

Intra-articular Adjuvant Analgesics Following Knee Arthroscopy: Comparison between Dexmedetomidine and Fentanyl

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Abstract:

This study was designed to compare the analgesic effect produced by intra-articular (IA) administration of either dexmedetomidine or fentanyl in combination with bupivacaine following arthroscopic knee surgery. Ninety ASA physical status I–II patients, scheduled for knee arthroscopic procedures were randomly assigned into three groups. The control group B received 30 ml 0.25% bupivacaine only; group B/D received 30 ml 0.25% bupivacaine and dexmedetomidine 1 µg/kg, and group B/F received 30 ml 0.25% bupivacaine and fentanyl 1 µg/kg at the end of arthroscopy. Postoperatively, pain visual analogue scale (VAS) at rest and during movement, the time to first postoperative analgesic request, and the total postoperative analgesic use during the first 24 h were recorded. The time to first postoperative analgesic request was longer in the B/D group (450 ± 85 min) and B/F group (465 ± 90 min) versus control B group (230 ± 85 min) ($P < 0.05$). Supplementary analgesic consumption during the first 24 h was almost equivalent for the B/D and B/F groups (mean meperidine consumption of 35.0 ± 11 and 33.5 ± 15 mg respectively), while consumption was greater in the control B group (75.7 ± 14 mg) ($P < 0.05$). No early side-effects were noted. It was concluded that, both dexmedetomidine, and fentanyl, provide a comparable analgesia after arthroscopic knee surgery when administered intraarticularly in combination with bupivacaine.

Key words: Knee Arthroscopy; Postoperative pain; Intra-articular Analgesia; Dexmedetomidine; Fentanyl

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INTRODUCTION

Knee arthroscopy is one of the most common orthopedic procedures performed on an ambulatory basis. Adequate postoperative analgesia is an essential requirement for day case surgery. Different analgesic agents for day case arthroscopy have been studied but an ideal agent is difficult to identify. It should be active upon cessation of surgery, have a prolonged duration of action, be easy to administer and be without serious side effects (Kaeding et al, 1990).

Lidocaine, prilocaine, and bupivacaine have all been administered intraarticularly to provide intraoperative local anesthesia and postoperative analgesia. Bupivacaine is often chosen because of its longer duration of action. Postarthroscopy analgesia has been provided with intraarticular (IA) bupivacaine, but the duration of analgesia may be only a few hours (Chirwa et al, 1989).

More recently, longer-lasting analgesia has been achieved using intraarticular morphine, although the onset of analgesia may be delayed. The combination of intraarticular morphine and bupivacaine has been suggested as an ideal analgesic after knee arthroscopy (Khoury et al, 1992). In contrast, other investigators have failed to demonstrate an analgesic effect of IA morphine (Laurent et al, 1994).

There is no explanation for these contradictory findings. While morphine is the classic mu-receptor agonist it may be an unfortunate choice for study of the clinical application of peripheral opioid analgesia. Morphine is well known to cause histamine release. Histamine is a powerful activator of nociceptors in the local tissues and induces substance-P release. Histamine and substance P produce vasodilatation and increased vascular permeability, which lead to the release of bradykinin. Substance P promotes additional release of histamine from mast cells and serotonin from platelets (Kalso et al, 1997).

Vita et al, 1999 hypothesized that the use of the non-histamine releasing opioid, **fentanyl**, would provide better peripheral analgesia than would morphine, and they concluded that intraarticular fentanyl provided postoperative analgesia that was superior to that provided by a relatively equipotent dose of intraarticular morphine.

Alpha-2-adrenergic agonists have also peripheral analgesic effects, and intra-articular clonidine has been shown to provide effective postoperative analgesia following knee arthroscopy (Gentili et al, 1996).

Dexmedetomidine is a potent and highly selective α_2 -adrenoreceptor agonist. It has sedative-hypnotic, anxiolytic, and analgesic, anaesthetic-reducing and sympatholytic effects (Ebert et al, 2004). Recently, intra-articular dexmedetomidine has been shown to enhance postoperative analgesia after arthroscopic knee surgery, with an increased time to first analgesic request and a decreased need for postoperative analgesia (Al-Metwalli et al, 2008).

However, there are no studies comparing the effects of intra-articular dexmedetomidine, and fentanyl.

The aim of this clinical study was to analyze and compare the analgesic effects of intra-articular dexmedetomidine versus fentanyl, in combination with bupivacaine in patients undergoing arthroscopic knee surgery.

PATIENTS AND METHODS

After approval by the local ethical committee, informed patient consent was obtained from all study patients. Ninety ASA physical status I–II patients, between the ages of 20 and 35 yr scheduled for knee arthroscopic procedures were included in this study. The exclusion criteria included chronic medications intake, relevant drug allergy and the need for postoperative intraarticular drainage.

All patients received 2 mg midazolam i.v. in the preparation room just before surgery. After placement of routine monitors, all operations were performed under general anaesthesia, which was induced with fentanyl 1–1.5 µg/kg and propofol 1.5–2.0 mg/kg i.v. Tracheal intubation was facilitated with vecuronium 0.1 mg/kg, and anaesthesia was maintained with N₂O 60% and O₂ 40% and isoflurane (1.0–2.0% inspired concentration). No further analgesic or sedative medications were given for the duration of the procedure.

All surgical procedures were done by the same surgeon and were consisted of arthroscopic removal of torn meniscus, debridement of chondromalacia, and diagnostic arthroscopy. A thigh pneumatic tourniquet was applied during surgery and until 10 min after the intraarticular injection of the tested drug into the knee joint at the end of the procedure.

Before the arthroscope was removed, a sealed envelope was opened to allocate patients randomly to one of three groups (n=30) for intraarticular injection as follow:

I: Group (B):

Received 30 ml 0.25% bupivacaine only and served as the control group,

II: Group (B/D):

Received 30 ml 0.25% bupivacaine and dexmedetomidine 1µg/kg,

III: Group (B/F):

Received 30 ml 0.25% bupivacaine and fentanyl 1µg/kg

The study drug was injected intraarticularly by the surgeon who performed the injection through the arthroscope at the end of the procedure (without knowing the contents) to ensure that the drug would be delivered into the joint.

All patients were instructed preoperatively in the use of the 100 mm Visual Analogue Scale (VAS) for pain (0 = no pain to 100 = the worst pain) (Chapman et al. 1985).

Pain levels at rest and during movement (active flexion of the knee) were evaluated. VAS scores were recorded preoperatively (baseline), and at 30 min, 1h, and then, every hour for 8 hours after the intraarticular injection. Scoring was conducted the postanesthesia care unit (PACU) by an observer blinded to patient group assignment.

Postoperative analgesic was available to the patients as meperidine (50 mg) was administered i.v. as an analgesic supplement if the recorded VAS pain score was 50 or greater. Bearable pain period of time was considered as the time from intra-articular injection of the study drug to the first requirement of meperidine. The total meperidine consumption during the first 24 h was also recorded.

Patient use of postoperative analgesics was recorded and summarized as total analgesic consumption for the first eight hours postoperatively.

The occurrence of side effects such as hypotension, bradycardia, nausea, vomiting, sedation, or pruritis was recorded for each patient at the same time points as those defined for VAS assessment.

Statistical Analysis:

Data were analyzed using computer statistical software system SPSS version 12.0 (SPSS Inc., Chicago, IL, USA). Patient characteristics data, operative time and time delay between intra-articular injection and supplementary analgesic administration were analyzed using two-tailed unpaired *t*-tests.

Differences in pain scores and total meperidine consumption between groups were analyzed using repeated-measures analysis of variance (ANOVA) to compare changes within each group. The results were reported as mean values \pm standard deviations (SD). $P < 0.05$ was accepted as statistically significant.

Sample size was estimated using pain scores as the primary variable. Assuming a SD of 10 mm, we calculated a group size of 30 patients would be sufficient to detect a difference of 10 mm on the VAS at an alpha threshold of 0.007 with 90% power.

RESULTS

As regards the demographic characteristics, there were no significant differences in the mean age, weight of patients, sex distribution, and ASA physical status, duration of anesthesia and tourniquet time among the three groups as seen in Table (1). Also, there were no significant differences among the three groups in terms of the type of operative arthroscopic procedure Table (2).

No side-effects were reported during the first 24 h after surgery. Arterial pressure and heart rate did not change significantly. No patient complained of nausea, vomiting, pruritis, sedation or other side effects.

Postoperatively, pain scores at rest (Figure 1) and during movement (i.e., active flexion of the knee) (Figure 2) were significantly higher in the control group than in the other two groups ($P < 0.05$),

But, the difference between the B/D and B/F groups were statistically non significant ($P > 0.05$).

The time to first postoperative analgesic request was longer in the B/D and B/F groups versus control B group; as it was (450 ± 85 min) for B/D group, (465 ± 90 min) for B/F, while in control B group it was (230 ± 85 min) ($P < 0.05$) (Figure 3).

Supplementary analgesic consumption postoperatively (Figure 4), was significantly decreased in the B/D and B/F groups versus control B group ($P < 0.05$), and the difference between the B/D and B/F groups were statistically non significant ($P > 0.05$).

Supplementary analgesic consumption during the first 24 h was almost equivalent for the IA- dexmedetomidine and IA- fentanyl groups as five patients in B/D group and seven patients in B/F group received one dose each of meperidine (mean consumption of 35.0 ± 11 and 33.5 ± 15 mg respectively). Also, supplementary analgesic consumption was greater in the control B group where mean meperidine consumption during the first 24 h was 75.7 ± 14 mg ($P < 0.05$) (Figure 4).

Pain scores both at rest and with movement (i.e., active flexion of the knee) diminished gradually over the testing period for both the IA- dexmedetomidine and IA- fentanyl groups but did not decrease between two and eight hours postoperatively for the bupivacaine control group (Figure 1-2).

(Table 1): Demographic data of the three groups (mean \pm SD):

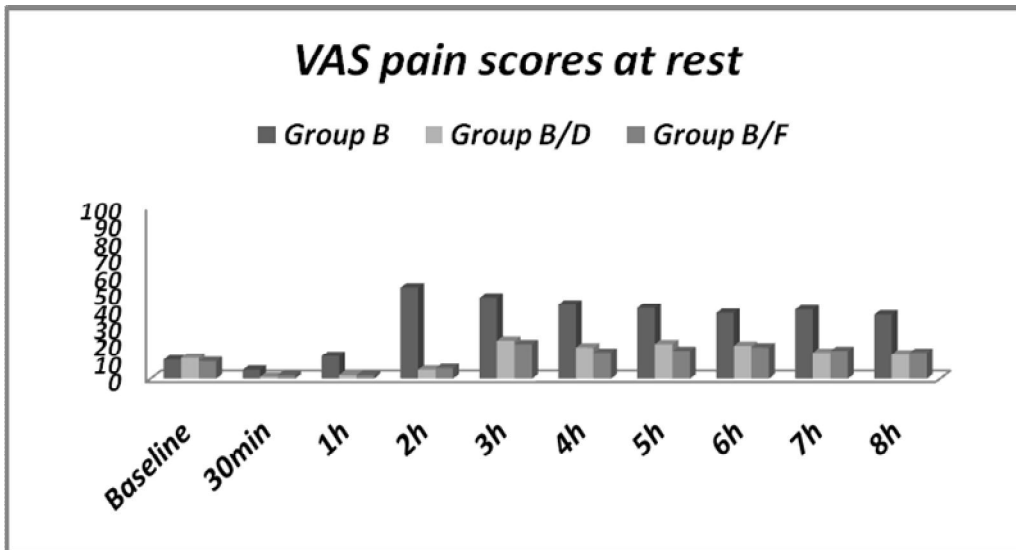
Parameter	Group B (n=30)	Group B/D (n=30)	Group B/F (n=30)
Age (yr)	33 \pm 13	34 \pm 12	32 \pm 12
Weight (kg)	83 \pm 12	85 \pm 17	81 \pm 19
Male/female	16/14	17/13	15/15
ASA class I/ II	18/12	16/14	19/11
Tourniquet time (min)	49 \pm 11	50 \pm 7	46 \pm 8
Duration of anaesthesia (min)	67 \pm 10	62 \pm 11	59 \pm 13

**No significant difference between the three groups.
B= Bupivacaine, D= Dexmedetomidine, F= Fentanyl.**

(Table 2): Types of arthroscopic procedure of the three groups (mean \pm SD):

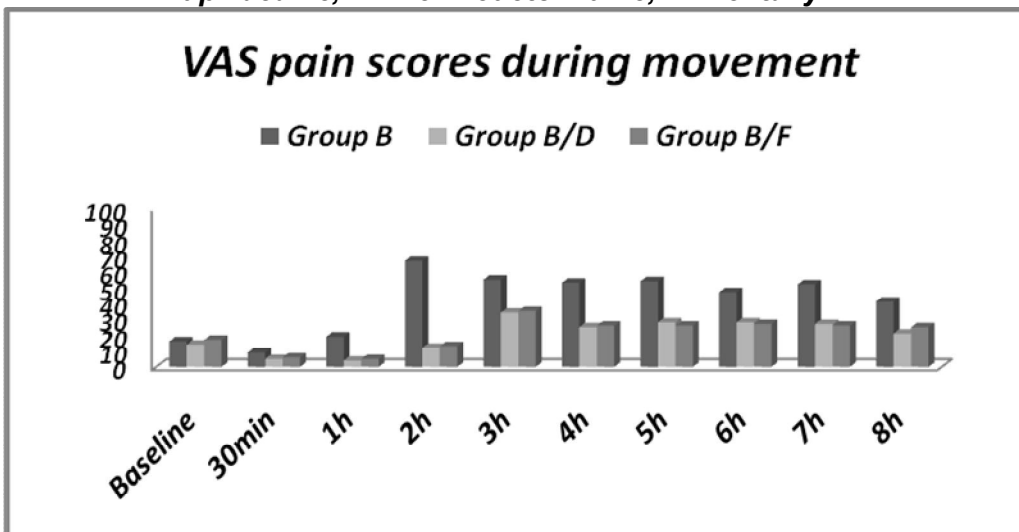
Parameter	Group B (n=30)	Group B/D (n=30)	Group B/F (n=30)
Diagnostic arthroscopy	8	7	7
Meniscectomy	12	10	14
Debridement	10	13	9

B= Bupivacaine, D= Dexmedetomidine, F= Fentanyl.



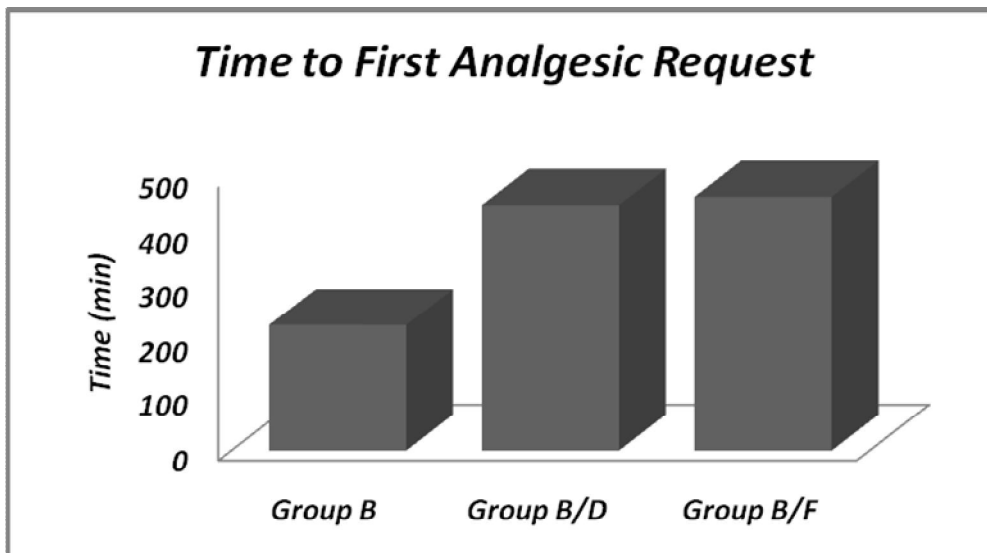
(Figure 1): Visual Analogue Scale (VAS) at rest in the three groups (mean \pm SD).

B= Bupivacaine, D= Dexmedetomidine, F= Fentanyl.

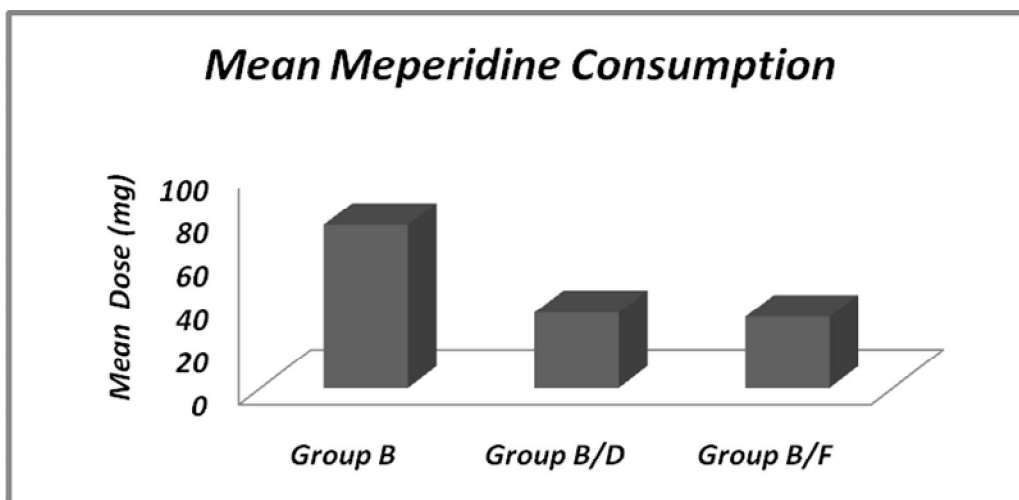


(Figure 2): Visual Analogue Scale (VAS) during movement in all groups (mean \pm SD).

B= Bupivacaine, D= Dexmedetomidine, F= Fentanyl.



(Figure 3): Time to the first analgesic request in all groups (mean \pm SD). B= Bupivacaine, D= Dexmedetomidine, F= Fentanyl.



(Figure 4): Mean Dose of Meperidine Consumption during the first 24 h in all groups (mean \pm SD). B= Bupivacaine, D= Dexmedetomidine, F= Fentanyl.

DISCUSSION

Fast rehabilitation after arthroscopic knee surgery requires the use of effective methods for postoperative pain control. To reduce pain after arthroscopy many analgesics such as NSAIDs (Dennis et al, 1995), intraarticular bupivacaine and/or intraarticular morphine (Kalso et al, 1997) have been used, and in an attempt to improve the results, research has been directed toward new techniques for postoperative analgesia.

The analgesic effect of intra-articular α_2 -adrenoreceptor agonist is evident. Several previous studies have revealed a beneficial analgesic effect of clonidine when injected into the knee joint after arthroscopic surgery, and the analgesic effect of bupivacaine was enhanced by the addition of IA clonidine (Reuben and Connelly, 1999). In another study done by (Joshi et al, 2000), they did not only confirmed this analgesic benefit, but also revealed that the addition of clonidine to bupivacaine and morphine provided even more effective analgesia.

Reuben and Connelly, 1999 found that the time for first analgesic request for intra-articular clonidine was 500 min, intra-articular bupivacaine 325 min and combined intra-articular clonidine and bupivacaine 700 min.

In the other study by Joshi and colleagues 2000, the time for first analgesic request for intra-articular bupivacaine was 280 min, intra-articular clonidine and bupivacaine 600 min, intra-articular bupivacaine and morphine 720 min and combined intra-articular clonidine, bupivacaine and morphine was 950 min.

More recently, dexmedetomidine, the more potent and highly selective α_2 -adrenoreceptor agonist, when injected intra-articularly, has been shown to enhance postoperative analgesia after arthroscopic knee surgery, with an increased time to first analgesic request and a decreased need for postoperative analgesia (Al-Metwalli et al, 2008). Al-Metwalli and colleagues 2008 found that the time to first postoperative analgesic request was 312.0 ± 120.7 min in the intra-articular dexmedetomidine group.

In the present study, it was shown that intra-articular administration of dexmedetomidine $1\mu\text{g}/\text{kg}$ ml in addition to bupivacaine 0.25% at the end of arthroscopic knee surgery improves postoperative pain scores when compared with bupivacaine 0.25% alone. It also increases the time to first rescue analgesic request and decreases the need for other postoperative analgesic medications.

In this study, the time for first analgesic request for intra-articular bupivacaine was 230 ± 85 min, intra-articular dexmedetomidine and bupivacaine 450 ± 85 min, and intra-articular fentanyl and bupivacaine 465 ± 90 min.

It seems that combined intra-articular dexmedetomidine and bupivacaine is much more efficient and causes more prolonged analgesia compared with either drug alone. It was detected that VAS scores of the bupivacaine/dexmedetomidine group in all measurement points, both at rest and with movement, were significantly lower than those of the control bupivacaine group.

Evaluation of pain scores both at rest and with movement (i.e., active flexion of the knee) is a more sensitive measurement of analgesic efficacy.

The mean finding of this study was that intraarticular dexmedetomidine provided postoperative analgesia that was comparable to that provided by intraarticular fentanyl in spite of different mechanisms of action. Both groups of patients receiving intraarticular dexmedetomidine or fentanyl had less postoperative pain than the control group who received only intraarticular bupivacaine.

In the present study, it was shown that intra-articular administration of dexmedetomidine $1\mu\text{g}/\text{kg}$ ml in addition to bupivacaine 0.25% produces analgesia comparable to that of intra-articular administration of fentanyl $1\mu\text{g}/\text{kg}$ ml in addition to bupivacaine 0.25%. There was no statistically significant difference between bupivacaine/dexmedetomidine group, and bupivacaine/ fentanyl group as regards duration of analgesia (450 ± 85 min, and 465 ± 90 min. respectively), and total dose of meperidine consumption as supplementary analgesic during the first 24 h (mean consumption of 35.0 ± 11 and 33.5 ± 15 mg respectively).

Peripheral opioid receptors may be activated only in the presence of tissue inflammation and opioid-binding sites have been identified in synovial tissue, indicating that analgesia is locally mediated (Söderlund et al, 1997).

Fentanyl being fat soluble opioid with less histamine release was proved in many studies to be more effective in intraarticular analgesia than morphine (Vita et al, 1999), and (Uysalel et al, 1995).

The volume of injected drug used in this study was the same that was used in previous studies. Volume of injected drug may increase the intraarticular pressure. Excessive pressure may facilitate systemic absorption once the tourniquet is released (Kaeding et al, 1990). The application of tourniquet and the time of its removal may be related to the duration of the local action of the tested drug and the rate of absorption of the drug from the joint (Whitford et al, 1997). Thus, in this study, after the administration of the tested drug was completed in all patients, the tourniquet was kept inflated for 10 minutes.

CONCLUSION

It was concluded that, both dexmedetomidine, an α_2 -agonist, and fentanyl, an opioid agonist provide a comparable analgesia after arthroscopic knee surgery when administered intraarticularly in combination with bupivacaine. Both drugs resulted in decreased postoperative pain scores, with an increased time to first analgesic request and a decreased need for postoperative analgesia, as well as an increased analgesic duration compared with bupivacaine alone.

REFERENCES

Al-Metwalli, R.R., Mowafi, H.A., Ismail, S., Siddiqui, A.K., et al. 2008. Effect of

- intra-articular dexmedetomidine on postoperative analgesia after arthroscopic knee surgery. *Br J Anaesth.*, 101 (3):395-9.
- Chapman, C.R., Casey, K.L., Dubner, R., et al. 1985. Pain measurement: an overview. *Pain*, 22: 1–31.
- Chirwa, S.S., MacLeod, B.A., Day, B., 1989. Intraarticular bupivacaine after arthroscopic meniscectomy: a randomized double-blind controlled study. *Arthroscopy*, 5:33-5.
- Dennis, A.R., Leeson-Payne, C.G., Hobbs, G.J. 1995. A comparison of diclofenac with ketorolac for pain relief after knee arthroscopy. *Anesthesia*, 50: 904–6.
- Ebert, T., Maze, M. 2004. Dexmedetomidine: another arrow for the clinician's quiver. *Anesthesiology*, 101(3):568-70.
- Gentili, M., Juhel, A., Bonnett, F. 1996. Peripheral analgesic effect of intra-articular clonidine. *Pain*, 64:593-6.
- Joshi, W., Reuben, S.S., Kilaru, P.R., Sklar, J., Maciolek, H. 2000. Postoperative analgesia for outpatient arthroscopic knee surgery with intra-articular clonidine and/or morphine. *Anesth Analg.*, 90:1102–6.
- Kaeding, C.C., Hill, J.A., Katz, J., Benson, L. 1990. Bupivacaine use after knee arthroscopy: Pharmacokinetics and pain control study. *Arthroscopy*, 6:33-39.
- Kalso, E., Tramer, M.R., Carroll, D., McQuay, H.J., Moore, R.A. 1997. Pain relief from intra-articular morphine after knee surgery: a qualitative systematic review. *Pain*; 71:127-34.
- Khoury, G.F., Chen, A.C.N., Garland, D.E., Stein, C. 1992. Intraarticular morphine, bupivacaine, and morphine/bupivacaine for pain control after knee videoarthroscopy. *Anesthesiology*, 77:263-266.
- Laurent, S.C., Nolan, J.P., Pozo, J.L., Jones, C.J. 1994. Addition of morphine to intra-articular bupivacaine does not improve analgesia after day-case arthroscopy. *Br J Anaesth.*, 72:170-3.
- Reuben, S.S., Connelly, N.R. 1999. Postoperative analgesia for outpatient arthroscopic knee surgery with intraarticular clonidine. *Anesth Analg.*, 88:729-33.
- Söderlund, A., Westman, L., Ersmark, H., et al. 1997. Analgesia following arthroscopy: a comparison of intraarticular morphine, pethidine and fentanyl. *Acta Anaesthesiol Scand.*, 41: 6–11.
- Uysalel, A., Keçik, Y., Kirdemir, P., Sayin, M., Binnet, M. 1995. Comparison of

for intraarticular bupivacaine with the addition of morphine or fentanyl

analgesia after arthroscopic surgery. *Arthroscopy*, 11:660-3.
Vita, V., Gershon, V., Ben-David, Bruce, B.D., Rayek, S., Bernard, G., Kurt, S.
1999.

following Intraarticular fentanyl compared with morphine for pain relief

arthroscopic knee surgery. *Can J Anesth.*, 46: 867-871.
Whitford, A., Healy, M., Joshi, G.P., McCarroll, S.M., O'Brien, T.M. 1997.
The effect of tourniquet release time on the analgesic efficacy of
intraarticular morphine after arthroscopic knee surgery.
Anesth Analg., 84:791-3.