ORIGINAL ARTICLE

Nefopam after total hip arthroplasty: Role in multimodal analgesia

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KEYWORDS
Nefopam; Multimodal analgesia; Ketamine; 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 (α = 0.05 and β = 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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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
of gastric or duodenal ulcer, allergy, and NSAID-induced asthma. In addition, 30–60 min before closure of the skin incision, the nefopam group patients were given 20 mg of nefopam (Acupan®, Biocodex, Gentilly, France) over 30 min followed by a continuous intravenous infusion for 48 h (120 mg/d). After extubation in the post-anaesthesia care unit (PACU), the patients used the NRS to evaluate their pain intensity. Patients reporting NRS scores greater than 30 mm received intravenous morphine titration (2–3 mg every 5 min). Once the NRS score fell below 30 mm, an intravenous PCA device was set up, for 1 to 4 days (bolus, 1 mg every 7 min; maximum, 15 mg/4 h; no continuous infusion). The device was loaded with 100 mg morphine and 5 mg droperidol. Patients with nausea were given a 4-mg ondansetron injection.

On the day after surgery, the oral route was substituted for the intravenous route for paracetamol (1 g qid until discharge) and ketoprofen (150 mg bid for 24 h). The PCA was replaced by 20 mg oral morphine sulphate as needed until discharge. The patients could return to their usual analgesic regimen 48 h after surgery, at their request.

Thromboembolism prophylaxis was with 2.5 mg/d fondaparinux injected subcutaneously. The drains were removed when they yielded less than 50 mL/d and on the third postoperative day at the latest. The patient was then encouraged to get up and, on the next day, to start ambulating.

Study parameters

For each patient, we collected data on demographics (age, weight, height, co-morbidities, preoperative treatment), the anaesthesia (doses of sufentanil, ephedrine or atropine; volume of crystalloids and colloids; blood transfusions; body temperature at completion of surgery; duration of general anaesthesia, and time spent in the PACU), and the surgery (whether the hip osteoarthritis was primary or not, history of surgery, approach, type of prosthesis, whether cement was used, and operative time).

The main evaluation criteria were morphine consumption and pain intensity. Cumulative morphine consumption during the first 7 postoperative days was computed as the sum of the dose used for morphine titration in the PACU, the dose delivered by PCA, and the intravenous equivalent of oral morphine doses (10 mg orally = 3 mg intravenously). The site and intensity of the pain were evaluated before surgery, in the PACU, and daily thereafter (in the morning at rest, by recording the maximal pain intensity during the 24-h cycle; at first arising, at first ambulation, and at discharge). Pain intensity was measured using the NRS and questionnaires used in a previous study in our department [9].

The secondary evaluation criteria were functional recovery assessed on the 7th postoperative day based on time to ambulation, leaving the room, and climbing stairs; side effects (experienced at least once by the patient) were reported during an interview at the bedside on the 7th postoperative day and recorded in the medical chart.

Statistics

Morphine consumption by H24 was 14 ± 13 mg in a previous study done at our department in patients receiving the paracetamol–ketoprofen–ketamine combination [9]. To detect a 40% decrease in morphine consumption with the alpha risk set at 0.05 and 80% power, we needed 86 patients in each group. We therefore included 90 patients per group.

The data are described as mean ± SD. Quantitative variables were tested using Student’s t test and qualitative variables using the Chi² test or Fisher’s test (Statview 5.0 for Windows, SAS Institute Inc., Cary, NC, USA). Values of P lower than 0.05 were considered significant.

Results

Of the 378 patients who underwent primary THA during the study period, 198 were excluded, for the following reasons: unwillingness to participate, n = 38; participation in another study, n = 110; daily use of opiates or drugs active against neuropathic pain, n = 20; inability to use the PCA system, n = 19; contraindication to nefopam therapy, n = 7; porphyria, n = 3; and surgery cancellation (anaphylactic shock at anaesthesia induction), n = 1. In the control group, one patient required repeat surgery at H30 for prosthesis dislocation; data acquisition was stopped at H24 in this patient. No statistically significant differences were found between the two groups regarding the preoperative and intraoperative characteristics (Tables 1 and 2).

Morphine consumption by H24 was not significantly different between the control group (13.8 ± 12.5 mg) and the nefopam group (12.9 ± 11.9 mg) (P = 0.62) (Table 3). Neither did the pain scores differ significantly between the two groups, except for the maximum pain intensity score in the PACU, which was significantly lower in the nefopam group (17 ± 26 mm versus 29 ± 31 mm in the control group, P = 0.007). Significantly lower rates were found in the nefopam group for ondansetron use, nausea, vomiting, pruritus, and visual disturbances (Table 4).

Discussion

This study shows that adding nefopam to the paracetamol–ketoprofen–ketamine combination has no significant effect on pain intensity or morphine consumption after THA. Paradoxically, nefopam diminishes several of the side effects of morphine therapy.

In theory, several factors might have masked an analgesic effect of nefopam in our study. One is the non-randomised study design. However, the two groups had no significant differences for multiple preoperative and intraoperative parameters related to the anaesthesia and surgical procedure. The higher preoperative use of analogics in the control group might have spuriously increased analgesic consumption in this group. Furthermore, the low morphine consumption in the control group made it difficult to detect a 40% decrease in morphine use. However, the study was designed to ensure that a 40% decrease could be detected with 80% power and 5% alpha risk. A 40% decrease was perhaps an excessively ambitious target. Nevertheless, a 30% to 50% decrease in morphine consumption has been reported with nefopam used alone [4, 14] or combined to paracetamol [11]. We hoped to obtain a greater than 40% decrease, since the nefopam–ketoprofen combination has been associated with a 16-fold decrease in nefopam dosage requirements.
Table 1  Preoperative features in the two groups of patients.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Control group (n = 90)</th>
<th>Nefopam group (n = 90)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean ± SD</td>
<td>65 ± 13</td>
<td>65 ± 15</td>
<td>0.67</td>
</tr>
<tr>
<td>Body mass index, kg/m², mean ± SD</td>
<td>26.9 ± 4.5</td>
<td>26.7 ± 4.5</td>
<td>0.81</td>
</tr>
<tr>
<td>Body mass index &gt; 30 kg/m², %</td>
<td>26</td>
<td>20</td>
<td>0.33</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>41</td>
<td>43</td>
<td>0.76</td>
</tr>
<tr>
<td>ASA III score, %</td>
<td>13</td>
<td>12</td>
<td>0.82</td>
</tr>
<tr>
<td>Previous surgery on same hip, %</td>
<td>20</td>
<td>9</td>
<td>0.06</td>
</tr>
<tr>
<td>Prosthesis on contralateral hip, %</td>
<td>29</td>
<td>24</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Characteristics of preoperative pain

| Pain in index hip at rest, NRS score, mean ± SD | 45 ± 34 | 44 ± 31 | 0.85 |
| Other pain at rest, NRS score, mean ± SD       | 38 ± 34 | 29 ± 32 | 0.08 |
| Pain in index hip during walking, NRS score, mean ± SD | 64 ± 26 | 61 ± 28 | 0.37 |
| Other pain during walking, NRS score, mean ± SD | 41 ± 35 | 42 ± 34 | 0.88 |
| Walking aid needed, %                          | 54       | 43       | 0.12 |

Treatment for chronic pain

| Antidepressant, %                           | 6        | 7        | 0.99 |
| Benzodiazepine, %                           | 10       | 14       | 0.50 |
| Non-steroidal anti-inflammatory drug, %     | 44       | 38       | 0.36 |
| Paracetamol, %                              | 70       | 40       | <0.0001 |
| Codeine/dextropropoxyphene/tramadol, %      | 41       | 27       | 0.04 |

NRS: numerical rating scale for pain intensity.

Table 2  Intraoperative features in the two groups of patients.

<table>
<thead>
<tr>
<th>Anaesthesia</th>
<th>Control group (n = 90)</th>
<th>Nefopam group (n = 90)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration in minutes, mean ± SD</td>
<td>181 ± 41</td>
<td>174 ± 35</td>
<td>0.20</td>
</tr>
<tr>
<td>Total sufentanil dose in µg/kg, mean ± SD</td>
<td>1.03 ± 0.36</td>
<td>1.05 ± 0.33</td>
<td>0.80</td>
</tr>
<tr>
<td>Core temperature at surgery completion in ºC, mean ± SD</td>
<td>36.1 ± 0.6</td>
<td>35.9 ± 0.6</td>
<td>0.06</td>
</tr>
<tr>
<td>Patients given ketoprofen, %</td>
<td>86</td>
<td>86</td>
<td>0.99</td>
</tr>
</tbody>
</table>

Surgery

| Diagnosis of primary hip osteoarthritis, %    | 68                     | 69                     | 0.87    |
| THA on the left hip, %                        | 44                     | 46                     | 0.88    |
| Operative time in minutes, mean ± SD          | 127 ± 37               | 123 ± 32               | 0.37    |
| Approach: posterior/anterior/trochanterotomy, % | 40/49/10  | 47/51/2            | 0.08    |
| Cemented femoral component, %                 | 79                     | 71                     | 0.23    |
| Cemented acetabular component, %              | 79                     | 72                     | 0.30    |

THA: total hip arthroplasty.

and a 7-fold decrease in ketoprofen dosage requirements, as well as with a reduction by half of the proportion of patients having a greater than 30-mm NRS score in the PACU [10]. In our nefopam group, 86% of patients received ketoprofen.

Several hypotheses can be put forward to explain the absence of an analgesic effect of nefopam in our study. First, continuous nefopam administration may be less effective than a 30-min intravenous infusion. Only two previous studies found no analgesic effect of nefopam, and both used continuous administration, after urological surgery [15] and after childbirth [16], respectively. This factor may explain that the only significant improvement in analgesia in the nefopam group was seen in the PACU, since a nefopam bolus was injected at the end of the surgical procedure. Second, the analgesic effect of ketamine may have masked that of nefopam. Two comparative studies suggest a stronger analgesic effect of ketamine compared to nefopam, resulting in decreased morphine titration in the PACU (9 ± 5 vs. 10 ± 5 mg after major surgery [17] and 8 ± 5 vs. 11 ± 4 mg after total knee arthroplasty [18]) and, above all, in improved functional recovery after total knee arthroplasty [18]. This strong effect may explain that adding ketamine to the paracetamol—nefopam combination improved analgesia after thoracotomy [19], whereas in our study adding nefopam to an analgesic combination including ketamine produced no further analgesia after THA. Experimental studies suggest that this effect may be related to several similarities in the mechanisms of action of the two
Nefopam, a direct-acting μ-opioid receptor agonist, is known to be associated with the side effects of morphine, including diplopia, nausea, vomiting, and pruritus. Although nefopam has been shown to have a lower risk of these side effects compared to morphine, it was found to be associated with an increased risk of urinary retention and hallucinations, and it required a higher dose of paracetamol–ketoprofen–ketamine combination for pain control after total hip arthroplasty (THA) [20,21].

Paradoxically, nefopam failed to decrease the morphine requirements in our study, which diminished several morphine side effects including visual disturbances, pruritus, and nausea/vomiting. A bias related to an abnormally high rate of these side effects in the control group is unlikely, since the observed rate of nausea/vomiting was consistent with that predicted by the Apfel score [13] (Table 4). Thus, the decrease in nausea and vomiting seen with nefopam may be attributable to a direct effect of this drug rather than to an indirect effect mediated by a decrease in morphine consumption, with the anatomical site of the anti-emetic effect being different from that of the analgesic effect.

This study shows that nefopam added to the paracetamol–ketoprofen–ketamine combination provides no additional analgesia after THA. Redundancy between nefopam and ketamine effects may explain this finding. Nevertheless, in this setting, despite the absence of a morphine-sparing effect, nefopam decreased some of the side effects of morphine. This unexpected finding needs to be confirmed by randomised trials.

### Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.
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