Regional Anesthesia and Pain

Timing of pre-emptive tenoxicam is important for postoperative analgesia

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Purpose: In this prospective randomized study, a comparison was made between the efficacy of 20 mg tenoxicam, administered either, 30 min preoperatively or at induction of anesthesia, for the relief of postoperative pain in patients undergoing ambulatory breast biopsy.

Methods. Seventy-three patients were recruited and all received a standard anesthetic consisting of induction with 2 $mg \cdot kg^{-1}$ propofol followed by 5 $\mu g \cdot kg^{-1}$ alfentanyl. No premedication was administered and at the end of the procedure the wounds were infiltrated with 10 ml of bupivacaine (0.5 %). Patients were randomized to receive 20 mg tenoxicam intraveneously either 30 min before surgery or at induction of anesthesia.

Results: Demographic criteria were similar in both groups. There were differences in pain scores at 30, 60, 120 and 240 min postoperatively (VAS at 30 min 3.2 ± 1.2 *vs* 5.5 ± 1.8; $P < 0.001$: VAS at 60 min 1.8 ± 1.2 *vs* 3.7 ± 1.9; $P < 0.001$: VAS at 120 min 0.9 ± 0.9 *vs* 1.7 ± 1.0; $P = 0.003$: VAS at 240 min 0.5 ± 0.5 *vs* 1.1 ± 0.8; $P < 0.001$: Expressed as mean ± SD). There was a difference in the number of patients requiring additional analgesia, in the first four hours postoperatively (12 (33%) *vs* 27 (73%); $P = 0.001$) and a difference in the time to additional analgesia in these patients (87.5 ± 32.5 *vs* 55.0 ± 26.8 min; $P = 0.002$).

Conclusion: Early administration of pre-emptive tenoxicam 30 min before induction of anesthesia improves postoperative analgesia in patients undergoing ambulatory breast biopsy.

Objectif : Notre étude porte sur la comparaison de l'efficacité de 20 mg de ténoxicam, administrés 30 min avant l'opération ou à l'induction de l'anesthésie pour le soulagement de la douleur postopératoire de patientes qui subissent une biopsie du sein en chirurgie ambulatoire.

Méthode : Nous avons recruté 73 patientes qui ont toutes reçu un régime anesthésique normal constitué d'une induction avec 2 $mg \cdot kg^{-1}$ de propofol suivi de 5$\mu g \cdot kg^{-1}$ d'alfentanil. Aucune prémédication n'a été administrée et, à la fin de l'intervention, 10 ml de bupivacaïne (0,5 %) ont été infiltrés dans la plaie chirurgicale. Les patientes, réparties de façon aléatoire, ont reçu 20 mg de ténoxicam intraveineux, soit 30 min avant l'opération, soit à l'induction de l'anesthésie.

Résultats : Les informations personnelles étaient similaires dans les deux groupes. Les scores de douleur ont été différents pour les mesures réalisées 30, 60, 120 et 240 min après l'opération (selon l'EVA à 30 min 3,2 ± 1,2 *vs* 5,5 ± 1,8; $P < 0,001$: EVA à 60 min 1,8 ± 1,2 *vs* 3,7 ± 1,9; $P < 0,001$: EVA à 120 min 0,9 ± 0,9 *vs* 1,7 ± 1,0; $P = 0,003$: EVA à 240 min 0,5 ± 0,5 *vs* 1,1 ± 0,8; $P < 0,001$: moyenne ± écart type). Un nombre différent de patientes a demandé de l'analgésie supplémentaire, pendant les quatre premières heures postopératoires (12 (33 %) *vs* 27 (73 %); $P = 0,001$). Le temps écoulé avant cette demande d'analgésie diffère également (87,5 ± 32,5 *vs* 55,0 ± 26,8 min; $P = 0,002$).

Conclusion : L'administration précoce de ténoxicam préventif, 30 min avant l'induction de l'anesthésie, améliore l'analgésie postopératoire chez des patientes qui subissent une biopsie du sein en clinique externe.

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POSTOPERATIVE analgesia is an important consideration in patients undergoing ambulatory surgery. A combination of opioids, NSAIDs, and local anesthetic agents provides good pain relief and this combination is effective for pain relief in ambulatory surgery. However, questions remain as to the optimum schedule for administration of these agents and attention has focused upon pre-emptive delivery. The concept of pre-emptive analgesia has gained popularity following experimental work demonstrating that early control of pain can alter its subsequent evolution, the recognition that nociception produces important physiological responses, even in adequately anesthetized individuals, and an understanding that for many individuals minimization of pain can improve clinical outcomes.[1–3]

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used in ambulatory surgery, are beneficial in mild to moderate pain, have a well recognized opioid sparing role and are effective when administered pre-, peri- and post-operatively.[4–6] Non-steroidal anti-inflammatory drugs have been developed which are suitable for intravenous administration and this facilitates examination of the role of NSAIDs as pre-emptive analgesic agents. A previous study from this institute demonstrated the value of pre-emptive tenoxicam, a NSAID, which may be administered intravenously, in patients undergoing ambulatory breast biopsy.[7] Tenoxicam administered 30 min preoperatively proved superior to administration post-incision. The present study was established to evaluate the efficacy of intravenous tenoxicam administered 30 min preoperatively, compared with the same dose of tenoxicam administered at induction of anesthesia, for the relief of pain after ambulatory breast biopsy.

Materials and methods

In this prospective randomized study pain scores and analgesic requirements were examined in 73 patients undergoing day case breast biopsy. All patients were ASA I or II and each gave informed consent for participation in the study, which was approved by the local ethics committee. Patients with contraindications to non-steroidal anti-inflammatory use and those undergoing fine wire localized breast biopsy were excluded from the study.

The patients were enrolled and randomized using a table of random numbers. The randomization schedules were drawn up by an individual with no further involvement in the study and were placed in a sealed envelope that was opened prior to surgery. The patients randomized to group A received 20 mg tenoxicam 30 min preoperatively. Those randomized to group B received the same dose at induction of anesthesia between five and ten minutes prior to incision.

All patients received a standard anesthetic and no premedication was administered. Anesthesia was induced with 2 $mg \cdot kg^{-1}$ propofol, followed by 5 $\mu g \cdot kg^{-1}$ alfentanyl and a laryngeal mask was inserted. The patients also received local subcutaneous infiltration with 10 ml of bupivacaine 0.5 % after completion of surgery while still under anesthetic. The patients were prescribed 50 mg meperidine *im* or 50 mg diclofenac *po* for postoperative analgesia and the choice of drug administered was left to the discretion of the recovery nurse who had no knowledge of the group to which the patient belonged. Following full recovery the patients were discharged home with an escort and with oral diclofenac.

A proforma was completed on all the patients detailing name, medical records number, age, sex, weight, length of wound, duration of surgery, diagnosis and any ill effects postoperatively. A record was kept of pain scores at 30, 60, 120, and 240 min postoperatively. The pain scores were assessed using a visual analogue scale (VAS) and these were scored from 0 to 10 (0 cm - no pain; 10 cm - worst possible pain). The time to first analgesia, from the time of arrival in the recovery room, within the four hours after surgery and the analgesics administered were recorded. An investigator, without any knowledge of the group to which the patient belonged, recorded the pain scores and analgesia requirements.

A formal sample size calculation was performed. From previous work the standard deviation of VAS pain scores was 1.5 cm. A two-sided significance level of 0.05 and a power of 80% were used with a specified mean difference of 1 cm. The calculated sample size was greater than 35 patients in each group. All enrolled patients completed the study. Statistical analysis was performed using standard parametric and non-parametric statistics; One-way ANOVA, Levene test of homogeneity of variances, the Mann Whitney U test, Chi-square test, and Spearman's correlation and significance was assumed at the 5% level.

Results

Seventy three patients were enrolled in the study with a mean ± SD age of 47.1 ± 11.2 yr. There were 37 patients in group A (tenoxicam 30 min preoperatively) and 36 patients in group B (tenoxicam at induction). There were no differences between the two groups with respect to age, duration of surgery, length of the wound or the weight of the patient (Table I).

Differences were observed between the two groups with respect to pain scores at 30, 60, 120 and at 240

TABLE I Comparing the two groups of patients.

Variable	*Group A*	*Group B*	*Significance*
n	37	36	
Age (yr)	46.4 ± 9.9 [43.1 – 49.7]	47.7 ± 12.5 [43.5 – 51.9]	NS
Weight (kg)	60.8 ± 5.5 [58.9 – 62.7]	62.6 ± 5.7 [60.7 – 64.5]	NS
Duration of surgery (min)	18.5 ± 2.6 [17.7 – 19.4]	18.2 ± 2.6 [17.3 – 19.0]	NS
Length of wound (cm)	3.1 ± 0.6 [2.9 – 3.3]	3.1 ± 0.7 [2.9 – 3.3]	NS

Group A tenoxicam administered 30 min preoperatively, group B tenoxicam administered at induction. Results given as mean ± Standard Deviation and [95% confidence intervals for the mean]. NS = not significant.

TABLE II Time to first analgesia, meperidine used in the first four hours postoperatively and pain scores at intervals postoperatively in the two groups.

Variable	*Group A*	*Group B*	*P*
n	37	36	
Additional analgesia	12 (33%)	27 (73%)	= 0.001
First analgesia (min)	87.5 ± 32.5 [66.8 – 108.2]	55.0 ± 26.8 [44.4 – 65.6]	= 0.002
Meperidine n (%)	1 (3%)	8 (22%)	= 0.016
Demerol (mg first 4 hr; whole group)	1.4 ± 8.3 [0 – 4.2]	10.8 ± 20.9 [3.8 – 17.8]	= 0.015
Diclofenac n (%)	11 (31%)	23 (62%)	= 0.006
Diclofenac (mg first 4 hrs; whole group)	15.3 ± 23.4 [7.4 – 23.2]	31.1 ± 24.6 [22.9 – 39.3]	= 0.006
VAS 30 min	3.2 ± 1.2 [2.8 – 3.6]	5.5 ± 1.8 [4.9 – 6.1]	< 0.001
VAS 60 min	1.8 ± 1.2 [1.4 – 2.2]	3.7 ± 1.9 [3.0 – 4.3]	< 0.001
VAS 120 min	0.9 ± 0.9 [0.6 – 1.3]	1.7 ± 1.0 [1.3 – 1.9]	= 0.003
VAS 240 min	0.5 ± 0.5 [0.3 – 0.7]	1.1 ± 0.8 [0.8 – 1.4]	< 0.001

Group A tenoxicam administered 30 min preoperatively, group B tenoxicam administered at induction. Results given as mean ± Standard Deviation and [95% confidence intervals for the mean] or as number (percent).

min post operatively (Table II). In addition, differences were observed between the need for additional analgesia, time to first analgesia and the doses of meperidine or diclofenac administered (Table II). More patients who received tenoxicam at induction required additional analgesia (Table II) and four patients in this group required both meperidine and diclofenac postoperatively.

Frozen sections were performed on clinically, cytologically, or mammographically suspicious lesions. Thirteen patients had carcinoma diagnosed: seven were in group A and six in group B. All patients with cancer were admitted for in-patient counseling and further treatment, as is standard practice in this unit. No patients in this study required admission because of poor postoperative pain control.

Discussion

In the present study, tenoxicam administered 30 min before surgery resulted in better postoperative analgesia than a similar dose administered at induction of anesthesia. A previous study from this institute confirmed the value of pre-emptive tenoxicam compared with a similar dose administered post-incision.[7] The present study demonstrates that early administration of tenoxicam (30 min preoperatively) resulted in better postoperative analgesia than a similar dose administered at induction.

Non-steroidal anti-inflammatory drugs (NSAIDs) are suitable for mild to moderate pain.[8–9] They inhibit the synthesis of prostaglandins and thromboxane by inhibition of the enzyme cyclo-oxygenase (COX). They decrease prostanoid synthesis and diminish post-injury hyperalgesia at sites of injury.[10–13] Tenoxicam is a thienothiazine derivative, belonging to the oxicam class of NSAIDs and is related to piroxicam. It is a non-selective NSAID, which is suitable for intravenous administration. The precise mode of action of tenoxicam in common with all non-steroidals is unknown and is probably multifactorial. It has a long half-life (60 hr), which enables it to be administered once daily. It is completely absorbed by the oral route and is about 99% protein bound. Because of its low lipophilicity and high degree of ionisation in blood (approximately 99%), the drug is poorly distributed and is slowly taken up by hepatocytes. A small apparent volume of distribution of 9.6 L (7.5 to 11.5L), and low total plasma clearance of 0.106 $L \cdot hr^{-1}$ (0.079 to 0.142 $L \cdot hr^{-1}$), have been reported in healthy volunteers after oral and intravenous administration.[14] After a single oral dose of 20 mg peak plasma concentrations of 2.7 $mg \cdot L^{-1}$ (range 2.3 to 3.0 $mg \cdot L^{-1}$) have been reported in groups of fasting healthy volunteers after 1.9 hr (1.0 to 5.0 hr). A mean elimination half-life of 67 hr (49 to 81 hr) has been estimated. Tenoxicam demonstrates linear single-dose pharmacokinetics in doses from 10 to 100 mg.[14] The pharmacokinetic behaviour of tenoxicam after intramuscular, intravenous and oral administration do not differ, with the exception that higher plasma concentrations are reached during the first two hours after parenteral

administration.[15] Intramuscular administration of tenoxicam takes 15 min to reach levels >90% of the maximally achieved concentration. The same dose administered intravenously reaches peak serum concentrations much faster and declines over the following two hours mainly due to distribution.[16] After both intramuscular and intravenous administration, tenoxicam shows a rapid onset of action, and reliable improvement of pain status.[15]

The role of pre-emptive analgesia has a sound theoretical and experimental basis but clinical studies have proved conflicting. Well-localized and brief noxious stimuli, perceived as pain, may result in long lasting neuronal sensitization resulting from alterations in central processing of stimuli with reduction in threshold, amplification of responses, expanded receptive fields and after discharges of dorsal horn neurons.[17–18] The noxious stimuli and the host response sensitize functional nociceptors and/or activate dormant ones. Sensitized nociceptors have an increased rate of basal discharge, a lowered stimulus threshold and exhibit a supra-normal increase in discharge rate with each increase in stimulus strength, or have a combination of these changes to produce sensitization. Endogenous analgesic responses are also mobilized along with processes of pain amplification and the balance between these processes may determine the responses after injury. When sensitization occurs, and it has been suggested that surgical trauma may lead to these alterations, innocuous stimuli may be perceived as pain. Central sensitization may be eliminated or reduced if afferent barrage can be prevented from reaching the central nervous system. These observations lead to the concept that analgesia administered before an initial noxious stimulus (e.g. skin incision) is more effective than the same dose given afterwards i.e. the concept of pre-emptive analgesia. Pre-injury neuronal blockade, with local anesthetics or opioids, has been shown to reduce sensitization and prevent the development of injury-induced hyperexcitability in animal studies.[19–20]

Initial perioperative control of pain may have long-term benefits. The biological and psychological foundation for persistent postoperative pain may be in place within hours of injury.[21] In adults, meticulous perioperative analgesia for radical prostatectomy lowered analgesic requirement and improved functional status for months postoperatively.[22]

Multiple factors interact to produce or prevent a pre-emptive analgesic effect. The nature and duration of the surgery, the type and extent of tissue damage, the timing and method of administration and the nature of agents used, interactions with other substances used intraoperatively, the afferent neuronal blockage produced and the time course of central sensitization all interact with the emotional, physiological and psychological state of the individual.[23,24] Small differences in the initial state of the host and in the intensity, quality, and meaning of the nociceptive stimulus can produce major differences in the final perception of pain. Many of these factors are difficult to control in clinical studies and may account for some of the discrepancies between studies on pre-emptive analgesia.

It has been suggested that the different drug classes have an additive analgesic effect and utilize distinct mechanisms. Strategies for pharmacological management of pain based on drugs which block all the transmitters may be more successful than those, based on antagonism of one specific transmitter alone. A triad of opioids, local anesthetic agents, and NSAIDs is necessary to produce maximal reduction in pain intensity. In the present study these three different classes of analgesics were employed and administration of tenoxicam 30 min preoperatively proved superior to the same dose administered at induction of anesthesia.

In the present study, beneficial effects were found for pain scores at 30, 60, 120, and 240 min postoperatively, time to first analgesia, opioid use, and additional analgesia use with tenoxicam administered 30 min preoperatively compared with the same dose administered at induction.

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