Randomized Controlled Trial

# Comparative Study Between Dexmedetomidine and Fentanyl as an Adjuvant to Intraarticular Bupivacaine for Postoperative Analgesia after Knee Arthroscopy

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**Background:** Intraarticular bupivacaine produces sufficient analgesia after arthroscopic knee surgery, but its analgesic duration is short. There is a need to search for an adjuvant with a longer duration of analgesia.

**Objectives:** This study aimed to compare the duration of analgesia, total rescue analgesic consumptions, pain intensity, adverse effects, and patient satisfaction of dexmedetomidine and fentanyl as adjuvants to intraarticular bupivacaine for analgesia after knee arthroscopy.

**Study Design:** A prospective double-blind randomized controlled study.

**Setting:** Zagazig University Hospitals.

**Methods:** After ending arthroscopy and 15 minutes before deflation of the tourniquet, 45 patients were randomly allocated into 3 equal groups: Group B (n = 15) received an intraarticular injection of 50 mg (20 mL) bupivacaine 0.25% plus 1 mL saline; group BD (n = 15): received an intraarticular injection of 20 mL bupivacaine 0.25% plus 100 µg (1 mL) dexmedetomidine; and group BF (n = 15) received an intraarticular injection of 20 mL bupivacaine 0.25% plus 50 µg (1 mL) fentanyl.

**Results:** The BF group had a statistically significant longest duration of analgesia (693.3 ± 22.6 minutes) compared to group the BD (505.8 ± 23.5 minutes) and group B (244.1 ± 17.5 minutes) ($P < 0.0001$). The total meperidine consumption was statistically significantly decreased in group BF (35 ± 12.6 mg) compared to the BD and B groups (60 ± 12.6 mg and 83.3 ± 15.4 mg respectively) ($P < 0.0001$). Groups BF and BD showed a highly statistically significant lower postoperative static and dynamic pain scores at 30 minutes, 1, 2, 4, and 6 hours compared to group B. However, group BF was comparable to group BD at the same time intervals. Postoperative static and dynamic pain scores showed a highly statistically significant higher values at 4 hours in group B, 8 hours in group BD, and 12 hours in group BF ($P < 0.0001$). No significant side effects were observed in the groups. The duration of analgesia was the most important parameter that determined patient satisfaction.

**Limitations:** Small sample size and lack of studies that compare both adjuvants.

**Conclusions:** Fifty µg of fentanyl as an adjuvant to intraarticular bupivacaine produces effective and safe analgesia after knee arthroscopy as 100 µg of dexmedetomidine and has a longer analgesia duration in the first postoperative 24 hours.

**Key word:** Dexmedetomidine, fentanyl, intra-articular bupivacaine, postoperative analgesia, knee arthroscopy

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The majority of knee arthroscopic surgeries are performed in ambulatory settings. Therefore, achievement of an efficient, simple, safe, and reliable analgesia technique with minimal side effects and longer duration after knee arthroscopic surgery is essential for rapid recovery and decreasing the hospital stay (1).

Intraarticular bupivacaine produced adequate

analgesia after knee arthroscopy but only lasts for 2 to 4 hours (2,3).

Intraarticular injection of opioids, clonidine, dexmedetomidine, or magnesium sulfate as an adjuvant to local anesthetics is effective in managing pain after knee arthroscopy but they all have a variable duration of action (4).

Intraarticular injection of dexmedetomidine has been investigated in the literature to reduce pain with a longer duration of analgesia and less postoperative analgesic consumption (5-7). It reduces pain after knee arthroscopy mainly by peripheral and central mechanisms through stimulation of presynaptic $\alpha$2-adrenoceptors. Dexmedetomidine as an adjuvant to local anesthetics exaggerates the motor and sensory blockade of local anesthetics, retards the neural rectifier of local anesthetics through inhibition of sodium and potassium currents, and inhibits tetrodotoxin-resistant $Na^+$ channels, hence facilitating the analgesic effect of local anesthetics (8,9).

Opioids are injected intraarticularly with local anesthetics in order to prolong their duration of action (10). Intraarticular injection of opioids has been established since the presence of μ-, κ-, and δ–opioid receptors were confirmed on peripheral nerve endings (11).

So, this study was established to investigate the best adjuvant to intraarticular bupivacaine with the longest duration of analgesia and minimal side effects.

Our primary outcome was to compare the duration of analgesia of dexmedetomidine and fentanyl as adjuvants to intraarticular bupivacaine for analgesia after arthroscopic knee surgery. Our secondary outcomes were to evaluate pain intensity, total rescue analgesic consumptions, incidence of adverse effects, and patient satisfaction.

## Methods

The protocol of this study was approved by our University's Institutional Review Board (IRB #5355-7-4-2020), the trial was registered at clinicaltrials.gov (ref: NCT04442906 at 19-6-2020) before patients' enrollment. Written informed consent was obtained from all patients.

A prospective double-blind randomized controlled study was conducted on 45 patients from July 2020 through December 2020.

Forty-five patients included in this study were of either gender, age range from 21-45 years, Body Mass Index (BMI) 20-30 $kg/m^2$, American Society of Anesthesiologists (ASA) physical status I – II scheduled for elective knee arthroscopy under general anesthesia.

Patients with a history of advanced renal and hepatic diseases, psychiatric disorders, prolonged intake of nonsteroidal anti-inflammatory drugs, pain killers, beta blockers, or tricyclic antidepressant or sensitivity to the study drugs were excluded.

After routine preoperative evaluation of patients, all patients were kept fasting for 8 hours preoperative and were informed about the use of the Visual Analog Scale (VAS) as a 10-cm line labeled with (0 = no pain and 10 = worst pain) (12); basal Static (VAS-s) at rest when knees are in the neutral position; and basal dynamic (VAS-d) at flexion and extension of the knees scores. Parameters were recorded for all patients. Also, basal heart rate, mean arterial blood pressure, and oxygen saturation were recorded.

For all patients, an intravenous (IV) line was inserted, and 0.05 mg/kg IV midazolam was given as a premedication 15 minutes before surgery. Then, 10 mL/kg IV crystalloids were started. Standard monitoring (electrocardiogram, pulse oximetry, and automated noninvasive arterial blood pressure) was applied to all patients. Induction of anesthesia was done with one μg/kg fentanyl and 2 mg/kg propofol. Placement of an endotracheal tube was facilitated with 0.5 mg/kg IV atracurium. Anesthesia was maintained by 1.2% isoflurane in 100% $O_2$, atracurium 0.1mg/kg was repeated every 30 minutes; fentanyl was not repeated during the operation. Mechanical ventilation was adjusted to maintain the end tidal $CO_2$ at 30 to 35 mm Hg. A pneumatic tourniquet was placed around the middle of the thigh and inflated to 300 mm Hg (13). Then, the arthroscopic technique was carried out by the same orthopedic surgeon through 2 portals: one anteromedial and one anterolateral.

At the end of arthroscopy, before skin closure and 10 minutes before tourniquet deflation, all patients were randomly allocated into 3 equal groups using a computer generated randomization table. Each group consisted of 15 patients:

- Group B (n = 15) (control group) received an intraarticular injection of 50 mg (20 mL) bupivacaine 0.25% plus one mL saline.
- Group BD (n = 15) received an intraarticular injection of 20 mL bupivacaine 0.25% plus 100 μg (one mL) dexmedetomidine.
- Group BF (n = 15) received an intraarticular injection of 20 mL bupivacaine 0.25% plus 50 μg (one mL) fentanyl.

The total volume injected in each group was 21 mL. Study solutions were prepared by the anesthesiolo-

gist and injected by the orthopedic surgeon in the knee joint and then the tourniquet was deflated.

Reversal of the muscle relaxant was done using neostigmine 0.05mg/kg plus atropine 0.02 mg/kg. Extubation was done after fulfilling the criteria of extubation. Then the patient was transferred to the postanesthesia care unit (PACU).

In the PACU, a monitor was attached to the patient and an anesthesiologist not sharing in the study (the outcome assessor) evaluated the primary and secondary outcomes.

Acetaminophen one g IV was given every 6 hours as a standard regimen for pain management.

The primary outcome was duration of analgesia defined as the time from intraarticular injection of the study drug solutions to the first call of meperidine (rescue analgesic) in minutes in the first 24 hours postoperative.

The secondary outcomes were:

1- Pain intensity was assessed using the VAS score at baseline then at 30 min, 1, 2, 4, 6, 8, 12, 18 and 24 hours postoperative on both VAS-s and VAS-d. (Rescue IV meperidine 25 mg was given if VAS ≥ 4; the total meperidine consumption was recorded.
2- Any adverse effects such as nausea or vomiting, hypotension (mean arterial blood pressure decreasing by > 20% of basal reading), bradycardia (heart rate decreasing by > 20% of basal reading), or pruritus were recorded and managed.
3- Patient satisfaction was recorded at the end of 24 hours postoperative using the 5-point Likert-like verbal rating scale (14) by asking the patient about "how he/she evaluated their experience with the analgesic management after the surgery?" The scale was 5 = very satisfied, 4 = satisfied, 3 = neutral, 2 = dissatisfied and 1 = very dissatisfied."

### Sample Size

Sample size was calculated based on the assumption of comparing the 3 investigated groups with regard to the time request for analgesia in minutes. The following parameters were considered: n (number of categories) = 3, f (effect size) = 0.5, power = 0.8 and cutoff level of significance (*P* value) = 0.05. This analysis was done using the R package "pwr," function "pwr.anova test" (15). Based on these calculations, 15 patients were included in each group (total n = 45 patients) considering a drop out error of one patient per group.

### Statistical analysis

To analyze the significance among the 3 groups, a Kolmogorov–Smirnov test was performed for verification of the assumption of normality. The continuous numerical variables were represented as mean ± SD and the overall significance of difference among the 3 investigated patient groups were determined by one-way analysis of variance (ANOVA). To determine if there were significant differences among the 3 groups, Tukey's test was used as a posttest to correct for multiple comparisons. The categorical variables were shown as numbers and frequencies (%), and the differences among groups were determined using the $\chi^2$ test applied on contingency tables. The *P* value was considered significant if $< 0.05$ and highly significant if $< 0.001$. This analysis was done using Graph Pad Prism software v. 8 (GraphPad Software, San Diego, CA).To reveal the patient parameters that best determine postoperative satisfaction, the patient's satisfaction degree (e.g., from dissatisfied to very satisfied) was considered as the outcome and other parameters (duration of analgesia, total meperidine consumption, age, gender, BMI, ASA physical status, treatment with either bupivacaine, bupivacaine plus dexmedetomidine and bupivacaine plus fentanyl) were used as predictor variables in a random Forest classification model. The ranked importance of the parameters was determined using the mean decrease in accuracy of the patient classification when the parameter was permuted. The larger the mean decreases in accuracy, the more important the parameter. The patient group "very dissatisfied" was not included in this analysis because it was represented by only one patient. This analysis was done using MetaboAnalyst web server that is based on the R programming language (https://www.metaboanalyst.ca/home.xhtml) (16).

## Results

Fifty-five patients were prepared for the study while 10 patients were excluded. Five patients refused to complete the study, 2 patients had a psychic disturbance on the antipsychotics drugs, while 3 patients were on prolonged intake of painkillers as shown in the Consolidated Standards of Reporting Trials Statement (Fig. 1). So, 45 patients were randomly allocated into the 3 equal groups (15 patients in each).

– Patient characteristics (age, gender, BMI, ASA physical status) and duration of surgery were comparable among the 3 groups (Table 1).
– The BF group had a highly statistically significant longest duration of analgesia (693.3 ± 22.6 min-

utes) compared to group BD (505.8 ± 23.5 minutes) and group B (244.1 ± 17.5 minutes) ($P < 0.0001$).

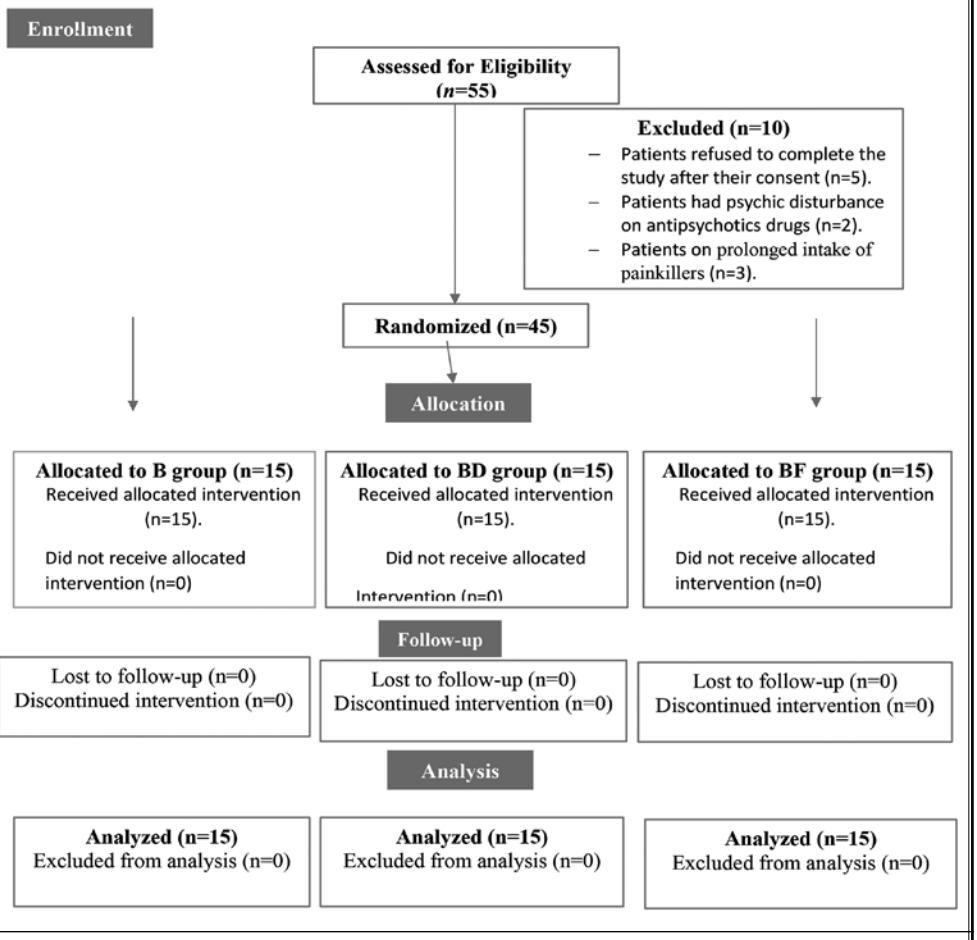


Fig 1. *Consort flow diagram.*

Moreover, group BD had a statistically significant longer duration (505.8 ± 23.5 minutes) compared to group B (244.1 ± 17.5 minutes) ($P < 0.0001$) (Table 2).

– The total meperidine consumption in group BF was highly statistically significant for lowest consumption (35 ± 12.6 mg) compared to the BD and B groups (60 ± 12.6 mg and 83.3 ± 15.4 mg) respectively ($P < 0.0001$). Also, group BD had a highly statistically significant lower total meperidine consumption (60 ± 12.6 mg) compared to group B (83.3 ± 15.4 mg) ($P < 0.0001$) (Table 2).

– Basal VAS-s and VAS-d scores were comparable among the 3 groups. Regarding postoperative VAS-s and VAS-d scores: Groups BF and BD showed a highly statistically significant lower VAS-s and VAS-d

Table 1. *Patient characteristics and duration of surgery among studied groups.*

| Group / Feature | | Group B (n = 15) | Group BD (n = 15) | Group BF (n = 15) | $\chi^2/f$ | *P* Value |
|---|---|---|---|---|---|---|
| Age (years) | | 32.3±5.8 | 35.6±5 | 34.6±5.5 | $f$ =1.44 | 0.24 |
| Gender | Male n (%) | 12 (80%) | 11 (73.3%) | 9 (60%) | $\chi^2$=1.5 | 0.46 |
| | Female n (%) | 3 (20%) | 4 (26.7%) | 6 (40%) | | |
| BMI (Kg/m$^2$) | | 25.3±2.5 | 27±2.3 | 25.6±2.5 | $f$ =2.06 | 0.13 |
| ASA | I | 12 (80%) | 14 (93.3%) | 11 (73.3%) | $\chi^2$=2.18 | 0.34 |
| | II | 3 (20%) | 1 (6.6%) | 4 (26.6%) | | |
| Duration of surgery (min.) | | 69.5±3.8 | 69.1±3.1 | 68.8±4.4 | $f$ =0.13 | 0.8 |

Data were expressed as mean±SD, or No (%). $P < 0.05$was significant. $\chi^2$ =chi square test.
ASA= American Society of Anesthesiologist. BMI=Body Mass Index. $f$ =one way analysis of varience.

scores compared to group B at 30 minutes, one, 2, 4 and 6 hours ($P < 0.0001$). However, group BF was comparable to group BD at the same time intervals ($P > 0.05$). VAS-s and VAS-d scores showed a highly statistically significant higher value at 4 hours in group B, 8 hours in group BD, and 12 hours in group BF compared to the other 2 groups ($P < 0.0001$). Otherwise, there were no statistically significant differences among the 3 groups at 18 and 24 hours (Fig. 2).

- There were no significant adverse effects observed among the groups.
- Patients in groups BF and BD were statistically significant satisfied with their analgesia compared to group B ($P = 0.03$). However, patients in groups BD and BF were comparable regarding satisfaction ($P < 0.05$) (Table 2).
- Duration of analgesia was the most important parameter determining patient satisfaction (Fig. 3).

## Discussion

This study demonstrates that the use of 50 µg fentanyl as an adjuvant to intraarticular bupivacaine produces effective and safe analgesia after knee arthroscopy compared to 100 µg dexmedetomidine but with a longer duration of analgesia in the first postop-

Table 2. *Analgesic parameters and patient satisfaction among the studied groups.*

| Groups / Feature | | B group (n=15) | BD group (n=15) | BF group (n=15) | $f$ / $\chi^2$ | $P$-value |
|---|---|---|---|---|---|---|
| Duration of analgesia (min) | | 244.1±17.5 | 505.8±23* | 693.3±22.6** | Ғ = 1661 | < 0.0001 |
| Meperidine consumption (mg) | | 83.3±15.4 | 60±12.6* | 35±12.6** | Ғ =46.9 | < 0.0001 |
| Patient satisfaction | Very satisfied | 2 (13.3%) | 6 (40%) | 7 (46.7%) | $\chi^2$=16.23 | 0.03 |
| | Satisfied | 3 (20%) | 6 (40%) | 7 (46.7%) | | |
| | Neutral | 6 (40%) | 3 (20%) | 1 (6.7%) | | |
| | Dissatisfied | 3 (20%) | 0 (0%) | 0 (0%) | | |
| | Very dissatisfied | 1 (6.7%) | 0 (0%) | 0 (0%) | | |

Data were expressed as mean±SD, or No (%). $P<0.05$ was significant. $P<0.0001$ was highly significant $\chi^2$ =chi square test.
Ғ =one way analysis of variance. **= statistically significant compared to groups BD and B. *= statistically significant compared to group B.

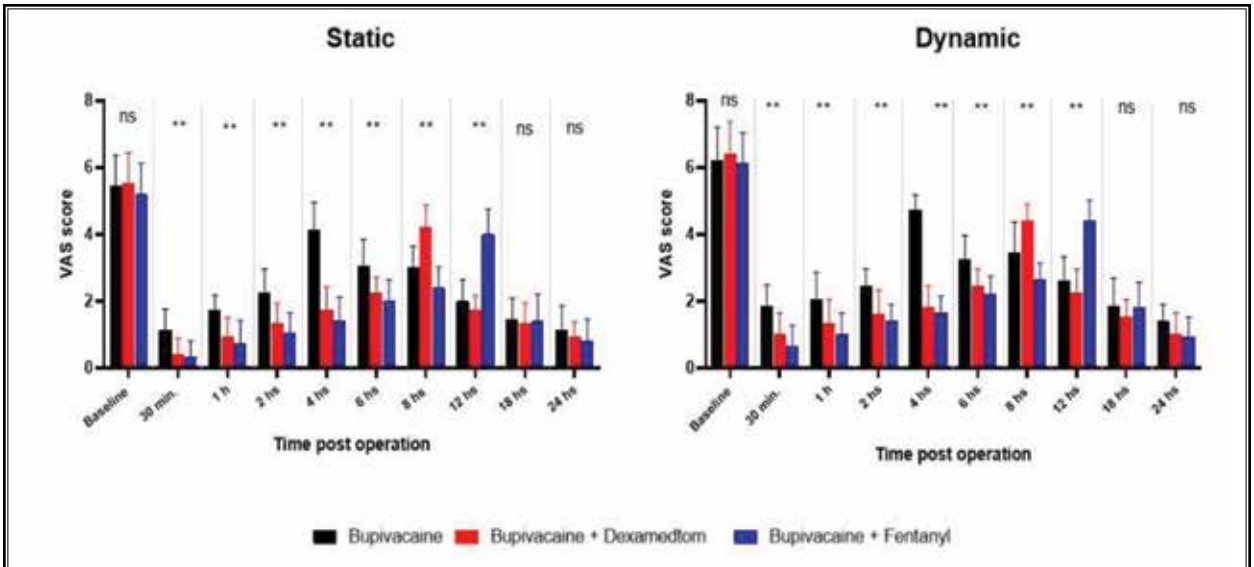


Fig 2. *Mean Visual analog scale (VAS) scores among the three studied groups on static (at rest) and on dynamic (at mobility) at the measured time points. ** = highly significant (p<0.0001). ns = non-significant*

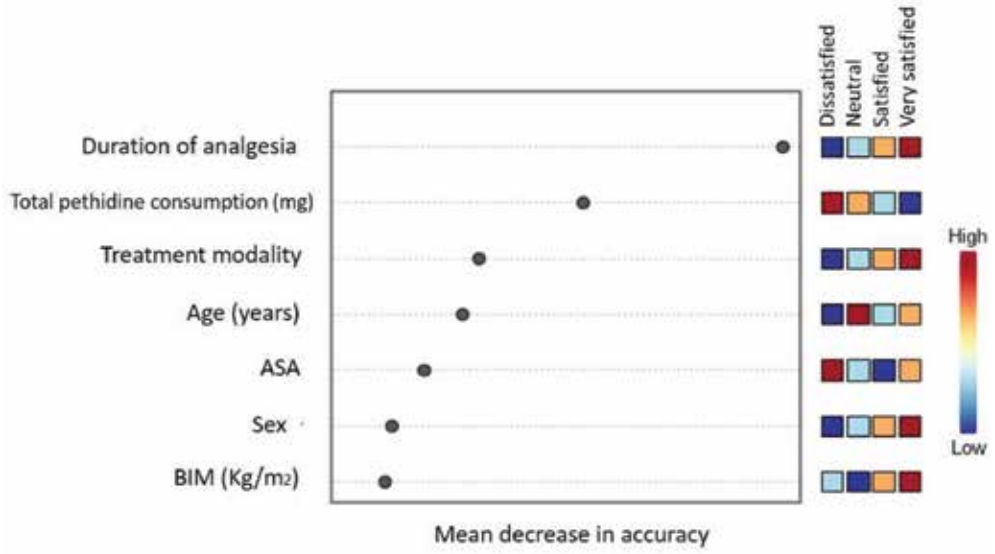


Fig 3. *Random forest classification model showing the parameters (Y-axis) that could predict patient's satisfaction ranked in a descending order by their importance as measured by the mean decrease in accuracy of classifying the patient satisfaction. The mini-heat maps on the right show a color-coded frequency of each parameter in the respective group. The duration of analgesia is the most important parameter that could determine patient's satisfaction after the operation.*

erative 24 hours.

To the best of our knowledge this is the first study that compares intraarticular fentanyl and intraarticular dexmedetomidine as an adjuvant to intraarticular bupivacaine regarding the quality of analgesia after knee arthroscopy.

In the current study, fentanyl as an adjuvant to intraarticular bupivacaine had the longest duration of analgesia (693.3 ± 22.6 minutes) and decreased meperidine consumption followed by dexmedetomidine (505.8 ± 23.5 minutes) then bupivacaine alone (244.1 ± 17.5 minutes).

Agrawal et al (17) published a comparative study that assessed the analgesic efficacy of intraarticular morphine compared to intraarticular dexmedetomidine added to levobupivacaine after knee arthroscopy. They concluded that intraarticular morphine revealed a highly statistically significant longer duration of analgesia (576.20 ± 67.09 minutes) compared to intraarticular dexmedetomidine (460.93 ± 38.95 minutes) with a significant lower total rescue analgesic consumption in the morphine group. Varkel et al (18) revealed that 50 µg intraarticular fentanyl had better pain relief than 3 µg intraarticular morphine following knee arthroscopy. These results were in alignment with ours; intraarticular fentanyl exerts its potent and significant clinical analgesic effects by activation of peripheral opioid receptors in the sensory neurons of the knee joint. In response to tissue injuries and local inflammatory process occurring in the surgical wound during the early postsurgical period, which is associated with activation of the inner immune system and production of chemokines and cytokines, the opioid receptors in the dorsal root ganglion of the peripheral neuron increase in synthesis, membrane-directed trafficking, axonal transport, and coupling to G proteins leading to enhancing the analgesic effect of intraarticular fentanyl. In addition, disruption of the perineural barrier by inflammation and low PH allows easier access of fentanyl to its opioid receptors and subsequent release of opioid peptides from immune cells that inhibit the nociceptive excitability of the sensory neurons as its release is dependent on $Ca^{++}$ release from the endoplasmic reticulum (19,20).

In agreement with our findings, Mostafa at al (21) reported that the duration of analgesia after knee arthroscopy was statistically significantly longer in the intraarticular dexmedetomidine added to bupivacaine group (458 ± 93.5 minutes) compared to the intraarticular bupivacaine only group (229.1 ± 83.7 minutes) with a significant decrease in total meperidine consumption.

In the present study, patients in the fentanyl group

started to report pain later at 12 hours postoperative. However, a recent meta-analysis by Lu et al (22) suggested that 50 µg intraarticular fentanyl lowered pain scores for only up to 8 hours postoperative for knee arthroscopy. That can be attributed to the limited number of randomized clinical trials (only 4) that they could find and include in their meta-analysis.

However, patients in the dexmedetomidine group showed significantly increased pain intensity at 8 hours postoperative (22). This was in agreement with studies by Ismail et al (23) and Mostafa et al (21). Moreover, there were statistically significant higher VAS values at 4 hours in the bupivacaine group, which correlates with Campo et al. (24).

Adequate analgesia is the cornerstone for patient satisfaction (25). Patients in the current study were satisfied with analgesia in the fentanyl and dexmedetomidine groups more than the bupivacaine group; the duration of analgesia was the most important parameter that determined patient satisfaction.

The results of this study reveal no significant side effects among the 3 studied groups. This could be explained as intraarticular injection of local anesthetics with different adjuvants improves analgesia locally by stimulation of peripheral joint receptors (24). Also, the absence of blood vessels on the articular surface minimizes systemic absorption (26). Lastly, fentanyl has a lipophilic property, and when injected locally it is not associated with hyperalgesia as there is no local release of histamine (27,28).

Effective analgesia with no side effects following knee arthroscopic surgeries was reported in Agrawal et al (17) and Lu et al (22).

### Limitation

A limitation of this study is the small sample size, but it didn't affect our results because of accepted type II error (power 80%). Another limitation is the lack of studies that compare the effects of fentanyl and dexmedetomidine as an adjuvant to intraarticular bupivacaine after knee arthroscopic surgeries. So, we recommend further studies with a larger sample size and different doses of intraarticular fentanyl or dexmedetomidine.

## Conclusion

The use of 50 µg fentanyl as an adjuvant to intraarticular bupivacaine produces effective and safe analgesia after knee arthroscopy compared to 100 µg dexmedetomidine and has a longer duration of analgesia in the first postoperative 24 hours.

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