Regional Anesthesia and Pain

Prior ibuprofen exposure does not augment opioid drug potency or modify opioid requirements for pain inhibition in total hip surgery

[L'exposition préalable à l'ibuprofène n'augmente pas l'effet des opiacés ou ne modifie pas les besoins d'opiacés pour l'analgésie de l'arthroplastie totale de la hanche]

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Purpose: In previous animal studies, a prior exposure to non-steroidal anti-inflammatory drugs (NSAID) augmented opioid drug potency. This study was designed to answer the question whether a similar effect can be attained in man. The objective was to use NSAID for preoperative pain reduction and at the same time use the NSAID exposure to reduce opioid requirements for pain inhibition in major orthopedic surgery.

Methods: In this double-blind, randomized study, 50 patients scheduled for total hip surgery were included. Patients of Group I received a placebo drug three times a day two weeks before surgery, and those allocated to Group II received ibuprofen (600 mg) three times a day. For surgical anesthesia, all patients received intrathecal bupivacaine 20 mg plus 0.1 mg morphine in a total volume of 4 mL.

Results: The preoperative or postoperative visual analogue scale pain scores or the amount of *iv* morphine showed no differences between the two groups in the first 24 hr after surgery. The median total blood loss in the ibuprofen group was 1161 mL *vs* 796 mL in the placebo group ($P < 0.01$).

Conclusion: Pretreatment with ibuprofen before major hip surgery does not improve the pain scores or reduce morphine requirement but significantly increases blood loss. Considering the presence of relevant adverse effects, pretreatment with a non-selective NSAID is not recommended.

Objectif : *Des études antérieures sur des animaux ont démontré qu'une exposition préalable aux anti-inflammatoires non stéroidiens (AINS) renforce l'effet des opiacés. Cette étude a été conçue pour savoir si le même effet peut être obtenu chez l'homme. L'objectif était de prescrire un traitement antalgique préopératoire aux AINS et en même temps, profitant de l'exposition aux AINS, de réduire le besoin d'opiacés pour diminuer la douleur après des opérations orthopédiques majeures.*

Méthode : *Cinquante patients opérés pour la mise en place d'une prothèse totale de la hanche ont été inclus dans cette étude randomisée et en double aveugle. Les patients du Groupe I prenaient un placebo trois fois par jour pendant deux semaines avant l'opération tandis que les patients du Groupe II prenaient de l'ibuprofène (600 mg) trois fois par jour. L'anesthésie pratiquée à l'ensemble des patients consistait en l'injection intrathécale de 20 mg de bupivacaïne et 0,1 mg de morphine dans un volume total de 4 mL.*

Résultats : *Aucune différence n'a été constatée entre les deux groupes dans les degrés de douleur mesurée par échelle visuelle analogique aussi bien en préopératoire qu'en postopératoire ou dans la dose de morphine injectée par voie iv pendant les 24 premières heures après l'opération. La perte totale de sang dans le groupe ibuprofène s'élevait à 1 161 mL et dans le groupe placebo à 796 mL.*

Conclusion : *Un traitement préalable à l'ibuprofène en chirurgie majeure de la hanche n'améliore pas la douleur et ne diminue pas le besoin de morphine postopératoire, mais est associé avec une perte de sang significativement plus élevée. Vu ces conséquences fâcheuses, il nous apparaît judicieux de s'abstenir d'un traitement préalable aux AINS non sélectifs avant ce type de chirurgie.*

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MORPHINE and other opioid analgesics produce potent analgesia by activating specific receptors on the spinal and supraspinal neurons involved in pain transmission. At the spinal level, opioids elicit analgesia partly by inhibiting the spinal release of substance P[1] or L-glutamate. These transmitters are localized in primary afferents that elicit pain behaviours by acting on the neurokinin and N-methyl-D-aspartate (NMDA) receptors, respectively. Evidence from experimental studies suggests that spinal prostanoids play an intermediary role in the expression of pain behaviours elicited by activity of these sensory transmitters.[2,3] It has been demonstrated that hyperalgesia produced by activation of spinal NMDA receptors is mediated by prostaglandins since intrathecal injections of cyclo-oxygenase inhibitors, agents that block prostanoid synthesis, inhibit this response.[4]

Like hyperalgesia, the development of opioid tolerance is recognized as an NMDA receptor- dependant phenomenon as NMDA antagonists attenuate this response.[5–9] A recent animal study[10] showed that co-administration of chronic morphine with cyclo-oxygenase inhibitors, ketorolac and ibuprofen, significantly attenuates the decline in opioid agonist potency occurring with repeated drug administration. This suggests that chronic opioid drug treatment likely mobilizes prostanoids[11] which act on presynaptic receptor sites[12] to stimulate release of nociceptive transmitters[13] and thus physiologically antagonize the analgesic action of the drug. However, it has also been observed that chronic spinal administration of the cyclo-oxygenase inhibitors alone significantly enhances the analgesic potency of acute morphine evaluated at the end of the treatment period, reflecting sensitization to the opioid action.[10] While the mechanisms underlying this sensitization are unclear, this observation has important clinical implications. It suggests that a prior exposure to cyclo-oxygenase inhibitors has the potential to augment opioid drug potency and thus reduce opioid requirements for pain inhibition.

Clinically the use of prior exposure to cyclo-oxygenase inhibitors carries some attractive potentials. First, the drug may result in a reduction of preoperative pain, and in a recent study we found that lower preoperative visual analogue scale (VAS) scores correlated with lower postoperative morphine requirements for postoperative analgesia.[14] Secondly, augmented opioid drug potency may contribute to reduction in opioid dosage and this may enhance safety. Intrathecal opiates are often used for postoperative pain control in major orthopedic surgery of the lower limb.[15,16] In our clinic, we showed that - for total hip surgery - 0.1 mg of intrathecal morphine and repeated *iv* morphine by patient-controlled analgesia (PCA) pump for 24 hr results in appropriate analgesia, defined by VAS scores < 3.[17] So far - in approximately 6,000 patients - the intrathecal dose of 0.1 mg morphine proved safe in that late respiratory depression did not occur. However, there continues to be a high incidence of other side effects such as urinary retention and itching.[18] Also, the total *iv* PCA morphine dose is highly variable and ranges from 10 to 100 mg·24 hr^{-1}.

The present double-blinded randomized study was designed to test whether a prior exposure to the cyclo-oxygenase inhibitor ibuprofen would reduce preoperative and postoperative pain and whether it would augment morphine's potency.

Methods and materials

The Ethical Committee of our hospital approved the study and written informed consent was obtained from all patients. Fifty consecutive patients with coxarthrosis scheduled for primary elective total hip replacement surgery under intrathecal anesthesia were included. Exclusion criteria were those that exclude spinal anesthesia or the use of non-steroidal anti-inflamatory drugs (NSAID) or opioids.

Patients were allocated and randomized to two groups in a double-blind manner. All patients were pretreated during a two-week period before surgery: Group I with placebo drug, and Group II with ibuprofen 600 mg. Placebo and ibuprofen were prepared as look-alike tablets by the pharmacist, who was the only person aware of the type of pretreatment, and were given orally three times a day. The day of surgery all patients started with 15 mg movicox orally one hour preoperatively. This was continued for three days postoperatively.

Prophylaxis against thromboembolism was started in all patients the evening before surgery with 3 mg acenocoumarol orally. On the day of surgery 2 mg acenocoumarol was given 24 hr after the initial dose. All patients were premedicated with 7.5 mg midazolam orally one hour before intrathecal anesthesia. Spinal anesthesia was induced by the administration of 20 mg bupivacaine plus 0.1 mg morphine dissolved in 4 mL (isobaric solution).

Adequate sedation was provided at the patient's request during the procedure: the anesthesiologist administered 1 mg midazolam at the minimum interval of five minutes until the patient indicated that the desired sedation was reached. Non-invasive blood pressure, heart rate (ECG), SpO_2, and respiratory rate were continuously monitored during anesthesia and in the intensive care unit during the first 24 hr after surgery.

TABLE I Patient characteristics

Group	*Ibuprofen*	*Placebo*
n	17	19
Age (yr)	63 (12)	59 (14)
Height (cm)	170 (8)	169 (11)
Weight (kg)	74 (13)	72 (14)
Gender (m/f)	6, 11	5, 14

Age, height, and weight are given as mean (SD) values. n = number of patients, m = male, f = female.

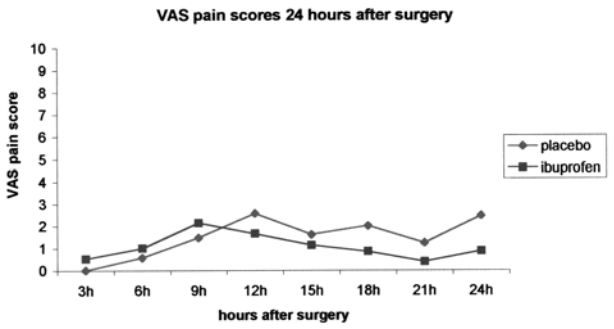

FIGURE 1 Visual analogue scale (VAS) pain scores in the first 24 postoperative hours for placebo and ibuprofen pretreated patients

Pain

Pain was evaluated using VAS scores. VAS scores were assessed: 1) before starting pretreatment; 2) preoperatively (i.e., after two weeks of pretreatment); and 3) postoperatively on rest (0–10; with 0 = no pain) every three hours. The patients could use a PCA device with *iv* morphine if pain was present. The settings of the PCA pump (Braun®, Melsungen, Germany): baseline 0.0 $mg \cdot hr^{-1}$, bolus dose 1.0 mg, bolus interval five minutes, maximum 30.0 mg per four hours.

Side effects

The presence or absence of itching, postoperative nausea and vomiting (PONV), urinary retention, sedation were noted at a three-hour interval during the 24-hr observation period. Also, medications to treat these side effects were recorded at the same interval during the 24-hr observation period.

Blood loss was measured by weighing the gauzes and inspection of collection reservoirs.

Statistical analysis

Pain scores were analyzed using a paired t test. The incidence of PONV and itching was compared between the groups with Fisher's exact tests. The amount of blood loss and morphine consumed was analyzed using a Mann Whitney U test, since they were non-normally distributed. It was planned to enroll 25 patients in each group to be able to detect a difference of one standard deviation in postoperative VAS pain score ($\alpha = 0.05$ two sided, ß = 0.10)

Results

Demographic data are represented in Table I. As shown, the two groups did not differ significantly in age, height, weight or gender. Likewise other variables, e.g., preoperative use of beta blockers, percentages of patients who required sedation during surgery, duration of surgery, use of bone cement and blood pressure decreases (> 25% decrease in mean arterial pressure after bone cement) were not different between groups. Surgery was postponed more than three days in 14 patients (and the medication not continued), so these patients had to be excluded from the analysis.

The VAS scores before treatment (6.7 ± 1.4 and 7.1 ± 1.6) did not differ between the two groups. After the two-week pretreatment period, VAS scores were not different for the two groups (6.4 ± 1.4 and 6.5 ± 2.6 for patients pretreated with placebo and ibuprofen, respectively). There was no difference in the postoperative VAS scores (Figure 1; $P = 0.35$). Likewise, the amount of morphine consumed by patients using the PCA pump (26.6 ± 18.6 mg and 22.1 ± 9.6 mg for placebo and ibuprofen pretreated patients respectively) was not different ($P = 0.52$).

The median perioperative blood losses and (interquartile range) are given in Table II. The median total perioperative blood loss in patients pretreated with ibuprofen was 1161 *vs* 796 mL in the placebo group: i.e., 30% higher after ibuprofen than after placebo ($P < 0.01$).

The incidence of PONV (Table III; Figure 2) was not significantly different between the two groups. Similarly, the incidence of postoperative itching was similar in both groups (Figure 3).

Discussion

Previous animal studies showed that a period of chronic *intrathecal* administration of ketorolac or S(+) ibuprofen increased the antinociceptive potency of acute morphine.[10] In man, VAS scores after orthopedic surgery were lower in patients treated with *iv* ketorolac before surgery than for patients treated with *iv* saline or postoperative ketolorac.[19] This prompted us to examine, in a clinical situation, whether prior

TABLE II Perioperative blood losses

Group	*Ibuprofen*	*Placebo*
Blood loss during surgery	700* (367)	416 (203)
Blood loss 24 hr after surgery	461 (312)	380 (169)
Total blood loss	1161* (472)	796 (337)

Blood loss is given as median and interquartile range, value in mL. *$P < 0.01$.

TABLE III Postperative nausea and vomiting

Group	*Ibuprofen*	*Placebo*
Incidence of postoperative nausea	52.9%	57.9%
Incidence of postoperative vomiting	41.1%	21.0%
%patients requiring anti-emetic drugs	52.9%	42.1%

No significant differences between groups.

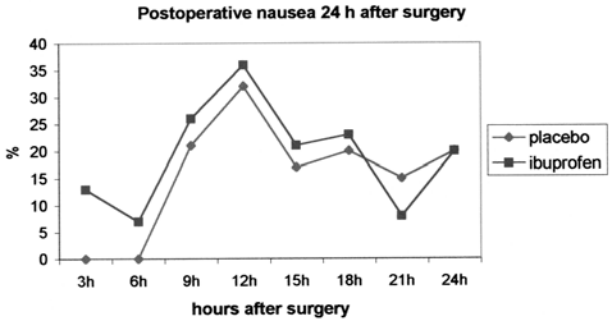

FIGURE 2 Incidence of postoperative nausea.

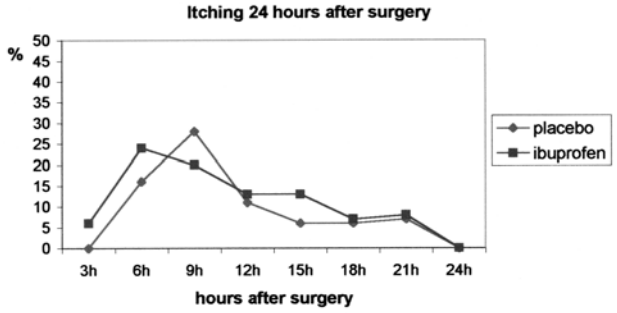

FIGURE 3 Incidence of postoperative itching.

treatment with a systemic NSAID would afford pain relief and reduce the requirements for morphine. Our main finding is that preoperative pretreatment with *oral* ibuprofen does not reduce VAS scores pre- or postoperatively and does not enhance the potency of morphine. Several factors may explain the absence of effect of NSAID on opioid requirements. In the surgical and immediate postoperative period, the combined administration of bupivacaine and morphine provides effective analgesia after total hip arthroplasty[17] and, thus, the prevailing low postoperative pain VAS scores may have prevented us from appreciating putative improvement from oral ibuprofen. For the subsequent period, pain was treated by the use of PCA morphine and systemic ibuprofen failed to reduce the amount and variability of analgesic consumption. Likewise, previous clinical trials that tested NSAID for their ability to effect "pre-emptive analgesia" showed no clinical improvement in postoperative pain control.[20] Finally, it should be noted that in the experimental study,[10] the NSAID was used intrathecally and it is likely that the oral dose of ibuprofen used clinically failed to reach the concentration that influenced morphine action at the spinal level. The use of higher doses of the drug in this respect is not advisable as the ibuprofen dose used already produces COX-1 related side effects. The inhibition of COX-1 may result in impaired platelet aggregation,[21–23] explaining the statistically and clinically relevant higher perioperative blood loss in patients pretreated with ibuprofen.

A potential clinical benefit pursued using pretreatment with ibuprofen was the possible reduction of opioid related side effects. We found no differences in the incidence of morphine side effects (urinary retention, itching, PONV) between the two groups. Consequently, we feel that there is no benefit in pretreating patients undergoing elective hip surgery with the NSAID ibuprofen. The use of COX-2 inhibitors may be more effective or ibuprofen might influence morphine action in other surgical situations, such as knee surgery when pain control is less optimal.

Conclusions

Preclinical research indicated that prior exposure to NSAID has the potential to augment opioid drug potency and thus reduce opioid requirements for pain control. This double-blind randomized human study showed no change in preoperative VAS pain scores, surgical spinal anesthesia, postoperative pain, or morphine consumption for pain relief after primary hip surgery and the use of ibuprofen lead to augmented blood loss.

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