Intra-articular tenoxicam improves postoperative analgesia in knee arthroscopy

Sallyann T. Colbert FFA RCSI,
Emer Curran FFA RCSI,
Deirdre M. O'Hanlon FRCSI,*
Ray Moran FRCSI,*
Maire McCarroll FFA RCSI

Purpose: Non Steroidal Anti-Inflammatory drugs have a well documented benefit in the relief of postoperative pain. This study was designed to compare the analgesic effect of intra-articular tenoxicam 20 mg with intravenous tenoxicam on postoperative pain in 88 patients undergoing day case knee arthroscopy.

Methods: A prospective, double blind, randomized trial was performed. All patients received a standard general anesthetic. Patients in group A received 20 mg tenoxicam made up to 40 ml with normal saline intra-articularly (*ia*) and 2 ml normal saline *iv*. Patients in group B received 40 ml normal saline intra-articularly and 2 ml, 20 mg of tenoxicam, *iv*.

Results: Both groups of patients were similar with respect to age, weight, sex and tourniquet inflation time. Patients receiving *ia* tenoxicam had lower pain scores (at rest and upon movement) at 30, 60, 120 and 180 min postoperatively (0.8 ± 0.2 *vs* 2.5 ± 0.2 at rest and 1.24 ± 0.2 *vs* 3.4 ± 0.2 at movement at 60 min; $P < 0.0001$). Fewer patients required additional analgesia in the first four hours postoperatively (33% *vs* 84%; $P < 0.00001$) and the time to first analgesia (23.7 ± 11.2 *vs* 9.4 ± 0.6; $P < 0.02$) was longer in those receiving *ia* tenoxicam.

Conclusion: Intra-articular tenoxicam provides superior postoperative analgesia and reduces postoperative analgesic requirements compared with *iv* tenoxicam in patients undergoing day case knee arthroscopy.

Objectif : Les anti-inflammatoires non stéroïdiens sont des médicaments bien reconnus pour le soulagement de la douleur postopératoire. La présente étude avait pour but de comparer l'effet analgésique de 20 mg de ténoxicam intra-articulaire à du ténoxicam intraveineux sur la douleur postopératoire chez 88 patients admis en chirurgie ambulatoire pour une arthroscopie du genou.

Méthode : On a procédé à un essai prospectif, randomisé et à double insu. Tous les patients ont reçu un anesthésique général standard. Les patients du groupe A ont reçu une injection intra-articulaire (*ia*) composée de 20 mg de ténoxicam complété à 40 ml par une solution salée et 2 ml de solution salée *iv*. Les patients du groupe B ont reçu 40 ml de solution salée en injection intra-articulaire et 2 ml, 20 mg de ténoxicam, *iv*.

Résultats : Les deux groupes présentaient des caractéristiques semblables quant à l'âge, le poids, le sexe et le temps de gonflement du garrot. Les patients qui ont reçu du ténoxicam *ia* ont eu des scores de douleur plus bas (au repos et en mouvement) à 30, 60, 120 et 180 min après l'intervention (0,8 ± 0,2 *vs* 2,5 ± 0,2 au repos et 1,24 ± 0,2 *vs* 3,4 ± 0,2 en mouvement à 60 min; $P < 0,0001$). Moins de patients ont eu besoin d'analgésie supplémentaire pendant les quatre premières heures postopératoires (33 % *vs* 84 %; $P < 0,00001$) et le temps écoulé avant la première analgésie (23,7 ± 11,2 *vs* 9,4 ± 0,6 $P < 0,02$) a été plus long pour les patients qui ont reçu du ténoxicam *ia*.

Conclusion : Le ténoxicam intra-articulaire, comparé au ténoxicam *iv*, fournit une analgésie postopératoire supérieure et réduit les besoins analgésiques postopératoires chez des patients qui subissent une arthroscopie du genou en chirurgie ambulatoire.

From the Departments of Anaesthesia and Surgery,* Cappagh Orthopedic Hospital, Finglas, Dublin 11, Ireland.
Address correspondence to: Dr. Sallyann Colbert, Department of Anaesthesia, Mater Misericordiae Hospital, Eccles Street, Dublin 7, Ireland.
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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.

Many studies have focused on the benefits of local application of different agents. The use of intra-articular (*ia*) steroids, opioids, local anesthetic agents and a combination of opioids and local anesthetic agents have been shown to achieve clinical benefits with respect to postoperative analgesia in many studies but others have failed to demonstrate a beneficial use and their use is controversial.[1-6] The advantage of the intra-articular route of drug administration is that it has therapeutic benefit with fewer systemic side effects.

Intra-articular administration of nonsteroidal anti-inflammatory drugs (NSAIDs) has received little attention. Non Steroidal Anti-Inflammatory Drugs are effective in reducing postoperative pain.[7] Tenoxicam is a potent analgesic and anti-inflammatory agent and has an established efficacy in postoperative pain relief.[8,9] In view of its long half-life (60-80 hr), once daily administration is sufficient. The parenteral formulation of tenoxicam has an aqueous base, without an organic stabilizer and since the solvent for injection is distilled water, this formulation offers the potential for intra-articular administration. Other non-steroidal drugs are unsuitable due to the solvents employed which cause problems with local tolerability. Tenoxicam has also been demonstrated to concentrate in the synovium rather than in the cartilage.[10]

The purpose of this study was to compare the benefits of intra-articular tenoxicam, 20 mg, and 20 mg tenoxicam *iv* on postoperative pain relief and further analgesic requirements in patients undergoing day case knee arthroscopy.

Materials and methods

A prospective randomized double blind trial was undertaken. Following informed written consent, Irish Medicines Board and local ethical committee approval, patients undergoing diagnostic day case knee arthroscopy were included in the study. Exclusion criteria were patients who were already receiving NSAID treatment or those who had evidence of severe cardiovascular, respiratory, metabolic or neurological disease. Patients in whom NSAIDs were contraindicated, i.e. those suffering from peptic ulcer disease, gastrointestinal bleeding, gastritis or renal failure were also excluded from the study. Patients were randomly allocated into one of two groups, using a table of random numbers. Ninety patients between 18 - 65 yr who were ASA I - II were enrolled into this prospective randomized trial. A study proforma was completed giving demographic, perioperative and postoperative details.

No premedication was administered. Intraoperative monitoring consisted of inspired oxygen concentration, ECG, oxygen saturation, $P_{ET}CO_2$ and non-invasive blood pressure. The anesthetic technique for both groups was standardized. Anesthesia was induced with 2.5-3 $mg \cdot kg^{-1}$ propofol and 1 $\mu g \cdot kg^{-1}$ fentanyl. Patients breathed spontaneously via a laryngeal mask airway, anesthesia being maintained by isoflurane and nitrous oxide 66% in oxygen.

At the conclusion of surgery, 10 min before deflation of the tourniquet, the surgeon injected the drug or placebo into the knee joint through the arthroscope. Patients in group A received 20 mg tenoxicam made up to 40 ml with normal saline intra-articularly and 2 ml normal saline *iv* administered by the anesthesiologist at the same time. Patients allocated to group B received 40 ml normal saline intra-articularly and 20 mg, 2 ml, tenoxicam *iv*.

Postoperative pain was assessed via a 10 cm visual analogue scale (VAS) ranging from no pain (0 cm) to unbearable pain (10 cm). These were recorded at rest and upon movement (the patient was asked to flex the knee joint 45°). The use of these measures was explained to patients before surgery. The scores were obtained by an independent investigator with no knowledge as to which group the patient belonged. The VAS scores were assessed at 30, 60, 120, and 240 min postoperatively. Supplemental postoperative analgesia consisting of 0.5 $mg \cdot kg^{-1}$ meperidine *iv* or 500 mg acetaminophen tablets up to eight tablets a day *po* was available on request. Time to first requesting analgesia and all analgesic agents administered to the patient in the first four hours postoperatively were recorded.

Statistical analysis was performed using standard non parametric statistics i.e., the Mann Whitney U test and Chi square test with significance assumed at the 5% level.

Results

Ninety patients were enrolled in the study and 88 completed the study. Two patients were excluded because they required admission; one patient has received *iv* tenoxicam and was admitted following an episode of an unexplained arrhythmia postoperatively and the second because of prolonged nausea and vomiting. No patient in this study required admission because of poor pain control.

TABLE I Detailing the demographic criteria and analgesic requirements in the two groups.

Variable	*Group A*	*Group B*	*P*
n	45	43	
Age (yr)	31.1 ± 1.1	33.5 ± 1.0	ns
Sex (n, male %)	23 (51%)	21 (49%)	ns
Weight (kg)	72.1 ± 1.4	70.9 ± 1.3	ns
Tourniquet Time (min)	30.9 ± 0.9	32.2 ± 0.7	ns
Additional analgesia (n first 4 hr)	15 (33%)	36 (84%)	< 0.00001
Meperidine use (no. of patients)	2	16	< 0.0001
Acetaminophen use (no. of patients)	13	20	ns
Time first analgesia (min)	23.7 ± 11.2	9.4 ± 0.6	0.02

Group A = Intra-articular tenoxicam. Group B = Intravenous tenoxicam.
Values expressed as mean ± SEM or as number (Percent), ns = not significant.

TABLE II Pain scores in each group at each of the time periods

Time period	*Group A*	*Group B*	*P*
Number	45	43	
Pain (R) at 30 min	1.4 ± 0.2	2.8 ± 0.2	< 0.0001
Pain (M) at 30 min	2.0 ± 0.2	3.9 ± 0.2	< 0.0001
Pain (R) at 60 min	0.8 ± 0.2	2.5 ± 0.2	< 0.0001
Pain (M) at 60 min	1.24 ± 0.2	3.4 ± 0.2	< 0.0001
Pain (R) at 120 min	0.5 ± 0.1	1.6 ± 0.2	< 0.0001
Pain (M) at 120 min	0.7 ± 0.2	2.2 ± 0.2	< 0.0001
Pain (R) at 180 min	0.1 ± 0.1	0.6 ± 0.1	= 0.001
Pain (M) at 180 min	0.2 ± 0.1	0.9 ± 0.2	= 0.001
Pain (R) at 240 min	0.0 ± 0.0	0.1 ± 0.0	NS
Pain (M) at 240 min	0.0 ± 0.0	0.1 ± 0.0	NS

Group A = Intraarticular tenoxicam. Group B = Intravenous tenoxicam.
Values expressed as mean ± SEM. R= at rest, M = upon movement, NS = not significant.

There were 45 patients in group A (20 mg tenoxicam *ia* and 2 ml normal saline *iv*) and 43 patients in group B (40 ml normal saline *iv* and 20 mg tenoxicam *iv*). Forty three of the patients were male.

There was no difference between the two groups with regard to age, sex, weight or tourniquet time (Table I). Differences were observed in the pain scores (at rest and upon movement) at 30, 60, 120, 180 min but not at 240 min postoperatively (Table II). There were differences between the two groups with respect to the number of patients requiring additional analgesia in the first four hours postoperatively, specifically meperidine, and the time to first analgesia (Table I). The mean ± SEM dose of meperidine consumed was 25 ± 0.0 mg in group A and 31.2 ± 2.8 mg in group B. Any patients who received acetaminophen had a 500 mg dose administered and the mean was 500 mg in both groups.

Discussion

In the present study examining Intra-articular *vs* intravenous tenoxicam, the local intra-articular route had benefits in terms of decreased postoperative pain scores both at rest and upon movement. In addition, the further analgesic requirements in the group receiving intra-articular tenoxicam were less than in those receiving systemic tenoxicam and the time to first additional postoperative analgesia was also prolonged.

Papathanassiou examined intra-articular injection of 20 mg tenoxicam in 28 patients with degenerative osteoarthritis of the knee joint[11] and demonstrated a 40% reduction in analgesia consumption and a 60% increase in joint movements lasting up to two months after a single injection. Two patients reported a slight allergic reaction: otherwise no other side effects were detected. Elhakim *et al.* evaluated the postoperative analgesic effects of *ia* tenoxicam compared with *iv* tenoxicam in 60 patients undergoing day case arthroscopy[12] and showed lower pain scores (at rest and upon movement) and reduced analgesic requirements postoperatively in the group who received *ia* tenoxicam. Similar results were obtained in the present study. There was a reduction in the number of patients requiring meperidine in the *ia* group than in the *iv* group. No difference was observed for acetaminophen consumption.

However, in contrast to these results Cook *et al.* examined 63 patients undergoing day case knee arthroscopy and compared *ia* tenoxicam with *ia* bupivacaine, and *ia* placebo[13] but failed to demonstrate any benefit in terms of pain scores following the use of tenoxicam or bupivacaine over placebo. Monahan *et al.* also found no benefit following the use of *ia* ketorolac *vs ia* bupivaciane in 40 patients undergoing day case knee arthroscopy.[14]

Reuben *et al.* evaluated ketorolac in 80 patients undergoing day case arthroscopy[15] and divided the patients into four groups; Group 1 *ia* ketorolac; Group 2 *ia* ketorolac and *ia* bupivacaine; Group 3 *ia* bupivacaine and *iv* ketorolac and Group 4 *ia* bupivacaine. Those receiving *ia* ketolorac combined with *ia* bupivacaine had better pain scores and consumed less analgesia postoperatively. In a second study, Reuben *et al.* [16] examined patients undergoing arthroscopic meniscus repair and concluded that intra-articular ketorolac improves pain scores in this patient population.

The intra-articular route of analgesic administration has been examined in a number of studies. Intra-articular opioids have been studied and encouraging results have been found with reduced pain scores and reduced postoperative analgesic consumption after knee surgery.[2,17,18] However, these findings have not been demonstrated in other studies.[19,20] Intra-articular administration of local anesthetic agents has also proved controversial. Geutjens *et al.*[21] found a beneficial effect following intra-articular bupivacaine in patients undergoing day case arthroscopy. Henderson *et al.*[22], in a similar study, found no benefit. A combination of agents has also been examined. McSwiney *et al.*[5] divided patients undergoing arthroscopy into four groups; Group 1 received normal saline, Group 2 bupivacaine , Group 3 morphine and Group 4 bupivacaine and morphine combined. All agents were administered intra-articularly. Group 4 patients had lower pain scores postoperatively. Similar results were produced by Boden *et al.*[23] Other studies have examined the use of intra-articular steroids. Excellent analgesia can be achieved but repeated use may cause problems with joint destruction.[1,17,24]

Experimental studies have implicated prostaglandin E_2, produced by synoviocytes, in joint inflammation.[25,26] NSAIDs inhibit prostaglandin synthesis and are potent anti-inflammatory agents. Many NSAIDs are currently available but only a few are suitable for Intra-articular administration because of formulation. In addition several NSAIDs have been shown to inhibit chondrocyte biosynthesis and have been implicated in cartilage destruction *in vitro* and *in vivo*. The aqueous based parenteral formulation of tenoxicam make this NSAID suitable for intra- articular administration. In contrast to other NSAIDs, tenoxicam has a chondroprotective effect in human cartilage *in vitro* and may have beneficial effects.[27]

The present study demonstrated considerable benefits with *ia* tenoxicam compared with the same dose administered *iv* in patients undergoing day case knee arthroscopy. The cost of 20 mg tenoxicam was $2.23 and was the same in both arms of the study as the same formulary was employed. Intra-articular administration of tenoxicam should be considered in all patients undergoing day case arthroscopy, who do not have contraindications to NSAID use.

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