

## RESEARCH ARTICLE

# Analgesia Following Arthroscopy – a Comparison of Intra-articular Bupivacaine and/or Midazolam and or Fentanyl

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## Abstract

**Background:** Arthroscopic intervention is very common for conducting orthopedic surgeries. After a knee arthroscopic surgery, different drugs are used through intra-articular administration to induce analgesia. The aim of this study was to evaluate analgesic effects of Bupivacaine (marcaine), Bupivacaine plus midazolam, and Bupivacaine plus fentanyl in reducing pain after knee arthroscopic surgery.

**Methods:** Fifty five patients who were candidate for knee arthroscopy were divided into three groups. Group A, B and C received Bupivacaine (50 mg), Bupivacaine (50 mg) plus midazolam (50 µg/kg), and Bupivacaine (50 mg) plus fentanyl (3 µg/kg), respectively. The analgesic solutions were diluted with normal saline up to 20 ml. The analgesic effects were evaluated by VAS during first 24 hrs after surgery. With the VAS > 4, extra analgesic (pethidine) was administered for patient.

**Results:** The amount of induced analgesia and need for extra analgesic was different between groups; however, it was not statistically significant ( $p < 0.109$ ). The amount of administered analgesic (pethidine) in first 24 hours post-operatively was 275 mg for group A, while it was 150 mg for group B and 75 mg for group C. In group A, 46.67% of patients required further analgesic while this was 26.67% and 13.34% for groups B and C respectively ( $p < 0.109$ ).

**Conclusion:** Intra-articular administration of studied drugs in all three groups reduced post-operation pain. The amount of induced analgesia was the highest for group C, while group B drugs induced better analgesia compared to group C.

**Keywords:** Analgesia, Bupivacaine, Fentanyl, Intra-articular, Knee arthroscopy, Midazolam

## Introduction

Arthroscopic surgery is one of the most common methods for performing orthopedic operations (1). Patients who undergo arthroscopy are not usually hospitalized before and after surgery. These surgeries can cause different level of pain for patients, which for some cases is considerable (2, 3). Thus, various strategies have been employed for analgesia after arthroscopic surgeries like administering systemic drugs such as NSAIDs, central and peripheral blocks, and intra-articular administration of drugs (4). Intra-articular injection of different drugs after arthroscopy can reduce the pain significantly and decrease the need for analgesic (5).

Intra-articular opiate can induce analgesia up to 24 hours and reduce the amount of chronic pain. Local anesthetic drugs including lidocaine and bupivacaine/marcaine, opiates like morphine and fentanyl, benzodiazepines such as midazolam,  $\alpha 2$ -agonists like clonidine, dexmedetomidine and even magnesium sulfate, alone or in combination with

others had been tested via intra-articular administration in previous studies (6-8).

Local anesthetics block transmission of action potentials through inhibition of related sodium channels (9). Intra-articular administration of midazolam may produce analgesic effects similar to its use in central neuraxial analgesia. Midazolam is a benzodiazepine agonist, which its peripheral analgesic effects are through benzodiazepine peripheral receptors that are distributed in different organs and joints. Gamma-aminobutyric acid (GABA) receptors exist in mitochondrial outer membrane and are bound to different benzodiazepines with different adhesive tendency (10-12). Peripheral opiate receptors exist at the end of primary afferent nerves and their number increases during inflammation in peripheral tissues (6,7). Opiates can induce strong analgesic effects by influencing opiates receptors in peripheral tissues (9, 12). In this study, we aimed to evaluate the analgesic effects of intra-articular administration of Bupivacaine alone or in combination

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with midazolam or fentanyl on pain control after knee arthroscopic surgery.

### Materials and Methods

This study was performed on patients within 18-55 years old with ASA class 1 and 2, who were candidate for knee arthroscopic meniscectomy at Ghaem Hospital affiliated with Mashhad University of Medical Sciences (MUMS). MUMS Institutional Review Board (IRB) approved the study. All volunteers were informed about the study and written consent was taken from them. The exclusion criteria included patients with liver, heart or renal diseases; patients with difficult postoperative pain assessment due to reasons such as lack of total consciousness, pre-operative use of oral or parenteral Narcotics; NSAID or opiates; allergy to any of studied drugs, addiction to opiates, patients who used neurological drugs, diabetics and patients with neuromuscular disease.

The study sample was calculated based on Adham *et al.* study in Egyptian Anesthetic Journal and Batra *et al.* study (4, 10). The mean of these two studies was calculated with mean comparison formula and study sample was determined with 95% confidence interval and 80% power for each group.

Fifty five patients participated in this study that were randomly assigned into three groups. The randomization method was based on blocks of four, and a person who was not aware of study goals placed the related codes in the confidential envelopes. The envelopes had been delivered to a person from research team who was not involved in patient pain evaluation and treatment. This person was responsible for preparing injection solutions based on assigned codes and delivering them to physician for injection. The visual analogue scale (VAS), a ten centimeter pain scale, was shown and explained to patients before surgery in which zero means no pain and ten means the maximum level of pain which is unbearable for patient.

In operation room all the patients had received standard monitoring including HR, ECG, SPO2, NIBP and then anesthesia was performed using the same protocol as follows.

To induce general anesthesia after pre-oxygenation, patients in all three groups had received fentanyl (2

µg/kg), propofol (2 mg/kg), and atracurium (0.25 mg/kg). Then patients' lung received mechanical ventilation by LMA with proper size and anesthesia was maintained using propofol (50-75 µg/kg/min) and atracurium (0.1-0.2 µg/kg) once required. Opiate was not repeated during operation. Patients of group A received only 50 mg of marcaine (Bupivacaine), while group B and group C received Midazolam (50 µg/kg) + Marcaine (50 mg); and Marcaine (50 mg) + Fentanyl (3 µg/kg), respectively. The analgesics for all three groups were diluted with normal saline up to total volume of 20 ml. A person unaware of the study protocol prepared them. The solutions were randomly coded and given to surgeon, who was also blinded to the study protocol, at the end of the operation for intra-articular injection. To induce hemostasis in operation site, a tourniquet that could induce pressures up to 300 mm/Hg was used. The intra-articular drainage was not used for the patients, and only a relative pressure bandage was employed for knee. A person blinded to the study protocol evaluated the analgesic effects of administrated drugs at hours of 1, 6, 12 and 24 post-operatively using VAS scale. If VAS score was higher than 4, patient received 25 mg of pethidine IV injection, which could be repeated every 4 hours if required. The time of first administration of analgesic in the first 24 hours of surgery was documented. SPSS v.13 was used to analyze collected data. To compare quantitative data with abnormal distribution, Kruskal Wallis test and for normal data chi square test were used. The  $P \leq 0.05$  was considered as significant level.

### Results

The difference between three study groups regarding age and gender was not significant. Table 1 shows the age and gender distribution of patients.

Patients' pain was evaluated based on VAS scale. The mean value of pain severity for three groups after 1, 6, 12 and 24 hours did not show significant difference ( $P=0.46$ ). The pain severity decreased over time, and the difference in pain reduction between the groups was statistically significant ( $P \leq 0.001$ ).

Table 2 shows the pain severity according to VAS scale in three study groups in different evaluation times. VAS

**Table 1. Patients' age and gender distribution**

(mean + SD)	Group A	Group B	Group C	Total
Age (year)	31.66±10.39	33.00±10.42	30.46±6.78	31.71±9.18
Gender (M/F)	(4/11)	(5/10)	(4/11)	$P$ value=0.9

Group A: Bupivacaine Group B: Bupivacaine+Midazolam Group C: Bupivacaine+ Fentanyl

**Table 2. Postoperation pain severity based on VAS (mean and SD)**

Study group	Group A		Group B		Group C	
	Mean	SD	Mean	SD	Mean	SD
6 h	2.44	1.88	2.40	1.84	2.60	1.22
12 h	2.03	1.78	1.33	1.17	1.36	1.24
24 h	1.20	1.30	0.56	0.82	0.55	0.55

Group A: Bupivacaine alone Group B: Bupivacaine + Midazolam Group C: Bupivacaine + Fentanyl

score was similar in all groups within the first hour after the operation, therefore it is omitted from the table.

Figure 1 compares the need for analgesic between three groups. 8 patients (53.33%) in group A, 11 patients (73.33%) in group B, and 13 patients (86.66%) in group C did not need analgesic ( $P=0.39$ ) and the difference between groups was not significant. However, the use of analgesic was the least for group C (Fentanyl+Bupivacaine), and for group B (Bupivacaine+Midazolam) was also less than group A (Bupivacaine). 7 out of 15 patients in group A required analgesics, which this number was 4 and 2 for groups B and C, respectively. We did not have a placebo group.

The amount of administered analgesic (pethidine) within the first 24 hours after operation for groups A, B and C was 275 mg, 150 mg, and 75 mg, respectively, as shown in Figure 2.

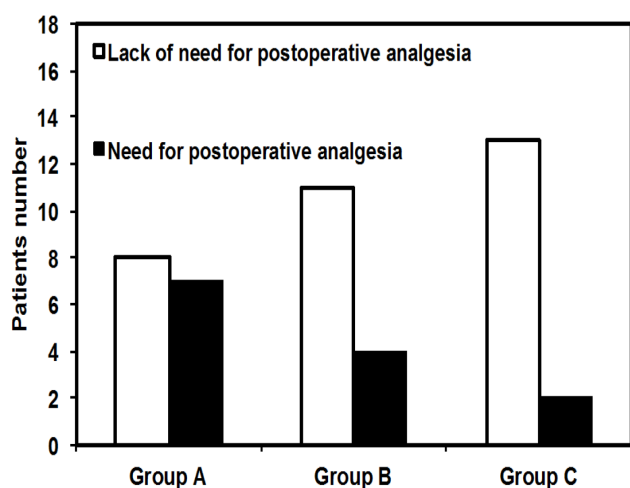


Figure 1. Comparison of need for postoperative analgesia among different groups.

Group A= Bupivacaine alone      Group B= Bupivacaine + Midazolam  
Group C= Bupivacaine + Fentanyl

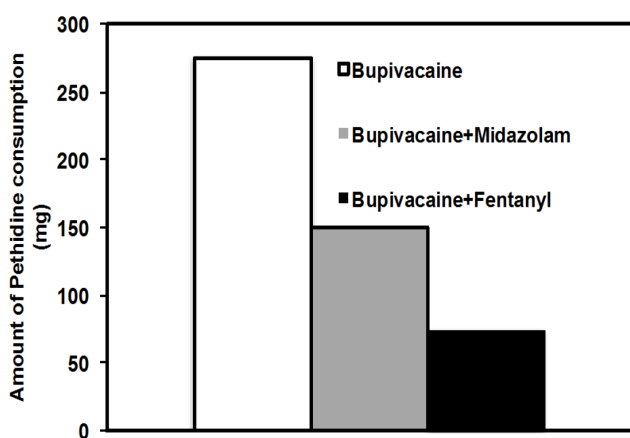


Figure 2. Amount of Pethidine consumption for different groups of A (Bupivacaine), B (Bupivacaine+Midazolam ) and C (Bupivacaine+Fentanyl).  $P$  value=0.109.

## Discussion

As it is known for pre-emptive analgesia, it must be given to patient before he/she asks to receive it. This is entirely possible with intra-articular analgesic technique.

Edham *et al.* has investigated the using analgesia after arthroscopy. Their results indicated that post-arthroscopy pain significantly decreased by midazolam intra-articular administration, however midazolam with Bupivacaine provided deeper and longer analgesia after knee arthroscopic surgery especially in first day compared with placebo (12).

In a study, performed by Batra *et al.* in Indian Anesthesiology Department, it was approved that intra-articular Midazolam significantly reduced post-operative pain compared with saline in the first day after surgery (10).

Hassani *et al.*, an anesthesiologist from Iran University of Medical Sciences, performed a study in 2006 and compared the analgesic effects of intra-articular injection of morphine, marcaine and both of them together on relieving knee arthroscopy pain (13). They concluded that morphine induces a delayed but long term analgesia while marcaine effect is fast and short (12).

The result of another study conducted by Dr. Heard in the Department of Anesthesiology and Surgery at Massachusetts University and in the hospital of Boston University Medical Center, showed that intra-articular injection of bupivacaine/marcaine after knee arthroscopy induces longer analgesia compared with morphine or placebo (14).

Aalipour *et al.* also performed a study at Ghaem Hospital from Mashhad University of Medical Sciences (MUMS) in 2013 on 46 patient candidates for arthroscopy. Patients were randomly divided into two groups and the study group received 1  $\mu$ g/kg Dexmedetomidine plus normal saline (total volume of 25 ml), and placebo group who received 25 ml of normal saline. Their results indicated that intra-articular administration of Dexmedetomidine after knee arthroscopy induces analgesia and increases the time interval between surgery and first analgesic administration with reduced need for analgesic injection (8).

The aim of present study was to approve the results of previous studies and to evaluate the additive effects of drugs like Midazolam, and fentanyl with Marcaine. Indeed the postoperative pain of arthroscopy could be varied considerably in different patients. Stimulation of free neural terminals of synovial tissue, frontal fat tissue and joint capsule following surgical incision are some reasons for pain (15). The reason that we did not find a significant difference between groups could be because of low study size or lack of placebo group.

However our results showed that intra-articular injection in all three groups induced the considerable analgesia in more than half of the patients. The amount of analgesia was higher in group C (Fentanyl+Marcaine, 13 patients out of 15) compared with two other groups of B (Midazolam+Marcaine,

11 patients out of 15) and group A (Marcaine alone, 8 patients out of 15) indicating the additive effects of drugs. The total amount of pethidine use in group C in first 24 hours after surgery was 75 mg, while it was 150 mg for group B and 275 mg for group A. Further studies with larger sample size and also with placebo group are recommended to reach better statistical difference.

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