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Randomized prospective study of the analgesic effect of nefopam after orthopaedic surgery†

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Background. Balanced postoperative analgesia combines non-narcotic drugs and opioids. We organized a large study to evaluate nefopam analgesia and tolerance in combination with morphine for patient-controlled analgesia (PCA) after orthopaedic surgery.

Methods. Two hundred and one patients scheduled to undergo hip arthroplasty were included in this multicentre (n=24), double-blind, randomized study comparing nefopam (20 mg every 4 h for 24 h) with placebo, the first dose being infused peroperatively. The primary outcome measure was the cumulative morphine dose received postoperatively by PCA over 24 h. Secondary outcome measures were the amount of morphine received as a loading dose in the postanaesthesia care unit (PACU) and during the 24-h observation period, and pain assessments using a visual analogue scale (VAS) and a verbal pain scale (VPS), patient's satisfaction with analgesia and treatment tolerance.

Results. The two groups were comparable with respect to their characteristics and preoperative pain assessment. PCA-administered morphine over 24 h was significantly less for the nefopam group than the control group (21.2 (15.3) and 27.3 (19.2) mg respectively; P=0.02). This morphine-sparing effect was greater (35.1%) for patients with severe preoperative pain (VAS>30/100). For the entire study period (loading dose and PCA), morphine use was less for the nefopam group (34.5 (19.6) *vs* 42.7 (23.6) mg; P=0.01). Pain VAS at PACU arrival and during the whole PACU period was significantly lower for the nefopam than for the placebo group (P=0.002 and 0.04 respectively). Patient satisfaction was similar for the nefopam and placebo groups.

Conclusion. In combination with PCA morphine, nefopam gives significant morphine-sparing with lower immediate postoperative pain scores without major side-effects. This analgesic effect seems to be particularly notable for patients with intense preoperative pain.

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Postoperative analgesia is required to achieve patient comfort and postoperative rehabilitation. As opioids alone can cause side-effects and have limited analgesic potency, it has been suggested that analgesic drug combinations may be useful to improve analgesia and limit side-effects.[1] Only a few non-narcotic analgesics are available (e.g. acetaminophen, non-selective non-steroidal anti-inflammatory drugs and selective inhibitors of cyclooxygenase 2).

Nefopam is chemically distinct and pharmacologically unrelated to any presently known analgesic.[2] It has been used in Europe for i.v. and oral administration since 1976, and has been available for i.v. administration in France since

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1981. Nefopam is a racemic mixture of its two enantiomers[3] and is a centrally acting non-narcotic analgesic. Its mechanisms of action are not fully understood, but *in vitro* analysis revealed inhibition of serotonin and norepinephrine reuptake in animal models.[4] The inhibiting effects of nefopam on noxiously evoked spinal c-Fos protein expression were shown recently.[5] Its intense inhibition of the nociceptive reflex in human volunteers confirms the central site of action.[6] Nefopam has the advantage of not affecting platelet aggregation and having no central nervous system depressive effect.[7 8] There have been rare fatal overdoses with the oral form of the drug, characterized by convulsions and arrhythmia.[9 10] Its sympathomimetic action renders it contraindicated for patients with limited coronary reserve, prostatitis and/or glaucoma. Nefopam causes minor side-effects (nausea, dizziness and sweating) in 15–30% of treated patients.

Despite its availability for many years, clinical data on the analgesic effect and tolerance of i.v. nefopam for postoperative pain relief are scarce. Before 1990, most of the studies evaluated the analgesic effect of a single oral or i.m. administration.[11–15] The results of these studies suggested that the analgesic effect of nefopam 20 mg equalled that of meperidine 50 mg or morphine 6–12 mg.

However, only a few studies have evaluated repeated administration of nefopam.[16 17] After abdominal surgery, i.m. administration of nefopam 80 mg allowed 30% morphine-sparing over 24 h with no reduction of the pain score and good tolerance.[16] More recently, an open study compared i.v. nefopam with i.v. propacetamol and placebo in addition to patient-controlled i.v. morphine for 24-h analgesia after hepatectomy.[17] A greater morphine-sparing effect with less nausea and vomiting was obtained with nefopam than propacetamol.

The purpose of this study was to ascertain in a large double-blind randomized study the analgesic effect and tolerance of i.v. nefopam in combination with morphine patient-controlled analgesia (PCA) after orthopaedic surgery.

Methods

Patient selection and randomization

After we had obtained ethics committee approval and written informed patient consent, 201 patients scheduled to undergo hip arthroplasty were included in this multicentre (n=24), double-blind, randomized study of nefopam *vs* placebo. To be included, patients had to be between 18 and 75 yr old, have an ASA score of I–III and require hip replacement with surgery performed under standard general anaesthesia.

The exclusion criteria were anterior surgical approach, surgery performed under regional anaesthesia, contraindications for nefopam or morphine use, severe cardiac disease, renal or hepatic insufficiency, and preoperative use of analgesics (corticosteroids, opioid). Before the start of the study, a randomization list, balanced by centre, was established and each centre enrolled patients and assigned treatments consecutively.

After inclusion, the preoperative pain score related to joint disease was assessed for all patients with a visual analogue scale (VAS, with end-points labelled 'no pain' and 'worst possible pain') and a verbal pain score (VPS: 0=no pain, 1=mild pain, 2=moderate pain, 3=intense pain).

All patients who received at least one dose of a study agent were included in the safety analysis (tolerance population). Among them, all those who participated in the PCA period were included in the intention-to-treat (ITT) analysis. The per protocol (PP) population excluded those patients in the ITT population with a major deviation of the protocol.

Anaesthesia

All patients were premedicated with oral hydroxyzine 1–2 mg kg^{-1}. Anaesthesia was induced with a combination of thiopental or propofol, atracurium, vecuronium or succinylcholine, and sufentanil (0.2–0.3 μg kg^{-1}). The patient's trachea was intubated and anaesthesia was maintained with oxygen–nitrous oxide and isoflurane. Sufentanil administration was allowed at the discretion of the anaesthetist; the last injection was before the beginning of deep wound closure. Extubation had to be during the hour after wound closure.

Administration of the analgesic drug

According to the randomization assignment, patients received every 4 h either i.v. nefopam 20 mg or placebo diluted in dextrose 5%, 100 ml. The first dose was infused over 15 min in the operating room at the onset of deep-wound closure. The five subsequent doses were infused over 30 min. For each patient, the study ended 24 h after administration of the first dose.

Upon arrival in the postanaesthesia care unit (PACU), pain was evaluated every 5 min using a simple verbal pain score (VPS). If the score was ⩾2, patients under 65 yr of age received morphine 3 mg while older patients were given 2 mg, every 5 min, if permitted according to the respiration rate (RR>10 bpm) and sedation score, until a VPS of 0 or 1 had been achieved. The sedation score was as follows: 0=no sedation; 1=intermittent drowsiness; 2=patient drowsy but could be aroused verbally; 3=impossible to arouse the patient verbally.

Once a VPS<1 had been achieved, spontaneously or after a loading dose of morphine, i.v. PCA with morphine was commenced (1-mg bolus, 8-min lockout time, no continuous infusion). If pain control proved insufficient, the bolus dose could be increased to 1.5 mg. However, when VPS⩾2 persisted for more than 1 h in the PACU despite morphine,

Table 1 Characteristics of the patients included in the study (n=200). Values are mean (SD) or number (%). The two groups were similar for all values tested; only body mass index tended towards significance (P=0.052)

Characteristic	Nefopam group (n=98)	Placebo group (n=102)	*P*
Men: no. (%)	54 (55.1)	48 (47.1)	0.26
Age (yr): mean (SD)	63.0 (9.5)	62.1 (9.3)	0.41
Weight (kg): mean (SD)	74.7 (4.2)	75.8 (14.5)	0.59
Height (cm): mean (SD)	168.0 (9.5)	166.0 (8.7)	0.13
Body mass index (kg cm $^{-2}$): mean (SD)	26.4 (4.1)	27.5 (4.6)	0.052
Pain score before surgery			
VPS score: mean (SD)	(n=98)	(n=101)	0.91
No pain	27 (27.6)	19 (18.8)	
Mild pain	26 (26.5)	41 (40.6)	
Moderate pain	34 (34.7)	31 (30.7)	
Intense pain	11 (11.2)	10 (9.9)	
VAS score	(n=87)	(n=97)	0.42
Mean (SD) score (mm)	27.7 (24.9)	29.4 (22.6	
VAS<30: no. (%)	49 (56.3)	59 (60.8)	
VAS>30: no. (%)	38 (43.7)	38 (39.2)	

the loading dose was considered a failure and the patient was withdrawn from the study.

Postoperative management and evaluation

The simple VPS described above and a 100-mm VAS were used to evaluate pain at rest and during mobilization. The intensity of the pain was evaluated before the loading dose and every 5 min during the titration period, then every 4 h (just before the administration of nefopam or placebo) for 24 h. The doses of morphine received during titration and by PCA were also recorded. At each evaluation, the site of the pain and the existence of side-effects (some were systematically sought: nausea, vomiting, itching, urine retention, drowsiness) were recorded. A score was used to quantify these side-effects: 0=none; 1=minor, no treatment necessary; 2=treatment required. The RR was similarly monitored. Respiratory depression was defined as the combination of RR<10 bpm and a sedation score of 3.

The primary outcome in this study was the cumulative dose of morphine given postoperatively by PCA during 24 h. Secondary outcomes were the quantity of morphine received during the 24-h observation period, quantity received by titration, VAS and VPS evaluations of pain, patient's overall assessment of satisfaction with analgesia at the end of the study, and treatment tolerance.

Statistical analysis

A clinically significant morphine-sparing effect was considered to be 15 mg over 24 h. According to previous data (SD 30),[18] for α risk of 0.05 and β risk of 0.10 it was necessary to include at least 86 patients per group. It was decided to include 200 patients to account for drop-outs.

Patient characteristics for the nefopam and placebo groups were compared using Fisher's exact test for qualitative variables, Student's t-test for quantitative variables, or a non-parametric test when an abnormal distribution of values was obtained. Results are expressed as mean (SD) or number (%).

The principal analysis compared the quantities of morphine consumed by PCA over 24 h using Student's t-test for the ITT and PP populations. Secondary criteria were analysed similarly. The treatment effect was also analysed after adjustment for supposed predictive factors (morphine loading dose injected in the PACU, duration of intervention). For this purpose, a general linear model was applied that included a fixed factor (treatment group), random factors (centre and centre $\times$ treatment group interaction), and predictive factors (qualitative or quantitative). In case of non-significance (P>0.05) the interaction was removed from the model.

Tolerance was analysed descriptively and the rates of side-effects in the two treatment groups were compared using Fisher's exact test.

Results

Patient characteristics and clinical variables

One placebo-group patient was withdrawn from the study at the start of the intervention, before administration of the study agent. This was at the request of the surgeon, who deemed it necessary to prescribe a non-steroidal anti-inflammatory drug (not allowed by the protocol) because of severe calcification of the joint. As a consequence, the population for the safety evaluation (tolerance population) included 200 patients (nefopam 98; placebo 102).

In addition, 17 patients had major deviations from the protocol (failure to administer the agent to be evaluated, use of another analgesic, older than 76 yr, final evaluation conducted too early, i.e. before 24 h). For the tolerance population, the groups were comparable at baseline, especially for the preoperative pain assessment (Table 1). Characteristics of the patients were similar except for body

mass index, which was slightly higher for the placebo group (27.4 *vs* 27.5; *P*=0.052).

Efficacy

The principal analysis of efficacy was conducted on the ITT population of 183 patients (nefopam 93; placebo 90). The amount of PCA-administered morphine over 24 h was significantly lower for nefopam than placebo recipients (21.2 (15.3) and 27.3 (19.2) mg respectively; *P*=0.02; i.e. 22.3% less for the nefopam group). For the entire study period (loading dose and PCA), morphine use was also significantly lower in combination with nefopam (34.5 (19.6) *vs* 42.7 (23.6) mg; *P*=0.01; i.e. 19.2% less for the nefopam group). Although morphine consumption for each time period was always lower for the nefopam group (ranging from –6 (T0–4; hours after peroperative administration of the first nefopam dose) to –31% (T20–24)) compared with placebo, only the overall between-group difference reached statistical significance (*P*=0.03). This morphine-sparing effect was even greater for patients with severe preoperative pain: 35.1% for the population with a VAS pain level >30 mm before surgery (nefopam 19.2 (14.2); placebo 29.6 (19.2) mg; *P*=0.01).

Examination of the influence of several factors on PCA-administered morphine showed that the quantity of self-injected morphine depended on that received during morphine loading in the PACU (*P*=0.004), without eliminating the difference between the two groups. The duration of surgery had no significant effect on PCA morphine consumption. During the titration period, morphine use was lower for the nefopam group, but not significantly (nefopam 13.3 (10.2) mg; placebo 15.4 (9.5) mg; *P*=0.15). The time until the first PCA request for analgesia was similar for the two groups (nefopam 74 (43) min; placebo 68 (36) min).

The initial VAS, that assessed at rest after 1 h in the PACU and that assessed during the whole PACU period were significantly lower for the nefopam group (*P*=0.002, *P*=0.03 and *P*=0.044 respectively) (Fig. 1). In contrast, the pain scores at rest and upon movement (data not shown) were comparable for the two groups during the PCA period. The overall levels of patient satisfaction with the quality of pain relief were also similar.

Although a centre effect was observed, each centre behaved in a homogeneous manner. Variation of results among the different centres was observed concerning PCA morphine use. The morphine-sparing effect was more remarkable in the centres that included more than eight patients, reaching 35% for this particular subpopulation, and 54% when the preoperative VAS-assessed pain score was >30 mm.

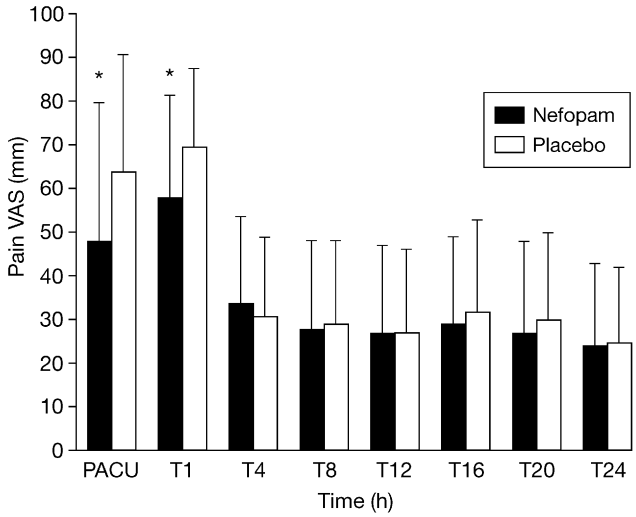

Fig 1 VAS pain score (mean and SD) assessed at rest at different times during the 24-h follow-up. PACU (post-anaesthesia care unit) assessment: **P*<0.05. T1, T4, T8, T12, T16, T20, T24 are time points (h) after the peroperative administration of the first nefopam dose.

Safety

Nefopam tolerance was comparable to that of the placebo. The incidence of sedation was the same in both groups. Adverse events were frequent, but typical of the post-operative period (drowsiness, nausea, vomiting, acute urine retention). No side-effect was reported at a higher frequency for the nefopam group (Table 2). Indeed, 79.6% of these patients experienced at least one adverse event (183 in all)

Table 2 Main or most frequent side-effects recorded for patients receiving nefopam (*n*=98) or placebo (*n*=102) during the 24 h after surgery according to their severity. Minor side-effects did not require any specific treatment. Moderate to severe side-effects required intervention, e.g. drug withdrawal, dose modification or symptomatic treatment. No significant between-group differences were found

Side-effect	Absent				Minor				Moderate to severe			
	Nefopam		Placebo		Nefopam		Placebo		Nefopam		Placebo	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Drowsiness	40	40.8	43	42.2	58	59.2	59	57.8	–	–	–	–
Nausea	59	60.2	60	58.8	27	27.6	26	25.5	16	16.3	19	18.6
Urine retention	74	75.5	78	76.5	8	8.2	13	12.7	16	16.3	11	10.8
Vomiting	77	78.6	83	81.4	9	9.2	14	13.7	12	12.2	6	5.9
Itching	96	98	94	92.2	2	2.0	7	6.9	–	–	1	1.0
Sweating	93	94.9	100	98.0	5	5.1	2	2.0	–	–	–	–

vs 87.3% of the patients who received the placebo (a total of 213 events). Overall, the most frequently observed undesirable effects were (globally, in both groups): drowsiness (58.5% of the patients), nausea (40.5%), vomiting (20%) and urine retention (24%). The severity of these side-effects was similar in the two groups (Table 2). Sweating was observed in five and two patients from the nefopam and placebo groups respectively. Two severe side-effects and four events leading to withdrawal from the study were recorded for the placebo group.

Discussion

Our study shows that nefopam administered i.v. for 24 h offers significant morphine-sparing with improved pain control during the immediate postoperative period and no significant side-effects attributed to nefopam.

Because the morphine dose administration during the titration phase in the PACU differed among the various centres and many protocol deviations were recorded, it was decided during the blind review to analyse the morphine-sparing effect on morphine consumed during PCA as the main criterion. This morphine-sparing effect of 22% was quite similar to that on total morphine consumption (19%). The PCA morphine-sparing effect during 24 h of i.v. nefopam (20 mg every 4 h started at the end of surgery) was reported to be 50% after hepatectomy in an open study.[17] After i.m. administration of nefopam 20 mg every 6 h, started before surgery, the morphine-sparing effect was estimated to be 30% during 24 h and 50% during the first postoperative hour.[16] Thus, the overall morphine-sparing effect of nefopam ranged from 20 to 50% depending on surgery and methodology, in agreement with that achieved with other non-narcotic analgesic drugs, such as paracetamol and non-steroidal anti-inflammatory drugs.[19] In our study, this effect varied as a function of the patient's preoperative pain score. It was previously observed in a similar surgical population that preoperative pain was predictive of postoperative analgesic requirements.[20] In our study, PCA morphine use was not affected by the preoperative pain. However, one pertinent observation was greater morphine-sparing for patients with intense preoperative pain. This result may suggest that nefopam could be particularly effective for these patients. The amount of analgesic used after surgery probably depends on the type of preoperative pain and hyperalgesia.[20 21] In our patients, intense preoperative pain may have been responsible for preoperative central nervous system sensitization, which might enhance the central action of nefopam on spinal and supraspinal monoaminergic modulation of pain.[5]

The pain scores of patients receiving nefopam were significantly lower upon arriving in the PACU and 1 h later. This finding supports a first administration of nefopam during wound closure. To the best of our knowledge, such benefit was previously shown only for peroperative administration of ketoprofen, another non-narcotic analgesic.[22] The morphine loading dose in the PACU was lower, but not significantly so. This absence of difference may reflect the wide variations of morphine doses administered during this phase, as mentioned above. That pain scores were not influenced during the PCA period indicates the adequate patient use of the device. Mimoz and colleagues[17] were the first to observe slightly lower pain scores at some time points, but this was not the case for patient-controlled i.v. morphine combined with propacetamol or other non-steroidal anti-inflammatory drugs, including the selective inhibitors of cyclooxygenase 2.[1 23 24] Only a few studies have described lower pain scores attributable to the combination of morphine and non-narcotic analgesics or non-steroidal anti-inflammatory drugs.[22 25]

Nefopam has previously been associated with a 15–30% incidence of minor side-effects, especially nausea, dizziness and sweating.[2] These events, although minor, were responsible for some reluctance to use the drug when it first became available in the 1970s in France. Four severe side-effects observed in our study occurred in the placebo group and led to patient withdrawal. Our data do not confirm a high frequency of minor side-effects with nefopam, because the global rates for nefopam and the placebo were similar. This similarity may reflect the modalities of administration (first administration in the anaesthetized patient, then slow i.v. infusion over 30 min). More specifically, unlike another study,[17] sweating was not more frequent with nefopam in our study. We have no precise explanation for this lower frequency of sweating, other than the difference in the type of surgery. Although side-effects were not increased by nefopam, the morphine-sparing effect was not sufficient to lower the nausea rate as reported by Mimoz and colleagues[17] for nefopam, and by others analysing the effect of combining non-narcotic analgesic with patient-controlled i.v. morphine.[1 19] Specifically, a reduction of morphine-related side-effects was never obtained when paracetamol was combined with patient-controlled i.v. morphine, and only a few reports describe less nausea and vomiting when non-steroidal anti-inflammatory drugs were combined with morphine.[1 19]

The limited effect of non-narcotic analgesic drugs combined with morphine on the rate of side-effects and quality of analgesia may lead some authors to question the validity of the balanced analgesia concept.[26] However, the minor influence is partially a result of the lack of power of most of the available data, as most studies included too few patients. To illuminate this debate, controlled clinical studies are needed on the opioid-sparing effect of new non-narcotic analgesics, preferably with multiple administrations of analgesics and a reasonably large patient population. Our findings clearly demonstrated both the advantages (i.e. lower initial pain scores in the PACU and morphine-sparing effect) and limitations of balanced analgesia (no fewer side-effects, no persistent reduction of pain scores). A possible way to enhance the analgesic effect of nefopam would be to combine it with another non-narcotic

analgesic, e.g. a non-steroidal anti-inflammatory drug. Indeed, it has been shown that the nefopam–ketoprofen interaction is synergistic.[27] This synergy suggests that such a combination with patient-controlled i.v. morphine may affect the quality of analgesia, as was achieved previously with the combination of paracetamol and a non-steroidal anti-inflammatory drug.[19]

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