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Multicentre, prospective, double-blind, randomised controlled clinical trial comparing different non-opioid analgesic combinations with morphine for postoperative analgesia: the OCTOPUS study

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Abstract

Background: Head-to-head comparisons of combinations of more than one non-opioid analgesic (NOA) with morphine alone, for postoperative analgesia, are lacking. The objective of this multicentre, randomised, double-blind controlled trial was to compare the morphine-sparing effects of different combinations of three NOAs—paracetamol (P), nefopam (N), and ketoprofen (K)—for postoperative analgesia.

Methods: Patients from 10 hospitals were randomised to one of eight groups: control (C) received saline as placebo, P, N, K, PN, PK, NK, and PNK. Treatments were given intravenously four times a day during the first 48 h after surgery, and morphine patient-controlled analgesia was used as rescue analgesia. The outcome measures were morphine consumption, pain scores, and morphine-related side-effects evaluated 24 and 48 h after surgery.
Results: Two hundred and thirty-seven patients undergoing a major surgical procedure were included between July 2013 and November 2016. Despite a failure to reach a calculated sample size, 24 h morphine consumption [median (interquartile range)] was significantly reduced in the PNK group [5 (1–11) mg] compared with either the C group [27 (11–42) mg; $P<0.05$] or the N group [21 (12–29) mg; $P<0.05$]. Results were similar 48 h after surgery. Patients experienced less pain in the PNK group compared with the C, N, and P groups. No difference was observed in the incidence of morphine-related side-effects.
Conclusions: Combining three NOAs with morphine allows a significant morphine sparing for 48 h after surgery associated with superior analgesia the first 24 h when compared with morphine alone.
Clinical trial registration: EudraCT: 2012-004219-30; NCT01882530.

Keywords: opioid sparing; non-opioid analgesics; postoperative analgesia; paracetamol; nefopam; ketoprofen; morphine

- Potential adverse effects, such as opioid-induced hyperalgesia and tolerance, from perioperative opioid use highlight the need for alternative analgesic strategies.
- The morphine-sparing effects of three different non-opioid analgesics (NOAs) (paracetamol, nefopam, and ketoprofen), alone or in combination, were evaluated in this multicentre study.
- Despite problems with attaining sample size, a benefit was found in using all three NOAs in combination.
- Further work is required to define the optimal combination and to assess potential opioid-related adverse effects.

Since its description in the early 1990s, the concept of balanced analgesia is part of the standard management of postoperative analgesia.[1] A survey conducted in France by Fletcher and colleagues[2] showed that patients often received one or more non-opioid analgesics (NOAs) associated with an opioid. The benefit and risk of the use of opioids associated with NOAs were recently reassessed as part of a formal recommendation of experts.[3] It is indeed recommended to combine at least one NOA with i.v. morphine. The goal is morphine sparing, which is expected when morphine is administered in combination with drugs acting on different pathways. Both improved analgesia and reduction of opioid-induced side-effects are expected when morphine sparing is significant enough. Many randomised studies and meta-analyses have studied the benefit of adding one NOA to morphine on postoperative analgesia.[4–6] However, evidence is lacking on the benefit of certain NOAs (e.g. nefopam), the majority of the literature being on NSAIDs. A recent network meta-analysis including 13 287 patients and assessing 14 analgesics other than morphine (including weak opioids) showed that morphine sparing was the highest with α-2 agonists, NSAIDs, and cyclooxygenase-2 inhibitors.[7] Moreover, comparisons of the combinations of more than one NOA with morphine for postoperative analgesia are also lacking in the literature. The aforementioned network meta-analysis reported that only 15 out of 135 trials assessed combinations of two analgesics and none the combination of three or more.[7] They showed that two combinations (paracetamol+NSAID or nefopam) were superior to analgesics used alone in reducing morphine consumption. Adverse events (AEs) were insufficiently reported to draw any conclusions. Randomised trials evaluating the associations of two or more NOAs are thus still needed. A number of definitive answers have therefore yet to be found: does NOA–morphine association allow an effective morphine-sparing effect? Is there a benefit in prescribing several NOAs in association? If yes, what are the optimal combinations in terms of morphine-sparing effect, reduction of morphine side-effects, and safety?

We therefore designed the OCTOPUS study in order to compare the morphine-sparing effect of different combinations of three NOAs—paracetamol (P), nefopam (N), and ketoprofen (K)—for postoperative analgesia. We studied, as a secondary objective, whether the morphine-sparing effect was associated with a reduction of the incidence of morphine side-effects or not.

Methods

Trial design and participants

This prospective, multicentre, double-blind, randomised controlled study on eight parallel groups was approved by an independent Ethics committee (Comité de Protection des Personnes Ouest V, Rennes, France; registration number: 12/36-869) and French Authorities (Agence Nationale de Sécurité du Médicament, Paris, France; registration number: 130505A-32). The trial was registered on EudraCT (2012-004219-30) and Clinicaltrials.gov (identifier: NCT01882530). Twenty-two centres agreed to participate, but only 10 enrolled patients, mainly because of logistical problems. After providing written informed consent, patients were assessed for eligibility between July 2013 and November 2016.

Patients older than 18 yrs, planned for scheduled surgery requiring the use of a morphine patient-controlled analgesia (PCA) to treat postoperative pain, affiliated to a social security system, and who had given written informed consent were included. Exclusion criteria were known allergy to morphine, paracetamol, nefopam, or ketoprofen, or to any of their excipients; use of morphine or NOA within 24 h before surgery; methadone consumption within 48 h of surgery; history of

epilepsy; renal insufficiency (creatinine clearance <30 ml min^{-1}; Modification of Diet in Renal Disease); hepatic insufficiency; severe respiratory insufficiency; pregnancy or breastfeeding; symptomatic prostatic disorders; angle-closure glaucoma; active peptic ulcer or active gastritis; severe heart failure; and history of asthma triggered by taking ketoprofen or similar substances.

Randomisation and masking

Randomisation was centralised and stratified according to the centre. Patients were randomly assigned to one of the eight treatment groups using permuted blocks of 16 (Fig. 1): the control group (C) received saline (100 ml) as placebo; the P group received paracetamol 4 g $(24\ h)^{-1}$; the N group received nefopam 80 mg $(24\ h)^{-1}$; the K group received ketoprofen 200 mg $(24\ h)^{-1}$; the PN group received paracetamol and nefopam; the PK group received paracetamol and ketoprofen; the NK group received nefopam and ketoprofen; and the PNK group received paracetamol, nefopam, and ketoprofen. In the four combination groups, each drug was administered at the same daily dose as in groups, in which it was given alone. All patients received their medications intravenously four times a day during the first 48 h after surgery. The first administration started at the end of surgery.

A randomisation list was sent to the pharmacy of each centre. To ensure blinding, treatments were prepared by the pharmacist in each centre and preparations were not distinguishable from each other. Each patient received three different preparations, respectively, containing P, N, and K, or their respective placebos intravenously every 6 h for 48 h. The pharmacist and the statistician were the only people aware of the patient treatment group during the study.

Intraoperative and postoperative care

Intraoperatively, patients received a balanced anaesthesia, including propofol followed by sevoflurane or desflurane, sufentanil, and neuromuscular blocking agent if necessary. Nitrous oxide, other analgesics than the one studied, and regional and local anaesthesia were not allowed in the study. The first set of study drugs was given at the end of surgery. To prevent postoperative nausea and vomiting (PONV), droperidol (1.25 mg) was administered at the end of surgery. In case of PONV, ondansetron (4 mg) was prescribed. After operation, all patients received morphine titration in PACU followed by morphine PCA for 48 h. As soon as the patient had pain higher than 3 on a 10-point numerical rating scale (NRS), morphine titration was administered (3 mg every 5 min) in PACU until the NRS was lower than 3. It was followed by morphine PCA,

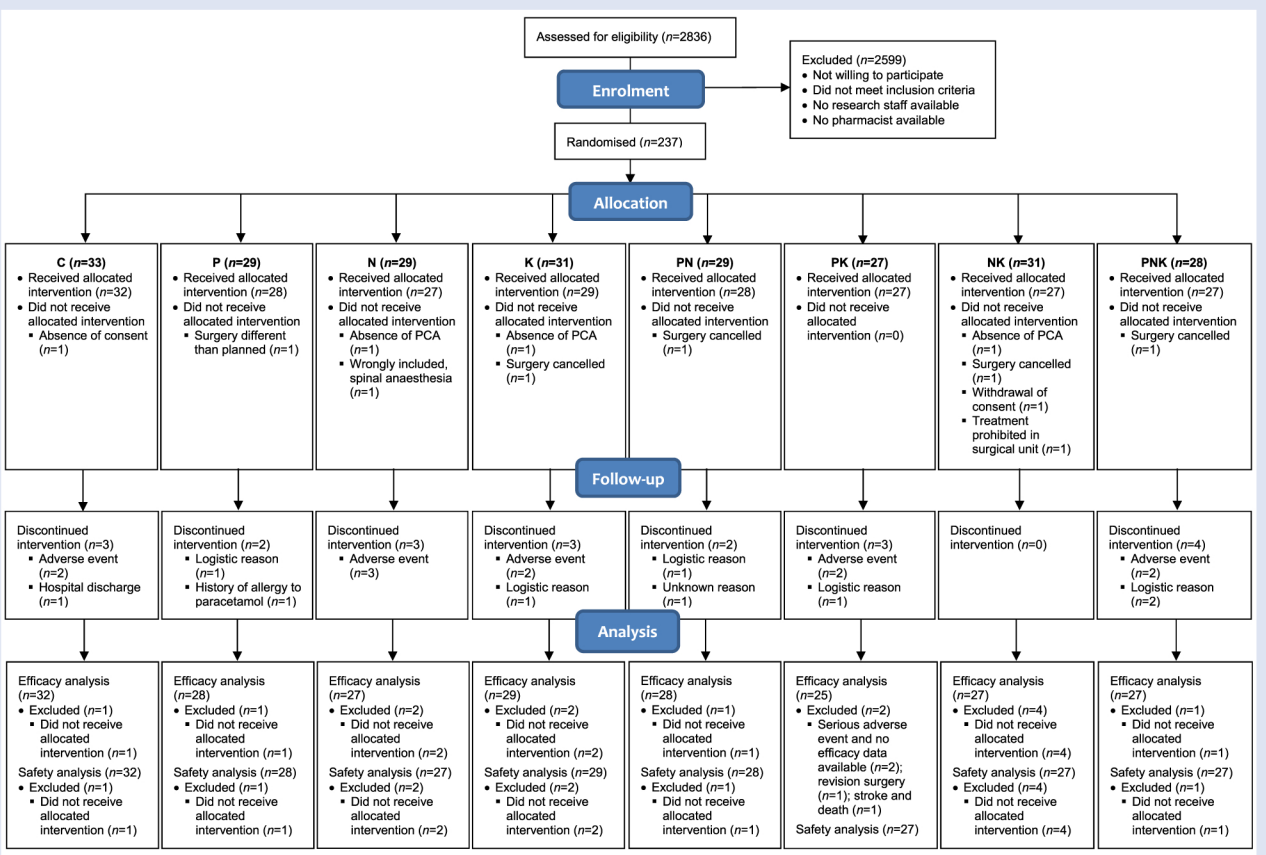

Fig 1. Flow chart. C, control; P, paracetamol; N, nefopam; K, ketoprofen; PCA, patient-controlled analgesia. No efficacy data were available for patients who did not receive the allocated intervention.

which was first set to deliver morphine bolus 1 mg with a lockout interval of 5 min. If pain relief was inadequate, the protocol allowed modifying the doses (up to 2 mg bolus). The PCA pump was continued for at least 48 h.

Outcome measures

The primary outcome was morphine consumption 24 h after surgery. Secondary outcomes were morphine consumption 48 h after surgery, pain scores 24 and 48 h after surgery, incidence of morphine-related side-effects (nausea, vomiting, sedation, urinary retention, pruritus, and respiratory depression), surface of hyperalgesia and persistent pain 3 months after surgery, and patient's global satisfaction (using the following scale: very satisfied, satisfied, not very satisfied, and not satisfied). Sedation was defined using the following 4-point scale, where 0=patient awake, 1=response only to verbal stimulation, 2=response only to contact stimulation, and 3=not arousable. Respiratory depression was defined as follows: SpO_2 <90% or ventilatory frequency <10 bpm.

Statistics

Based on previous literature, the 24 h morphine consumption measured by PCA in controls was estimated at 45 (22) mg {mean [standard deviation (SD)]}.[4] To detect a difference of 9 mg in 24 h morphine consumption with 90% power in a statistical test performed with a 5% Type I error, we calculated that it was necessary to include 1000 patients (i.e. 125 per group). Continuous variables are presented as medians and interquartile range (IQR), or means and SDs as appropriate. Categorical variables are presented as number of patients and percentages. Comparisons between the eight groups (C, P, N, K, PN, PK, NK, and PNK) were made using analysis of variance for continuous data followed by Tukey's *post hoc* tests if normal distribution. In case of non-normal distribution, we performed Kruskal–Wallis test and *post hoc* Dunn's tests, and we added median differences between groups and 95% bias-corrected bootstrap confidence intervals (CIs). Logistic regression models were made for categorical data. When the group was significant, Tukey's tests were used for multiple comparisons. Missing data were not replaced. Statistical analyses were performed using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA) and R software (GNU General Public license, www.r-project.org), version 3.4.1. All statistical tests had a significance level of 0.05.

Results

Study population

During the study period, from July 23, 2013 to November 21, 2016, a total of 2836 patients were screened for eligibility, and 237 patients were enrolled and randomised (Fig. 1). Data on primary and secondary outcomes were available for 223 patients. The calculated sample size was not reached for two reasons: first, the heavy logistics of the study, as a result of the necessity of preparing each treatment in sterile conditions in the pharmacy of each centre, markedly slowed down the inclusions from the start by preventing some centres to participate and by impeding the inclusion of several patients simultaneously in the great majority of others. Second, the practice on postoperative pain management progressively changed during the course of the study. The emergence of routine use of i.v. lidocaine and ketamine during surgery, and the concerns about administering morphine alone in the placebo group led to increasing difficulties of inclusion, as more and more investigators considered that administering morphine alone to manage postoperative pain raised ethical concerns. The data monitoring and safety committee decided to stop the study after 42 months, as it was no longer possible to include enough patients to reach the required sample size.

The eight groups were well balanced at baseline (Table 1). A substantial number of patients were in pain before surgery, with 35% describing pain intensity higher than 3 on an NRS. Twenty patients did not receive all study medications, either for logistic reasons or for patient's decision or investigator's decision because of side-effects. The number of patients who did not complete the 48 h treatment was not significantly different between the eight groups (C: 3, P: 2, N: 3, K: 3, PN: 2, PK: 3, NK: 0, and PNK: 4; P=0.89). Patients underwent orthopaedic (44%), cardiac (19%), urological (21%), abdominal (15%), and gynaecologic (1%) surgeries with no differences between treatment groups. The median duration of surgery was 3.3 (IQR: 2.0–4.8) h, and not different between groups.

Outcomes

There was a significant difference between groups (P<0.01) on the primary outcome (i.e. morphine consumption 24 h after surgery). Global 24 h morphine consumption was 14 (IQR: 5–30) mg. It was significantly lower in the PNK group [5 (IQR: 1–11)] compared with either the C group [27 (IQR: 11–42) mg; P<0.05; median difference of 21 mg (95% CI: 9–30)] or the N group [21 (IQR: 12–29) mg; P<0.05; median difference of 16 mg (95% CI: 6–22); Fig. 2;

Results were similar 48 h after surgery: morphine consumption was lower in the PNK group [6 (IQR: 2–27)] compared with either the C group [32 (IQR: 13–55) mg; P<0.05; median difference of 26 mg (95% CI: 9–44)] or the N group [34 (IQR: 12–50); P<0.05; median difference of 28 mg (95% CI: 11–34); Fig. 2;

NRS measurements showed that 43% of patients had pain (NRS ≥3/10) on the first day (i.e. 24 h after surgery) and that they were still 28% on the second day (48 h after surgery). A statistical difference was found between groups 24 h after surgery (P=0.003). Patients experienced less pain in the PNK group compared with the C group (P<0.05), the N group (P<0.05), and the P group (P<0.05) (Fig. 3;

Morphine-related side-effects did not differ significantly across the eight groups whether viewed individually (P-value for each >0.30 except for dry mouth P=0.06) or collectively (P=0.26). Half of the patients (51%) experienced side-effects (Table 2). Patients were globally satisfied with their pain management, with 33% being very satisfied and 60% being satisfied. There was no difference between groups (P=0.75). Twenty-seven patients experienced at least one AE and five experienced a serious AE (SAE)

Amongst the five SAEs, three patients were excluded because of one death after a stroke, one early re-intervention, and one treatment failure and intense pain (NRS=9/10). Data on the occurrence of hyperalgesia and persistent pain 3 months after surgery were not assessed.

Discussion

Despite the failure to reach the calculated sample size (the *a posteriori* power with the initial hypothesis and n=28 in each

Table 1 Patient characteristics. Data are presented as means (standard deviation), except age as mean (range), medians (Q1–Q3), or numbers (%); ^{n}: number of missing data. DN4, Neuropathic Pain Diagnostic questionnaire; NRS, numerical rating scale

	Global (*n*=223)	C (*n*=32)	P (*n*=28)	N (*n*=27)	K (*n*=29)	PN (*n*=28)	PK (*n*=25)	NK (*n*=27)	PNK (*n*=27)
Age (yr)	61 (12)	61 (12)	62 (14)	60 (12)	63 (12)	63 (11)	58 (12)	62 (14)	63 (12)
Sex (men/women)	144/79	19/13	17/11	18/9	14/15	21/7	17/8	17/10	21/6
Height (cm)	169 (9)[1]	170 (10)	169 (7)	168 (9)[1]	166 (11)	167 (7)	169 (10)	171 (9)	172 (9)
Body weight (kg)	75 (15)	74 (17)	71 (14)	73 (13)	69 (13)	76 (17)	80 (16)	75 (14)	80 (17)
BMI (kg m^{-2})	26.1 (4.7)[1]	25.6 (4.7)	24.7 (3.8)	25.8 (4.9)[1]	25.1 (3.5)	27.1 (5.1)	28.0 (5.7)	25.6 (4.4)	27.0 (4.9)
ASA physical status									
1	67 (30.0)	7 (21.9)	9 (32.1)	12 (44.4)	9 (31.0)	8 (28.6)	8 (32.0)	9 (33.3)	5 (18.5)
2	114 (51.1)	19 (59.4)	16 (57.1)	10 (37.0)	15 (51.7)	10 (35.7)	13 (52.0)	16 (59.3)	15 (55.6)
3	42 (18.8)	6 (18.8)	3 (10.7)	5 (18.5)	5 (17.2)	10 (35.7)	4 (16.0)	2 (7.4)	7 (25.9)
NRS score	0 (0–4)[5]	0 (0–4)	3 (0–5)	0 (0–3)	0 (0–3)[1]	0 (0–4)	0 (0–3)[3]	0 (0–4)	0 (0–4)[1]
NRS score ≥3	76 (34.9)[5]	11 (34.4)	14 (50.0)	8 (29.6)	10 (35.7)[1]	9 (32.1)	6 (27.3)[3]	8 (29.6)	10 (38.5)[1]
DN4 score ≥4 (in patients with NRS score ≥3)	12 (17.4)[7]	1 (11.1)[2]	4 (30.8)[1]	0 (0.0)	1 (12.5)[2]	1 (11.1)	2 (33.3)	1 (16.7)[2]	2 (20.0)
Analgesic treatment before inclusion	16 (7.2)	3 (9.4)	0 (0.0)	2 (7.4)	3 (10.3)	3 (10.7)	1 (4.0)	2 (7.4)	2 (7.4)
Type of surgery									
Cardiac	43 (19.3)	6 (18.8)	5 (17.9)	6 (22.2)	5 (17.2)	6 (21.4)	4 (16.0)	5 (18.5)	6 (22.2)
Abdominal	33 (14.8)	4 (12.5)	4 (14.3)	3 (11.1)	3 (10.3)	4 (14.3)	5 (20.0)	4 (14.8)	6 (22.2)
Gynaecology	3 (1.3)	1 (3.1)	1 (3.6)	1 (3.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Orthopaedic	98 (43.9)	16 (50.0)	11 (39.3)	11 (40.7)	15 (51.7)	12 (42.9)	13 (52.0)	10 (37.0)	10 (37.0)
Urology	46 (20.6)	5 (15.6)	7 (25.0)	6 (22.2)	6 (20.7)	6 (21.4)	3 (12.0)	8 (29.6)	5 (18.5)
Duration of surgery (h)	3.3 (2.0–4.8)[1]	2.9 (1.9–4.2)	3.7 (1.8–5.0)	3.9 (1.8–5.5)[1]	3.2 (2.0–4.8)	3.7 (2.4–4.5)	3.1 (2.5–4.0)	3.3 (1.8–4.8)	3.7 (2.0–5.0)
Premedication (hydroxyzine 1.5 mg kg^{-1})	128 (57.4)	19 (59.4)	18 (64.3)	16 (59.3)	16 (55.2)	16 (57.1)	13 (52.0)	19 (70.4)	11 (40.7)
Intraoperative sufentanil doses (μg)	49 (35–75)[1]	43 (31–58)	45 (36–80)	54 (40–90)[1]	40 (35–55)	58 (40–73)	41 (35–70)	45 (35–75)	50 (35–90)
Intraoperative propofol doses (mg)	200 (200–345)[1]	200 (200–373)	225 (155–260)	260 (200–702)[1]	200 (187–300)	225 (200–483)	250 (200–350)	200 (160–300)	200 (200–600)
Halogenated gases	[3]	[1]		[1]					[1]
Desflurane	64 (29.1)	10 (32.3)	9 (32.1)	6 (23.1)	8 (27.6)	10 (35.7)	6 (24.0)	8 (29.6)	7 (26.9)
Sevoflurane	141 (64.1)	17 (54.8)	18 (64.3)	18 (69.2)	19 (65.5)	16 (57.1)	18 (72.0)	16 (59.3)	19 (73.1)
None	15 (6.8)	4 (12.9)	1 (3.6)	2 (7.7)	2 (6.9)	2 (7.1)	1 (4.0)	3 (11.1)	0 (0.0)

group was 32%), the OCTOPUS study showed a clear benefit of combining three NOAs (paracetamol, nefopam, and ketoprofen) for postoperative analgesia after surgery. This association led to a reduction of morphine consumption and to a better analgesia as compared with those observed in the control group or the nefopam group.

Randomised trials evaluating associations of two or more NOAs are lacking. To the best of our knowledge, this study is the first attempt to conduct an RCT to evaluate the benefit of the association of the three most commonly prescribed NOAs for postoperative analgesia. No previous study met the methodological requirements to be included in the most recent network meta-analysis on the subject.[7] Gilron and colleagues[8] failed to demonstrate a benefit with the addition of a third NOA to double-drug regimens, including acetaminophen, meloxicam, and gabapentin. In the present study, we showed that three NOAs, including one NSAID, allowed a significant reduction in morphine consumption. Previous meta-analyses and retrospectives studies on the subject also reported the superiority of analgesic associations containing NSAIDs.[6,7,9,10] The lack of power of our study did not allow to show any significant superiority of the triple-drug regimen over any double-drug regimen. The recent retrospective study by Memtsoudis and colleagues[10] utilising a database of more than 1.5 million patients who underwent total hip or knee arthroplasties reported that morphine consumption decreased by up to 18.5% in patients receiving more than two modes of analgesia compared with opioids only. We also did not show any difference between drugs when they were used as monotherapy or in bi-therapy. The morphine-sparing effect of paracetamol, nefopam, and ketoprofen used alone has already been proved.[11] It is weak for paracetamol and nefopam, as it does not allow an important-enough reduction of morphine, which would be associated with a reduction of morphine-related side-effects.[6,12] When administered alone, NSAIDs have the most potent morphine-sparing effect. They allow a 30% reduction of morphine consumption and a reduction of PONV.[6] RCTs are scarce on bi-therapies, but

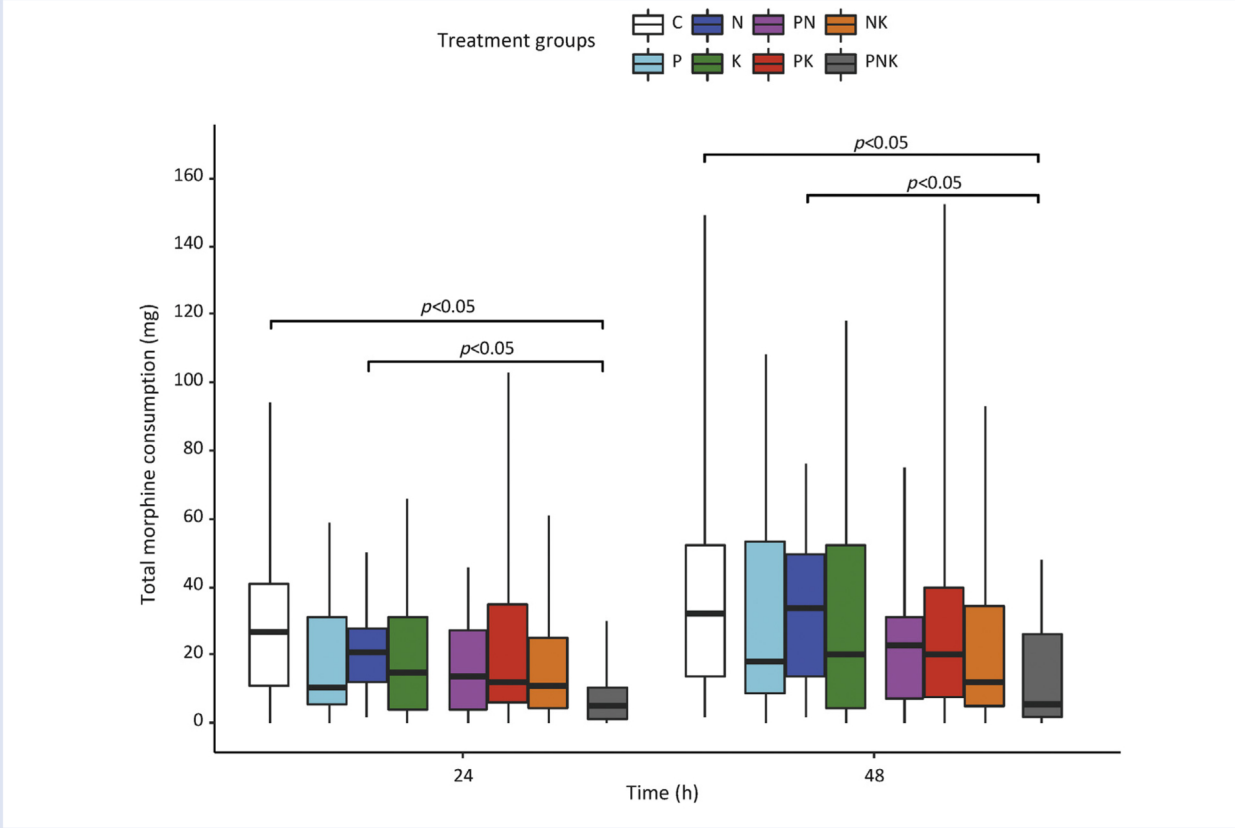

Fig 2. Morphine consumption. Box plots represent median (Q1–Q3), and whiskers represent range values for morphine consumption at different times according to treatment group. Morphine consumption was significantly different between the eight groups 24 and 48 h after surgery ($P=0.001$ and $P<0.007$, respectively). C, control; P, paracetamol; N, nefopam; K, ketoprofen.

Martinez and colleagues[7] in their network meta-analysis reported that paracetamol combined with NSAIDs or with nefopam is superior to most analgesics used alone in reducing morphine consumption. Altogether, these results suggest that, whenever NSAIDs are part of a multimodal analgesia, they provide a significant benefit. As recently stated by Martinez and colleagues,[7] NSAIDs should now be used as the reference treatment. Comparing NOA *vs* placebo should not be done anymore, because the efficacy of these treatments has been demonstrated. Different authors recently pointed out that the reference treatment has to be defined.[7,13] Indeed, the 'gold standard' at the time of the design of a study should be defined as the control group. Therefore, a new study would assess if the addition of an analgesic intervention further improves analgesia or reduces side-effects.[13] However, this does not take into consideration the rapid changes in clinical practice. Indeed, at the time of the proposal of our study (2011), morphine was still prescribed alone after surgery. Few years later, pain management had changed drastically with intraoperative ketamine and lidocaine, and the systematic use of a NOA combination. Investigators in our study found it unethical to take the risk of administering only morphine after surgery (control group), and became more and more reluctant to include patients. With the increasing evidences published on the consequences of high doses of morphine prescribed alone after surgery[14] and the proven benefit of adding NSAIDs, future studies should not be using morphine alone as a reference treatment. Unfortunately, studies comparing one weak NOA (paracetamol) and morphine have still been recently published.[15]

We did not observe any benefit in terms of morphine-related side-effects. Given the large differences in morphine consumptions, one can hypothesise that enhanced power might not alter them. These side-effects are not only morphine related, but rather consequences of the surgery or anaesthesia. As in many previous studies, power was, however, lacking to show any statistically significant difference. All previous reviews and meta-analyses highlighted the lack of data on side-effects and SAEs.[6,7,16] This lack of documentation on side-effects associated with multimodal regimens should be a matter of concern, as considerable numbers of patients are treated with combinations of analgesics for which the benefit has not always been proved, and therefore, introducing an increased risk of AEs. Very recently, the large retrospective study by Memtsoudis and colleagues[10] brought new data showing that multimodal regimens were associated with reduced rates of complications that are commonly associated with opioids (19% fewer respiratory complications when compared with an 'opioid only' regimen). Despite the obvious limit of the lack of power because of the failure to recruit, our study presented some strength, as it was the first prospective, double-blind, multicentre RCT comparing single- to double- to triple-NOA regimens in the postoperative period. The design of our study, including different types of surgical procedures,

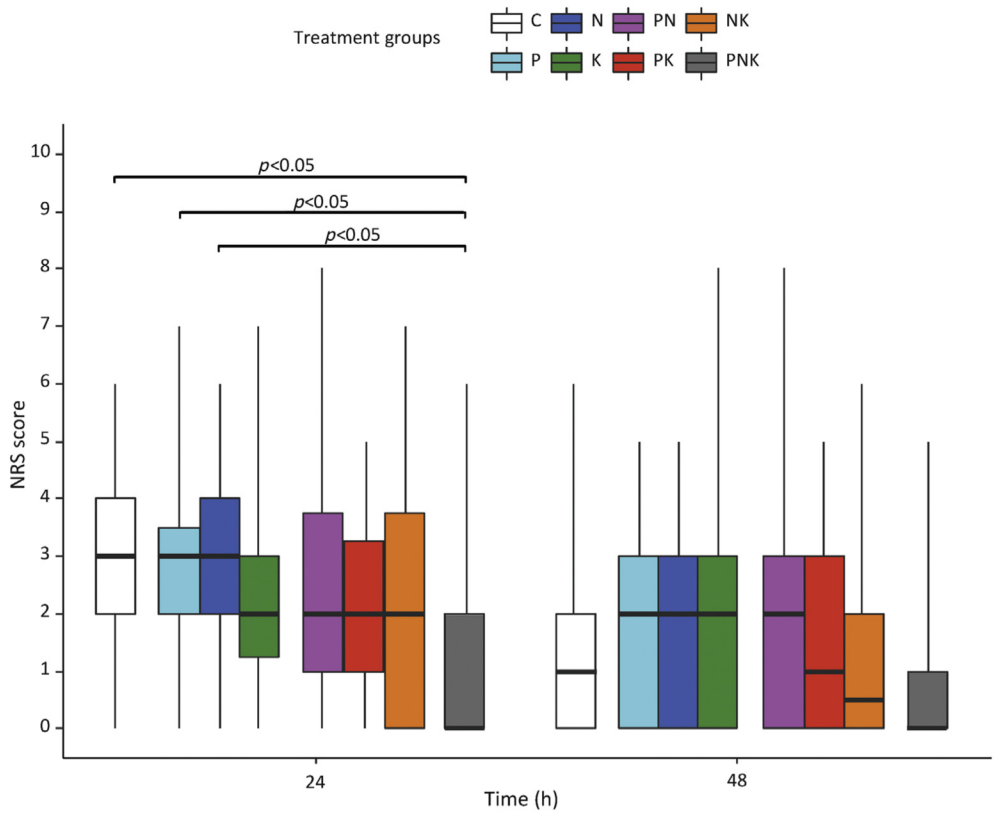

Fig 3. Pain measured with numerical rating scale (NRS) 24 and 48 h after surgery. Box plots represent median (Q1–Q3) and whiskers represent range values for NRS at different times according to treatment group. NRS was significantly different between the eight groups 24 h after surgery (P=0.003). C, control; P, paracetamol; N, nefopam; K, ketoprofen.

Table 2 Morphine-related side-effects. Data are presented as numbers (%). SpO_2, oxygen saturation

	Global (*n*=223)	C (*n*=32)	P (*n*=28)	N (*n*=27)	K (*n*=29)	PN (*n*=28)	PK (*n*=25)	NK (*n*=27)	PNK (*n*=27)	P-value
Side-effects	114 (51.1)	15 (46.9)	16 (57.1)	19 (70.4)	14 (48.3)	17 (60.7)	10 (40.0)	10 (37.0)	13 (48.1)	0.26
Sweating	31 (13.9)	5 (15.6)	4 (14.3)	8 (29.6)	2 (6.9)	3 (10.7)	3 (12.0)	3 (11.1)	3 (11.1)	0.44
Nausea	42 (18.8)	5 (15.6)	3 (10.7)	6 (22.2)	6 (20.7)	8 (28.6)	4 (16.0)	5 (18.5)	5 (18.5)	0.84
Vomiting	14 (6.3)	1 (3.1)	2 (7.1)	3 (11.1)	1 (3.4)	2 (7.1)	0 (0.0)	1 (3.7)	4 (14.8)	0.67
Treated for vomiting: ondansetron 4 mg i.v.	19 (8.5)	1 (3.1)	2 (7.1)	1 (3.7)	3 (10.3)	5 (17.9)	2 (8.0)	2 (7.4)	3 (11.1)	0.66
Vertigo	6 (2.7)	0 (0.0)	1 (3.6)	1 (3.7)	1 (3.4)	1 (3.6)	1 (4.0)	1 (3.7)	0 (0.0)	0.99
Dry mouth	41 (18.4)	2 (6.3)	5 (17.9)	11 (40.7)	5 (17.2)	5 (17.9)	2 (8.0)	4 (14.8)	7 (25.9)	0.06
Tachycardia (HR >120 beats min^{-1})	8 (3.6)	0 (0.0)	0 (0.0)	2 (7.4)	2 (6.9)	0 (0.0)	0 (0.0)	1 (3.7)	3 (11.1)	0.58
Hypertension (MAP >120 mm Hg)	9 (4.0)	0 (0.0)	3 (10.7)	1 (3.7)	1 (3.4)	1 (3.6)	1 (4.0)	1 (3.7)	1 (3.7)	0.90
Respiratory depression (SpO_2 <90% or ventilatory frequency <10 bpm)	8 (3.6)	1 (3.1)	2 (7.1)	0 (0.0)	0 (0.0)	3 (10.7)	0 (0.0)	1 (3.7)	1 (3.7)	0.73
Urine retention	18 (8.1)	1 (3.1)	3 (10.7)	3 (11.1)	1 (3.4)	4 (14.3)	2 (8.0)	3 (11.1)	1 (3.7)	0.73
Pruritus	7 (3.1)	0 (0.0)	1 (3.6)	2 (7.4)	3 (10.3)	0 (0.0)	1 (4.0)	0 (0.0)	0 (0.0)	0.63
Sedation	36 (16.1)	5 (15.6)	6 (21.4)	4 (14.8)	4 (13.8)	5 (17.9)	2 (8.0)	4 (14.8)	6 (22.2)	0.91
Sedation score										0.32
1	17 (47.2)	1 (20.0)	3 (50.0)	1 (25.0)	3 (75.0)	3 (60.0)	0 (0.0)	3 (75.0)	3 (50.0)	
2	16 (44.4)	4 (80.0)	2 (33.3)	2 (50.0)	1 (25.0)	2 (40.0)	1 (50.0)	1 (25.0)	3 (50.0)	
3	3 (8.3)	0 (0.0)	1 (16.7)	1 (25.0)	0 (0.0)	0 (0.0)	1 (50.0)	0 (0.0)	0 (0.0)	
Treated for sedation	8 (3.6)	2 (6.3)	2 (7.1)	0 (0.0)	1 (3.4)	1 (3.6)	0 (0.0)	2 (7.4)	0 (0.0)	0.87

could also be challenged. Indeed, the efficacy of an analgesic intervention could depend on the nature and location of the surgery.[13,17,18] However, this approach is still a matter of debate, as some authors reported no differences in analgesic efficacy (when assessed with the number needed to treat) between the different types of surgical procedures.[19–21] Finally, the difficulties we encountered whilst conducting the OCTOPUS study are a consequence of the rapid change in clinical practice. It is also a call for a more patient-centred approach of postoperative analgesia. Individualised or tailored care is indeed recommended.[22] Indeed, morphine sparing can be considered as a substitute endpoint. Pain and medication side-effects are the endpoints patients care about.

Our results show that combining three NOAs (paracetamol, nefopam, and ketoprofen) with morphine allows a significant morphine sparing for 48 h after surgery associated with a superior analgesia the first 24 h after surgery when compared with morphine alone.

Authors' contributions

Research protocol conception/design: HB, EB, AR.
Critical input for the methodology: EB.
Statistical analysis: AR, ER.
Writing of first draft: HB.
Critical revision/modification of the manuscript: PA, VM, SL, EF, DV, VM, CF, ABe, FA.
HB was the principal investigator. HB, PA, VM, SL, EF, DV, VM, CF, ABe, FA, AS, MD, ER, GC, SJ, ADJ, FF, and ABl. included patients in their centres.
All authors approved the final version of the manuscript.

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Declaration of interest

The authors declare that they have no conflicts of interest.

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