# Analgesic efficacy and haemodynamic effects of nefopam in critically ill patients

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**Background.** Pain management is challenging in intensive care unit (ICU) patients. The analgesic efficacy, tolerance, and haemodynamic effects of nefopam have never been described in critically ill patients.

**Methods.** In consecutive medical–surgical ICU patients who received 20 mg of nefopam i.v. over 30 min, we measured pain, Richmond Agitation Sedation Scale (RASS), respiratory parameters, and adverse drug events at T0 (baseline), T30 (end-of-infusion), T60, and T90 min. Haemodynamic variables were assessed every 15 min from T0 to T60 and T90. Pain was evaluated by the behavioural pain scale (BPS, 3–12) or by the self-reported visual numeric rating scale (NRS, 0–10) according to communication capacity.

**Results.** Data were analysed for 59 patients. As early as T30, median NRS and BPS decreased significantly from T0 to a minimum level at T60 for NRS [5 (4–7) *vs* 1 (1–3), $P<0.001$] and T90 for BPS [5 (5–6) *vs* 3 (3–4), $P<0.001$]. No significant changes were detected for RASS, ventilatory frequency, or oxygen saturation. Increased heart rate and decreased mean arterial pressure, defined as a change $\geq$15% from baseline, were found in 29% and 27% of patients, respectively. For the 18 patients monitored, cardiac output increased by 19 (7–29)% and systemic vascular resistance decreased by 20 (8–28)%, both maximally at T30. Heat sensation, nausea/vomiting, sweating, and mouth dryness were found, respectively, in 6%, 9%, 22%, and 38% of patients.

**Conclusions.** A single slow infusion of nefopam is effective in critically ill patients who have moderate pain. The risk of tachycardia and increased cardiac output and also hypotension and decreased systemic vascular resistance should be known to evaluate the benefit/risk ratio of its prescription.

**Keywords:** adverse drug reaction; analgesia; intensive care unit; nefopam; pain

Moderate-to-severe pain has been reported in at least 50% of critically ill adult patients at rest during their hospitalization in the intensive care unit (ICU), for both surgical and medical, intubated or non-intubated patients.[1–4] Pain is one of the most stressful events experienced by ICU patients,[5] and it has been suggested that pain experienced during the ICU stay may contribute to an increased stress response[6 7] and risk of post-traumatic stress disorder[8] or chronic pain.[9–11] Although medical societies[12 13] have recommended pain level evaluation and analgesic drug titration for ICU patients, underutilization of analgesia has been reported in the ICU setting in several countries.[4 14–16] It has been suggested that the paradox between clinical recommendations and practice is due, in part, to the perceived risk of side-effects associated with analgesic use in critically ill patients.[17 18] In a study including 400 medical ICU patients, analgesia was associated with an impaired outcome in the 35% of patients who received any analgesic.[15] Although opioids are the drug group most frequently implicated in surgical ICU adverse drug events (ADEs),[19] hypotension has also been reported after acetaminophen infusion in ICU patients.[20] Nevertheless, a study which measured the impact of systematic pain and agitation evaluation and management in a medical–surgical ICU showed

that a decreased incidence and intensity of pain and agitation is associated with a better outcome.[6] This improved pain management included a systematic and rational therapeutic approach with regard to the benefit/risk ratio for the use of each analgesic drug in different clinical situations.[6] Awareness of the efficacy and tolerance of each analgesic drug is important in the ICU setting because of the fragility of critically ill patients who suffer from organ dysfunctions.

Nefopam is a non-opioid analgesic whose action is spinal and supraspinal, including an inhibition of dopamine, norepinephrine, and serotonin recapture.[21] A 20 mg dose has an analgesic action comparable with 6 mg of morphine.[22] Nefopam has been reported to be administered in 14–40% of ICU patients in France.[4 6] Unlike anti-inflammatory drugs and acetaminophen, it has no detrimental effects on haemostasis,[23] gastric mucosa,[24] or on renal or hepatic function.[25] Hence, nefopam could be a safe and effective drug in ICU patients because of their high risk of organ vulnerability. However, ADEs have been documented in postoperative non-critically ill patients and an anticholinergic effect has been suggested. ADEs include tachycardia, hypertension, urine retention, sweating, dryness of the mouth, nausea, vomiting, hot flushes, heat sensation, confusion, and convulsions.[26–30] A quantitative systematic review of nefopam use in surgical patients showed that only tachycardia and sweating were revealed as significant ADEs.[31] The method of administration for reported serious ADEs was either a single bolus infusion,[26] a larger dose via oral route (60 mg),[27] prolonged continuous perfusion during 6 days,[29] or was not reported.[30] No serious ADEs were reported in a study performed in 36 patients who received a slow infusion of 20 mg of nefopam in combination with patient-controlled analgesia with morphine.[28] In this study, patients were admitted to an ICU after a planned surgery, were extubated during the first 4 h, and able to use a patient-controlled analgesia.[28] There is a paucity of studies about nefopam in critically ill patients.

The objective of the present study was to measure the analgesic efficacy, tolerance, and haemodynamic effects of a slow, 30 min infusion of nefopam in critically ill patients which was routinely prescribed according to local guidelines.

## Methods

### Ethics approval

Because of the strictly observational study design which is an evaluation of the routine use of nefopam in an ICU, and the absence of modification in patient clinical management, the need for written consent was waived. The local scientific and ethics committee of Comité d'Organisation et de Gestion de l'Anesthésie Réanimation du Centre Hospitalier Universitaire de Montpellier (COGAR) approved the design of the study.

### Patient population

This prospective study took place in the 16-bed medical–surgical ICU of St Eloi Hospital, a 660-bed teaching and referral facility of the University of Montpellier in France.

All consecutive patients >18 yr old hospitalized in the ICU from January 2005 to January 2006 were included in the study if they had acute pain of at least moderate intensity (see below) requiring, for the first time, an infusion of nefopam, as prescribed by the bedside physician according to local guidelines.[6] Surgical patients were admitted after general surgery. No neurosurgical patients were admitted to the ICU. Non-inclusion criteria were patients whose haemodynamic status had changed during the last 2 h, defined by an increase or a decrease in dose of vasoactive drugs, a fluid challenge, or both, and awakening, defined by a modification of their vigilance level by more than one point (see below) during the 2 h after interruption of sedatives or anaesthesia.

### Conduct of the study

Upon prescribing nefopam, the bedside physician alerted an independent observer, who was either a pharmacy or a medical student. Twenty milligrams of nefopam, diluted in 40 ml of 0.9% sodium chloride solution, were administered by the bedside nurse with a syringe pump during a period of 30 min. Evaluation parameters were assessed and recorded by the observer. If there was a major ADE, the nefopam infusion was interrupted by the bedside nurse or the physician.

### Data handling

The following patient characteristics were evaluated upon admission: age, sex, body mass index (kg $m^{-2}$), calculated as weight (kg) divided by height$^2$ ($m^2$), Simplified Acute Physiological Score II (SAPS II),[32] and Sequential Organ Dysfunction Score (SOFA)[32] calculated 24 h after ICU admission, and admission type. A medical admission was defined by the absence of surgical intervention in the last 7 days. After inclusion, SAPS II and SOFA were calculated again and the main cause of pain was determined.

During the observation period, pain and vigilance were assessed and recorded by the observer at baseline just before the beginning of the infusion (T0), at the end of the infusion that is to say 30 min after baseline (T30), and at 60 and 90 min after baseline (T60 and T90). The observer asked the patient to rate his/her pain using a numeric rating scale (NRS) from 0 (no discomfort) to 10 (maximum imaginable discomfort). This scale was adapted to intubated and non-intubated ICU patients by enlarging the printed scale to make it more easily visible (10×30 cm).[6 33] The behavioural pain scale (BPS)[34] was used for pain evaluation in intubated patients if they were not able to use the NRS. The BPS is a score of three components (facial expression, upper limb movements, and compliance with ventilator) which has been validated in surgical[34] and medical[35] ICU patients. Scores range from 3 (absence of pain behaviour) to 12 (maximal pain behaviour). Moderate-to-severe pain was defined by an NRS level $\geq$4[36] or a BPS score $\geq$5.[34 35] The level of vigilance was measured using the Richmond Agitation Sedation Scale (RASS)[37 38] translated and validated into the French language.[39] The RASS is a scale validated in medical and surgical ICU patients, ventilated and

non-ventilated.[37–39] Scores range from −5 (unarousable) to +4 (combative agitation). A RASS level of 0 defines a calm and alert patient.

Heart rate (HR) and ventilatory frequency were measured continuously by electrocardiographic monitoring (Hewlett-Packard, Palo Alto, CA, USA). Arterial pressure was measured continuously by an arterial catheter or a non-invasive automatic cuff. These haemodynamic variables were recorded at T0, T15, T30, T45, T60, and T90.

A more detailed evaluation of haemodynamic effects associated with the nefopam infusion was done in patients who had cardiac output monitoring: either jugular triple-lumen flow-directed Swan-Ganz continuous thermodilution pulmonary catheter (Edwards Lifesciences, Irvine, CA, USA) or femoral thermodilution pulse contour cardiac output (PV2015L20, Pulsion Medical Systems AG, München, Germany) which was calibrated at baseline. HR, mean arterial pressure (MAP), central venous pressure, and cardiac index were recorded at T0, T15, T30, T45, T60, and T90. Systemic vascular resistance index was calculated by the monitor and recorded at each time.

ADEs associated with nefopam infusion were assessed at T30, T60, and T90. An increase or a decrease in HR and MAP ≥15% from T0 was assessed for all patients, as this threshold is considered physiologically relevant in ICU patients.[40] The observer assessed sweating in all patients by looking at the face and feeling the palms. Communicating patients were questioned about nausea and vomiting, dryness of the mouth, and heat sensation.

### Statistics

Qualitative data are expressed as number of events (%) and continuous data as mean (SD) deviation, or as median and inter-quartile range when they were not normally distributed. Parametric or non-parametric tests were used for continuous variables, as appropriate, after the normality of distribution was tested by the Kolmogorov–Smirnov test.

Repeated-measures ANOVA was used to analyse continuous variables over time. We considered a *P*-value of $<0.05$ to be statistically significant. Data were analysed using SAS software, version 6.12 (SAS Institute, Cary, NC, USA).

## Results

During the period of the study, 225 patients were eligible and 60 patients were included. One patient was excluded because of an intense hot flash sensation that occurred after <5 min due to an error in the infusion rate setting. In all, 59 patients were included for analysis. Figure 1 shows the study flow chart. Patient characteristics are shown in

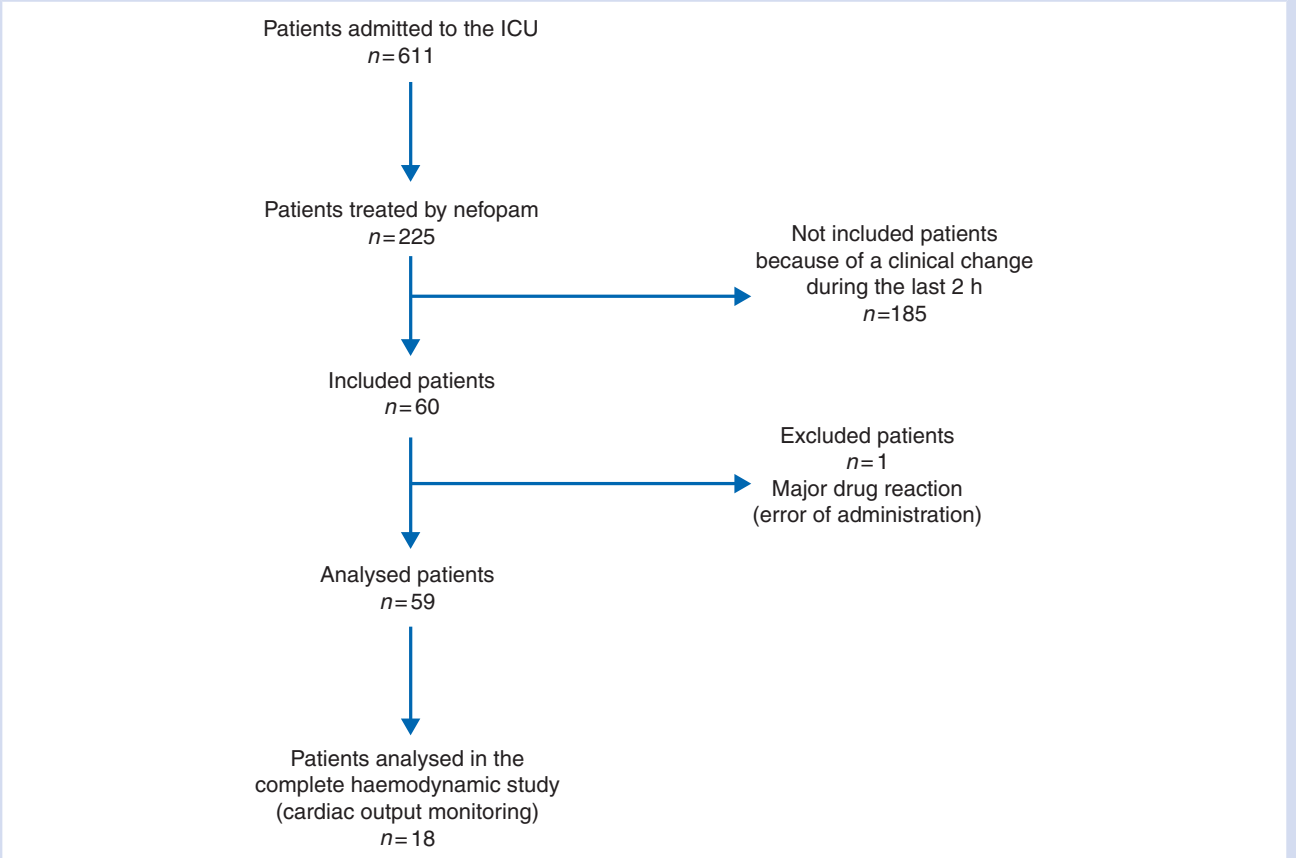


**Fig 1** Patient flow chart.

**Table 1** Characteristics of the 59 patients included for analysis. Continuous data are expressed in median (25th–75th percentiles). SAPS II, Simplified Acute Physiological Score II;[54] SOFA, Sequential Organ Failure Assessment Score;[32] RASS, Richmond Agitation Sedation Scale[37–39]

| | |
|---|---|
| Age (yr) | 57 (49–63) |
| Sex (F/M) | 15/44 |
| Body mass index (kg $m^{-2}$) | 25 (23–28) |
| Type of admission [*n* (%)] | |
| Medical | 11 (19) |
| Surgical | 48 (81) |
| Time between admission to ICU and inclusion (days) | 1 (0–2) |
| SAPS II at admission | 30 (24–40) |
| SAPS II at inclusion | 28 (22–37) |
| SOFA at admission | 4 (2–6) |
| SOFA at inclusion | 4 (2–6) |
| Mechanical ventilation upon inclusion [*n* (%)] | 29 (49) |
| Infusion of vasoactive drugs at the time of inclusion [*n* (%)] | 12 (20) |
| Haemodynamic parameters of all 59 patients at baseline | |
| Heart rate (beats $min^{-1}$) | 87 (74–104) |
| Mean arterial pressure (mm Hg) | 92 (86–103) |
| Haemodynamic parameters of the 18 patients monitored for cardiac output at baseline | |
| Heart rate (beats $min^{-1}$) | 75 (70–93) |
| Mean arterial pressure (mm Hg) | 96 (91–105) |
| Cardiac index (litre $min^{-1}$ $m^{-2}$) | 4 (3–4) |
| Systemic vascular resistance index (dyn $s^{-1}$ $cm^5$ $m^{-2}$) | 487 (386–612) |
| Infusion of at least one analgesic drug [*n* (%)] | 36 (61) |
| Acetaminophen | 26 (44) |
| Tramadol | 9 (15) |
| Morphine | 14 (24) |
| Fentanyl | 7 (12) |
| Non-steroidal anti-inflammatory drug | 3 (5) |
| Infusion of continuous sedation [*n* (%)] | 14 (24) |
| Propofol | 11 (19) |
| Midazolam | 3 (5) |
| Median RASS level of sedated patients at inclusion time | −1 (−2 to 0) |

Table 1. The main sources of pain among the 11 (19%) medical patients were acute pancreatitis ($n=6$), back or limbs ($n=3$), and abdomen ($n=2$). After infusion of nefopam in the 37 (63%) communicating patients, self-rated pain, as measured by the NRS, decreased significantly between T0 and T60 [5 (4–7) to 1 (1–3), $P<0.001$] (Fig. 2). In the 22 (37%) non-communicating patients, pain, as measured by the BPS, decreased significantly, as early as T30, to a minimum level at T90 [5 (5–6) at T0 to 3 (3–4) at T90, $P<0.001$] (Fig. 2). To take into account the norepinephrine reuptake inhibition property of nefopam, we compared its analgesic efficacy in patients who were receiving infusions of vasopressors or with those who were not.

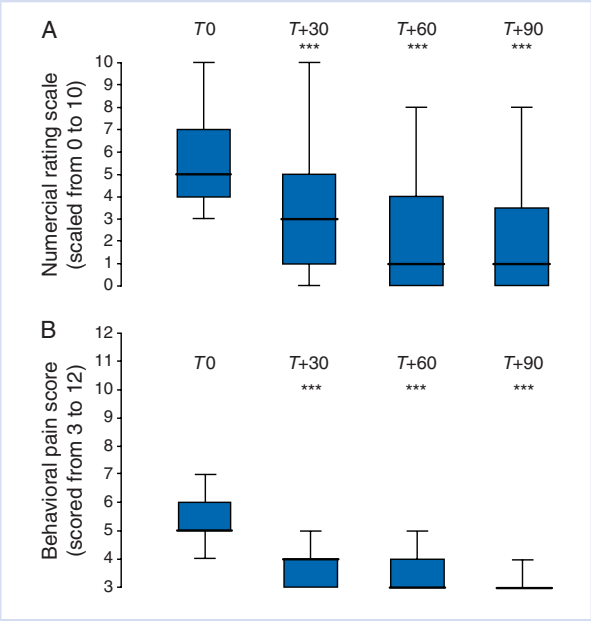


**Fig 2** Analgesic efficacy of nefopam infusion. This figure shows the effect of nefopam on pain. (A) Pain was self-rated by the 37 communicating, intubated, or non-intubated, patients using an NRS from 0 (no discomfort) to 10 (maximum imaginable discomfort). This scale was adapted to intubated and non-intubated ICU patients, who often suffer from sensorial deficiencies, by enlarging the printed scale to make it more easily visible (10×30 cm).[6] (B) Pain was measured by the observer using the BPS[34] for evaluation of pain in the 22 intubated patients who were unable to perform the NRS. The BPS is a score of three components (facial expression, upper limb movements, and compliance with ventilator).[34] It ranges from 3 (absence of pain behaviour) to 12 (maximal pain behaviour). Moderate-to-severe pain was defined by an NRS level ≥4[36] or a BPS score ≥5.[34 35] Data are given as median shown by plots, with 25th–75th quartile shown by boxes, and 95th confidence interval shown by bars. ***$P<0.001$ from baseline (T0) and other time of observation (repeated-measures ANOVA).

Changes in pain scores were not significantly different between these groups (data not shown).

No significant change in vigilance level, as rated by RASS, was shown after the infusion of nefopam [median RASS of 0 (0; −1) at each evaluation time]. Among the 29 mechanically ventilated patients, nine were breathing spontaneously with a pressure support mode. The median oxygen saturation and ventilatory frequency, which were assessed in these patients and in the 30 non-intubated patients ($n=39$), did not vary significantly over the period of evaluation. Table 2 shows the prevalence of ADEs observed after the beginning of the nefopam infusion. An overall prevalence rate above 20% was observed for sweating, dryness of the mouth, increased HR, and decreased arterial blood pressure (MAP), defined by a change ≥15% from baseline. Six (10%) and five (8%) patients had, respectively, an increased HR or a decreased MAP ≥25% compared with that at T0. Among the 40 patients who had an HR <100 beats $min^{-1}$ at baseline, five (13%) had

**Table 2** Prevalence of ADEs associated with nefopam infusion. T0, start of nefopam administration; MAP, mean arterial pressure; RASS, Richmond Agitation Sedation Scale.[37–39] *The rate of quantitative parameters was calculated among all patients included for analysis ($n$=59). †The rate of qualitative symptoms was calculated among patients who had no symptoms at T0. The rate of sweating was calculated among patients who had no sweating at T0 ($n$=51). The rate of nausea and vomiting, dryness of the mouth, and sensation of flush were calculated among the 37 patients who were able to communicate and had no nausea or vomiting ($n$=33), no dryness of the mouth ($n$=21), no heat sensation ($n$=35) at T0

| | *T*+30 (min) | *T*+60 (min) | *T*+90 (min) | All time |
|---|---|---|---|---|
| Change of observed quantitative parameters from T0 [*n* (%)]* | | | | |
| Increased heart rate ≥15% | 16 (27) | 10 (17) | 8 (14) | 17 (29) |
| Decreased heart rate ≥15% | 0 (0) | 1 (2) | 4 (7) | 4 (7) |
| Increased MAP ≥15% | 4 (7) | 6 (10) | 3 (5) | 8 (14) |
| Decreased MAP ≥15% | 5 (8) | 11 (19) | 9 (15) | 16 (27) |
| Observed qualitative symptoms in patients without symptoms at T0 [*n* (%)]† | | | | |
| Sweating | 8 (16) | 5 (10) | 5 (10) | 11 (22) |
| Nausea or vomiting | 2 (6) | 2 (6) | 1 (3) | 3 (9) |
| Dryness of mouth | 5 (24) | 7 (33) | 7 (33) | 8 (38) |
| Sensation of heat | 1 (3) | 1 (3) | 0 (0) | 2 (6) |

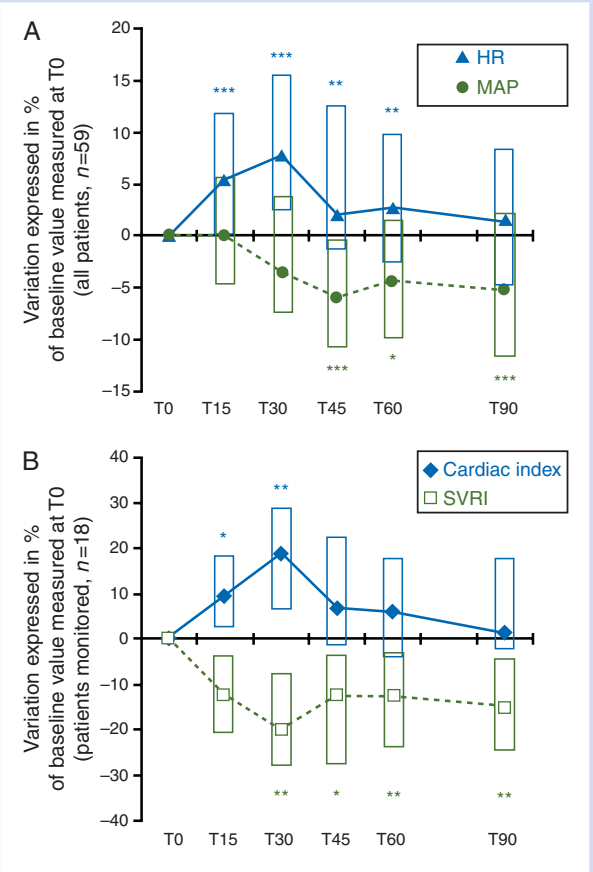


**Fig 3** Haemodynamic effects of nefopam infusion in the 59 patients ($n$=59) (A) and in the 18 patients monitored for the cardiac index (B). Haemodynamic data were measured just before the beginning of the infusion (T0), 15 min after the beginning (T15), at the end of the infusion that is to say 30 min after baseline (T30), and at 45, 60, and 90 min after baseline (T45, T60, and T90). (A) The variation of HR and MAP in the 59 patients included for analysis. HR increased significantly from baseline, as early as 15 min after the beginning of infusion, up to 30 min after the end of infusion, whereas MAP decreased significantly after the end of infusion. Data are shown as medians for HR and MAP, and 25th–75th quartiles (boxes). (B) The change of cardiac index and systemic vascular resistance index (SVRI) in the 18 patients monitored for cardiac index. Data are shown as medians for cardiac index and SVRI, and 25th–75th quartiles (boxes). *$P$<0.05; **$P$<0.01; ***$P$<0.001 from baseline (T0) and other time of observation, either for HR, MAP, cardiac index, or SVRI (repeated-measures ANOVA).

an increase in HR >110 beats min$^{-1}$ at any time during the study. Among the 58 patients who had an MAP >65 mm Hg at baseline, three (5%) patients had a decrease in MAP <60 mm Hg at any time during the study. This was considered clinically significant for only one patient according to the bedside physician who decreased the infusion rate of propofol at the end of the study.

Figure 3 shows the variation of haemodynamic parameters from baseline. HR increased significantly from baseline, as early as 15 min after the beginning of infusion, to 30 min after the end of infusion, whereas the MAP decreased significantly after the end of infusion (Fig. 3A). In the 18 monitored patients, cardiac index increased significantly as early as T15, and up to T30, whereas the systemic vascular resistance index decreased significantly as early as the end of infusion, and during the following 60 min (Fig. 3B). No significant variations in central venous pressure were detected [median value of 12 (11–12) mm Hg at each evaluation time]. The change of MAP was not associated with receipt of an infusion of acetaminophen in the 4 h before the study or not (data not shown).

## Discussion

The main finding of this study is that nefopam is an effective analgesic drug in critically ill patients who have moderate-to-severe pain. However, in at least one-quarter of patients, slow infusion of the drug during 30 min is associated with an increased HR and a decreased MAP, defined as a change ≥15% from baseline. Only one patient in our study needed a therapeutic intervention to prevent the decrease in arterial pressure. Increased HR was the most clinically relevant side-effect associated with nefopam infusion. At least 10% of patients had an HR increase ≥25% or had an HR >110 beats min$^{-1}$ when it was <100 beats min$^{-1}$ at baseline. No drug was added to treat this increased HR. Finally, we observed no effects of nefopam on respiratory function or vigilance

status. Hence, nefopam could be an alternative to opioids in ICU patients but should be used with caution particularly in patients at risk such as patients who have haemodynamic instability, a history of coronary artery disease, or both.

In the present study, we found that the onset time and peak effect of nefopam seem to be at least 30 and 60 min, respectively, after the beginning of the infusion. A study done in 10 volunteers showed that the onset of analgesia occurred at least 30 min after a 5 min infusion of 20 mg.[41] As in our study, pain intensity was not evaluated before 30 min. The onset of analgesia was reported as at least 15 min after an i.v. injection,[42] whereas the peak effect was reported from 30 to 60 min after the beginning of injection,[41 43] although dose, time, and number of infusions differed among these studies. The analgesic efficacy of nefopam has previously been described, but its usefulness remains unclear according to some authors.[31]

Awareness of individual analgesic drug tolerance is important in the ICU setting, not only because of the fragility of critically ill patients, but also to avoid impaired outcomes associated with inadequate pain management.[6 15] In the present study, we found that nefopam could be considered for use in the ICU setting because of the absence of respiratory and vigilance impairment, contrary to opioids.[17] Sweating and dryness of the mouth observed after the beginning of the nefopam infusion may not be caused only by nefopam infusion. At baseline, these two symptoms were observed in 14% and 37% of the patients, respectively. The high prevalence of discomfort, particularly dryness of the mouth, is consistent with a previous report.[2] This may be related either to the pathology (e.g. sepsis, ileus, dehydratation) or the medical treatment (e.g. tracheal or gastric tubes, high flow oxygen therapy). Moreover, these patients are often treated with many drugs, making it difficult to attribute an ADE to one given drug.[44]

In the same way, about two-thirds of patients in our study had already received analgesia. The interaction with nefopam is pertinent because this drug is associated with decreased opioid need in postoperative patients[22 28 45] and it has been shown that nefopam has at least an additive analgesic effect when associated with acetaminophen.[46] The multimodal approach to analgesia, using a combination of several analgesics, is recommended for the management of postoperative pain and rehabilitation[47–49] but rather poorly applied for sedation-analgesia in the ICU setting.[4 14] Haemodynamic effects of nefopam are relevant for the ICU physician. However, this has been reported mainly by previous studies many years ago and nefopam was administered as a bolus.[26 50 51] A bolus i.v. injection of nefopam increased HR, cardiac output, and arterial pressure moderately. Haemodynamic effects of nefopam were explained by a possible anticholinergic property which has never been tested to our knowledge. Although hypertension has been reported in patients receiving nefopam, this was not found in our study.[26] A recent study performed by the Toulouse center of pharmacology vigilance from 1985 to 2004 in France did not report any incidents of hypertension associated with nefopam infusion.[30] On the contrary, we found a moderate, but significant, decrease in arterial pressure and systemic vascular resistance in critically ill patients. One explanation for the decrease in arterial pressure may be the analgesic effect of nefopam and the associated decrease in stress response. However, the increased HR and cardiac output during infusion of nefopam are not consistent with this explanation. A second explanation is that increased cardiac output may decrease arterial pressure and systemic vascular resistance after inducing endothelium-dependent vasodilatation mediated by nitric oxide (NO).[52] Finally, another explanation may be a direct effect of nefopam on the endothelium. This explanation is suggested by an experimental study which showed that phenylephrine-precontracted rat aortic strips with intact endothelium were relaxed by nefopam in a concentration-dependent manner.[53] Removal of endothelium, inhibition of guanylate cyclase, inhibition of NO biosynthesis, and inactivation of NO significantly reduced nefopam-induced vascular relaxation.[53] Hence, the increase in the biological activity of NO by nefopam may contribute to decreased arterial pressure.

Our study has several limitations. Neither repeated infusions nor continuous infusion of nefopam over several days were evaluated. As for any drug, the benefit/risk ratio for the prescription of nefopam should be frequently assessed to avoid an ADE.[6] Finally, nefopam infusion was not compared with other analgesic drugs. This could be explained by a multimodal approach of analgesia in our ICU for most patients. Only a randomized controlled study comparing nefopam with placebo or other analgesics could answer this question. Selection criteria of patients included in a further randomized controlled study should take into account the haemodynamic side-effects of nefopam in critically ill patients highlighted by the present study.

In conclusion, a single and slow infusion of nefopam is effective in critically ill patients who have moderate-to-severe pain. It is a good alternative to opioids for these patients because of the absence of associated respiratory and neurological effects. However, ICU physicians should be aware of the haemodynamic effects of nefopam. An increase in HR $\geq$15% was found in at least one-quarter of patients. An increased cardiac output during the infusion and a decreased arterial pressure during and after the infusion could be explained in part by a direct effect of nefopam on the cardiovascular system. These results should guide the choice of analgesics for critically ill patients taking into account their respective side-effects.

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## Conflict of interest

None declared.

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