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ORIGINAL ARTICLE

Nefopam after total hip arthroplasty: Role in multimodal analgesia

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Nefopam;
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Hip arthroplasty;
Postoperative nausea/vomiting;
Postoperative pain

Summary
Background: Multimodal analgesia combining several non-opioid analgesics is recommended for pain control after surgery. In one study of total hip arthroplasty (THA), pain relief achieved by adding ketamine to the paracetamol—ketoprofen combination was statistically significant but remained inadequate in most patients. In two other studies, the analgesic effect of nefopam was synergistic with that of ketoprofen and additive with that of paracetamol. Adding nefopam to the paracetamol—ketoprofen-ketamine combination has not been evaluated.
Hypothesis: Adding nefopam to the paracetamol—ketoprofen—ketamine combination significantly improves analgesia after THA.
Material and methods: A prospective single-centre comparative non-randomised study (control group then nefopam group) was conducted in patients undergoing THA under general anaesthesia. All patients received paracetamol—ketoprofen—ketamine and morphine/droperidol patient-controlled analgesia. The nefopam group also received a continuous infusion of nefopam (120 mg/d for 48 h). Pain was evaluated daily for 7 days. The main evaluation criteria were morphine consumption, and pain intensity evaluated using a numerical rating scale and a validated questionnaire. To detect a 40% morphine-sparing effect by H24 ($\alpha = 0.05$ and $\beta = 0.2$), 85 patients were needed in each group.
Results: The two groups (90 patients/group) had no significant differences for perioperative characteristics, pain scores, morphine consumption at H24 (nefopam, 13 ± 12 mg and control, 14 ± 13 mg, $P = 0.39$), or functional recovery. Compared to the control group, the nefopam group had lower rates of nausea/vomiting ($P < 0.0001$), pruritus ($P = 0.002$), and visual disturbances ($P = 0.02$).

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Discussion: Nefopam failed to improve pain relief when added to a multimodal analgesia regimen but alleviated several morphine-induced side effects. Redundancy between nefopam and ketamine may explain the absence of greater pain relief. This study emphasises the need for clinical evaluations of every analgesic regimen, as the available data were not sufficient to predict these results.
Level of evidence: Level III, case-control study.

Introduction

Effective analgesia is crucial to expedite and improve functional recovery after orthopaedic surgery [1]. Postsurgical rehabilitation can be adversely affected by the side effects of opioids (drowsiness, respiratory depression, nausea, vomiting, and urinary retention). Most of these side effects are dose-dependent. Multimodal analgesia seeks to decrease their incidence by limiting the need for opioids. Multimodal analgesia consists in combining several non-opioid analgesics to obtain additive or even synergistic effects [2]. However, among combinations of non-opioid drugs, only paracetamol plus a non-steroidal anti-inflammatory drug (NSAID) has been adequately studied.

When used alone, paracetamol, nefopam, and ketoprofen have a morphine-sparing effect after total hip arthroplasty (THA) [3—5]. The paracetamol-NSAID combination has been proven effective [6—8]. Adding ketamine to the paracetamol—ketoprofen combination improved pain relief after THA, for up to 6 months [9]. Nevertheless, most of the patients in the ketamine add-on group reported persistent moderate to severe pain (mean maximum pain score during the first 3 days, 41 ± 28 mm) and 41% of them required anti-emetic treatment within the first 24 h after surgery. Thus, further optimisation of this analgesia protocol is needed. Nefopam and ketoprofen act synergistically in relieving moderate to severe pain after minor surgery [10]. Adding nefopam to paracetamol decreases the morphine requirements after abdominal surgery [11]. However, no studies have evaluated nefopam added to ketamine therapy.

The objective of this study was to evaluate the effect of nefopam added to the paracetamol—ketoprofen—ketamine combination after THA, based on both the consumption of morphine after surgery and pain intensity measured using a numerical rating scale (NRS) and a validated questionnaire [9]. Our hypothesis was that adding nefopam improves pain control after THA and decreases morphine requirements, thereby diminishing morphine-induced side effects such as nausea.

Materials and methods

Patient inclusion

The research project was approved by the local ethics committee (*Comité de Protection des Personnes*). Patients scheduled for primary THA (regardless of the surgical approach and type of prosthesis) were invited to participate in the study during the pre-anaesthesia evaluation. At our institution, THA is performed under general anaesthesia. Written informed consent to study participation was obtained from each patient on the day before surgery. Non-inclusion criteria were surgery for cancer, contraindications to nefopam (acute angle-closure glaucoma, epilepsy, allergy, nocturnal frequency with more than two bathroom visits per night, coronary artery disease), contraindications to paracetamol (liver failure, allergy), contraindication to ketamine (porphyria), chronic morphine use in a daily dosage greater than 10 mg, inability to understand the use of patient-controlled analgesia (PCA) or of a NRS for self-evaluating pain intensity, and refusal to participate.

We used a prospective controlled design with two successive enrolment periods. Between February 2007 and February 2008, the study patients received the control treatment regimen, namely, paracetamol—ketoprofen—ketamine. During the second period, from February to November 2008, nefopam was added to the paracetamol—ketoprofen—ketamine combination.

Anaesthesia

During the pre-anaesthesia evaluation, the patients were informed about the use of PCA and about pain self-evaluation using the NRS. To use the NRS, the patient rated pain intensity from 0 (no pain) to 100 (worst pain imaginable). Premedication with hydroxyzine (100 mg) or alprazolam (0.5 mg) was given 1 h before surgery. General anaesthesia was induced using propofol (2—3 mg/kg), sufentanil (0.3—0.5 μg/kg), and atracurium (0.5 mg/kg). After oral endotracheal intubation, anaesthesia was maintained using inhaled sevoflurane/nitrous oxide, together with additional sufentanil and/or atracurium injections as needed. The patient was operated on in the lateral decubitus position under a hot air blanket.

Analgesia

Ketamine was injected after anaesthesia induction and before the incision in a dose of 0.5 mg/kg (up to 50 mg) then given as a continuous intravenous infusion (2 mcg/kg per minute) for 24 h, through a dedicated line in a three-way extension tubing with anti-reflux valves [12]. Ketoprofen (50 mg) and paracetamol (1 g) were injected 30—60 min before closure of the skin incision then every 6 h. Contraindications to ketoprofen were creatinine clearance (by the Cockcroft formula) lower than 30 mL/min, any history