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Adding ketamine to morphine for patient-controlled analgesia after thoracic surgery: influence on morphine consumption, respiratory function, and nocturnal desaturation

P. Michelet[1]*, C. Guervilly[1], A. Hélaine[1], J. P. Avaro[2], D. Blayac[1], F. Gaillat[1], T. Dantin[3], P. Thomas[2] and F. Kerbaul[1]

[1]Department of Anesthesiology and Intensive Care, [2]Department of Thoracic Surgery and [3]Department of Pharmacy, University Hospital of Sainte Marguerite, 13274 Marseille Cedex 9, France

**Corresponding author. E-mail: pierre.michelet@ap-hm.fr*

Background. I.V. patient-controlled analgesia (PCA) with morphine is often used for postoperative analgesia after thoracic surgery, but the required doses may increase postoperative respiratory disorders. Adjunction of ketamine could reduce both doses and related respiratory side-effects.

Methods. The main objective of this prospective, randomized double-blinded study was to evaluate the influence of adding ketamine to PCA on morphine consumption and postoperative respiratory disorders. Consecutive patients undergoing lobectomy (n=50) were randomly assigned to receive, during the postoperative period, either i.v. morphine 1 mg ml^{-1} or morphine with ketamine 1 mg ml^{-1} for each. Morphine consumption was evaluated by cumulative doses every 12 h for the three postoperative days. Postoperative respiratory disorders were assessed by spirometric evaluation and recording of nocturnal desaturation.

Results. The adjunction of ketamine resulted in a significant reduction in cumulative morphine consumption as early as the 36th postoperative hour [43 (SD 18) *vs* 32 (14) mg, P=0.03] with a similar visual analogue scale. In the morphine group, the percentage of time with desaturation <90% was higher during the three nights [1.80 (0.21–6.37) *vs* 0.02 (0–0.13), P<0.001; 2.15 (0.35–8.65) *vs* 0.50 (0.01–1.30), P=0.02; 2.46 (0.57–5.51) *vs* 0.55 (0.21–1.00), P=0.02]. The decrease in forced expiratory volume in 1 s was less marked in the ketamine group at the first postoperative day [1.04 (0.68–1.22) litre *vs* 1.21 (1.10–0.70) litre, P=0.039].

Conclusions. Adding small doses of ketamine to morphine in PCA devices decreases the morphine consumption and may improve respiratory disorders after thoracic surgery.

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After thoracic surgery, pulmonary changes can lead to hypoxaemia, atelectasis, pneumonia, and then respiratory failure. In this high-risk setting, analgesic strategies using local anaesthetics for paravertebral or epidural blockade represent the gold-standard technique to relieve pain.[1] Nevertheless and related to technique failures or patient's refusal, morphine analgesia is still widely used, despite a potential harmful influence on postoperative function.[2–4] The large doses needed to provide an optimal analgesic control may be associated with an impairment in pulmonary function that could counteract the first analgesic benefit.[5] Therefore, adjunction of another type of i.v. analgesic agent that could reduce the opioid doses and prevent morphine-related adverse effects appears of great interest. The potential benefit of adding ketamine to morphine for patient-controlled analgesia (PCA) has been reported by randomized controlled studies in several types of surgery.[6–9] Nevertheless, other studies focusing on major abdominal surgery did not confirm any benefit of adding ketamine.[10]

Moreover, only few data are available concerning analgesic strategy for thoracic surgery and pulmonary

function-related effects.[11] This aspect is of paramount importance since thoracic surgery is characterized by a postoperative impairment of pulmonary function and a significant alteration in the physiology of sleep.[12 13] The severity of sleep disturbance could be associated with respiratory disorders leading to nocturnal arterial oxygen desaturation.[5 14 15]

The goal of this double-blinded, randomized study was to investigate if the addition of ketamine to i.v. morphine for PCA could result in a sparing effect in opioid consumption and improvement in postoperative respiratory disorders after thoracotomy for lobectomy. These respiratory disorders were assessed by spirometric evaluation and analysis of nocturnal oxygenation during the first three postoperative days.

Methods

Patient selection and study design

From November 2004 to May 2005, patients undergoing lobectomy were consecutively included from the Thoracic surgical unit of a University Teaching Hospital. This prospective, randomized, and double-blinded study was conducted after the approval of the ethics committee of the hospital and in accordance with good clinical practice and the guidelines set out in the Declaration of Helsinki. Informed consent was obtained from each patient.

Eligible patients met the following criteria: age of 18 yr or older, planned lobectomy by posterolateral thoracotomy incision, and the choice of PCA in preference to other forms of postoperative analgesia.

Exclusion criteria included the existence of a New York Heart Association class III–IV, a moderate to severe preexisting chronic obstructive pulmonary disease (forced expiratory volume in 1 s $<$50% predicted),[16] or a chronic renal insufficiency (creatinin clearance $<80\ ml^{-1}\ min^{-1}\ 1.73\ m^{-2}$).

Patients were randomly assigned to two groups (PCA consisting of either morphine or morphine with ketamine) using a table of random order. All mixtures were prepared and marked in the hospital pharmacy by a pharmacist who did not take part in the study. Patients, nurses in charge of postoperative care, and staff members, who informed the patient performed analgesia, and collected data were blinded to the PCA regimen used.

General anaesthesia and postoperative analgesia

After inclusion criteria were checked and informed consent was obtained, patients were instructed before surgery on the use of PCA and the visual analogue scale (VAS). They assessed pain using a VAS ranging from 0 (no pain) to 100 mm (worst imaginable pain). All of them received the same premedication with oral hydroxyzine ($1.5\ mg\ kg^{-1}$) 1 h before surgery. Anaesthetic management was standardized for all study patients. Induction of anaesthesia was performed with propofol ($2\ mg\ kg^{-1}$), sufentanil ($0.3\ \mu g\ kg^{-1}$), and cisatracurium ($0.15\ mg\ kg^{-1}$). Anaesthesia was maintained with sevoflurane, sufentanil, and cisatracurium titrated according to the patients' needs. Additional analgesia, such as non-steroidal anti-inflammatory drugs, regional or local anaesthetic techniques were not allowed during the operative period. After the operation, patients were transferred to the post-anaesthesia care unit for 2 h, then to the surgical unit. In the post-anaesthesia unit, immediately after extubation time, a morphine titration was performed until a VAS score below 30 was obtained. After morphine titration, patients received PCA device (APM®, Abbott Laboratories), containing either morphine $1\ mg\ ml^{-1}$ (Group M) or morphine with ketamine $1\ mg\ ml^{-1}$ for each (Group MK) as the optimal combination of morphine–ketamine has been reported to be a ratio of 1:1.[17] The stability of this solution has been tested with success previously at a wide range of pH values for at least 4 days.[18] They were allowed to have bolus doses of morphine or morphine/ketamine at the dosage of $0.015\ ml\ kg^{-1}$ every 10 min without any limitation. All patients received i.v. acetaminophen 1 g every 6 h for 3 days. All additional analgesia such as i.v. ketoprofene and nefopam administered to patients during the following 3 days in order to lower the VAS to under 40 at mobilization were considered as rescue analgesia and recorded as such. The protocol for rescue analgesia consisted of the first administration of i.v. ketoprofen (first rescue analgesia line) 100 mg twice a day for 2 days. The second rescue analgesic line consisted of the possible adjunction of i.v. nefopam (100 mg first in a perfusion of 30 min followed by continuous infusion of 400 mg per day for 2 days) in the case of residual pain with a VAS higher than 40.

Diurnal oxygen supply was delivered by a nasal specs device. The first oxygen level was adjusted in the recovery room in order to obtain an oxygen saturation up to or equal to 95%. Thereafter, the level was adjusted by increments of 1 litre min^{-1} or kept constant to maintain this level. These adjustments were performed three times a day by the nurse in charge of the patient. During the night, this saturation was evaluated with the last diurnal adjustment with the pulse oximeter device. Thus, the oxygen supply was adjusted if necessary (for a $Sp_{O_2}>95\%$). From this moment, the oxygen supply was adjusted only if an Sp_{O_2} level $<90\%$ was noted during the nurse examination three times a night or when the alarm incorporated in the pulse oximeter (Pulsox–3iA, Minolta, Osaka, Japan) ($<90\%$ for more than 30 s) rang. In the case of desaturation $<90\%$, the oxygen supply was increased and recorded as such. If the increase in oxygen did not improve the saturation, a respiratory complication was suspected, complementary exams performed, and a potential complication notified. Physiotherapy was performed once a day by the same physiotherapist according to a standardized 30-min procedure. Clinical respiratory complications were systematically assessed daily and included bronchial secretions accumulation, atelectasis, or

pneumonia requiring intervention other than physiotherapy (fibroscopic suctioning, non-invasive ventilation, antibiotherapy, and intensive care unit admission).

Data collection

The first end-point was the cumulative morphine consumption during the first three postoperative days to maintain an intensity of pain (VAS) at mobilization (i.e. when the patient moved from his bed to the chair or walked) under 40. This choice was based on the fact that postoperative rehabilitation first requires a rapid mobilization and the recovery of ambulatory status. Therefore, VAS at mobilization appeared to be the most accurate score to evaluate the clinical effectiveness of analgesic strategy. Arterial pressure, heart rate, respiratory rate, morphine consumption, and side-effects were also evaluated every 12 h for 3 days. Twice a day, patients were asked if they had experienced any of the following: nausea, pruritus, dreams, hallucinations, blurred vision, agitation, sedation, or oral secretions. On the third postoperative day, they were also asked about satisfaction with regard to the analgesic strategy used (satisfied or not satisfied) based on the choice of the same analgesic strategy in the case of new surgical procedure.

Oxygen saturation was measured from the first to the third postoperative nights with a pulse oximeter using a finger probe (Pulsox–3iA, Minolta, Osaka, Japan). Data were analysed using the manufacturer's software (Pulsox Sp_{O_2} Analysis DS-3, Minolta). All patients completed at least 10 h of continuous monitoring on each study night, from 22:00 to 08:00. We evaluated episodes of pulse oximetry saturation (Sp_{O_2}) levels less than 95% and 90% during the measurement period. To prevent artifact bias, only dips in the Sp_{O_2} level >4% for longer than 10 s were recorded and analysed.[15 19] Diurnal and nocturnal oxygen supplies were also recorded. Patients also benefited from a spirometry before surgery and repeated on the second and the third morning after operation. Forced vital capacity (FVC), forced expired volume in 1 s (FEV_1), and forced expiratory volume in 1 s over FVC were measured using a Vitalograph spirometer (Vitalograph, Hamburg, Germany) by the same investigator. At each measurement, spirometry was performed three times and the best of three attempts was recorded.

Statistics

Data were analysed using the SPSS 12.0 package (SPSS Inc., Chicago, IL, USA). The primary end-point was cumulative morphine consumption during the first three postoperative days in order to obtain a VAS<40 at mobilization. On the basis of a pilot study, we hypothesized a 25% reduction in morphine consumption with an expected standard deviation of 30%. Therefore, the calculated sample size was 24 subjects per group in order to detect a difference with a power of 0.80 and a 5% risk of type I error. Results were expressed as the mean (SD) after verification of normal distribution or median (inter-quartile range) for quantitative variables, and as percentages for qualitative variables. Student's *t*-test or Mann–Whitney *U*-test was used for quantitative variables. Pearson's χ^2 or Fisher's exact test was applied for qualitative variables. A two-way repeated measures analysis of variance (ANOVA) followed by a Tukey's *post hoc* test was used to evaluate the effects of time and PCA mixture (treatment) on morphine consumption.

Results

Patients

Among patients undergoing lobectomy by posterolateral thoracotomy incision during the study period, only two patients declined to participate in the study, 46 patients preferred the use of epidural or paravertebral analgesia, and 13 presented exclusion criteria. Thus, 50 patients were assessed for eligibility. Two patients did not benefit from an evaluation of morphine consumption, spirometric, and nocturnal desaturation assessment because of operative findings resulting in pneumonectomy (morphine/ketamine group) and early postoperative respiratory failure (morphine group) before PCA initiation. Therefore, 48 patients were completely studied (24 in each group). Patient baseline characteristics, preoperative data, and intraoperative data were similar among groups (Table 1). Moreover, the perioperative consumption of sufentanil was similar between groups [42 (7) μg in the morphine group *vs* 41 (8) μg in the morphine/ketamine group].

Morphine consumption

The association of ketamine with morphine in the PCA device resulted in a significant reduction in cumulative

Table 1 Demographic characteristics and perioperative data of the patients. Data are expressed as mean (range) for age or mean (SD). FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; OLV, one-lung ventilation; NYHA, New York Heart Association. There was no significant difference between groups

	Morphine group (*n*=25)	**Ketamine group (*n*=25)**
Age (yr)	63 (42–76)	64 (42–77)
Sex (M/F)	17/8	19/6
Body mass index	24 (4)	25 (4)
ASA physical status (I/II/III)	5/15/5	7/15/3
NYHA (I/II/III)	9/15/1	11/11/3
Prior chemo-radiotherapy	6	7
Smoking history *n* (pack yr^{-1})	17 [52 (22)]	15 [42 (18)]
FEV_1 (% predicted)	2.4 (0.8) [87 (17)]	2.5 (0.6) [4 (15)]
FVC (% predicted)	3.4 (1.1) [92 (18)]	3.2 (0.8) [94 (18)]
Surgery duration (min)	83 (33)	86 (36)
OLV duration (min)	61 (26)	62 (26)
Perioperative mechanical ventilation (min)	148 (39)	155 (53)
Perioperative blood loss (ml)	186 (150)	201 (201)
Perioperative sufentanil consumption (μg)	42 (7)	41 (8)

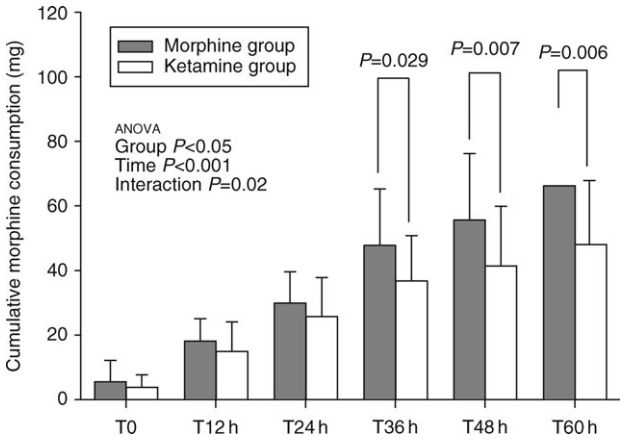

Fig 1 Cumulative morphine consumption by 12 h period between the morphine group and morphine/ketamine group. Data are expressed as means (SD).

morphine consumption as early as the 36th postoperative hour ($P<0.05$ by ANOVA, Fig. 1). This reduction was associated with lower pain scores during mobilization at the 48th and 60th postoperative hours (Table 2). The needs for rescue analgesia were not different between groups (16 patients in the morphine group, 11 patients in the morphine/ketamine group). Rescue analgesia consisted of ketoprofen for all 27 patients associated with nefopam in 10 cases (six patients in the morphine group and four patients in the morphine/ketamine group).

Nocturnal desaturations

During the study period, the percentage of desaturation duration differed significantly between groups, with a greater percentage <95% for the first and the second nights (Fig. 2) and a greater percentage of recording time <90% for the three postoperative nights (Fig. 3) in the morphine group. These results were associated with a lower value in diurnal saturation in the morphine group from the 48th postoperative hour (Table 2), despite a higher level in oxygen supply requirements (Table 2). There was no correlation between the reduction in spirometric measurements and the percentage of time with desaturation.

Spirometric measurements

Preoperative and postoperative pulmonary function data are shown in Figures 2 and 3. Comparing preoperative values, we noted significant decreases in FEV_1 and FVC in both groups after operation (Figs 4 and 5). Furthermore, there was a significant difference between groups with a greater decrease in the morphine group for FEV_1 at the first postoperative day (Fig. 4). The FEV_1/FVC ratio did not demonstrate any significant variation with time or between the morphine and the morphine/ketamine groups [72 (12) *vs* 75 (9), 79 (13) *vs* 80 (14), and 80 (9) *vs* 79 (13)%, respectively, before operation and at the first and second postoperative day].

Table 2 Respiratory and haemodynamic variables. Evolution of respiratory and haemodynamic variables during the protocol for the morphine group (M) and the morphine–ketamine group (K). Data are expressed as means (SD) or medians (25th–75th percentile). Sp_{O_2}, diurnal saturation; RR, respiratory rate; VAS, visual analogue scale; SAP, systolic arterial pressure; HR, heart rate. $^{\dagger}P<0.05$ *vs* morphine group

	T baseline		T 12 h		T 24 h		T 36 h		T 48 h		T 60 h	
	M	K	M	K	M	K	M	K	M	K	M	K
Oxygen supply (litre min^{-1})	4 (3–6)	4 (3–6)	3 (3–5)	3 (2–4)	3 (2–3)	2.5 (2–3)	2 (2–4)	2 (2–3)	2.75 (2–5)	2 (1–2)†	2.75 (2–5)	1 (1–2)†
Sp_{O_2} (%)	98 (96–99)	98 (96–100)	98 (2)	98 (2)	97 (96–98)	98.5 (96–99)†	96 (2)	97 (2)	96 (94–97)	98 (95–99)†	96 (2)	97 (3)
RR (min^{-1})	17 (5)	20 (6)	14 (4)	17 (5)†	16 (4)	16 (3)	16 (4)	16 (3)	15 (5)	16 (3)	14 (3)	16 (3)†
VAS	50 (26)	50 (27)	45 (20)	38 (20)	40 (20)	30 (14)	38 (22)	28 (12)	42 (21)	29 (16)†	36 (20)	24 (13)†
SAP (mm Hg)	132 (16)	133 (23)	130 (16)	123 (18)	125 (18)	115 (12)†	124 (16)	123 (13)	125 (16)	121 (17)	124 (18)	125 (9)
HR (beats min^{-1})	82 (14)	84 (16)	81 (18)	80 (16)	87 (16)	79 (12)	92 (21)	81 (11)†	92 (19)	82 (10)†	87 (15)	79 (11)

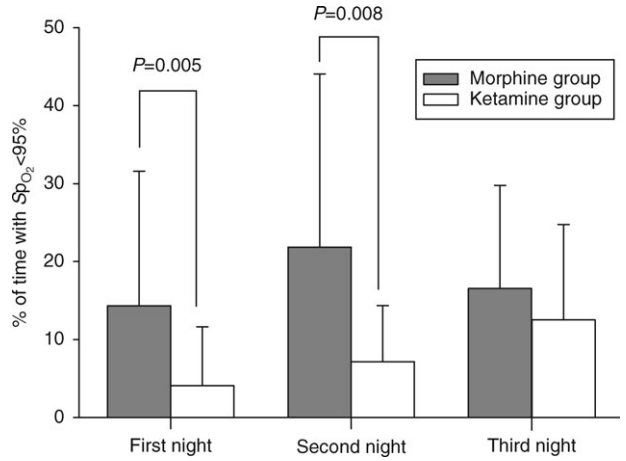

Fig 2 Percentage of time with Sp_{O_2} desaturation <95% during the three first postoperative nights between the morphine group and the morphine/ketamine group. Data are expressed as means (SD).

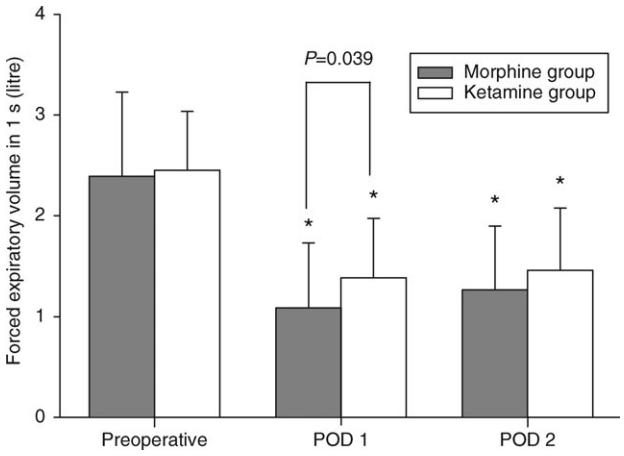

Fig 4 FEV_1 at the different times of spirometric assessment between the morphine group and the morphine/ketamine group. Data are expressed as means (SD); POD, postoperative day. *P<0.001 *vs* preoperative values.

Side-effects and complications

No psychological alteration nor side-effect related to ketamine use was noted. There was no difference between groups with respect to spontaneous diuresis recovery [9.1 (5.2) h in the morphine group *vs* 7.3 (3.9) h in the ketamine group], urinary retention (5 in the morphine group *vs* 3 in the ketamine group), time to bowel transit recovery [33 (16) h in the morphine group *vs* 29 (18) h in the morphine/ketamine group], nausea–vomiting requiring treatment (seven patients in the morphine group *vs* six patients in the morphine/ketamine group), and satisfaction with the analgesic strategy (15 patients in the morphine group *vs* 20 patients in the morphine/ketamine group). The incidence of respiratory complications revealed no difference between the two groups. In the morphine group, one patient presented an early postoperative respiratory failure (before PCA initiation), three patients developed atelectasis requiring bronchial suctioning, two patients presented pneumonia with transfer to the intensive care unit, and non-invasive ventilation for one patient. In the morphine/ketamine group, one patient required bronchial suctioning for atelectasis and one developed pneumonia.

Discussion

The main finding of this study was that the adjunction of small doses of ketamine in combination with morphine allowed a significant reduction in cumulative morphine consumption associated with a reduction in nocturnal desaturation.

Conflicting results still exist concerning the potential benefit of adding ketamine to morphine for PCA. Indeed, whereas positive results have been reported by randomized controlled studies in several types of surgery,[6–9] others,

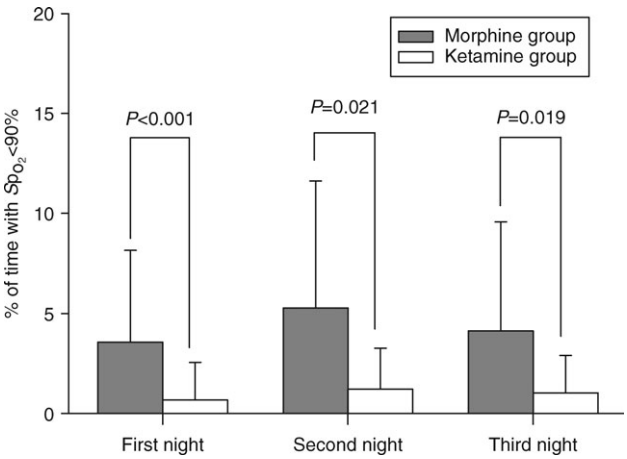

Fig 3 Percentage of time with Sp_{O_2} desaturation <90% during the first three postoperative nights between the morphine group and the morphine/ketamine group. Data are expressed as means (SD).

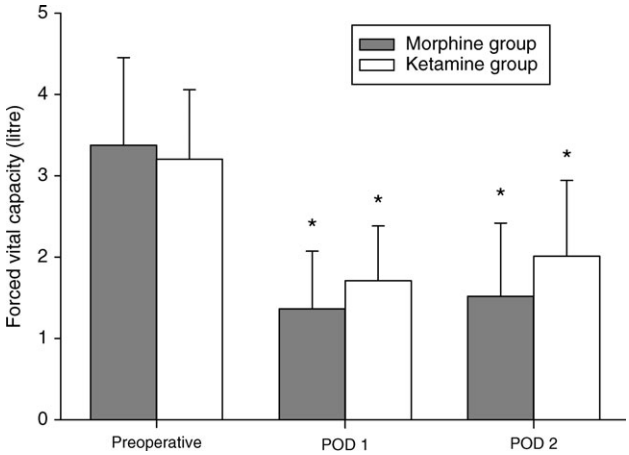

Fig 5 FVC at the different times of spirometric assessment between the morphine group and the morphine/ketamine group. Data are expressed as means (SD); POD, postoperative day. *P<0.001 *vs* preoperative values.

especially after major abdominal surgery, have failed to confirm these.[10] These discrepancies could be partly explained by differences in methodologies between studies. Indeed, the lack of sparing effect and the adverse cognitive effect reported by Reeves and colleagues[10] could be related to the absence of rescue analgesia and the consecutive higher doses of morphine and ketamine required. Conversely, several studies have reported a benefit of ketamine use with no difference for cognitive adverse events and lower cumulative analgesic doses for quite better analgesic control.[7–9] Furthermore, the doses and nature of analgesics used perioperatively appear of importance. In this sense, Reeves and colleagues[10] have mentioned a similar morphine requirement during surgical procedures, but the doses reported were limited in regard to the surgical procedure, and the pain assessment before the fourth postoperative hour was not reported whereas the first pain assessment was high. From these considerations, it could be assumed that the ketamine adjunction to the PCA device should be evaluated in analgesic protocols, including a sufficient perioperative and postoperative pain control, notably by a multimodal strategy.

In this study, ketamine has been used only for the postoperative period without pre- or perioperative administration. Although there is growing evidence that the adjunction of ketamine to general anaesthesia (with a preemptive effect) is beneficial in a variety of surgical procedures,[20 21] our study focused on the postoperative analgesic effect. Our design allowed the discrimination between a sparing effect on perioperative and postoperative opioids consumption with a specific assessment of the influence of ketamine on use of the PCA device. Knowing the interindividual variability in analgesic drug requirement, this design also permitted an adaptative dosage. Moreover, some authors consider that an activated open state of *N*-methyl-D-asparate (NMDA) receptors by nociception stimulation is required for an optimal effect of ketamine.[9 22] Our protocol included a small dose of ketamine for each patient's requirement. This choice was supported by the comparison between the studies using ketamine in PCA devices, which indicated that there was no increased morphine-sparing effect by increasing the ketamine dose above an estimated dose of 25–30 mg per day.[21] As recently highlighted in reviews and studies focusing on selected patients who traditionally require large doses of opioids, the adjunction of ketamine in our specific population allowed a decrease in postoperative morphine consumption.[9 21 23] Additionally, the reduction in morphine consumption could be related to the prevention of acute tolerance to morphine by ketamine.[7 24] Indeed, nociceptive stimulation induces activation of the NMDA receptors which could be enhanced by high-dose opioids and could worsen postoperative pain.[25 26] The adjunction of ketamine may prevent this process.[26]

After major abdominal surgery,[27] episodic arterial hypoxaemia could occur during the first postoperative nights resulting from the combination of alteration of pulmonary function and changes in sleep pattern with breathing disturbances.[28] Kawai and colleagues[15] have recently reported that the frequency of hypoxaemia after lung resection which was higher than in a gastrectomy control group. Similarly, our results showed a high incidence of nocturnal hypoxaemia in the first postoperative nights. These events were observed, despite adequate oxygen supply during the postoperative days with saturation maintained above 95%. The predominance of nocturnal desaturation and the lack of correlation between the duration of nocturnal desaturation and spirometric impairments seem to confirm the implication of sleep disorders in the genesis of these events.[15] Furthermore, a significant difference in the duration of nocturnal desaturation between groups was observed. Our study was the first to compare the effects of the analgesic strategy on the occurrence of nocturnal desaturation in the specific setting of thoracic surgery. In the same respect, few data are actually available to explain our results, and the mechanisms involved are still not well known. Nevertheless, mechanisms implicated could include both a sparing effect on opioids consumption and a ketamine-specific effect. Although patients vary greatly in their response to opioids administration, the cumulative doses could induce sleep disturbances with erratic breathing patterns[5 13 29] and ensuing profound hypoxaemia.[12] Moreover, if oxygen therapy is able to increase mean arterial oxygenation, the narcotic-induced abnormalities persist.[30] Therefore, the improvement observed in our study, with ketamine adjunction, could be partly explained by the reduction in morphine consumption. Concerning the specific effect of ketamine adjunction, a positive effect on respiratory control has already been reported and may counteract the opioids-induced hypoventilation.[31 32]

After thoracic surgery, pulmonary dysfunction is mainly characterized by a decrease in lung volumes. In this sense, we have observed a significant impairment in both the FVC and FEV_1 without any decrease in the FEV_1/FVC ratio. These results were in accordance with previous data.[33 34] Indeed, Boisseau and colleagues[34] have reported a similar decrease of about >50% of preoperative values for FVC and FEV_1, highlighting the post-thoracotomy restrictive syndrome. In our study, the analysis of the evolution of spirometric values during the first 2 days also demonstrated a faster improvement in the ketamine group for FEV_1. Although significant, this advantage appeared limited in time and did not influence the restrictive postoperative syndrome. According to our results, previous studies have already reported that even more powerful analgesic techniques such as thoracic epidural analgesia did not result in improved respiratory mechanics.[34] Since high doses of ketamine could be responsible for ventilatory depressive effects,[35] it seems that the beneficial effect of ketamine on respiratory function is not related mainly to the influence on respiratory mechanics.

There are some limitations in our study. No gazometric measurement was planned in our study protocol, which limits the interpretation of the spirometric results between groups. Furthermore, our study design included a small number of time-evaluation for analgesic efficacy with an assessment limited to postoperative mobilization. Nevertheless, the present study was mainly designed to evaluate the effect on sparing of morphine and consequences on the respiratory disorders with the PCA device use. Finally, the benefit of ketamine adjunction in regard to respiratory disorders did not influence the respiratory morbidity in our study. Considering this last issue, a specifically designed study including a larger number of patients should be conducted.

In conclusion, adding small doses of ketamine to morphine in PCA devices appears to be an alternative strategy for limitation of postoperative respiratory disorders and for pain control when an i.v. analgesia is scheduled after thoracic surgery. Further investigations are warranted to determine the effect of this combination on respiratory morbidity and thoracotomy-related chronic pain. Moreover, the clinical relevance of nocturnal desaturation in the specific setting of thoracic surgery needs complementary researches.

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References

1 Gottschalk A, Cohen S, Yang S, Ochroch E. Preventing and treating pain after thoracic surgery. *Anesthesiology* 2006; **104**: 594–600

2 Stone J, Cozine K, Wald A. Nocturnal oxygenation during patient-controlled analgesia. *Anesth Analg* 1999; **89**: 104–10

3 Tsui S, Irwin M, Wong C, *et al.* An audit of the safety of an acute pain service. *Anaesthesia* 1997; **52**: 1042–7

4 Soto R, Fu E. Acute pain management for patients undergoing thoracotomy. *Ann Thorac Surg* 2003; **75**: 1349–57

5 Catley D, Thornton C, Jordan C, Lehane J, Royston D, Jones J. Pronouced episodic oxygen desaturation in the postoperative period: its association with ventilatory pattern analgesic regimen. *Anesthesiology* 1985; **63**: 20–8

6 Lahtinen P, Kokki H, Hakala T, Hynynen M. S(+)-Ketamine as an analgesic adjunct reduces opioid consumption after cardiac surgery. *Anesth Analg* 2004; **99**: 1295–301

7 Adriaenssens G, Vermeyen K, Hoffmann V, Mertens E, Adriaensen H. Postoperative analgesia with i.v. patient controlled morphine: effect of adding ketamine. *Br J Anaesth* 1999; **83**: 393–6

8 Javery K, Ussery T, Steger H, Colclough G. Comparison of morphine and morphine with ketamine for postoperative analgesia. *Can J Anaesth* 1996; **43**: 212–5

9 Guillou N, Tanguy M, Seguin P, Beranger B, Campion J, Malledant Y. The effect of small-dose ketamine on morphine consumption in surgical intensive care unit patients after major abdominal surgery. *Anesth Analg* 2003; **97**: 843–7

10 Reeves M, Lindholm D, Myles P, Fletcher H, Hunt J. Adding ketamine to morphine for patient-controlled analgesia after major abdominal surgery: a double-blinded, randomized controlled trial. *Anesth Analg* 2001; **93**: 116–20

11 Chow T, Penberthy A, Goodchild C. Ketamine as an adjunct to morphine in postthoracotomy analgesia: an unintended N-of-1 study. *Anesth Analg* 1998; **87**: 1372–4

12 Rosenberg-Adamsen S, Kehlet H, Dodds C, Rosenberg J. Postoperative sleep disturbance: mechanisms and clinical implications. *Br J Anaesth* 1996; **76**: 552–9

13 Knill R, Moote C, Skinner M, Rose E. Anesthesia with abdominal surgery leads to intense REM sleep during the first postoperative week. *Anesthesiology* 1990; **73**: 52–61

14 Gogenur I, Rosenberg-Adamsen S, Lie C, Carstensen M, Rasmussen V, Rosenberg J. Relationship between nocturnal hypoxaemia, tachycardia and myocardial ischaemia after major abdominal surgery. *Br J Anaesth* 2004; **93**: 333–8

15 Kawai H, Tayasu Y, Saitoh A, *et al.* Nocturnal hypoxemia after lobectomy for lung cancer. *Ann Thorac Surg* 2005; **79**: 1162–6

16 Pauwels R, Buist A, Calverley P, Jenkins C, Hurd S. Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2001; **163**: 1256–76

17 Sveticic G, Gentilini A, Eichenberger U, Luginbühl M, Curatolo M. Combination of morphine with ketamine for patient-controlled analgesia. *Anesthesiology* 2003; **98**: 1195–205

18 Schmid R, Koren G, Klein J, Katz J. The stability of a ketamine-morphine solution. *Anesth Analg* 2002; **94**: 898–900

19 Thompson J, Boyle J, Thompson M, Bell P, Smith G. Nocturnal hypoxaemia and respiratory function after endovascular and conventional abdominal aortic aneurysm repair. *Br J Anaesth* 1999; **82**: 129–31

20 Himmelseher S, Durieux M. Ketamine for perioperative pain management. *Anesthesiology* 2005 **102**: 211–20

21 Bell R, Dahl J, Moore R, Kalso E. Peri-operative ketamine for acute post-operative pain: a quantitative and qualitative systematic review. *Acta Anaesthesiol Scand* 2005; **49**: 1405–28

22 Arendt-Nielsen L, Petersen-Felix S, Fisher M, Bjerring P, Zbinden A. The effect of N-Methyl-D-aspartate antagonist (ketamine) on single and repeated nociceptive stimuli: a placebo controlled experimental human study. *Anesth Analg* 1995; **81**: 63–8

23 Unlugenc H, Ozalevli M, Guler T, Isik G. Postoperative pain management with intravenous patient-controlled morphine: comparison of the effect of adding magnesium or ketamine. *Eur J Anaesthesiol* 2003; **20**: 416–21

24 McQuay H, Bullingham R, Moore R. Acute opiate tolerance in man. *Life Sci* 1981; **28**: 2513–7

25 Mao J. NMDA and opioid receptors: their interactions in antinociception, tolerance and neuroplasticity. *Brain Res Rev* 1999; **30**: 289–304

26 Celerier E, Rivat C, Jun Y, *et al*. Long-lasting hyperalgesia induced by fentanyl in rats: preventive effect of ketamine. *Anesthesiology* 2000; **92**: 465–72

27 Rosenberg J, Dirkes W, Kehlet H. Episodic arterial oxygen desaturation and heart rate variation following major abdominal surgery. *Br J Anaesth* 1989; **63**: 651–4

28 Rosenberg J, Wildschiodts M, Pedersen F, von Jessen F, Kehlet H. Late postoperative nocturnal episodic hypoxemia and associated sleep pattern. *Br J Anaesth* 1994; **72**: 145–50

29 Bouillon T, Bruhn J, Roepcke H, Hoeft A. Opioid-induced respiratory depression is associated with increased tidal volume variability. *Eur J Anaesthesiol* 2003; **20**: 127–33

30 Rosenberg J, Pedersen F, Gebuhr P, Kehlet H. Effect of oxygen therapy on late postoperative episodic and constant hypoxaemia. *Br J Anaesth* 1992; **68**: 18–22

31 Persson J, Scheinin H, Hellstrom G, Bjorkman S, Gotharson E, Gustafsson L. Ketamine antagonises alfentanil-induced hypoventilation in healthy male volunteers. *Acta Anaesthesiol Scand* 1999; **43**: 744–52

32 Pierrefiche O, Foutz A, Denavit-Saubie M. Pneumotaxic mechanisms in the non-human primate: effect of the N-methyl-D-aspartate (NMDA) anatagonist ketamine. *Neurosci Lett* 1990; **119**: 90–3

33 Bastin R, Moraine J, Bardocsky G, Kahn R, Melot C. Incentive spirometry performance: a reliable indicator of pulmonary function in the early postoperative period after lobectomy. *Chest* 1987; **111**: 559–63

34 Boisseau N, Rabary O, Padovani B, *et al*. Improvement of dynamic analgesia does not decrease atelectasis after thoracotomy. *Br J Anaesth* 2001; **87**: 564–9

35 Mildh L, Taittonen M, Leino K, Kirvela O. The effect of low-dose ketamine on fentanyl-induced respiratory depression. *Anaesthesia* 1998; **53**: 965–70