofol (2.5 mg/kg Intravenous (IV)) and fentanyl (1μg/kg IV) were used in anesthesia induction. After IV injection of rocuronium (0.5 mg/kg), endotracheal intubation was facilitated, and anesthesia was sustained with 1.5%-2% sevoflurane and 50% nitrous oxide in oxygen. After the initial dose of fentanyl, no other analgesic was given during the surgery. The same surgeon performed all meniscectomies under tourniquet application. Patients were divided into four groups of 15 patients in each group. Randomization was based on a computer-generated code that was prepared at a remote site and sealed in opaque, sequentially numbered envelopes. Randomization was based on blocks of 60 patients using randomly sealed envelopes. The sterile needle is inserted lateral to the patellar tendon (for the anterolateral approach) approximately 1 cm above the tibial plateau and directed 15-45° from the anterior knee surface vertical midline toward the intra-articular joint space. Intra-articular injection was administered to the intra-articular joint space by the surgeon. The Control Group (Group 1) patients received 0.9% isotonic (20mL). The Levobupivacaine Group (Group 2) patients received levobupivacaine 0.5 mg/kg plus 0.9% isotonic (total volume 20 mL), the Dexmedetomidine Group (Group 3) patients received 1μg/kg dexmedetomidine plus 0.9% isotonic (total volume 20 mL), and the Levobupivacaine + Dexmedetomidine Group (Group 4) patients received levobupivacaine 0.5 mg/kg plus 1μg/kg dexmedetomidine and 0.9% isotonic (total volume 20 mL) at the end of surgery. The pneumatic tourniquet stayed inflated for 10 minutes after the injection. Only the surgeon knew the exact groups. Postoperative follow-up, evaluating the pain scores, and deciding the analgesic need were made by a second anesthesiologist who was blinded to the groups. The anesthesiologist in the operating room, the second anesthesiologist who followed up the patients postoperatively, and the patients were blinded. The drugs were prepared by an anesthetist, who was not one of the observers. The weight and sex of the patients were recorded preoperatively. Heart rate, mean arterial pressure, allergic reactions, nausea, and headache were recorded for the first postoperative 24 hours. Pain levels at rest were evaluated by using a Visual Analog Scale (VAS). Also, the Verbal Rating Scale (VRS) at rest was used to assess the pain. VRS is based on the values of 0 as "no pain", 1 as "mild pain", 2 as "severe pain", and 3 as "intolerable pain". VAS and VRS for pain scores were recorded preoperatively and they were recorded at intervals of 15th and 30th minutes and 1, 2, 4, 6, 12, and 24 h after the intra-articular injection.

HIGHLIGHTS

- Dexmedetomidine commonly used intravenously in intensive care units for sedative, analgesic, and sympatholytic purposes.
- When dexmedetomidine is used as an adjuvant to levobupivacaine, dexmedetomidine increases the duration and the quality of postoperative analgesia.
- Dexmedetomidine had no side effects on cardiac or other systems when it was used at a dose of 1 μg/kg intra-articularly.

When there is a need for analgesic requirement, paracetamol (500 mg) was administered. If there was no pain relief, 1μg/kg intramuscular (IM) morphine was injected. Total analgesic consumption and time to first analgesic requirement were recorded.

None of the patients had physical therapy for their operated knees. All of the patients succeeded in weight bearing without the use of crutches in the first 24 postoperative hours.

Statistical analysis

Pains in rest, movement, and postoperative periods were evaluated in four different groups. The intergroup comparison of the related measurements during the same period was examined by the Kruskal–Wallis *H*-test, and in case of differences, with the Mann Whitney *U*-test. Pain severities of the same groups at different times were compared with the Friedman *F*-test. In the case of differences, the Wilcoxon signal test revealed the difference between the two time periods. At the same time, the first analgesic duration and the total amount of analgesic consumption were compared with the Kruskal–Wallis *H*-test. All tests were interpreted as a 95% confidence level.

Results

The mean age of the patients was 43.37 ± 12.45. A total of 31 (51.7%) of the patients were male, and 29 (48.3%) were female. Demographic data of the groups are shown in Table 1.

When blood pressure and heart rate values that were recorded postoperatively were compared between the groups, the difference was not significant ($P > 0.05$). There was no nausea-vomiting or other side effects.

When the means of postoperative VAS values in rest were assessed in the groups, all the values were significant ($P < 0.001$). The analyses of the postoperative VAS values in the groups are shown in Table 2.

When the means of VRS values at rest were evaluated in the groups, the results were significant ($P < 0.05$) except for the values that were recorded at the postoperative 6th hour, and the values that were measured preoperatively (Table 3).

When we evaluated the mean arterial pressure (MAP) and heart rate (HR) values, there was no significant difference between the groups ($P > 0.05$).

When the VAS values at rest were analyzed, it was determined that there were statistically significant differences between the values of Group 1 and Groups 2, 3, and 4 at postoperative 15th and 30th minutes and at 1st, 2nd, 4th, 6th, 12th, and 24th hours ($P < 0.05$).

When the VRS values at rest were analyzed, it was determined that the were statistically significant differences between the values of

Table 1. Demographic Data According to the Groups

	Age (year)	Sex (*n*)		Weight (kg)		
	Mean ± SD	Male	Female	Mean ± SD	Minimum	Maximum
Group 1	46.70 ± 13.13	8	7	79.1 ± 8.94	63	90
Group 2	42.60 ± 12.18	7	8	78 ± 8	60	90
Group 3	43.80 ± 12.63	8	7	74.8 ± 7.91	60	86
Group 4	40.40 ± 11.79	7	8	73.8 ± 11.41	52	86

SD, standard deviation; Group 1, placebo; Group 2, levobupivacaine; Group 3, dexmedetomidine; Group 4, levobupivacaine + dexmedetomidine.

Table 2. The Mean VAS Values at Rest in Groups

	Groups				
	(Group 1) Placebo	(Group 2) Levobupivacaine	(Group 3) Dexmedetomidine	(Group 4) Levobupivacaine + Dexmedetomidine	
The Time of VAS values at Rest	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation	*P* (Between the Groups)
Preoperative	0.40 ± 0.70	0.00 ± 0.00	0.20 ± 0.42	0.40 ± 0.52	0.185
Postop 15th minute	4.20 ± 2.39	0.30 ± 0.48	0.30 ± 0.67	0.10 ± 0.32	<0.001*
Postop 30th minute	4.70 ± 1.34	0.60 ± 0.84	0.90 ± 0.88	0.20 ± 0.42	<0.001*
Postop 1st hour	5.20 ± 1.69	0.70 ± 1.06	1.60 ± 1.17	0.10 ± 0.32	<0.001*
Postop 2nd hour	4.40 ± 1.90	1.20 ± 0.92	1.90 ± 0.88	0.10 ± 0.32	<0.001*
Postop 4th hour	4.00 ± 1.41	1.40 ± 0.97	2.00 ± 0.82	0.70 ± 0.95	<0.001*
Postop 6th hour	3.00 ± 0.82	1.20 ± 1.14	2.00 ± 1.25	0.80 ± 0.79	<0.001*
Postop 12th hour	2.50 ± 0.85	0.60 ± 1.07	0.60 ± 0.70	0.30 ± 0.42	<0.001*
Postop 24th hour	1.50 ± 0.97	0.40 ± 0.52	0.30 ± 0.48	0.10 ± 0.20	<0.001*
P (within the groups)	<0.001*	<0.001*	<0.001*	0.001*	

*$P < 0.05$ is significant.
Postop, postoperative; VAS, visual analogue scale.

Table 3. The Means of the VRS Values at Rest in Groups

	Groups				
	(Group 1) Placebo	(Group 2) Levobupivacaine	(Group 3) Dexmedetomidine	(Group 4) Levobupivacaine + Dexmedetomidine	
The Time of VRS values at Rest	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation	Mean ± Standard Deviation	*P* (Between the Groups)
Preoperative	0.30 ± 0.48	0.00 ± 0.00	0.10 ± 0.32	0.10 ± 0.32	0.237
Postop 15th minute	1.60 ± 0.70	0.10 ± 0.32	0.10 ± 0.32	0.00 ± 0.00	<0.001*
Postop 30th minute	1.90 ± 0.74	0.20 ± 0.42	0.40 ± 0.52	0.00 ± 0.00	<0.001*
Postop 1st hour	2.10 ± 0.57	0.40 ± 0.52	0.70 ± 0.82	0.00 ± 0.00	<0.001*
Postop 2nd hour	1.70 ± 0.82	0.70 ± 0.67	0.90 ± 0.57	0.20 ± 0.42	0.001*
Postop 4th hour	1.40 ± 0.70	0.80 ± 0.63	1.30 ± 0.48	0.60 ± 0.70	0.027*
Postop 6th hour	1.20 ± 0.42	0.80 ± 0.79	1.00 ± 0.47	0.60 ± 0.52	0.114
Postop 12th hour	1.40 ± 0.70	0.40 ± 0.70	0.15 ± 0.32	0.00 ± 0.00	<0.001*
Postop 24th hour	0.70 ± 0.48	0.00 ± 0.00	0.10 ± 0.21	0.00 ± 0.00	<0.001*
P values (Within the groups)	<0.001*	<0.001*	<0.001*	<0.001*	

*$P < 0.05$ is significant.
Postop, postoperative; VRS: verbal rating scale.

Table 4. The Time to Take the First Analgesic (minute)

Groups	Mean ± Standard Deviation	*P*
Placebo	72.00 ± 65.12	<0.001*
Levobupivacaine	538.00 ± 337.67	
Dexmedetomidine	308.00 ± 106.09	
Levobupivacaine + dexmedetomidine	964.00 ± 288.19	

*$P < 0.05$ is significant.

Group 1 and Group 4 at postoperative 15th and 30th minutes and at 1st, 2nd, 4th, 6th, 12th, and 24th hours ($P < 0.05$). Also, there were no statistical differences between Group 1 and Group 3 according to VRS values at rest in all times ($P > 0.05$).

When the mean values of the time to take the first analgesic were evaluated, the patients of Group 4 had the longest time to take the first analgesic. The mean times of the other groups to take the first analgesic are shown in Table 4.

If the values of the time to take the first analgesic were compared between the groups, significant differences were found between Group 1 and Groups 2, 3, and 4 ($P < 0.05$). Also, there was a statistically significant difference between Group 3 and Group 4 according to the time to take the first analgesic ($P < 0.05$). The other comparisons between the groups were insignificant ($P > 0.05$).

When we look at the total analgesic consumption data, Group 1 patients had the highest analgesic consumption while Group 4 patients had the lowest (Table 5).

Discussion

An important finding of this study is that, although intra-articular dexmedetomidine has a weaker analgesic effect than intra-articular levobupivacaine alone, this effect is increased when dexmedetomidine is used in combination with levobupivacaine. Dexmedetomidine is known to have some side effects on cardiac functions when used systemically, and no cardiac or systemic side effects were found in the present study when used at a dose of 1 μg/kg intra-articularly. In addition, patients' need for postoperative analgesics occurred at a later timein the Dexmedetomidine + Levobupivacaine group, and the total analgesic consumption was at the lowest level.

Postoperative pain is an important problem in arthroscopic knee meniscectomy surgeries in terms of early discharge from the hospital. Therefore, several drugs such as lidocaine, prilocaine, bupivacaine,

Table 5. Total Analgesic Consumption

Groups	Statistic	Not Taking Analgesic	*n* and % of Patients Who Took 500 mg Paracetamol	*n* and % of Patients who Took Morphine	*P*
Placebo	*n*	0	9	6	0.001*
	%	0.0%	60.0%	40.0%	
Levobupivacaine	*n*	9	6	0	
	%	60.0%	40.0%	0.0%	
Dexmedetomidine	*n*	6	9	0	
	%	40.0%	60.0%	0.0%	
Levobupivacaine + dexmedetomidine	*n*	12	3	0	
	%	80.0%	20.0%	0.0%	
Total	*n*	27	27	6	
	%	45%	45%	10.0%	

*$P < 0.05$ is significant.
n = number of patients.

and levobupivacaine are used intra-articularly to reduce postoperative pain which occurs due to arthroscopic knee meniscectomy surgeries.[7-10]

Dexmedetomidine has a local anesthetic effect with the inhibition of nerve impulses through C and Aδ fibers; analgesic effect is achieved by modulating the opioid analgesic pathway and by stimulating the release of enkephalin-like substances in the peripheral regions.[13–15] Dexmedetomidine is also a selective alpha-2 adrenoreceptor agonist, and its binding to the alpha 2 receptor is eight times greater than clonidine.[13] Therefore, its mechanism of intra-articular effect can be similar to clonidine. Also, it must be considered that systemic absorption of dexmedetomidine can cause this analgesic effect by its systemic mechanism.

Intra-articular dexmedetomidine use was researched in several studies to decrease postoperative pain after knee meniscectomy; and these studies showed that the patients who took intra-articular dexmedetomidine as an adjuvant had lower analgesic consumption, and their time to first analgesic requirement increased.[16–18]

In the study of Paul et al., the addition of intra-articular dexmedetomidine as an adjuvant drug to intra-articular ropivacaine augmented the postoperative analgesia duration after knee arthroscopy and reduced the requirement of fentanyl with an average of 10.84 ± 2.6 hours between intra-articular injection and complementary analgesic administration by a Patient-Controlled Analgesia (PCA) pump.[19] According to our data, while the Levobupivacaine Group had postoperative analgesic effect of 8.96 ± 5.61 hours, addition of dexmedetomidine to levobupivacaine increased this effect up to 16.06 ± 4.8 hours. It is an interesting result that Paul et al. found the postoperative analgesic effect of ropivacaine alone as 5.38 ± 1.4 hours; and addition of dexmedetomidine prolonged the analgesic effect by approximately twice. Our results given in Table 4 also show this similar prolongation by addition of dexmedetomidine to levobupivacaine. Paul et al. preferred to use dexmedetomidine at a standard dose of 100 μg but we have chosen the dose 1 μg/kg. All of the patients received the dose of dexmedetomidine below 100 μg, and similar results were obtained with a lower dose in this study.

Reuben and Connelly demonstrated that the first analgesic demand following knee arthroscopy was 500 minutes after intra-articular clonidine administration, 325 min after intra-articular bupivacaine, and 700 min after combined intra-articular clonidine and bupivacaine.[20] It was shown in the study of Reuben et al. that addition of another alpha-2 agonist, clonidine, enhances bupivacaine's analgesic effect approximately 2 times, which is again, similar to our results.

In the study of Shaima et al. it was showed that bupivacaine plus 100 μg dexmedetomidine was superior to bupivacaine alone on postoperative analgesia outcomes.[18] The present study is distinct from their study in the point of dexmedetomidine dose. None of our patients' weight was above 100 kg; therefore, all of our dexmedetomidine doses were lower than 100 μg. However, we also found similar results to those of Shaima et al.'s study with lower doses of dexmedetomidine.

Tarlika et al. also showed that intra-articular dexmedetomidine at a dose of 1μg/kg as an adjuvant to ropivacaine had better outcomes in the case of postoperative analgesia in knee arthroscopies. However, the study of Tarlika et al. was based on patients with spinal anesthesia, unlike the current study. We have to say that spinal anesthesia can affect the evaluation of postoperative analgesia.[21] Because of this, we chose standardized general anesthesia for our patients.

A meta-analysis that included 12 randomized controlled trials involving 594 participants reported that intra-articular dexmedetomidine use decreased postoperative pain and opioid consumption in patients undergoing arthroscopic surgery.[22] In that meta-analysis, it was reported that the incidence of side effects was low with intra-articular dexmedetomidine administration. This may be due to the lack of vascularization in the articular surface. Since the drug applied to an area without vascularization will take a long time to be removed from the region, the duration of the drug's local effect will also be prolonged and the possibility of drug-related side effects will be low since its accession into the systemic circulation will be limited.[23]

According to the results, the patients of the Levobupivacaine + Dexmedetomidine Group had the longest analgesia, followed by the Levobupivacaine Group and the Dexmedetomidine Group. If we analyze the VAS and VRS scores of the patients in Tables 2 and 3, we can say that postoperative analgesia was prolonged in the Levobupivacaine + Dexmedetomidine Group, which also had better quality in analgesia. This can show us that intra-articular dexmedetomidine itself has a a lower analgesic effect than levobupivacaine; however, when it is used at a dose of 1μg/kg as an additive drug to levobupivacaine, dexmedetomidine augments the postoperative analgesic effect of intra-articular levobupivacaine obviously.

Animal studies are also available on intra-articular non-steroidal anti-inflammatory drug (NSAID) injections. These studies generally aim to observe the effect of NSAIDs on the inflammatory process in the joint after injection. In one of these studies, Kütahya et al.'s study, ibuprofen injection was applied to rats into the knee joint and an inflammatory process was followed up for up to 21 days.[24] Hematoma was observed in 10 rats in the group that received ibuprofen injection while hematoma was not observed in any rats in the saline injection group and the sham group. The cause of hematoma was associated with ibuprofen because of its inhibitory effect on platelet aggregation. On the 1st, 2nd, 7th, and 14th days, inflammation scores were found to be higher in the group that was administered ibuprofen. Although pain scores were not studied in that study, hematoma and high inflammation scores would likely lead to higher pain scores in human patients. As a result, more studies are needed on the effects of intra-articular NSAID injections on pain and local inflammatory process.

This study has some limitations. Plasma concentrations of the drugs were not measured and possible chondrotoxic effects were not controlled. In clinical practice, local anesthetic toxicity has been mainly seen in continuous infusions via pain pumps. We did not measure the plasma concentrations of the drugs because we thought that local anesthesia toxicity would be very unlikely in a study about intra-articular injection. Limited number of cases in each group was also another limitation.

As a result, intra-articular dexmedetomidine itself has a weaker effect than intra-articular levobupivacaine; however, when it is used as an adjuvant to levobupivacaine, dexmedetomidine increases the duration and the quality of postoperative analgesia without causing any side effect. Future studies must be based on higher numbers of cases using intra-articular dexmedetomidine routinely.

Ethics Committee Approval: This study was approved by local committee on ethics in research on humans (B.30.2.CUM.0.1H.00.00-08/17). This study is designed on principles of Helsinki Declaration properly.

Informed Consent: Written informed consents were taken from the patients.

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