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Nefopam for the prevention of postoperative pain: quantitative systematic review

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Nefopam, a centrally acting analgesic, has been used in the surgical setting in many countries since the mid-1970s. However, clinical trials provide contflicting results for its analgesic potency. We performed a systematic search (multiple databases, bibliographies, any language, to January 2008) for randomized, placebo-controlled trials of nefopam for the prevention of postoperative pain. Data were combined using classic methods of meta-analyses and were expressed as weighted mean difference (WMD), relative risk (RR), and number needed to treat/harm (NNT/H) with 95% confidence interval (CI). Nine trials (847 adult patients, 359 received nefopam) were included. Nefopam (cumulative doses, 20–160 mg) was given orally or i.v., as single or multiple doses, or as a continuous infusion. Compared with placebo, cumulative 24 h morphine consumption was decreased with nefopam: WMD −13 mg (95% CI −17.9 to −8.15). Pain intensity at 24 h was also decreased: on a 100 mm visual analogue scale, WMD −11.5 mm (95% CI −15.1 to −7.85). The incidence of tachycardia was increased with nefopam (RR 3.12, 95% CI 1.11–8.79; NNH 7), as was the incidence of sweating (RR 4.92, 95% CI 2.0–12.1; NNH 13). There is limited evidence from the published literature that nefopam may be a useful non-opioid analgesic in surgical patients. The analgesic potency seems to be similar to non-steroidal anti-inflammatory drugs. However, dose responsiveness and adverse effect profile remain unclear, and the role of nefopam as part of multimodal analgesia needs to be established. Data in children are lacking.

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In the early 1970s, nefopam was developed as an antidepressant and was also used as a myorelaxant for the treatment of spasticity.[15] The additional analgesic property was soon recognized,[10] and although the mechanism of analgesia is not completely understood, it appears that nefopam is a centrally acting, non-opioid analgesic that inhibits reuptake of serotonin, norepinephrine, and dopamine.[23]

Nefopam is a benzoxazocine and is a cyclized analogue of diphenhydramine (an antihistamine), and its chemical structure is close to orphenadrin (an antimuscarinic). Nefopam is synthesized in four steps from *O*-benzoyl benzoic acid and is pharmacologically unrelated to any other known analgesic.[13] Plasma half-life is 3–5 h; plasma peak concentrations are reached 15–20 min after i.v. injection, and after 30 min during a continuous infusion. Owing to a first-pass metabolism, oral bioavailability is only 40%. Nefopam undergoes extensive hepatic biotransformation to desmethylnefopam (which seems to be biologically active) and *N*-oxide-nefopam.[2] Protein binding is 75%, and the major route of elimination (87%) is renal whereas a small part (8%) is excreted in the faeces. Ninety-five per cent of an initial dose is excreted within 5 days, 5% as unchanged substance.[13]

Nefopam has been used extensively in many countries for the treatment of acute and chronic malignant and non-malignant pain, often despite the lack of valid clinical trial data. Some studies have suggested that in the surgical setting, nefopam 20 mg was equipotent to morphine 6–12 mg,[26] or to meperidine 50 mg.[28] Some authors also reported on a morphine-sparing effect of 30–50%.[18 20] However, others were unable to confirm these results,[19] and the role of nefopam as an adjuvant to opioid-analgesia in patients undergoing surgery has remained obscure.

Nefopam is generally considered to be safe and well tolerated. Reported adverse effects are mostly minor and include drowsiness, nausea and vomiting, and sweating.[6 14 20] Potentially more serious adverse effects are confusion and tachycardia.[20 30] Unlike non-steroidal anti-inflammatory drugs, nefopam has no effect on platelet function,[5] and, in

contrast to opioids, this drug does not seem to increase the risk of respiratory depression.[11] In this quantitative systematic review, we aimed to quantify the analgesic efficacy and the adverse effect profile of nefopam when used as an analgesic for the prevention of postoperative pain.

Methods

Literature search

MEDLINE, the Cochrane Library, EMBASE, WHOLIS, the African Index Medicus, and LILACS were searched using the term 'nefopam' either alone or in association with 'pain'. Trials studying the anti-shivering effect of nefopam[16] were excluded using the command 'NOT shivering' in the title, abstract, and keywords. Additional trials were identified from the reference lists of retrieved reports. The last search was performed in January 2008. Searches were without language restriction and authors were contacted for supplemental data or specific questions about their trials.

We included trials that compared nefopam with an inactive control group (placebo or no treatment) for the prevention of postoperative pain and that reported on pain outcomes or adverse effects. We limited our search to randomized trials in humans. Data from abstracts, letters, experimental studies in healthy volunteers, narrative reviews, animal studies, and studies with <10 patients per group were not considered.

One author (M.S.E.) extracted information on patients, surgery, anaesthesia, nefopam and postoperative analgesic regimens, pain outcomes, and adverse effects. Two other authors independently checked all extracted data. Appropriate pain outcomes were pain intensity at rest and on movement (or during coughing), and cumulative postoperative morphine consumption.

Continuous outcomes were extracted as means and standard deviations or standard errors. When these data were not reported, we contacted the authors. If they did not respond, and the data were presented graphically, we attempted to extract the data from the graphs. Data from continuous 0–10 cm visual analogue scales for pain intensity were converted to a 0–100 mm scale. Binary outcomes (for instance, adverse effects) were extracted as the presence or absence of the effect. Definitions of adverse effects were taken as reported in the original trials.

We applied a modified four-item, seven-point Oxford scale to assess the adequacy of data reporting (randomization, concealment of treatment allocation, blinding, description of withdrawals) of all included trials.[8] As we included only randomized trials, the minimum score was 1. One author scored all included studies (M.S.E.). Scores were independently checked by the two other authors and discrepancies were resolved by discussion.

Meta-analysis

For continuous outcomes, we computed weighted mean differences (WMD) with 95% confidence interval (CI). For dichotomous outcomes, we calculated relative risks (RR) with 95% CI. If the 95% CI around the WMD or RR did not include 1, we assumed that the difference between nefopam and control was statistically significant at the 5% level. To estimate the clinical relevance of a beneficial or harmful effect, we calculated numbers needed to treat (NNT) or to harm (NNH); a 95% CI around the NNT/H point estimate was computed when the difference was statistically significant.[29] We were using a fixed effect model throughout. Heterogeneity was formally tested using both the conventional χ^2 statistics and the I^2 statistics (i.e. the proportion of total variation in the estimates of a treatment effect that is due to heterogeneity between the studies). Analyses were conducted using Review Manager (version 4.2, Cochrane Collaboration) and Microsoft Excel® 2003 for Windows XP®.

Results

Retrieved trials

We identified 70 trials but subsequently excluded 61 (Fig. 1). Two reports were unavailable,[4 27] and one was excluded as data reporting was inappropriate.[31] One report was published twice.[1 25] We included the more recently published study[1] as the data reported were more complete.

We contacted three authors for supplementary information.[19 20 30] One answered and the data were included in our analyses.[20] One was unable to provide the necessary data, but some information could be extracted from the published figures.[30] Finally, one did not answer, and as no relevant efficacy data could be extracted from the published report, only data on drug-related harm could be used for analysis.[19]

We eventually analysed data from nine valid randomized trials, published between 1974 and 2007, with data from 847 adult patients, of which 359 received nefopam, 136 received another analgesic drug (ketamine, diclofenac, tilidine, propoxyphene, or proparacetamol), and 352 received an inactive control treatment (placebo or no treatment).[1 3 6 12 14 18–20 30] Five studies were performed in France, two in the UK, one in Belgium, and one in the USA. Group sizes ranged from 20 to 102 patients. The median score for quality of data reporting was 4 (range 1–7). Surgery was major abdominal in four trials, episiotomy in two, and hip arthroplasty, gynaecologic or orthopaedic, or dental extraction in one each. All patients underwent general anaesthesia (Table 1).

A large variety of nefopam regimens were tested. In two trials for each regimen, nefopam was administered as a continuous i.v. infusion, as repeat i.v. injections, or as a

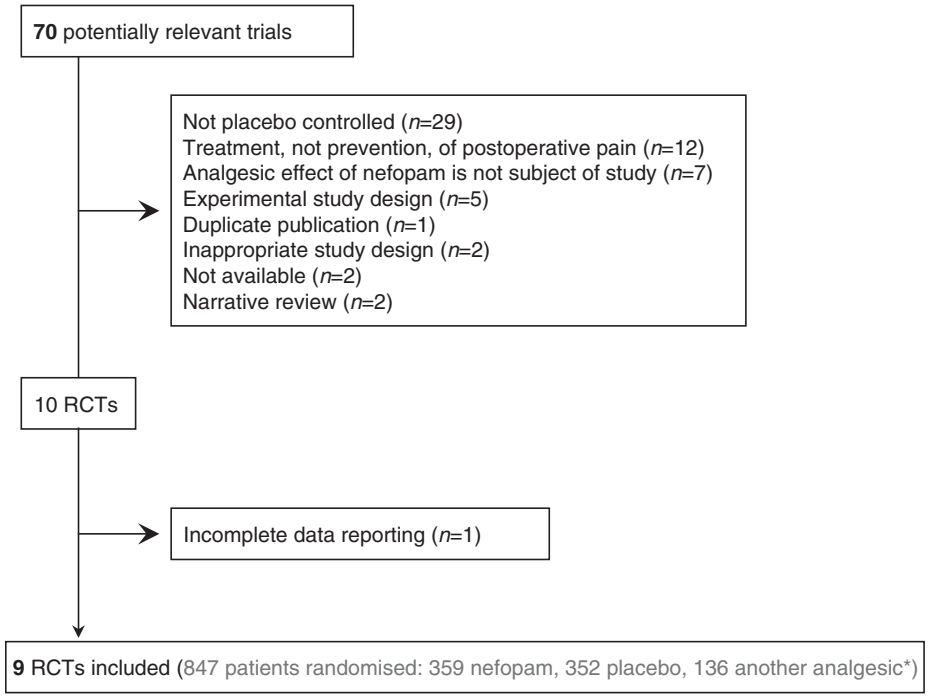

Fig 1 Flow chart of retrieved, excluded, and analysed trials. RCT, randomized controlled trial. *Ketamine, diclofenac, tilidine, and propoxyphene.

single i.m. injection; in one trial for each, it was administered as repeat i.m. injections, as a single i.v. injection, or as a single oral dose. Cumulative doses ranged from 20 to 160 mg for i.v., from 45 to 90 mg for oral, and from 20 to 100 mg for i.m. regimens (Table 1). Follow-up was 60 min in one trial, 6 or 7 h in two further trials, 24 h in four, and 48 h in two trials.

Pain outcomes

The studies reported on a large variety of pain outcomes, and few of these were reported in more than two trials.

Six trials reported on cumulative morphine consumption at various postoperative times: three of those reported on cumulative morphine consumption at 24 h.[6 18 20] They used nefopam 20 mg i.m. every 6 h for 24 h (cumulative dose, 100 mg) in patients undergoing upper abdominal surgery,[18] or 20 mg i.v. every 4 h for 24 h (cumulative dose, 120 mg) in patients undergoing hepatic resection,[20] or hip arthroplasty.[6] Average cumulative 24 h morphine consumption in controls was 47 mg. When the data were combined, cumulative 24 h morphine consumption was significantly decreased with nefopam: WMD −13 mg (95% CI −17.9 to −8.15) (Fig. 2). The data were too sparse to allow testing for dose–response.

Seven studies reported on postoperative pain intensity, but only three used a conventional 0–10 cm or 0–100 mm visual analogue pain scale. All three reported on pain intensity at rest at 24 h.[6 20 30] Two of them tested nefopam 20 mg i.v. every 4 h for 24 h (cumulative dose, 120 mg) in patients undergoing hepatic resection,[20] or hip arthroplasty.[6] The third trial tested a continuous infusion of nefopam (80 mg during 24 h) during 2 days (cumulative dose, 160 mg) in patients undergoing abdominal laparotomy.[30] In controls, average pain intensity at 24 h ranged from 24 to 40 mm on the 100 mm visual analogue scale. When the data were combined, average pain intensity was significantly decreased in patients receiving nefopam: WMD −11.5 mm (95% CI −15.1 to −7.85) (Fig. 3). The data were too sparse to allow testing for dose responsive.

One trial reported on pain intensity during coughing.[20] In controls, average pain intensity on coughing at 24 h was 60 mm on the 100 mm visual analogue scale; in the nefopam group, average pain intensity on coughing at 24 h was 45 mm, an improvement that was statistically significant.

Data from active controlled trials

Five studies had a supplementary group with an active comparator.[1 3 12 14 20] In patients following hepatic resection, supplemental morphine requirements were significantly decreased and analgesia was consistently superior with nefopam 20 mg i.v. 4 hourly compared with propacetamol 2 g i.v. 6 hourly.[20] There was no difference between diclofenac 75 mg i.m. and nefopam 20 mg i.m. in relieving pain in outpatients who received general anaesthesia for surgical removal of third molars.[12] Postoperative morphine requirements were similar with nefopam 20 mg i.v. and ketamine 10 mg i.v. in patients undergoing major surgery.[14] Finally, the analgesic efficacy of nefopam 0.66 mg kg^{-1} i.m. was similar to tilidine 1.67 mg kg^{-1} i.m. after gynaecologic or orthopaedic surgery,[1] and nefopam

Table 1 Included trials testing nefopam for the management of postoperative pain. Randomization: 0, none; 1, mentioned; 2, described+adequate. Concealment: 0 no, 1 yes. Blinding: 0 none, 1 mentionend but unclear, 2 described+adequate. Follow-up: 0, not adequately described; 1, described but incomplete; 2, described+adequate. PACU, post-anaesthetic care unit; PCA, patient-controlled analgesia. All trials were performed in adults. *(), no. of analysed patients; [], data not considered

Reference	Comparison*	Nefopam regimen		Surgery	Anaesthesia	Postoperative pain management	Quality of data reporting			
		Time point of administration	Cumulative dose				Randomization	Concealment	Blinding	Follow-up
Abeloos and colleagues[1]	1. Nefopam 0.66 mg kg^{-1} i.m. (34) [2. Tilidine 1.67 mg kg^{-1} i.m. (34)] 3. Placebo (33)	End of surgery	40 mg	Gynaecologic, orthopaedic	Halothane or enflurane, nitrous oxide	N/A	1	1	1	2
Bloomfield and colleagues[3]	1. Nefopam 90 mg p.o. (25) 2. Nefopam 45 mg p.o. (25) [3. Propoxyphene 65 mg p.o. (25)] 4. Placebo (25)	After intervention	1. 90 mg 2. 45 mg	Episiotomy	No information	N/A	2	1	2	2
Du Manoir and colleagues[6]	1. Nefopam 20 mg i.v. (98) 2. Placebo (102)	At skin closure	20 mg	Hip arthroplasty	Thiopental or propofol, sufentanil, isoflurane, nitrous oxide	PCA morphine	1	0	1	2
Goucke and colleagues[12]	[1. Diclofenac 75 mg i.m. (23)] 2. Nefopam 20 mg i.m. (22) 3. No treatment (21)	After induction of anaesthesia	20 mg	Dental extraction	Methohexitone, halothane, nitrous oxide	Acetaminophen on demand	1	0	0	0
Kapfer and colleagues[14]	1. Placebo (21) [2. Ketamine 10 mg i.v. (22)] 3. Nefopam 20 mg i.v. (22)	After surgery in PACU	20 mg	Major	Thiopental, sufentanil, isoflurane, nitrous oxide	Morphine on demand	2	1	1	2
McLintock and colleagues[18]	1. Nefopam 20 mg i.m. (23) 2. Placebo (26)	At skin closure	100 mg	Abdominal	Thiopental or propofol, sufentanil, isoflurane, nitrous oxide	PCA morphine	1	0	1	2
Merle and colleagues[19]	1. Nefopam 20 mg i.v.+80 mg 24 h^{-1} infusion (20) 2. Nefopam 20 mg i.v.+120 mg 24 h^{-1} infusion (20) 3. Placebo (20)	End of surgery	1. 100 mg 2. 140 mg	Urologic laparotomy	Propofol, sufentanil, desflurane, nitrous oxide	PCA morphine	2	1	2	2
Mimoz and colleagues[20]	1. No treatment (38) 2. Nefopam 20 mg 4 h^{-1} i.v. (39) [3. Proparacetamol IV (38)]	End of surgery	120 mg	Hepatic resection	Pentobarbital, midazolam, sufentanil, nitrous oxide	PCA morphine	1	1	0	2
Tramoni and colleagues[30]	1. Nefopam 160 mg 48 h^{-1} infusion (31) 2. Placebo (31)	End of surgery	160 mg	Abdominal laparotomy	Thiopental, remifentanil, isoflurane	PCA morphine	1	0	1	2

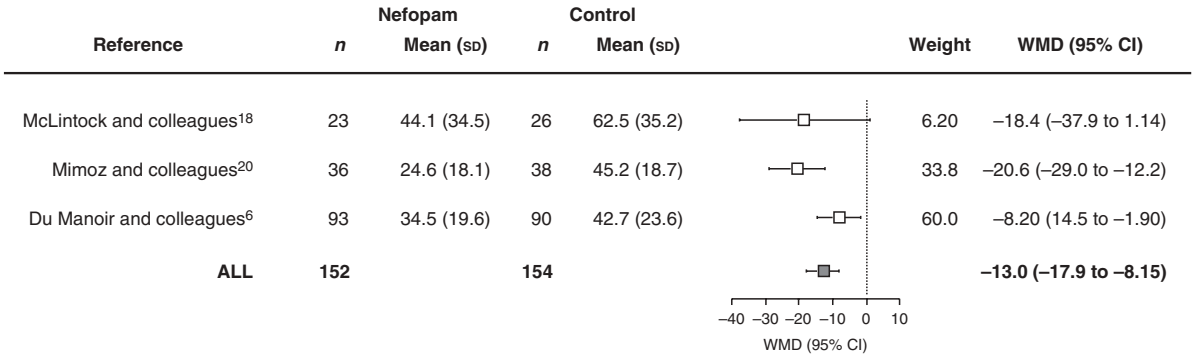

Fig 2 Cumulative 24 h morphine consumption. WMD, weighted mean difference; CI, confidence interval. Test for heterogeneity $P=0.06$, $I^2=64.8\%$.

45 or 90 mg orally was more efficacious than propoxyphene 65 mg orally in the relief of post-episiotomy pain.[3]

Adverse effects

Two trials reported on the incidence of postoperative tachycardia.[14 20] Tachycardia was defined as a heart rate >100 beats min^{-1} for at least 5 min,[14] or as ≥ 120 beats min^{-1} for more than 30 min.[20] When the data were combined, the risk of tachycardia was significantly increased in patients receiving nefopam: RR 3.12 (95% CI 1.11–8.79), NNH 7 (Table 2).

Seven trials reported on the incidence of postoperative sweating.[1 3 6 14 18 20 30] When the data were combined, the risk of sweating was significantly increased with nefopam: RR 4.92 (95% CI 2.0–12.1), NNH 13 (Table 2). Other reported adverse effects were sedation, nausea or vomiting, drowsiness, dry mouth, dizziness, and confusion: none of these was significantly associated with nefopam (Table 2).

Discussion

There are three main findings from this meta-analysis. First, nefopam, when used in adults undergoing surgery has a morphine-sparing effect in the postoperative period. Secondly, nefopam decreases pain intensity at 24 h. Thirdly, nefopam increases the risk of tachycardia and of sweating.

These results suggest that nefopam has a potential in the control of postoperative pain as demonstrated by the finding that cumulative 24 h morphine consumption was decreased by almost 30%. However, this outcome has to be interpreted with caution as it was reported in only three trials with data on 306 patients. Postoperative morphine-sparing *per se* is a surrogate of the efficacy of an adjuvant analgesic that is used in the perioperative period. However, the degree of morphine sparing may be used to compare indirectly the efficacy of analgesic adjuvants. For instance, nefopam's morphine-sparing effect appeared to be more pronounced in comparison with acetaminophen,[9 24] but similar to ketamine or non-steroidal anti-inflammatory drugs.[8 9] We were unable to establish dose responsiveness for nefopam's morphine-sparing effect as the data were too sparse and the nefopam regimens were too variable. Despite nefopam's statistically significant morphine-sparing effect, there was no evidence of a decrease in the incidence of morphine-related adverse effects. This phenomenon has been observed with other non-opioid analgesics, and thus the clinical relevance of the morphine sparing is controversial.[7]

There was a statistically significant decrease in pain intensity at rest at 24 h. As with the morphine sparing, this outcome has to be interpreted with caution due to the small number of trials. However, the result suggests that a patient who receives nefopam as an adjuvant to a morphine-based analgesic regimen is likely to have the pain intensity at rest decreased from 50 to 40, or from 40 to 30, on a 100 mm scale. This degree of efficacy may be regarded as clinically relevant, and again, it seemed to be more pronounced in comparison with acetaminophen,[9] and to be similar to ketamine or non-steroidal anti-inflammatory drugs.[8 9] Pain intensity on movement, perhaps the most relevant endpoint in this context, was reported in one single study only.

Indirect comparisons from placebo-controlled trials suggest that nefopam was more analgesic than acetaminophen and equianalgesic with ketamine or non-steroidal anti-inflammatory drugs. Direct comparisons between nefopam and other analgesics may be used to validate these findings. Indeed, nefopam appeared to be more analgesic than propacetamol,[20] equianalgesic with diclofenac[12] or ketamine,[14] and similar or even more analgesic compared with the weak opioids, tilidine or propoxyphene.[1 3]

Nefopam was generally well tolerated. The incidence of sweating increased significantly with nefopam, but this side-effect could be classified as uncomfortable rather than a true medical problem. About one in 13 patients complain of sweating. Tachycardia was also significantly more frequently associated with nefopam: one in seven patients develop tachycardia when exposed to this drug. Tachycardia may be undesirable in patients with limited cardiac function.

Life-threatening adverse effects have been reported in relation to nefopam overdose. An accidental overdose was

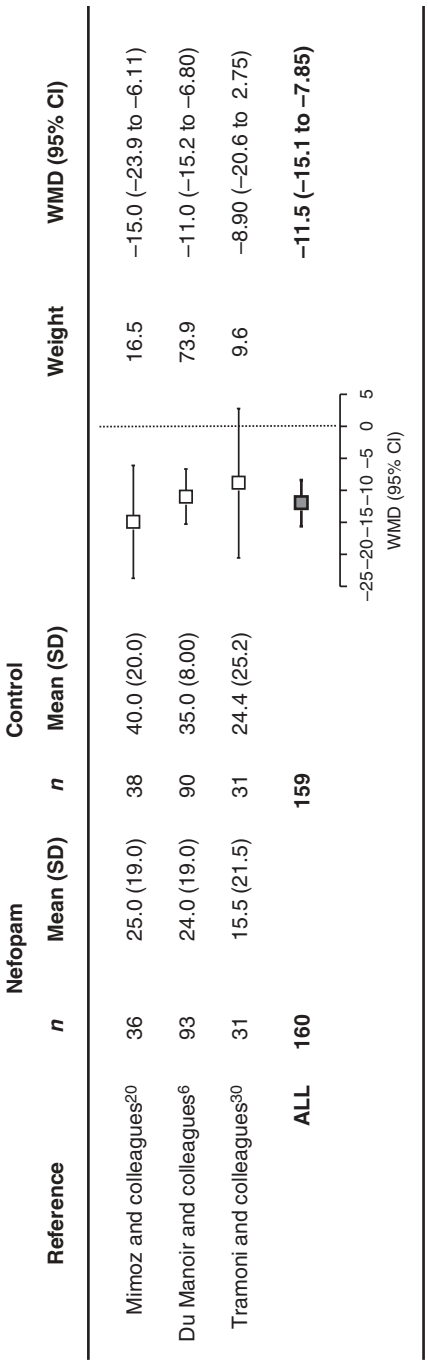

Fig 3 Pain intensity at 24 h. WMD, weighted mean difference; CI, confidence interval. Test for heterogeneity $P=0.66$, $I^2=0\%$.

reported in a 77-yr-old man who was undergoing splenectomy.[22] The postoperative analgesic regimen consisted of patient-controlled analgesia with morphine, wound infiltration with ropivacaine, acetaminophen, and a continuous infusion of nefopam 100 mg day^{-1}. One hour after the initial 20 mg loading dose, nefopam plasma level was 73 ng ml^{-1}, corresponding to plasma levels previously reported after similar doses.[2 17] After a 14 h continuous infusion, nefopam plasma concentration rose unexpectedly to 135 ng ml^{-1}. At this time, the patient developed acute neurological impairment with disorientation, confusion, mydriasis, tachyarrhythmia with a heart rate of 120 beats min^{-1}, and respiratory depression necessitating tracheal intubation. Acute renal failure and hypoproteinaemia were diagnosed. It remained unclear whether the nefopam caused the renal failure, or whether nefopam accumulated due to renal failure and drug displacement related to hypoproteinaemia. Treatment was symptomatic and the outcome was good.[22]

Our systematic review has limitations. First, several retrieved reports could not be used for meta-analysis as they compared nefopam with another analgesic and did not incorporate a placebo group. As there is no gold standard analgesic against which nefopam could be tested, combination of data from active controlled trials would be inappropriate. However, direct comparisons from the retrieved reports could be used to validate the findings of our analysis. Secondly, most trials were of limited size; only two contained more than 40 patients per group.[3 6] Small studies of pain are more likely to report on beneficial outcomes by random chance.[21] In addition, small studies are unlikely to report on rare but clinically relevant adverse effects. The large variety of reported outcomes made it difficult to combine data from more than two trials. Many of these outcomes were non-validated and were invented by the authors. For instance, pain intensity was not only reported on the widely accepted and standardized linear 10 cm or 100 mm visual analogue scale but also on a variety of custom numerical and verbal scales, preventing comparison across trials. The clinical relevance of many reported outcomes remained unclear, for example, in one trial, patients were followed up for 60 min and pain intensity was recorded every few minutes.[14] Only one study reported pain intensity both at rest and during coughing.[20] Adequate relief of dynamic pain allows for early mobilization and respiratory physiotherapy and is therefore crucial in the postoperative period. There was no agreement on the optimal dosage regimen for nefopam. It was given i.m., i.v., or orally, as a single or multi-dose regimen, or as a continuous infusion. Combining such diverse raw material data may be questionable, and testing for dose–response was impossible. Finally, relevant data from patient groups, such as pregnant women, the elderly, or children, were unavailable.

Table 2 Adverse effects. hetero, heterogeneity; CI, confidence interval. NNT, number-needed-to-treat (a negative NNT is a number-needed-to-harm); 95% CIs around the NNT/NNH point estimate are shown only for statistically significant results. Order of adverse effects according to increasing relative risks

Outcome	No. of trials	No. receiving nefopam/no. with outcome (%)	No. receiving placebo/no. with outcome (%)	Relative risk (95% CI)	P_{hetero}	NNT (95% CI)	References
Sedation	2	18/61 (29.5)	20/59 (33.9)	0.87 (0.52–1.47)	0.54	23	14, 20
Nausea	4	60/202 (29.7)	68/184 (37.0)	0.89 (0.68–1.17)	0.50	14	6, 18, 26, 30
Nausea or vomiting	4	39/123 (31.7)	33/98 (33.7)	0.95 (0.64–1.40)	0.02	50	12, 14, 19, 20
Drowsiness	2	61/148 (41.2)	63/127 (49.6)	0.97 (0.77–1.22)	0.16	12	3, 6
Vomiting	3	24/171 (14.0)	24/153 (15.7)	1.02 (0.61–1.70)	0.70	60	3, 6, 18
Dry mouth	3	14/111 (12.6)	9/84 (10.7)	1.41 (0.67–2.97)	0.50	−53	3, 14, 20
Dizziness	3	11/111 (9.9)	4/84 (4.8)	1.76 (0.54–5.77)	0.15	−19	3, 14, 20
Confusion	2	6/71 (8.5)	2/51 (3.9)	2.05 (0.55–7.63)	0.35	−22	19, 30
Tachycardia	2	13/61 (21.3)	4/59 (6.8)	3.12 (1.11–8.79)	0.59	−7 (−41 to −3)	14, 20
Sweating	7	26/297 (8.8)	3/276 (1.1)	4.92 (2.00–12.1)	0.97	−13 (−24 to −9)	1, 3, 6, 14, 18, 20, 30

In conclusion, there is some evidence that nefopam may be a useful non-opioid adjuvant to opioid-based, multimodal analgesia in patients undergoing surgery. Further research into this drug is necessary to establish the dose–response of the analgesic efficacy and to define the most useful regimen and the adverse effect profile. Trials should be of reasonable size and should report on validated outcomes for the measurement of pain intensity and pain relief. Pain intensity should be recorded at rest and during coughing or on movement. Studies of other patient populations, especially children, are warranted.

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