Egyptian Journal of Anaesthesia

ISSN: (Print) 1110-1849 (Online) Journal homepage: https://www.tandfonline.com/loi/teja20

Effect of intra-articular injection of midazolam and/or bupivacaine on postoperative analgesia after arthroscopic knee surgery

Salwa M.S. Hayes, Emadeldeen S. Nasr, Enas A.A. El Motilb & Adham A. El Geidi

To cite this article: Salwa M.S. Hayes, Emadeldeen S. Nasr, Enas A.A. El Motilb & Adham A. El Geidi (2012) Effect of intra-articular injection of midazolam and/or bupivacaine on postoperative analgesia after arthroscopic knee surgery, Egyptian Journal of Anaesthesia, 28:2, 143-147, DOI: 10.1016/j.egja.2011.11.004

To link to this article: https://doi.org/10.1016/j.egja.2011.11.004

Published online: 17 May 2019.

Egyptian Journal of Anaesthesia (2012) **28**, 143–147

Egyptian Society of Anesthesiologists

Egyptian Journal of Anaesthesia

www.elsevier.com/locate/egja
www.sciencedirect.com

Research Article

Effect of intra-articular injection of midazolam and/or bupivacaine on postoperative analgesia after arthroscopic knee surgery

Salwa M.S. Hayes [a,*], Emadeldeen S. Nasr [a], Enas A.A. El Motilb [a], Adham A. El Geidi [b]

[a] *Department of Anesthesiology and ICU, Mansoura University, Faculty of Medicine, Mansoura University Hospital, 02050, Egypt*
[b] *Department of Orthopedic, Mansoura University, Faculty of Medicine, Mansoura University Hospital, 02050, Egypt*

Received 28 September 2011; revised 12 November 2011; accepted 16 November 2011
Available online 24 December 2011

KEYWORDS

Intra-articular midazolam bupivacine;
Knee arthroscopic surgery

Abstract *Background:* A variety of analgesic techniques have been used to manage postoperative pain after arthroscopic knee surgery. We investigated the hypothesis that intra-articular midazolam would result in lower pain score and reduced analgesic requirements.
Methods: One-hundred patients undergoing arthroscopic meniscectomy were allocated randomly to receive intra-articular 20 mL of isotonic saline containing 50 μg/kg midazolam (midazolam group (group M),the bupivacaine group (group B) received 0.25% (20 mL) bupivacaine, and the midazolam with bupivacaine group (group MB) received bupivacaine 0.25% and 50 μg/kg of midazolam in 20 mL. The postoperative analgesia was assessed using visual analog score at rest and during movement at 1/2 h, 1 h, 2 h, 6 h, 12 h, and 24 h.
Results: Patients in group MB showed significantly lower visual analog scores, both at rest and during movement, long time to first postoperative analgesic request, as well as reduced total analgesic consumption than the other two groups.

* Corresponding author. Address: Department of Anesthesiology and ICU, Mansoura University, Faculty of Medicine, Mansoura University Hospital, 02050, Egypt. Tel.: +20 102223272.
E-mail address: salwa.hayes@yahoo.com (S.M.S. Hayes).

Peer review under responsibility of Egyptian Society of Anesthesiologists.
doi:10.1016/j.egja.2011.11.004

Conclusion: Intraarticular administration of midazolam in combination with bupivacaine improves the quality of postoperative analgesia after arthroscopic meniscectomy.

1. Introduction

Arthroscopic knee procedures are commonly performed for outpatients setting using different anesthetic techniques including general, spinal, epidural, regional nerve block and local anesthesia, one of the important regime is the intra-articular injection of various drugs such as opioid, non-steroidal anti-inflammatory, clonidine, neostigmine, local anesthetics and ketamine [1–4].

The use of intra-articular bupivacaine for knee arthroscopy has been gained worldwide popularity either alone or in combination with other intra-articular additives [5,6].

Midazolam, a benzodiazepine (BDP) agonist has a well settled peripheral analgesic effect, via the peripheral benzodiazepine receptors which distributed in various organs and joints, these receptors are present in the outer mitochondrial membrane and bind with a different affinities to various benzodiazepines [7].

The present study was performed to investigate the effects of intra-articular injection of midazolam with or without bupivacaine on the postoperative visual analog pain scores (VASs) and postoperative analgesic consumption after knee arthroscopic surgery.

2. Patients and methods

After obtaining local ethics committee approval and an informed written consent, one-hundred patients with ASA I and II undergoing arthroscopic meniscectomy were enrolled in this randomized, prospective, blinded study.

Patients with cardiac, hepatic or renal disorder, patients less than 18 years old, patients with communications barriers for the interpretation of VAS, patients with drug allergy, and preoperative use of oral narcotics, non-steroidal anti-inflammatory, and opioid were excluded from the study.

Patients were randomly assigned into three groups (25 patients for each), using a computer generated randomization code included in sequentially numbered, sealed, opaque envelopes. Patients in group M received (intra-articular injection of midazolam 50 μg/kg in 20 mL isotonic saline). Patients in group B received (intra-articular injection of 20 mL bupivacaine 0.25%). Patients in group MB received (intra-articular injection of midazolam 50 μg/kg and bupivacaine 0.25% in 20 mL isotonic saline) at the end of surgery.

The study solutions look identical and were prepared before surgery by a blind investigator to the study protocol and the patient's randomization code.

The primary objective included the postoperative VAS pain scores, Secondary outcome variables included the time of the first analgesic request and the total doses of first 24 h postoperative ketorolac consumption.

The studied populations were instructed about the postoperative assessment of pain severity using a 10 cm visual analog scale (VAS) with 0, no pain, with 10, the worst pain.

Standard intraoperative monitoring included 3-lead ECG, pulse oximeter, capnography and non-invasive arterial blood pressure were applied. Baseline heart rate (HR) and mean arterial blood pressure (MAP), were recorded.

Anesthetic management was standardized in all studied population, no premedications were given and surgery was done under general anesthesia, after preoxygenation, anesthesia was induced by using IV fentanyl 2 μg/kg, propfol 2 mg/kg and tracheal intubation was facilitated by atracurium 0.5 mg/kg, the lungs were mechanically ventilated to maintain normocapnia. Anesthesia was maintained using isoflurane 1 MAC in 100% of oxygen and atracurium increments of 0.1–0.2 mg/kg.

A pneumatic tourniquet was applied to the operative side and inflated to 300 mmHg to provide surgical homeostasis. At the end of surgery, a blind surgeon to the study protocol injected the prepared study solution intra-articularly into the knee joint using the arthroscopic guidance 10 min before the tourniquet release. No postoperative intra-articular drainage was used for any patients.

At the completion of surgery, isoflurane was discontinued and the residual neuromuscular blockade was reversed using neostigmine 50 μg/kg and atropine 20 μg/kg and the patients were extubated. Patients were admitted to the recovery room.

Postoperative monitoring of patients included heart rate (HR), mean arterial blood pressure (MAP) and oxygen saturation.

Postoperative analgesia was assessed by using VAS at 0.5, 1, 2, 6, 12, 24 h, evaluation was done both at rest and during movement (active movement of the knee joint), all data were collected by a blinded observer who was unaware of the patients' assignment group.

Postoperative analgesia was achieved using IV ketorolac (30 mg) per dose every 8 h if required with a maximum daily dose of 120 mg. Tramadol 50 mg i.v was used as a rescue analgesic if the patients continued to suffer pain after ketorolac administration .

The time from completion of surgery until the first analgesic dose requirements and the total analgesic dose during the first 24 h after the operation were also recorded.

Side effects from intra-articular injection of midazolam and bupivacaine such as significant reduction in arterial blood pressure or heart rate (more than 15% from baseline), arrhythmia, flushing, nausea, vomiting, or respiratory depression, were recorded during the first 24 h period after surgery.

3. Statistical analysis

The statistical analysis of data done by using *SPSS* (SPSS, Inc., Chicago, IL) version 16. Kolmogorov–Smirnov test was done to test the normality of data distribution .The description of the data done in form of mean (+/−) SD for quantitative data, and Frequency & proportion for Qualitative data. Repeated measure analysis of variance was done. One way ANOVA and Tukey-Honest post hoc tests were used to compare the

parametric data between the studied groups. Chi square test was used for categorical data.

P value less than 0.05 was considered significant.

We calculated the needed sample size from our preliminary data. We found that 22 patients were needed in each group. The total number of studied patients in each group would be 25 patients after the adding of 10% to compensate for the dropped cases during the study.

4. Result

All patients completed the study protocol, as regard the patients age, gender, body weight and height, are shown in (Table 1), with no statistical significant difference among the studied groups.

Tourniquet time and duration of surgery were similar among the studied groups (Table 2).

There were no statistical significant difference between groups as regard the perioperative hemodynamic changes, O_2 saturation, and end-tidal CO_2.

Postoperative pain scores at rest were significantly lower in group MB in comparison to group M at 0.5, 1, 2, 6, and 12 h after surgery (*p*-value $\leqslant$0.003) (Graph 1).

Postoperative pain scores in the patients in group MB were significantly lower at rest than those in group B at 2 h and 6 h (*p*-value $\leqslant$0.03) (Graph 1).

Pain scores in the patients in group MB were significantly lower during movement than in group M and group B at 0.5, 1, 2, 6, 12, and 24 h after surgery (*p*-value $\leqslant$0.02) (Graph 2).

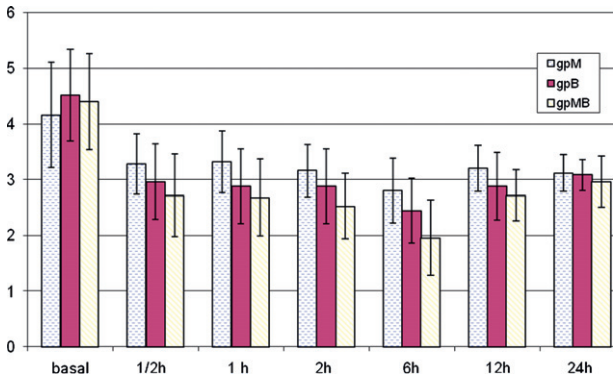
There were no statistical significant difference as regarding postoperative pain scores at movement in groups B and group M, although postoperative pain scores at rest were lower in group B than in group M at 1, 6 and 12 h after surgery (*p*-value $\leqslant$ 0.01) (Graphs 1 and 2).

Postoperative heart rate (HR), mean arterial blood pressure (MAP) and oxygen saturation showed no significant difference between groups.

Total analgesic consumption during first 24 h postoperative were significantly lower in group MB than in groups M and group B (Table 2).

The time to first request for analgesic after surgery was significantly longer in the patients in group MB than those in groups M and group B (Table 2).

There were no noted side effects (such as nausea and vomiting, bradycardia and hypotension) among the studied patients in the three groups during the 24 h after surgery.



Graph 1

Visual analog score at rest preoperative and postoperative

gpM ---midazolam group

gpB --- bupivacaine group

gpMB -- midazolam+ bupivacaine

significant reduction of VAS in gpMB in comparison to gpM and gpB

Graph 1 Visual analog score at rest preoperative and postoperative gpM – midazolam group gpB – bupivacaine group gpMB – midazolam + bupivacaine significant reduction of VAS in gpMB in comparison to gpM and gpB.

Table 1 demographic data.

Variable	GpM	GpB	GpMB
Age (year)	43.68 ± 8.68	43.68 ± 8.68	44.12 ± 8.44
Male	12(48.0%)	11(44.0%)	13(52.0%)
Female	13(52.2%)	14(56.0%)	12(48.0%)
Body weight (kg)	79.40 ± 7.11	77.96 ± 7.82	78.08 ± 5.63
Height (cm)	165.04 ± 1.01	165.84 ± 1.81	165.60 ± 1.35

GpM – midazolam group.
GpB – bupivacaine group.
GpMB – midazolam + bupivacaine.
No statistical significant difference among groups.

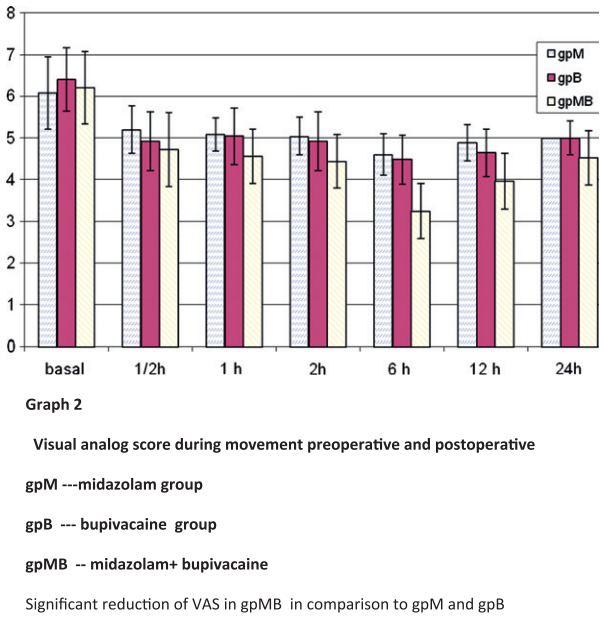
5. Discussion

Arthroscopic surgery is associated with variable amount of post operative pain which caused by an irritation of free nerve

Table 2 Tourniquet time, duration of operation, total analgesic dose, first analgesic request.

Variable	GpM	GpB	GpMB
Tourniquet time (min)	49.88 ± 2.48	49.84 ± 2.19	50.40 ± 2.27
Duration of operation (min)	66.44 ± 1.70	66.72 ± 2.09	64.76 ± 2.22
Total analgesic dose (mg)	40.71 ± 14.91†	39.00 ± 20.24*	21.42 ± 8.01
First analgesic request (min)	342.85 ± 265.66†	361.00 ± 295*	682.85 ± 169.48

GpM – midazolam group.
GpB – bupivacaine group.
GpMB – midazolam + bupivacaine.
$P < 0.05$ significant compared GPM† and GpB*.
GpM† and GpB* had a significantly shorter time to first analgesic request than GpMB.



Graph 2 Visual analog score during movement preoperative and postoperative gpM – midazolam group gpB – bupivacaine group gpMB – midazolam + bupivacaine significant reduction of VAS in gpMB in comparison to gpM and gpB.

ending of the synovial tissue, anterior fat pad, and joint capsule result from surgical excision and resection [8].

The main findings in this study were that the addition of midazolam to bupivacaine achieved more effective analgesia. Patients received intra-articular midazolame and bupivacaine had lower postoperative pain scores, a longer analgesic duration, and lower 24-h analgesic consumption compared with those received intraarticular either bupivacaine, or midazolam individually.

In this study, the use of intra-articular midazolame alone achieved comparable post operative analgesia with intra-articular bupivacaine.

The action of midazolam on peripheral receptors has been substantiated by its efficacy in enhancing the duration of analgesia when used in conjunction with bupivacaine for brachial plexus block [9]. A similar action of midazolam on GABA-A receptors in afferent nerve endings in the knee joint may be responsible for its analgesic action [7], Various authors have demonstrated the presence of the GABA-A receptors in peripheral nerves, which may have served as the mechanism of action for IA midazolam [10].

Batra and colleagues [11], studied different doses of intra-articular midazolam (50 μg/kg, 75 μg/kg),and they concluded in similar to our study that The addition of intra-articular midazolam significantly reduced visual analog pain scores in the early postoperative period compared with saline, they suggested that midazolame may act at a peripheral site in the joint, which was confirmed in the present study, They reported mild nausea in three patients after the use of 75 μg/kg of intra-articular midazolam, and in two patients each after the use of 50 μg/kg midazolam or placebo, this may be due to artial vascular uptake and subsequent transport to the central nervous system. The side effects are short-lived due to the high lipophilicity, rapid clearance (6–11 mL/kg/min), and short half-life (1.7–2.6 h) of midazolam [9,12], so, we selected in our study to use intra-articular midazolam in a dose of 50 μg/kg rather than 75 μg/kg.

He et al. [13] studied of the analgesic effects of intra-articular midazolam after knee arthroscopy they found that intra-articular midazolam significantly reduced visual analog pain scores in the early postoperative period (4 h) compared with saline [(2.0 ± 0.3) vs (4.8 ± 0.4), $P < 0.05$], while did not increase adverse effects, they concluded that intra-articular midazolam might be an ideal choice for postoperative analgesia after knee arthroscopy.

In the present study there were no noted complications with the use of intra-articular injection of midazolam which may be due to injection in a relatively avascular area.

Elsharnouby and coworkers [14] reported that intra-articular bupivacaine after arthroscopic surgery has been safely used with significant decrease postoperative pain scores, reduction of the postoperative analgesic consumption and increase the time to take first analgesic dose which was confirmed in the present study.

The analgesic effect of intra-articular bupivacaine after arthroscopic surgery has been demonstrated by different studies, it was safely used after arthroscopic knee surgery with significant reduction in postoperative analgesic consumption as well as increasing the time to first analgesic dose demanded [5,15,16].

In conclusion, Intra-articular administration of both midazolam and bupivacaine improves the quality of postoperative analgesia after arthroscopic meniscectomy.

References

[1] Kaeding CC, Hill JA, Katz J, Benson L. Bupivacaine use after knee arthroscopy: pharmacokinetics and pain control study. Arthroscopy 1990;6:33–9.
[2] Chirwa SS, Macleod BA, Day B. Intraarticular bupivacaine(marcaine) after arthroscopic meniscectomy: a randomized double-blind controlled study. Arthroscopy 1989;5:33.
[3] Gentili M, Houssel P, Osman M, Henel D, Jubel A, Bonnet F. Intra-articular morphine and clonidine produce comparable analgesia but the combination is not more effective. Brit J Anaesth 1997;79:660–1.
[4] Yang LC, Chen LM, Wang CJ, Buerkle H. Postoperative analgesia by intraarticular neostigmine in patients undergoing knee arthroscopy. Anesthesiology 1998;88:334–9.
[5] Allen GC, St Amand MA, Lui AC, et al. Postarthroscopy analgesia with intraarticular bupivacaine/morphine: a randomized clinical trial. Anesthesiology 1993;79:475–80.
[6] Reuben SS, Connelly NR. Postoperative analgesia for outpatient arthroscopic knee surgery with intraarticular clonidine. Anesth Analg 1999;88:729–33.
[7] Bazzichi L, Betti L, Giannaccini G, Rossi A, Lucacchini A. Peripheral type benzodiazepine receptors in human mononuclear cells of patients affected by osteoarthritis, rheumatoid arthritis or psoriatic arthritis. Clin Biochem 2003;36:57–60.
[8] Dye SF, Vaupel GL, Dye CC. Conscious neurosensory mapping of the internal structures of the human knee without intraarticular anesthesia. Am J Sports Med 1998;26:773–7.
[9] Jarbo K, Batra YK, Panda NB. Brachial plexus block with midazolam and bupivacaine improves analgesia. Can J Anaesth 2005;52:822–6.

[10] Goodchild CS, Guo Z, Musgreave A, Gent JP. Antinociception of intrathecal midazolam involves endogenous neurotransmitter acting at spinal cord delta opioid receptor. Brit J Anaesth 1996;77:758–63.
[11] Batra YK, Mahajan R, Kumar S, Rajeev S, Singh Dhillon M. A dose-ranging study of intraarticular midazolam for pain relief after knee arthroscopy. Anesth Analg 2008;107:669–72.
[12] Reves JG, Fragen RJ, Vinik HR, Greenblatt DJ. Midazolam: pharmacology and uses. Anesthesiology 1985;62:310–24.
[13] He Xing-ying, Shi Xue-yin, Yuan Hong-bin, XU Hai-tao, Ning Hui-jie. Study of intraarticular midazolam for postoperative analgesia after knee arthroscopy. Chin J Clin Pharmacol 2010;26(1).
[14] Elsharnouby NM, Eid HE, Abou Elezz NF, et al. Intraarticular injection of magnesium sulphate and/or bupivacaine for postoperative analgesia after arthroscopic knee surgery. Anesth Analg 2008;106:1548–52.
[15] Raja SN, Dickstein RE, Johnson CA. Comparison of postoperative analgesic effects of intra-articular bupivacaine and morphine following arthroscopic knee surgery. Anesthesiology 1992;77:263–6.
[16] Karlsson J, Rydgren B, Eriksson B, Järvholm U, Lundin O, Swärd L, Hedner T. Postoperative analgesic effects of intraarticular bupivacaine and morphine after arthroscopic cruciate ligament surgery. J Knee Surg Sports Traumatol Arthrosc 1995;3:55–9.