THE EFFECT OF THE ADDITION OF LORNOXICAM (XEFOCAM) INTRARTICULARLY ON THE WOMAC SCALE IN PATIENTS UNDERGOING ARTHROSCOPIC ANTERIOR CRUCIATE LIGAMENT RECONSTRUCTION

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Abstract

Effective pain relief is important after diagnostic and therapeutic arthroscopic knee surgery to permit early discharge and improve comfort and mobility at home. We compared the intraarticular analgesic effects of ropivacaine and morphine with or without Xefocam and the need for rescue IV morphine at rest and during movement in patients undergoing anterior cruciate ligament reconstruction under spinal anesthesia. Anterior cruciate ligament reconstruction (ACLR) is associated with moderate to severe postoperative pain.

Patients and Method: Forty five patients undergoing anterior cruciate ligament reconstruction (ACLR) under spinal anesthesia were enrolled in this study. Patients were divided into three equal groups (15 each); the *C* group received saline. The *RM* group received 0.25% ropivacaine and morphine 0.2 mg/mL; the *RMX* group received 0.25% ropivacaine, morphine 0.2 mg/mL and Xefocam 0.8 mg/mL postoperatively they received intraarticular patient-controlled analgesia. The study drug was given in a volume of 10-mL bolus and a 60-min lockout interval. If needed, *rescue morphine* 2 mg was self-administered IV with 10-min lockout intervals. Pain scores and patient satisfaction were assessed at *rest and during movement*. There were significant differences among the groups in *pain scores* and *patient satisfaction* and in the *Western Ontario and McMaster Universities Osteoarthritis Index* (WOMAC) Classification. Daily morphine consumption was significantly smaller in the RMX group (7 ± 6 mg) compared with the RM group (23 ± 20 mg; $P = 0.002$) and in both groups compared with control (46 ± 21 mg; $P < 0.001$). We conclude that intraarticular patient-controlled regional analgesia provides effective pain relief after anterior cruciate ligament reconstruction. The combination of intraarticular ropivacaine, morphine, and xefocam was superior to control or to a combination of ropivacaine and morphine.

Introduction

Lornoxicam [Xefocam (Nycomed Pharma AS, Roskilde, Denmark)], is a new NSAID it is nonopioid analgesic that is available in parenteral form. Postoperatively it is as effective as morphine[1,2], pethidine[3], tramadol[4,5], or fentanyl[6], but produces fewer adverse effects than those drugs. Lornoxicam is more potent than many other nonopioid analgesics and is well tolerated by patients.

It is rapidly eliminated, having a short plasma elimination half-life of 3-5 h[4,5], which suggests its suitability for acute use in the postoperative period[6,7]. Lornoxicam is also as effective as morphine but better tolerated when administered intravenously by patient-controlled analgesia in the treatment of moderate postoperative pain after laminectomy or discectomy[6] Furthermore, wound infiltration with a combination of LA plus lornoxicam improved postoperative pain control and

patient comfort, and decreased the need for opioid as compared with the use of either drug alone suggesting a local effect[7]. It is also added to local intravenous analgesia as it enhances the effect of lidocaine[8].

The aim was to compare the IA analgesic effects of intraarticular ropivacaine/morphine/xefocam (RMX) mixture with ropivacaine/morphine (RM) to the traditional intravenous PCA using Morphine on pain at rest and during movement and the need for supplemental IV morphine consumption.

Material and Methods

After patient informed consent and Hospital institutional approval**,** 45 patients scheduled for anterior cruciate ligament (ACL) reconstruction under spinal anesthesia, were enrolled in this study. They were randomly divided into 3 groups (15 each) (n = 15).

- **Group C** (control group) received no research drug intraarticularly.
- **Group RM** received morphine, ropivacaine, mixture as patient controlled intraarticular patient controlled analgesia.
- **Group RMX** received morphine, ropivacaine, xefocam mixture as patient controlled intraarticular patient controlled analgesia.

All groups received patient controlled analgesia (PCA) morphine intravenous as a rescue drug.

Exclusion criteria included, history of chronic pain, regular medication with analgesics, drug or alcohol abuse, psychiatric disorder, unable to understand the patient-controlled analgesia [PCA] device).

Preoperatively, all patients were instructed how to use the 10-cm visual analog scale (VAS) were 0 = "no pain" and 10 = "worst pain imaginable," VAS was recorded at rest. Also the patient was instructed to the use of patient-controlled analgesia (PCA) pump before surgery. *As premedication***,** midazolam was administered IV (0.03 mg/kg) before the start of anesthesia. *Intraoperatively*, a subarachnoid blockade at L3-4 interspace performed with the patient in the lateral position. Three millilitres of heavy bupivacaine were injected (Marcaine spinal 0.5%, Astra Laboratories, Sweden).

The arthroscopic ACLR was performed by the same surgeon using an autologous quadriceps tendon graft with adjacent bone block from the patella of the same knee. Before closing the wounds, epidural catheter (Portex clear 18-gauge catheter) was placed intraarticularily (IA) through a Tuohy needle. Its position was confirmed arthroscopically. The catheter was secured to the skin by a sterile transparent dressing, flushed with 5 mL of saline, and connected to a Microject® PCA pump (Sorenson Medical, West Jordan, UT), using a Microject® cassette with incorporated 1.2-µm antimicrobial filter.) The pump was programmed to administer a bolus of 10 mL with a 60-min lockout interval each with its own study drug.

Forty milliliters of analgesic mixtures were prepared in 50 ml syringe. The analgesic mixture was prepared as follows.

RM group 20 ml ropivacane 0.5%, 8 mg morphine in 8 ml and 12 cm saline Thus every ml of the solution contain ropivacaine 0.25%, 0.2 mg/ml morphine.

RMX group The mixture was as follows 20ml ropivacane 0.5%. 40 mg xefocam dissolved in 8 ml saline 8 mg morphine in 8 ml and 4 cm saline were added up to make the total volume = 40 ml. Thus every ml of the solution contain ropivacaine 025%, 0.2 mg/ml morphine and xefocam 1 mg/ml.

After closure of the wound a bolus dose of 10 milliliters of study drug was administered to every patient. Whenever the patient experienced pain (VAS >3) rescue morphine 2 mg was self-administered by a PCA pump IV with 10-min lockout intervals.

To avoid confusing the patients, the IA PCA pump was marked with a green tape and the IV PCA pump was marked with a red tape. The numbers of IA boluses and the morphine total IV consumption were recorded.

VAS at rest was recorded at the following intervals 4, 8, 16, and 24 hours postoperatively. The presence of side effects (dizziness, nausea, vomiting, pruritus, and urinary retention) were recorded at 24 h after surgery. Patients were asked to rate their satisfaction with pain treatment on a 3-point scale: 1 = pain relief worse than expected, 2 = as expected, 3 = better than expected. In addition to properly

evaluate the joint a WOMAC Score (Western Ontario and McMaster Universities Osteoarthritis Index) was used. It tests the *function, pain and stiffness* on the 1st, 2nd, 3rd postoperative days. The (WOMAC) questionnaire was designed to measure these components by assessing 17 questions *for functional activities*, five questions for pain related activities, and two for stiffness criteria. The 17 questions for assessing the joint function are ability to (1) bathe, (2) step in the car, (3) out of the car, (4) going upstairs, (5) downstairs, (6) lying down, (7) bending, (8) putting on socks, (9) walking on flat surface, (10) on the toilet, (11) off the toilet, (12) rise from bed, (13) rise from seat, (14) light chores, (15) heavy chores, (16) standing, (17) sitting. The scale is from 0 to 170, were zero is fully functioning and 170 is no function of the joint at all. *As regard the stiffness two questions were asked* (1) fully bend the knee (2) fully extend the knee the score is from 20 to 0 where 0 is full range of motion and 20 is no joint movement. *As regards the pain* five questions were asked about pain experienced during (1) sitting, (2) standing, (3) walking, (4) Up the stairs, (5) night pain. The score is from 50 with 0 being no pain at all and 50 is the worst pain. Hospital stay was recorded in all groups.

Results

No significant differences were noted among study groups as regards demographic data and duration of surgery Table 1.

Table 1
Demographic Data

Variables	Group C	Group RM	Group RMX
Age(yrs)	35 ± 3	27 ± 3	32 ± 3
Weight(kg)	86 ± 2	86 ± 2	86 ± 2
Sex (male/ female)	12/3	13/2	12/3
Duration of surgery(min)	89 ± 16	88 ± 6	94 ± 8

Values are mean ± SD C is the control group, RM is ropivacaine/ morphine RMX ropivacaine/morphine/xefocam.

VAS score-VAS After 4 hours there was no statistical significance between the three groups. After 8 hours RMX group was significantly lower than Group RM and Group C. However, there was no statistical significance between C group and the RM group. After 16 hours postoperatively group RMX was significantly lower than group RM and C there was no statistical significance between C group and the RM group. After 24 hours RM and RMX were significantly lower than group C. RMX group was significantly lower than group RM (Fig. 1).

Fig. 1
VAS scores at 4, 8, 16, and 24 hours postoperatively. C is the control group, RM is ropivacaine/morphine, RMX ropivacaine /morphine/xefocam

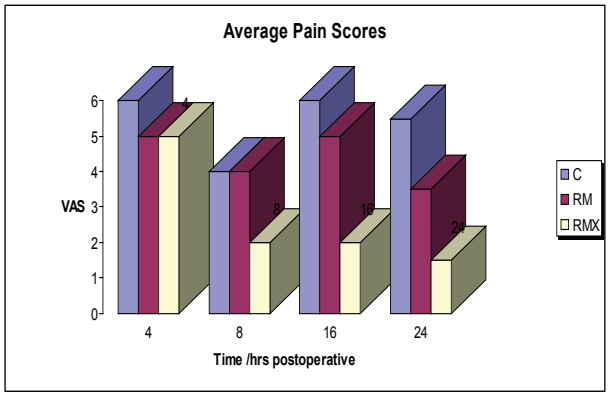


Fig. 2
Showing Western Ontario and McMaster Universities Osteoarthritis Index) WOMAC classification testing (A) Pain (B) Function (C) Stiffness (Bellamy et al. 1988)[10]

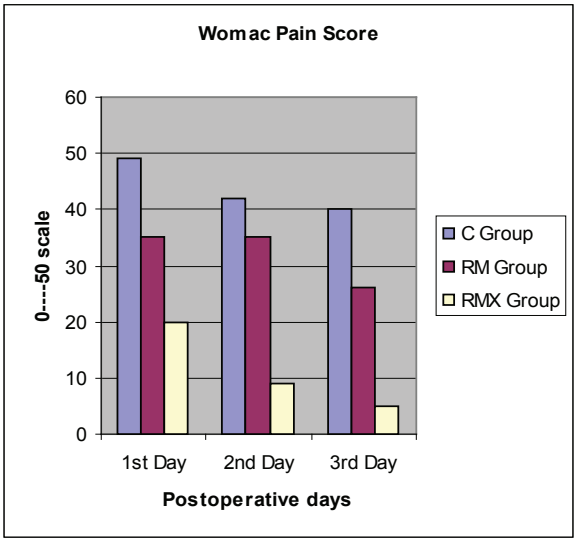


Fig. 2 (A)
Shows that the WOMAC pain score in group RMX is significantly less than group RM and C group. It was 20, 9, 5 on 1st, 2nd, 3rd postoperative days, versus 35, 35, 26 in RM group versus 49, 42, 40 in Group C.

Fig. 2 (B)
Shows the WOMAC Function score. Group RMX is significantly less than Group RM and C group it was 70, 60, 28 on 1st, 2nd, 3rd postoperative days, versus 90, 88, 88 and 140, 130, 100 in group RM and group C respectively.

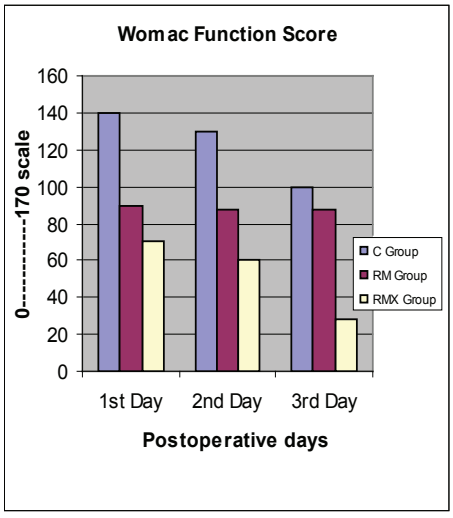
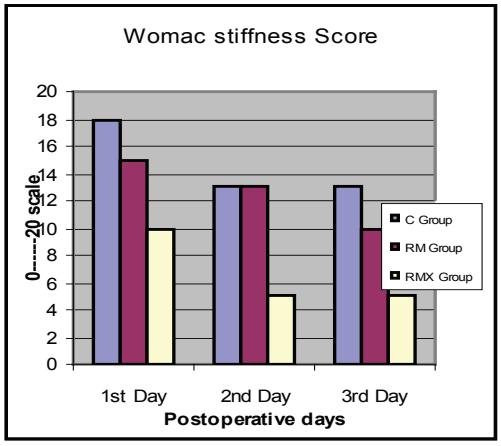


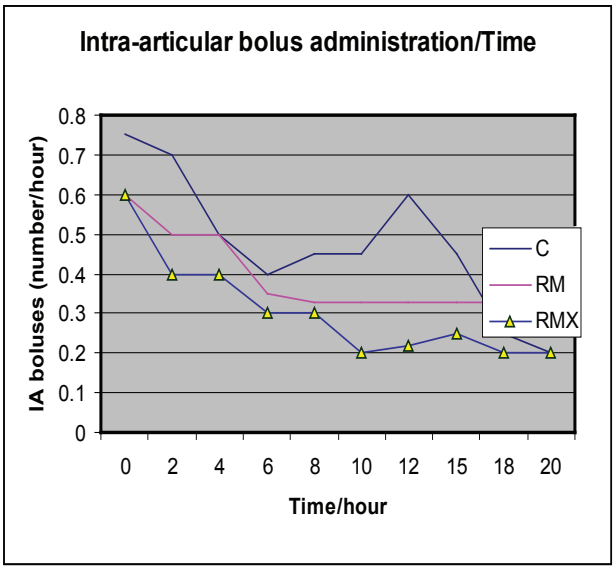
Fig. 2 (C)
Shows the WOMAC stiffness score. In Group RMX it is significantly less than Group RM and C group it was 10, 5, 5 on 1, 2, 3 postoperative days versus 15, 13, 10 and 18, 13, 13 in group RM and C respectively. Group RM was significantly less than Group C in all WOMAC three scores on the 1st, 2nd, 3rd postoperative days.



Requirements of intraarticular analgesia

Patients in all groups required intraarticular analgesia, however in RMX group the analgesic requirements were significantly lower than RM Group and C group. In group RMX highest demand was recorded in the first hour with an average of 0.6 bolus/hour and lowest demand after 18 hours with an average of 0.2 bolus/hour. As regards RM group the highest demand was within the first hour with an average of 0.6 bolus/hour and reached 0.35 after 20 hours. As regard C group the demand was highest at the first hour at 0.75 bolus/hour and lowest was 0.2 bolus/hr after 20 hours (Fig. 3).

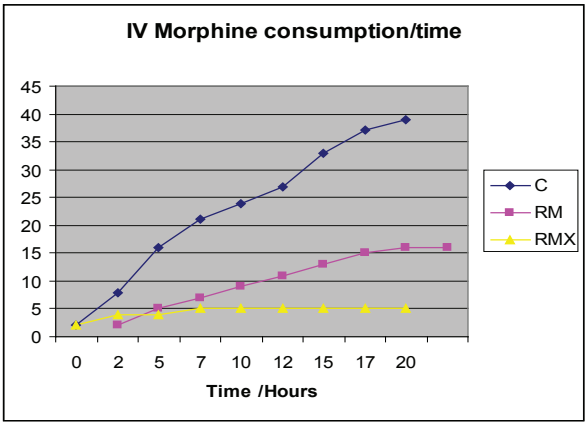
Fig. 3
Intraarticular (IA) bolus administration over time. RMX = ropivacaine/morphine/xefocam; RM = ropivacaine/morphine; C = saline control.



Rescue IV morphine

The total dose of 24-h rescue IV morphine was 8 ± 8 mg in the RMX group versus 23 ± 3.6 mg and 46 ± 1.3 mg in the RM group and C group. Morphine consumption was significantly smaller in the RMX group (RMX versus RM and control group, P <0.001; RM versus the C group, P = 0.002) Fig. (4).

Fig. 4
Total Intravenous consumption of Morphine /time in the first 24 hours postoperatively



Patient Satisfaction Score

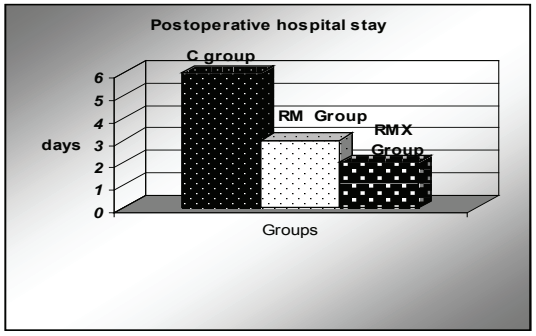
Patients in group RMX had significantly better satisfaction score when compared to RM and C group. Group RM showed more satisfaction than group C (Table 2).

Table 2
Patient Satisfaction Score

Patient's Satisfaction	Group C N = 15	Group RM N = 15	Group RMX N = 15
1	6	4	0*
2	7	4	6*
3	2	7†	9*

C control group, **RM,** Ropivicaine Morphine **RMX** Ropivicaine Morphine Xefocam.
1 = pain relief worse than expected, 2 = as expected, 3 = better than expected.
* is significant in comparison to group RM and Group C † Significant in comparison to group: C

Fig. 5
Postoperative hospital stay



*The days spent in hospital in **C** control group, **RM,** Ropivicaine Morphine **RMX** Ropivicaine Morphine xefocam*

Incidence of complications

Group RMX showed the lowest incidence of complications as only 2 patients complained of dizziness. While Group C showed the highest incidence of complications (Table 3).

Table 3
Incidence of complications

Side effect	Group C N = 15	Group RM N = 15	Group RMX N = 15
No side effects	1	7	13*
Dizziness	6†	4	2
Urinary retention	2	0	0
Pruritis	3	0	0
Vomiting	3	0	0
Nausea	4	1	0
Vertigo	2	1	0

* is significant in comparison to group RM and Group C † versus RM and RMX.

Discussion

After arthroscopy of the knee joint, patients regularly suffer from severe pain. Although the degree of superficial trauma is less with these procedures, the internal surgical site of repair, including the synovial tissue, the anterior fat pad, and the joint capsule, have free nerve endings that are capable of transmitting painful stimuli and producing severe pain[10]. A variety of treatment modalities have been applied for postoperative pain relief after arthroscopic knee surgery and many efforts have been made to maximize analgesia and minimize side effects[11]. In recent years, intraarticular analgesia has been used for arthroscopy in an attempt to establish the smallest drug dose providing effective analgesia with minimum side effects.

Local anesthetics were the first of such drugs to be given intraarticularly for purposes of postoperative analgesia, and they remain in wide use[12]. However as Sorensen et al observed in most cases that the reduction in postoperative pain are small to moderate and short lasting and patients may need supplementary analgesia, which delays their discharge[13]. Intraarticular multimodal regimens after arthroscopic knee surgery may provide enhanced effects on postoperative pain. White et al emphasized that many studies have focused on the benefits of the addition of different drugs such as bicarbonate, adrenaline, opioids, and NSAIDs to intraarticular local anesthetic[14] as with the opioids. El Hakim et al said that, intraarticular administration of NSAIDs after knee arthroscopy has been found to provide variable results with respect to their analgesic efficacy. Different types of NSAIDs[15,16], such as ketorolac[17] and tenoxicam[18], have been used alone or in combination with intraarticular local anesthetics or morphine in a number of clinical studies[19].

The administration of NSAIDs decreases the inflammatory response associated with arthroscopic knee surgery, resulting in diminished pain and facilitating earlier ambulation and faster rehabilitation The literature on single-dose IA analgesia is controversial because of different concentrations and volumes of local anesthetics and also as a result of the use of several drugs and drug combinations A systematic review of single-dose IA local anesthesia for postoperative pain relief after arthroscopic knee surgery reported a small to moderate effectiveness

of short duration. This is in contrast with our current study which showed long postoperative good analgesia in RMX group, evidenced by early ambulation, better patient satisfaction, lower intravenous rescue drug administration[20]. Less side effects were encountered and less postoperative hospital stay was recorded. Therefore it is advisable to use the analgesia according to the patient's requirements rather than giving it as a single intraarticular dose.

In our study, xefocam was used in combination with ropivacaine and morphine. Lornoxicam (Xefo@; Nycomed Pharma AS, Roskilde, Denmark) is a new NSAID belonging to the enolic acid chemical class shared by piroxicam and tenoxicam. Its analgesic potency in animal pain models exceeds that of piroxicam by approximately 12- and 3-fold, respectively, and that of indomethacin and diclofenac by 4- and 6-fold, respectively[5]. Lornoxicam is rapidly eliminated, having a short plasma elimination half-life of three to five hours[6,7], which suggests its suitability for acute use in the postoperative period[6]. The principal therapeutic effect of NSAIDs is the inhibition of prostaglandin synthesis. The NSAIDs were given IA combined either with bupivacaine or with morphine and the authors suggest the synergistic action of the drugs[21]. They all agree that the IA application of NSAIDs compared with IV administration is more effective, but the doses in those studies were large (60 mg and 30 mg of xefocam). A reduced dose of locally applied xefocam (5 mg of xefocam in a 5-mL volume and 0.25% bupivacaine 20 mL) provided comparable analgesia to a systemic dose (6 mg xefocam IV) after arthroscopy of the knee, which has the potential of minimizing the systemic side effects of xefocam while conferring the analgesic benefit of the drug. There are some concerns about the effects of xefocam on wound healing. In the studies regarding IA administration, xefocam was given as a single shot and no such effects were reported. The combination of the three drugs in the RMX group allowed us to use small doses intraarticulary thus decreasing all the disadvantages and side effects of the other drugs.

In the study of Dauri et al.[22] the IA analgesia with ropivacaine plus sufentanil was found insufficient for pain relief after ACLR. Similarly in our study the combination of ropivacaine and morphia gave a lower analgesic effect than group RMX. And this may prove the beneficial effect of the addition of xefocam to ropivacaine and morphine.

Alford and Fadale[23] showed only mild analgesic effects of IA bupivacaine infusion after ACLR. In our study, better effects of IA analgesia in the RM and RMX groups can be attributed to a combination of drugs.

The main findings of our study are: i) IA PCA with a combination of ropivacaine and morphine with or without xefocam provided effective postoperative pain relief after ACLR with few side effects, ii) daily morphine consumption was smaller in the RM and RMX groups compared with Control group and iii) consumption of IV morphine was smaller in the RMX group compared with the RM group.

In conclusion, This study showed the feasibility and efficacy of the IA regional PCA technique for pain relief after ACLR. The combination of IA RMX was superior to RM group. The addition of xefocam resulted in reduced consumption of narcotics, reduced occurrence of side effects, reduced length of stay, and also improved early walking ability. In many countries ACLR is not done as a day-case procedure because of moderate to severe pain despite oral analgesics Our results may encourage more day-case surgery for ACLR.

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