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Research Article

Comparative study of intra-articular dexmedetomidine versus ketamine as adjuvant analgesics after knee arthroscopy

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KEYWORDS

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Postoperative pain;
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Abstract *Background:* Knee arthroscopy is one of the day case procedures which may be diagnostic or therapeutic. Postoperative analgesia is important for early ambulation and short hospital stay. This prospective randomized study was designed to compare the analgesic effect of intra-articular dexmedetomidine versus ketamine as adjuvant to bupivacaine following knee arthroscopy.
Method: 75 patients ASA physical status I and II undergoing knee arthroscopy under general anesthesia were included in this study. Patients were divided into three groups according to intra-articular injected combination at the end of the arthroscopy. Group B/D received 25 ml 0.25% bupivacaine and dexmedetomidine 1 μg/kg, group B/K received 25 ml 0.25% bupivacaine and ketamine 1 mg/kg, and control group B received 25 ml 0.25% bupivacaine only. Postoperative pain using visual analogue score (VAS), the time to the first postoperative analgesic request, the total dose of postoperative analgesia during the first 24 h, and possible side effects were recorded.
Results: Visual analogue score (VAS) was significantly less in B/D group in comparison with B/K group after the 1st hour and thereafter. Also VAS was higher in B group compared to the other two groups ($P < 0.05$). Time to first postoperative analgesic request was longer in the B/D group (479.2 ± 34.9 min) than in B/K group (356.7 ± 39.2 min), but in both groups it was longer than in B group (312.4 ± 18.8 min), ($P < 0.05$).
The total dose of postoperative analgesia (paracetamol consumption) during the first 24 h was significantly low in B/D group (758.0 ± 153.0 mg) compared to both B/K and B groups (1041.2 ± 178.6 mg and 1368.0 ± 227.2 mg) respectively ($P < 0.05$).
Conclusion: Intra-articular bupivacaine/dexmedetomidine provides better analgesia compared to bupivacaine/ketamine and both are superior to bupivacaine alone following knee arthroscopy.

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1. Introduction

Knee arthroscopy is a minimally invasive day case procedure which may be done for diagnosis, meniscectomy or debridement. Arthroscopic surgery is associated with a variable degree of postoperative pain, which is caused by an irritation of free nerve endings of the synovial tissue, anterior fat pad, and joint capsule due to surgical excision and resection [1]. Postoperative pain control is very important for early rehabilitation and short hospital stay. Several postoperative analgesic modalities were tried such as systemic drugs, central or peripheral nerve blocks and intra-articular injections aiming at reaching the ideal technique for postoperative pain control [2]. Many studies were done using different intra-articular agents as local anesthetics, opioids, ketamine, NSAIDS and α2-adrenergic agonists for prevention and treatment of pain after knee surgeries [3]. Dexmedetomidine is a potent and highly selective α2-adrenoreceptor agonist. It has sedative-hypnotic, anxiolytic, analgesic, anesthetic and sympatholytic effects [4].

Intra-articular dexmedetomidine was used in several studies to enhance postoperative analgesia after knee arthroscopy with an increased time to first analgesic request and a decreased need for postoperative analgesia [2]. Ketamine has been introduced into clinical practice for nearly 46 years, with the objective to act as an anesthetic substance with analgesia, amnesia, unconsciousness, and immobility properties. Ketamine has been found to interact with a number of receptors such as opioids, muscarinic and N-methyl-D-aspartate receptors (NMDAr) [5].

Although central NMDAr, especially when located in the spinal cord have received a great deal of attention, recent evidence suggests that NMDAr located in peripheral somatic and visceral pain pathways play an important role in nociception [6]. NMDAr have been found to exist in joints, as demonstrated in the rat model by Yu et al. [7].

The intra-articular application of ketamine after arthroscopic knee surgery leads to a significant decrease of postoperative analgesic demand and decreases patients' subjective level of pain compared to intra-articular application of bupivacaine or placebo [8]. However, there is no study comparing the effect of intra-articular dexmedetomidine versus ketamine. The aim of this prospective randomized study was to evaluate the effect of adding dexmedetomidine versus ketamine as adjuvant to intra-articular bupivacaine for postoperative analgesia after knee arthroscopy.

2. Patients and methods

2.1. Study design

This is a randomized parallel-group controlled study with allocation ratio (1:1:1) was done in orthopedic theater in Kasr Alaini hospital in the period between October 2013 and August 2014 after approval of ethics committee and obtaining written informed consent from all patients. Patients recruited in this study were scheduled to knee arthroscopy under general anesthesia to evaluate the postoperative analgesic effect of intra-articular dexmedetomidine versus ketamine as adjuvant to bupivacaine in comparison with bupivacaine alone.

2.2. Patient

75 patients aged 20–50 years of both sexes, ASA physical status I–II were enrolled in this study. Fig. 1 shows a flowchart of participants in the study. Patients with history of cardiac, hepatic, renal diseases, and hypertension treated with ß-adrenergic blockers, α-2-adrenergic agonists, α-methyldopa, or known allergy to the used drugs were excluded.

In the preparation room under local anesthesia intravenous cannula was inserted, midazolam 2 mg and ranitidine 50 mg were given to all patients. Then patient was transferred to the operating room, standard monitors were applied (noninvasive blood pressure, pulse oximetry, electrocardiogram) and capnography after induction of anesthesia.

General anesthesia was induced with Propofol 2 mg/kg and fentanyl 2 μg/kg, endotracheal intubation was facilitated with atracurium 0.5 mg/kg, mechanical ventilation was adjusted to keep the end tidal carbon dioxide between 30–35 mmHg and anesthesia was maintained with 50% O2, 50% Air and isoflurane 1–1.5% with topup doses of atracurium 0.15 mg/kg every 20 min. Surgical pneumatic tourniquet was applied to the thigh during the procedure till 15 min after intra-articular injection. Patients were randomly assigned into one of three groups (25 patients each). Randomization was done using Computer-generated random numbers inserted into opaque concealed envelopes; inside these envelopes was a number, which indicates the group to which the patient was allocated. Group (B) received intra-articular injection of 25 ml 0.25% bupivacaine only and considered as the control group, group (B/D) received intra-articular injection of combination of 25 ml 0.25% bupivacaine and dexmedetomidine 1 mcg/kg, and group (B/K) received intra-articular injection of combination of 25 ml 0.25% bupivacaine and ketamine 1 mg/kg. The study drugs were injected by the surgeon through the arthroscopy port at the end of the procedure (Neither the surgeon and the anesthesiologist nor the nurse looking after the patient postoperatively was aware of the randomization sequence or the content of the injected drugs), and if a drain was inserted it was closed for one hour. At the end of the surgery isoflurane inhalation was stopped and 100% O2 was inhaled. The neuromuscular block was reversed with neostigmine (0.05 mg/kg) and atropine (0.02 mg/kg), and then tracheal extubation was done after complete recovery of the patient with sufficient muscle power.

The use of the 10 cm Visual Analogue Scale (VAS) for pain was explained to all patients preoperatively (0 = no pain to 10 = the worst pain). The primary outcome of the study was the duration of postoperative analgesia guided by the pain score. Secondary outcome variables were the total paracetamol consumption and the requirement of meperidine rescue analgesia between the study groups.

VAS scores were recorded at 30 min, 1, 2, 4, 6 and 12 h after the intra-articular injection. Scoring was conducted postoperatively by an observer who was blinded to the study drugs. For postoperative pain control paracetamol intravenous infusion was given if the recorded VAS was 4 or more (with minimum 4 h time interval between successive doses of paracetamol and rescue analgesia with meperidine 50 mg intravenous if the VAS score was 4 or more within this time interval). The time to first analgesic request and the total dose of paracetamol during the first 24 h as well as the total dose of

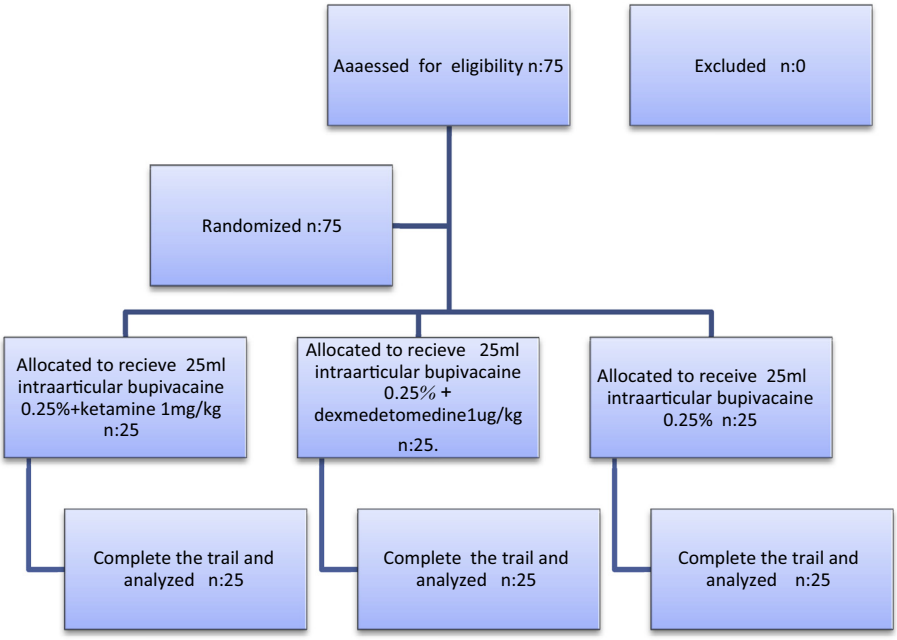

Figure 1 Flowchart of participants in the study.

meperidine rescue analgesia was recorded. The occurrence of any side effects as hypo- or hypertension, tachy- or bradycardia, nausea, vomiting, sedation, and hallucinations was recorded for all patients at the same time points as those defined for VAS.

3. Statistical analysis

Data were expressed using mean ± SD for quantitative variables and frequency and percentage for qualitative ones. Comparison between groups was performed using one way ANOVA with posthoc Tukey's test (if parametric) or Kruskal Wallis test followed by Mann Whitney test (if non-parametric) for quantitative variables and Chi square or Fisher's exact test for qualitative ones. *P* value less than 0.05 was considered statistically significant. Computer Statistical Package of Social Science Software program, version 21 (SPSS) was used. Sample size estimation has not been done prior to the study; instead the power was calculated after we finished our study. At an alpha threshold of 0.001 with a group size of 25 patients and mean difference 0.5, the estimated study power was 93.9%.

4. Results

There was no statistically significant difference between the three groups as regarding demographic data (age, sex, weight, ASA physical status and duration of anesthesia) and postoperative clinical variables (Table 1).

No serious adverse effects were recorded in the first 24 h in all patients. No postoperative sedation, hallucination, nausea, vomiting, allergy or significant heart rate and blood pressure changes were reported.

Postoperative pain scores were significantly less in B/D group compared to B/K group after the first hour and in the next time intervals ($p < 0.05$). Also VAS scores were significantly lower in B/D group than in B (control) group in all measurement points, and significantly higher in B (control) group in comparison with B/K group till the 4th hour reading, and then it was statistically insignificant thereafter (Table 2, Fig. 2).

Table 1 Demographic data – clinical variables.

Parameter	B/D group (n:25)	B/K group (n:25)	B group ctrl (n:25)
Age (years)	36.5 ± 10.4	32.9 ± 9.7	33.6 ± 10.3
Weight (kg)	76 ± 7.8	75.4 ± 7.5	74.2 ± 10.3
Sex (male/female)	14/11	15/10	16/9
ASA (I/II)	20/5	18/7	18/7
Duration of anesthesia (min)	72.8 ± 12.7	69.9 ± 8.1	71.0 ± 11.2
Heart rate (min)	64.5 ± 6	69 ± 5.2	70 ± 6.2
Mean blood pressure (mmHg)	89.9 ± 5.6	90.4 ± 5.2	91.5 ± 4.3

B: bupivacaine, D: dexmedetomidine and K: ketamine. Values are mean ± SD and ratio. No significant difference between the study groups, ($P > 0.05$).

Table 2 Visual analogue score (Mean ± SD).

	B/D group	B/K group	B group ctrl	*P*-value	Pairwise comparisons
VAS 30 MIN	0.5 ± 0.5	0.7 ± 0.5	1.2 ± 0.5	< 0.001	G1 * G2 = 0.086 G1 * G3 = < 0.001 G2 * G3 = 0.001
VAS 1H	1.3 ± 0.5	1.7 ± 0.5	2.7 ± 0.7	< 0.001	G1 * G2 = 0.004 G1 * G3 = < 0.001 G2 * G3 = < 0.001
VAS 2H	1.7 ± 0.5	2.8 ± 0.4	3.2 ± 0.4	< 0.001	G1 * G2 = < 0.001 G1 * G3 = < 0.001 G2 * G3 = 0.002
VAS 4H	2.3 ± 0.5	3.3 ± 0.5	3.4 ± 0.5	< 0.001	G1 * G2 = < 0.001 G1 * G3 = < 0.001 G2 * G3 = 0.243
VAS 6H	3.9 ± 0.4	4.7 ± 0.6	4.6 ± 0.5	< 0.001	G1 * G2 = < 0.001 G1 * G3 = < 0.001 G2 * G3 = 0.739
VAS 12H	4.3 ± 0.5	4.8 ± 0.6	5.0 ± 0.5	< 0.001	G1 * G2 = 0.001 G1 * G3 = < 0.001 G1 * G2 = 0.198

B: bupivacaine, D: dexmedetomidine and K: ketamine. Values are mean ± SD and ratio. No significant difference between the study groups, ($P > 0.05$).
B: bupivacaine, B/D: bupivacaine/dexmedetomidine and B/K: bupivacaine/ketamine. Values are mean ± SD *: statistically significant ($P < 0.05$). G1: B/D group, G2: B/K group, G3: B group.

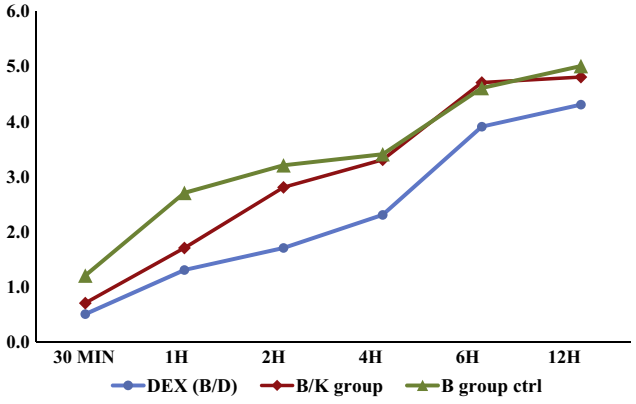

Figure 2 Visual analogue score (mean ± SD). B: bupivacaine B/D: bupivacaine/dexmedetomidine and B/K: bupivacaine/ketamine

The time to postoperative analgesic requirement was significantly longer in B/D group (479.2 ± 34.9 min) compared to B/K group (356.7 ± 39.2 min) and control group (312.4 ± 18.8 min). ($P < 0.05$) (Table 3).

The total dose of postoperative supplementary analgesia (intravenous paracetamol infusion) in the first 24 h was significantly lower in B/D group (758 ± 153 mg) in comparison with B/K (1041.2 ± 178.6 mg) and control group (1368 ± 227.2 mg) ($p < 0.05$) (Table 3). No need for meperidine rescue analgesia was recorded in any patient.

5. Discussion

The present study demonstrated that the use of intra-articular dexmedetomidine and ketamine as adjuvant to bupivacaine for postoperative analgesia after knee arthroscopy is safe and effective with reduced postoperative pain and analgesic request during the first 24 h compared to bupivacaine alone. Also it was noticed that intra-articular dexmedetomidine is associated with significant lower VAS scores and longer time to first analgesic request with reduced analgesic consumption in comparison with intra-articular ketamine.

Dexmedetomidine is an alpha-2 agonist which produces its effect through spinal, supraspinal and peripheral actions [9].

Table 3 Time to first analgesic request and total dose of paracetamol.

Parameter	B/D group (n:25)	B/K group (n:25)	B group (n:25)	Pairwise comparisons
Time to first analgesic request (min)	479.2 ± 34.9	356.7 ± 39.2	312.4 ± 18.8	G1 * G2 = < 0.001* G1 * G3 = < 0.001* G2 * G3 = < 0.001*
Total dose of paracetamol (mg)	758.0 ± 153.0	1041.2 ± 178.6	1368.0 ± 227.2	G1 * G2 = < 0.001* G1 * G3 = < 0.001* G2 * G3 = < 0.001*

B: bupivacaine, B/D: bupivacaine/dexmedetomidine and B/K: bupivacaine/ketamine. Values are mean ± SD.
* Statistically significant ($P < 0.05$). G1: B/D group, G2: B/K group, G3: B group.

The analgesic effect of intra-articular dexmedetomidine appears to be mainly due to direct local action. However, a central analgesic effect resulting from systemic absorption cannot be excluded. The mechanism of analgesic effect of intra-articular dexmedetomidine might be similar to that of intra-articular clonidine.

Clonidine produces analgesia mainly through inhibition of the transmission of nociceptive stimulation in the dorsal horn of spinal cord [10]. Clonidine is reported to mimic the effect of noradrenaline release by descending inhibitory control pathways [11]. Topical administration of clonidine may reduce pain intensity in patients with sympathetically maintained pain, suggesting a peripheral site of action [12]. Dexmedetomidine, like clonidine, may provide local anesthetic effects that inhibit the conduction of nerve signals through C and Aδ fibers and may stimulate the release of enkephalin-like substances at peripheral sites [13,14].

The results of our study are in agreement with the study of El-Hamamsy et al., who showed that intra-articular dexmedetomidine 1 mcg/kg as adjuvant to bupivacaine significantly enhanced the postoperative analgesia after arthroscopic knee surgery, with an increased time to first analgesic request (450 ± 85 min) in comparison with bupivacaine alone (230 ± 85 min), and decreased total postoperative meperidine requirement during the first 24 h [15].

A study was done to investigate the effect of intra-articular magnesium versus dexmedetomidine for postoperative analgesia after knee arthroscopic meniscectomy concluded that both intra-articular magnesium sulfate and dexmedetomidine enhance postoperative analgesia after knee arthroscopic meniscectomy with significantly longer time to postoperative analgesic request 461.5 ± 39.2 min and 354 ± 34 min respectively without adverse systemic side effects of these drugs [16].

Paul et al. demonstrated that, administration of dexmedetomidine as adjuvant to local anesthetic ropivacaine improves the quality and duration of postoperative analgesia and reduces the consumption of fentanyl citrate, with delay time 10.84 ± 2.6 h between intra-articular injection of ropivacaine with dexmedetomidine and supplementary analgesic administration by PCA pump [17].

In the present study the analgesic effect of intra-articular ketamine in combination with bupivacaine was superior to bupivacaine alone with significantly lower VAS at 30 min, 1 h and 2 h. Also the time to first analgesic request was significantly longer with decreased mean consumption of paracetamol analgesia in the first 24 h.

Ketamine is proved to have local effects; it interacts with multitude of receptors including opioid, cholinergic, adrenergic, serotonergic and NMDAr, all of which have significant role in analgesia [18].

Dal et al used ketamine intra-articularly and reported a significant analgesic effect that was comparable to intra-articular neostigmine, without reported side effects [19].

The study investigating the analgesic effect of intra-articular ketamine and tramadol revealed that both ketamine and tramadol produce peripheral analgesic effect when injected intra-articularly in the knee following arthroscopic surgeries. Both agents reduced pain scores and opioid consumption and had no systemic side effects [20].

Lashgarinia et al. demonstrated that, the addition of ketamine 2 mg/kg to 5 mg/kg lidocaine 1.5% in ultrasound-guided brachial plexus block decreases the postoperative pain and the time to first analgesic request in the ketamine group was significantly longer than in the control group (8.93 ± 1.0 vs. 7.30 ± 1.9), respectively. Therefore, it could be considered as an option in the brachial plexus block to enhance the analgesic action of lidocaine [21].

Ayoglu et al. concluded that administration of intra-articular tramadol-ketamine combination was found to be more effective in decreasing postoperative analgesic consumption in comparison with intra-articular tramadol alone with lower postoperative pain scores [22].

The results of the study done by Batra et al. showed that intra-articular injection of a combination of 1 mg/kg ketamine and 0.25% bupivacaine to a total volume of 20 mL following surgery provides better pain relief with longer duration of analgesia 5.1 ± 1.1 h compared to ketamine 1 mg/kg alone which was 1.7 ± 0.9 h. However, 24 h consumption of analgesic was similar [23].

A limitation of our study is that, there was no follow-up to detect any local tissue damage in the intra-articular space following injection of the study drugs which require long time. Further studies are also needed to define the optimal analgesic dose without hemodynamic changes of intra-articular dexmedetomidine and ketamine in combination with bupivacaine for control of pain after knee arthroscopy.

6. Conclusion

Both dexmedetomidine and ketamine are safe and effective when added to intra-articular bupivacaine but dexmedetomidine/bupivacaine has better analgesic profile with lower perception of pain, as assessed by the VAS score, longer time to analgesic request and reduced total dose of analgesia during first 24 h after knee arthroscopy in comparison with ketamine/bupivacaine or bupivacaine alone.

Conflict of Interest

Author states that there is no conflict of interest.

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