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Perioperative ketamine does not prevent chronic pain after thoracotomy

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ABSTRACT

Thoracotomy is often responsible for chronic pain, possibly of neuropathic origin. To confirm preclinical studies, the preventive effects of perioperative ketamine were tested in a randomized, double-blind, placebo-controlled clinical trial on persistent neuropathic pain after thoracotomy. Eighty-six patients scheduled for thoracotomy under standardised general anaesthesia were randomised to receive either ketamine (1 mg kg^{-1} at the induction, 1 mg kg^{-1} h^{-1} during surgery, then 1 mg kg^{-1} during 24 h; $n = 42$) or normal saline ($n = 44$). Postoperative analgesia included a single dose of intrapleural ropivacaine, intravenous paracetamol and nefopam, and patient-controlled intravenous morphine. Vital parameters and analgesia were recorded during the 48 first postoperative hours. Seventy-three patients were followed up. The patient's chest was examined 1–2 weeks, 6 weeks and 4 months after surgery. At the last two observations, spontaneous pain score over a one-week period (visual analogue scale), neuropathic pain score (NPSI), and intake of analgesics, were assessed. No drug affecting neuropathic pain (except opiates) was given during the follow-up. Two patients in each group were lost to follow-up after the 6 week visit. Ketamine improved immediate postoperative pain, but the groups were similar in terms of neuropathic pain and intake of analgesics, 6 weeks (NPSI score: ketamine: 1.25 [0–4.125]; placebo: 1 [0–4]) and 4 months after surgery. Thus, ketamine given in 24-h infusion failed to prevent chronic neuropathic pain after thoracotomy. Other perioperative preventive long-lasting treatments or techniques could be tested in this context.

1. Introduction

Thoracotomy is one of the most painful surgical procedures. It has been shown that 5–80% of patients still suffer from thoracic pain 2–3 months after surgery, such cases having been reported up to 7 years after surgery (Macrae, 2001; Eisenberg, 2004; Maguire et al., 2006). Hetereogenity between reported incidence is explained by the methods used for evaluation and by the difficulties in following up a population with a high rate of mortality in the first years. However, a recent study reported that 57% of the patients surviving in the year after thoracotomy reported persistent pain, this pain being severe in almost 8% of cases (Maguire et al., 2006). Out of the various mechanisms involved (Conacher, 1990; Hamada et al., 2000), the observed symptoms (Maguire et al., 2006) and evidence of intercostal nerve injury due to rib retraction during surgery (Benedetti et al., 1998; Rogers et al., 2002) suggest a neuropathic aetiology.

Preventing post-surgical pain is an important challenge for anaesthetists and surgeons (Kehlet et al., 2006; Gottschalk et al., 2006). Not only surgical procedures but also perioperative interventions must now be tested in clinical trials. One of the most promising interventions requiring investigation is the reduction of central sensitisation by inhibitors of the NMDA amino-acid receptors (NMDA-R), such as ketamine. Ketamine has been reported to prevent signs of neuropathic pain in animals (Burton et al., 1999), and to prevent post-surgical pain (Petrenko et al., 2003) with long-term effects (De Kock et al., 2001). The aim of this clinical trial was to test the preventive effects of perioperative ketamine (at a dose sufficient to prevent hyperalgesia) on the development of chronic pain after elective thoracotomy.

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2. Methods

This study was approved by the local institutional review board (CCPPRB d'Auvergne) and was registered on ClinicalTrials.gov under the number NCT00313378. The patient's inclusion, care and observation until the 6th week were undertaken at the Thoracic Surgery unit of the University Hospital of Clermont-Ferrand (Pr. G. Escande). The monitoring and the outpatient follow-up at 4 months were undertaken at the Clinical Pharmacology Center (Pr. C. Dubray) of the same institution. All patients between 20 and 75 years of age scheduled for elective partial pneumonectomy under thoracotomy were considered for inclusion. Enrolment began in April 2004 and ended in February 2007. At the first visit (1–2 weeks before surgery), the patients were informed about the study and, if willing to participate, were pre-included by an anaesthetist (Y.A.G., H.T. or L.V.). Formal inclusion was made the day before surgery, after obtaining written consent. The exclusion criteria were: patient refusal, previous thoracic chronic pain, previous neuropathic pain (whatever the site), analgesic treatment (opiates, tricyclic antidepressants or venlafaxin, gabapentin or pregabalin, clonazepam, carbamazepine, NMDA-R blockers), contraindication to bupivacaine, morphine, paracetamol, nefopam or ketamine, emergency surgery, poor physical status or advanced phase of cancer, predicted use of epidural anaesthesia or paravertebral block. Total pneumonectomies were excluded because of frequent serious complications, and because an intercostal pedicle flap was made to protect and revascularise bronchial anastomoses. Randomisation was undertaken by a research assistant who was not involved in the observations. An inclusion number was allocated randomly and kept in a sealed envelope.

All the patients were given 1 mg lorazepam on the night preceding surgery, and 1 h before the intervention. Surgery was always scheduled in the morning. When the patient arrived at the operating theatre, the anaesthetist checked the randomisation, which was kept secret to the patient throughout the study. Induction of anaesthesia involved intravenous midazolam 0.05 mg kg^{-1}, propofol 2.5 mg kg^{-1} or etomidate 0.3 mg kg^{-1}, sufentanil 0.5 μg kg^{-1}, cistracurium 0.2 mg kg^{-1}; selective intubation was undertaken with a double-lumen tube. The patient was maintained with desflurane 4–6%, sufentanil 0.5–1 μg kg^{-1} h^{-1}, cistracurium 0.1 mg kg^{-1} h^{-1}. Ventilation and haemodynamics were adapted to obtain optimal conditions. Surgery was performed following standardised procedures by a senior surgeon. Before skin closure, the edges of the thoracotomy as well as the chest drainage orifices were infiltrated with 0.1% ropivacaine.

Patients were allocated either to the ketamine or the placebo group. Racemic ketamine (Kétamine Panpharma, Ivry-sur-Seine, France) was diluted to 500 mg in 500 mL of isotonic saline (1 mg = 1 mL). Then, 1 mL kg^{-1} of the solution was given 5 min before surgical incision, and 1 mL kg^{-1} h^{-1} until skin closure. For the postoperative period, 1 mg kg^{-1} of ketamine was diluted in isotonic saline in a 48 mL-syringe, then infused at the rate of 2 mL h^{-1} (i.e. 1 mg kg^{-1} for 24 h), then discontinued. In the placebo group, isotonic saline was given alone following the same protocol. At the end of surgery, the anaesthetist confirmed the inclusion by fax to the monitoring research assistant. All the observers of the study (i.e. nurses in recovery room and surgical ward, investigators and research assistants) were unaware of the treatment given, throughout the study.

In addition to the intraoperative ropivacaine infiltration, postoperative analgesia was ensured with interpleural 0.2% ropivacaine (40 mL into the chest tube clamped for 20 min), intravenous paracetamol (1 g every 6 h), nefopam (80 mg per 24 h in continuous infusion) and morphine. Morphine treatment was initiated in the recovery room at the first patient demand, 5 mg intravenously per bolus was given until the pain score went below 30/100 on visual analogue scale (VAS), then it was delivered via a patient-controlled device (1 mg per mL of isotonic saline, bolus = 1 mL, refractory period = 6 min, maximal dose = 12 mg per 4 h, no continuous infusion).

T0 was the time of the patient's arrival in the recovery room. The parameters for assessment of efficacy and tolerance to analgesia were recorded at T0, T0 + 1, 2, 4, 8, 12, 16, 24, 32, 40 and 48 h. These parameters were: morphine consumption (in mg), pain at rest (VAS from 0 to 10), sedation (scale from 0 to 3), nausea, vomiting, dizziness, pruritus, sensation of dry mouth, and current vital parameters. In the case of severe vomiting or nausea, 8 mg of ondansetron were injected intravenously. If ondansetron was unsuccessful, or in the event of unpleasant pruritus or a life-threatening event, the anaesthetist gave intravenous naloxone (0.4 mg).

At the 14th day after surgery, or earlier in case of early discharge of the patient to home, one of two investigators (C.D. or F.S.) met the patient. The existence of ongoing pain at that time was noted and an analgesic treatment (paracetamol ± codeine) was prescribed if necessary. The patient was given a personal booklet including practical instructions and a questionnaire to be completed during the 7 days before the next visit. The questionnaire asked about all treatments taken each day, existence of pain in the operated region ("side of the scar"), and pain intensity by a mark on a VAS (100 mm-line). Instructions were given to the referring general practitioner about permitted and excluded analgesics with respect to the study protocol (permitted: paracetamol and opiates; excluded: tricyclic antidepressants/venlafaxin, gabapentin /pregabalin, clonazepam, carbamazepine, or drugs possibly acting on NMDA receptors).

At the 6th week after surgery, the same investigators met the patient after the systematic post-surgical visit. The operated side of the chest was examined. Clinical signs were recorded in order as follows. Hypoesthesia was defined as an area where the light touch of the blunt end of a paintbrush was felt less precisely than in referent healthy areas (shoulder and contralateral side). Hyperalgesia was defined as an area where the pain induced by the tip of a plastic sterile cone applied perpendicular to the skin was felt abnormally strongly. Static allodynia was defined as an area where the application of a Von Frey hair no. 13 (8 g) was unpleasant. Dynamic allodynia was defined as an area where three successive gentle strokes of an 8 mm-width paintbrush over a 40 mm-distance were unpleasant. The investigator waited for pain provoked by one test to disappear completely before the next test was applied. The pathological areas were traced onto an anatomical graph, and a size score was given to each pathological area after approximate evaluation of the surface (0: none; 1: small, <2 cm^2; 2: medium, between 2 and 10 cm^2; 3: wide, >10 cm^2). The data provided by the patient on the personal booklet were recorded on a case report form, and the patient was asked to complete the Neuropathic Pain Symptom Inventory (NPSI) (Bouhassira et al., 2004), and the Health-Related Quality of Life questionnaire SF-36 (Niv and Kreitler, 2001). The same instructions as those previously described were given to the patient for the following period. Four months after surgery, the patient visited the research centre, and the same procedure was repeated. The questionnaires were collected (by V.G.). The patients who suffered from pain at that time and who required care were addressed to the referent practitioner in charge of pain management.

The per-study exclusion criteria before discharge from the surgery ward were extension of resection (to whole lung, pleura, chest wall or other side), major complication, reoperation, major loss of information and patient's wish for withdrawal. The per-study exclusion criteria after discharge from the surgery ward were the same as previously, plus major medical events and loss to follow-up.

Morphine consumption was defined as the cumulative dose (in mg) given to the patient from T0 to T0 + 24 h. For the T0–T0 + 24 h and for the T0 + 24 to T0 + 48 h periods, the area under the curve (AUC) for pain was calculated, as the sum of the VAS values [(pain at t_n + pain at t_{n+1})/2] × [time (h) between t_n and t_{n+1}] calculated for each interval between observations. The other criteria considered for pain analysis were the number of observations when the pain score was superior to 3/10, and when it was superior to 7/10. For the parameters relative to the possible side effects of the studied treatment, only the period of treatment (the first 24 postoperative hours) was considered for analysis. All data were treated as nominal, according to the following definitions: bradypnea = respiratory rate <13 min^{-1}; hypoxemia = oxygen saturation <90% (treated with high-flow oxygen on mask); hypotension = systolic arterial pressure <95 mmHg; bradycardia = heart rate < 49 min^{-1}; strong sedation = sedation score of 3. Mean arterial pressure was treated as a continuous variable.

The patient's auto-evaluation booklet was analyzed by the main investigator. If spontaneous pain was reported and if it was located at a relevant site (i.e. excluding head, limbs, contralateral chest wall, low back or pelvis), the pain intensity was measured on the 100 mm-line as the distance (in mm) between the left end and the drawn mark. Then, the mean pain intensity (out of 100) was calculated as an average of the seven daily scores. The intake of opiates was noted and the data were converted to oral morphine-equivalents (in mg), by multiplication by a factor depending of the drug taken (codeine: 0.15; dextropropoxyphen: 0.17; hydrocodone: 3.3; hydromorphone: 7.5; oxycodone: 2; tramadol: 0.17) (Fukshansky et al., 2005; VIDAL, 2007). The intake of paracetamol (in mg per week), other analgesic drugs (as anti-inflammatory or other relevant drugs) and drugs possibly responsible for neuropathy (such as chemotherapy for cancer), was also noted, as nominal. The NPSI questionnaire was analysed to calculate a total neuropathic pain score (Bouhassira et al., 2004). Out of the intermediate scores used for the calculation of the total score, those corresponding to clinically relevant dimensions in the study's context were considered, such as ongoing pain [burning pain + (squeezing pain + pressure pain)/2] and evoked pain [(pain at brushing + pain at pressure + pain at contact with something cold)/3]. Ongoing pain and evoked pain were treated as nominal data (yes: score > 0; no: score = 0). The data given by the clinical examination were the surface size scores of pathological areas, treated as ordinal as well as nominal data (yes: = size > 0; no: size = 0).

To analyze the patient's answers to the SF-36 questionnaire, data were scored and interpreted following the French manual (Leplège et al., 2001). Hence, 35 of the 36 items were converted to eight scales representing the following health concepts: physical functioning, role function-physical aspect, bodily pain, general perception of health, vitality, social functioning, role function-emotional aspect, and mental health. Scores for each of the eight scales range from 0 to 100, a higher score indicating better health in that aspect.

The quantitative data were expressed as mean and standard deviation if normally distributed and as quartiles and range otherwise. The categorical data were expressed as number of cases (patients or observations) and percentage of the total. For comparisons between the two groups, the Student's *t*-test (numerical Gaussian), the Mann–Whitney test (other numerical or ordinal), and the Chi-square or Fischer's exact test (categorical) were used. The normality of distribution was checked with a Shapiro–Wilk test. The primary endpoint was to assess whether ketamine was able to reduce the pain score at the 6th week after surgery, compared to placebo. The secondary endpoints were to compare the early postoperative pain parameters, the rate of side effects, the late parameters of pain and the quality of life between the two groups. A preventive effect on the development of chronic pain was to be considered if the pain score was significantly lower in the ketamine group at both the 6th week and the 4th month postoperative observation, with a Bonferroni correction for multiple comparisons. The sample size calculation was made on the basis of data from a previous pilot cohort study undertaken in the same service on 49 patients who rated their spontaneous pain on a VAS (0/10) 6 months after thoracotomy (3.9 ± 2.5). With an expected reduction of pain to 2 on the VAS, with $\alpha = 5\%$, $1 - \beta = 90\%$ and a bilateral hypothesis, the necessary sample size was estimated at 36 per group.

3. Results

The flow of patients enrolled in the study is shown in Fig. 1. Missed inclusions occurred mostly at the start of the study (before the anaesthetists were fully aware of the protocol) and at the end of 2006, with a 5-month gap. As the reasons for withdrawal were mostly due to a change in the clinical context (i.e. total instead of partial pneumonectomy), a per-protocol analysis was undertaken to ensure that the patients belonged to a homogeneous population. This was further justified as there was no possibility for the patients to receive the treatment allocated to the other initial group. The first postoperative in-patient visit was at 11 ± 6 days after surgery. The out patient visits were at 46 ± 10 days and 125 ± 12 days after surgery, respectively. There was no difference in the delay of the visits between the two groups of the study. Table 1 shows the demographic characteristics of the patients at crucial times during the study.

Data concerning the quality of the immediate postoperative analgesia are shown in Table 2 and Fig. 2. It appears that ketamine administered during the 24 h after surgery improved analgesia, reducing the global intensity of pain and the number of observations in which pain (VAS > 3/10) was noted. There was also a statistically non-significant reduction in morphine consumption. However, these effects of ketamine were no longer observed after discontinuation of the drug. During the period of treatment, there was no difference between the two groups in the rate of the possible adverse events of analgesic drugs (Table 3). No major event (such as respiratory depression or delirium) imputable to morphine or ketamine had occurred, and naloxone was never used. The mean arterial pressure (time by time analysis) was also similar in the two groups of the study ($p > 0.05$). During the visit before discharge, 16 patients reported spontaneous pain in a site related to surgery in the ketamine group (45.7%), vs. 13 patients (35.1%) in the placebo group ($p = 0.36$).

Six weeks after surgery, 39 patients reported spontaneous pain (mean pain score >0) on autoevaluation (55.7% of the available questionnaires). For these patients, the mean pain score was 23.5 ± 22.2 (range 0.9–82.6). In 46 patients (63.0%), the total NPSI score was positive. Four months after surgery, 21 patients reported spontaneous pain (mean pain score > 0) on autoevaluation (30.9% of the available questionnaires). In these patients, the mean pain score was 23.7 ± 23.2 (range 1–90). In 40 patients (58.0%), the total NPSI score was positive.

Table 4 shows the data concerning persistent pain and the other neuropathic symptoms observed 6 weeks and 4 months after surgery. For all of the parameters, at any time of observation, no difference was shown between the ketamine and the placebo group. The distribution of mean pain score and NPSI score in the two groups 6 weeks and 4 months after surgery is shown in Fig. 3. There was a relationship between presence of spontaneous pain on autoevaluation and a positive total NPSI score ($p = 0.006$ at 6 weeks; $p = 0.0004$ at 4 months).

The data reporting health-related quality of life are shown in Table 5. As observed for the pain and other neuropathic symptoms,

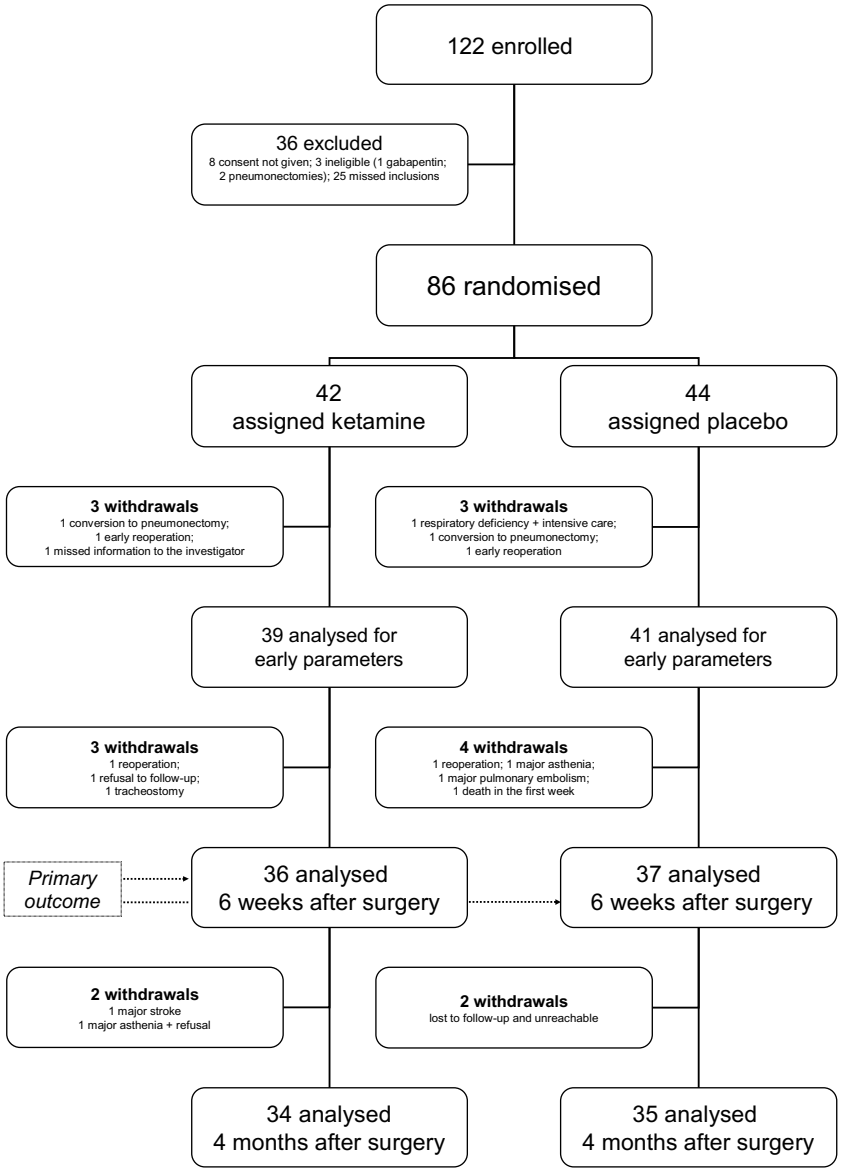

Fig. 1. Diagram showing the flow of the patients enrolled in the study.

Table 1
Demographic and surgical characteristics of the patients, at the time of randomisation and collection of the primary outcome

	Ketamine	Placebo	*p* value
Randomisation			
Number of patients	42	44	
Age (years)	61.9 ± 8.3	58.5 ± 8.5	0.071
Sex (F/M)	11/31 (26/74)	15/29 (34/66)	0.425
Six weeks after surgery			
Number of patients	36	37	
Age (years)	61.0 ± 8.1	58.1 ± 8.8	0.148
Sex (F/M)	9/27 (25/75)	13/24 (35/65)	0.345
Duration of thoracotomy (min)	158 ± 40	158 ± 54	0.990

Numerical data are expressed as means ± SD. Categorical data are expressed as number of patients and %.

the perioperative administration of ketamine had no preventive impact.

Out of the 79 patients that completed the study, 10 patients (12.7% of all; 5 in the ketamine and 5 in the placebo group) asked for additional analgesic treatment and were addressed to a referent practitioner.

4. Discussion

This project was initiated in 2003, in response to growing evidence that thoracotomy could induce chronic pain. Since then, interest has increased in developing preemptive treatments, and it was hypothesised that ketamine given during – and possibly after – surgery could prevent the processes involved in neuropathic pain. This was supported by the following arguments: (i) ketamine is a non-competitive inhibitor of the NMDA-R that can be easily administered perioperatively, and that is often reported for preemptive effects on early postoperative pain (Adam et al., 2005; Bell et al., 2005), (ii) the NMDA-R may be implicated in the development of neuropathic pain (Gao et al., 2005), (iii) inhibitors of these receptors impair the cellular and behavioural response to spinal ligation (Mao et al., 1993; Suzuki et al., 2001), and can alleviate neuropathic pain in patients (Leung et al., 2001; Jorum et al., 2003; Maier et al., 2003; Gottrup

Table 2
Quality of the immediate postoperative analgesia

Period	Parameter	Ketamine (n = 39)	Placebo (n = 41)	p value
T0–T0 + 24 h	Morphine consumption (mg)	37 (24–49) *39 ± 23*	41 (32–59) *48 ± 28*	0.068[b]
	Pain score (AUC)	73 ± 40	88 ± 34	0.039[b]
	Pain score >3/10	127 (39)	190 (56)	<0.0001
	Pain score >7/10	10 (3)	24 (7)	0.022
T0 + 24 to T0 + 48 h	Pain score (AUC)	69 ± 38	73 ± 45	0.672
	Pain score >3/10	29 (28)	32 (32)	0.523
	Pain score >7/10	2 (2)	4 (4)	0.438
Before return to home	Spontaneous pain[a]	16 (45.7)	13 (35.1)	0.360

Numerical data are expressed as median and (interquartile range). Italics: means ± SD, for indication. AUC: area under curve. Categorical data are expressed as number of events and (% of available observations, except a: % of patients). b: unilateral hypothesis.

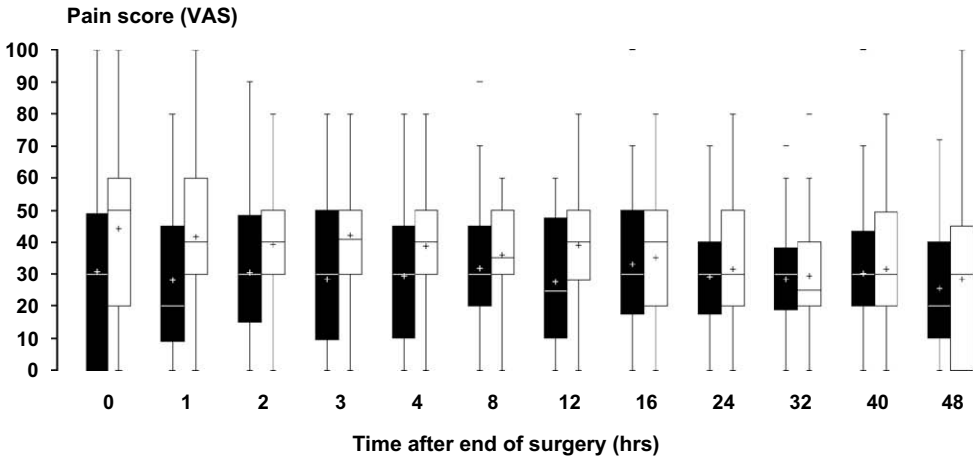

Fig. 2. Time course of pain score during the first postoperative 48 h, expressed as VAS out of 100. The box plots display the quartile values as follows: range (indents), limits for outliers (whiskers), interquartile range (ends of the box), mean (cross) and median (line inside the box). Black boxes: ketamine; white boxes: placebo.

Table 3
Adverse events in the immediate postoperative period, from T0 to T0+24 hrs

Type of event	Ketamine (n = 39)	Placebo (n = 41)	p value
Strong sedation (score = 3)	7 (2.4)	7 (2.2)	1.000
Pruritus	5 (1.5)	4 (1.2)	0.749
Nausea	19 (5.7)	15 (4.3)	0.482
Vomiting	3 (0.9)	0 (0)	0.117
Dizziness	8 (2.4)	8 (2.4)	1.000
Dry mouth sensation	170 (51.1)	189 (55.9)	0.206
Bradypnea < 13 min^{-1}	69 (21.1)	89 (25.4)	0.183
Hypoxemia (SpO_2 < 90%)	3 (0.9)	0 (0)	0.114
Hypotension (SAP < 95 mmHg)	11 (3.2)	19 (5.3)	0.195
Bradycardia < 49. min^{-1}	0 (0)	0 (0)	1.000

SAP: systolic arterial pressure. Categorical data are expressed as number of events and (% of available observations).

et al., 2006), and (iv) in the rat, a single administration – prior to spinal nerve ligation – of either intraperitonal or intrathecal ketamine may prevent neuropathic pain behaviour (Burton et al., 1999). Furthermore, in a study performed in patients undergoing rectal surgery, ketamine given intravenously during surgery (at doses about the half of those used here) was shown to reduce the level of pain 1 and 2 months after surgery (De Kock et al., 2001). However, the conclusions of this study can be contested because of the multiple comparisons and the low baseline risk 1 year after surgery, probably due to the systematic epidural anaesthesia. In another study involving patients undergoing thoracotomy, 1 mg kg^{-1} of ketamine injected epidurally before surgery reduced the surface of pin-prick hyperalgesia and brush allodynia around the scar 30 days after surgery (Ozyalcin et al., 2004). The same single dose given intramuscularly had no significant effects.

In this study, precise information about the neuropathic features of chronic pain after thoracotomy was collected, with long term follow up to investigate chronicity (Macrae, 2001). Medium-term follow-up was chosen, as later observations would have increased the loss to follow-up and the confounding effect of cancer evolution and treatment, and would have unacceptably delayed initiation of management for confirmed cases of neuropathic pain. It was hypothesised that a relevant preventive effect of ketamine would be observable at both 6 weeks and 4 months after surgery, rather than only at one of the two times. Our results show that ketamine, administered at sufficient doses to prevent central sensitisation (De Kock et al., 2001; Joly et al., 2005; Bell et al., 2005), did not prevent the development of chronic pain. This negative result is supported by internal homogeneity, as it was noted for all relevant criteria at all times of observation, while the expected co-analgesic effects of ketamine were observed during infusion of the drug. Possible technical or pharmacological problems, confounding factors, and the possibility of an erroneous hypothesis need therefore to be discussed.

Ketamine was given throughout surgery and continued for about 24 h, as it was considered that this would be sufficient to block the initial phase of central sensitisation. However, the neuropathic processes evoked by the nerve lesion may develop over a wider time range, as increased synthesis in nerve growth factors is observed 7 days after lesion (Obata et al., 2006). Giving NMDA-R inhibitors over several days might be recommended for preventing chronic pain, but ketamine would not be appropriate

Table 4
Pain and other neuropathic symptoms observed 6 weeks and 4 months after surgery

Time after surgery	Six weeks			Four months		
Type of event	Ketamine	Placebo	*p* value	Ketamine	Placebo	*p* value
Number of patients	36	37		34	35	
Anticancer chemotherapy since surgery	7 (19.4)	10 (27.0)	0.441	12 (35.3)	14 (40.0)	0.685
Spontaneous pain (mean VAS out of 100)[a]	3.7 (0–15.4) [0–70.6]	4.7 (0–19.2) [0–82.6]	0.878	0 (0–4.7) [0–90]	0 (0–1.9) [0–61.1]	0.770
Paracetamol intake over 7 days (g)[a]	3.5 (0–11.5) [0–28]	7 (1–13.5) [0–28]	0.211	0 (0–1.875) [0–18]	0 (0–5.5) [0–28]	0.393
Opiate intake over 7 days (mg of morphine equivalent)[a]	0 (0–30) [0–335]	0 (0–86) [0–630]	0.413	0 (0–0) [0–126]	0 (0–0) [0–630]	0.742
Other analgesics (yes/no)[a]	8 (22.9)	9 (25.7)	0.780	5 (14.7)	6 (17.1)	0.782
NPSI (total score)	1.25 (0–4.125) [0–27.5]	1 (0–4) [0–9]	0.825	0 (0–4) [0–37.25]	1 (0–3.7) [0–12.5]	0.264
Neuropathic pain (NPSI total score > 0)	23 (63.9)	23 (62.1)	0.879	16 (47.1)	24 (68.6)	0.070
Ongoing pain (from NPSI)	12 (33.3)	6 (16.2)	0.090	8 (23.5)	12 (34.3)	0.325
Evoked pain (from NPSI)	15 (41.7)	14 (37.8)	0.738	13 (38.2)	16 (45.7)	0.529
Hypoesthesia (yes/no)	24 (66.7)	25 (67.6)	0.935	15 (44.1)	15 (42.9)	0.916
Hypoesthesia (surface)	2 (0–3)	2 (0–3)	0.592	0 (0–2)	0 (0–2)	0.860
Hyperalgesia (yes/no)	8 (22.2)	15 (40.5)	0.092	12 (35.3)	8 (22.9)	0.255
Hyperalgesia (surface)	0 (0–0)	0 (0–2)	0.068	0 (0–0)	0 (0–1.75)	0.269
Static allodynia (yes/no)	3 (8.3)	3 (8.1)	0.972	4 (11.8)	3 (8.6)	0.660
Static allodynia (surface)	0 (0–0)	0 (0–0)	0.974	0 (0–0)	0 (0–0)	0.452
Dynamic allodynia (yes/no)	7 (19.4)	6 (16.2)	0.719	5 (14.7)	3 (8.6)	0.426
Dynamic allodynia (surface)	0 (0–0)	0 (0–0)	0.642	0 (0–0)	0 (0–0)	0.278

Numerical data are expressed as means ± SD or median, (interquartile range) and [range]. Categorical data are expressed as number of patients presenting the event and % of patients. a: data missing because of loss of the autoevaluation questionnaire (at 6 weeks: 1 patient in the ketamine group and 2 in the placebo group; at 4 months: 1 patient in the placebo group); per-protocol analysis.

for technical reasons, and because a drug taken per-os would be more suitable in this context (Cohen et al., 2004; Snijdelaar et al., 2004; Duedahl et al., 2006). However, a recent clinical trial with amantadine given orally for 2 weeks from the day before mastectomy, failed to evidence any prevention of postmastectomy pain syndrome (Eisenberg et al., 2007). To act closer to the site of sensitisation, ketamine could also be injected perispinally, but despite previous promising results (Burton et al., 1999; Ozyalcin et al., 2004), this route is not acceptable in humans because of local toxicity (Vranken et al., 2006).

Partial pneumonectomy was chosen as a model in this study to reduce the rate of postoperative complications compared to total resection, but it may have induced less chronic pain because of a lower number of nerve lesions. This is illustrated by the lower main level of pain in the present study, compared to that was observed during the pilot study (see methods, last paragraph). For future trials, all types of pneumonectomy may be considered despite a strong risk of loss to follow-up that would lower the size of a positive effect. In addition, females were underrepresented in this study compared to other reports (Maguire et al., 2006), as the prevalence of lung cancer in France follows a different sex-ratio. However, despite these factors that may have reduced the baseline risk of persistent pain, the prevalence observed was similar to that found by a more recent retrospective report (Maguire et al., 2006). Finally, many other confounding factors were avoided in the current study, such as drugs or techniques that could prevent the development of chronic pain (non-steroidal anti-inflammatory drugs, steroids, or epidural/parabrachial block) (*cf. infra*).

The main conclusion is that intervention on the NMDA-R may have no effect in preventing neuropathic pain. This can be supported by some data from electrophysiological studies in the rat, as (i) neuropathy induced by spinal nerve ligation is not associated with a reduction in thresholds (Chapman et al., 1998b; Suzuki et al., 1999, 2000, 2001; Kontinen and Dickenson, 2000; Kontinen et al., 2001), and (ii) some criteria of central sensitisation, such as temporal summation and long-term potentiation, are paradoxically reduced in the neuropathic model (Chapman et al., 1998a; Suzuki et al., 1999; Rygh et al., 2000; Suzuki et al., 2001; Kontinen et al., 2001). However, this hypothesis contradicts the results of a recently published randomised and double-blind clinical trial, in which the effects of intravenous ketamine were compared to placebo in patients undergoing thoracotomy (Suzuki et al., 2006). Ketamine was infused with a target-controlled program to obtain a blood concentration of 20 ng mL^{-1}, during the 72 h following the start of surgery. Patients were observed 1, 3 and 6 months after surgery. The main differences with this study were (i) lower doses of ketamine, (ii) systematic epidural analgesia during surgery and the following 48 h, (iii) less patients observed ($n = 44$ at 3 months), and (iv) a different main outcome (number of patients with numerical rating scale of pain > 1). Ketamine was shown to have a preventive effect at 3 months (relative risk = 0.5, $CI_{95\%}$ [0.25; 0.995], $p = 0.048$). However, it should be noted that the difference was no longer significant 6 months after surgery, and that the multiple analyses performed without correction may have inflated the type I error (Lord et al., 2004).

Other drugs or techniques should be tested in the future, both on relevant animal models and in clinical trials. To reduce nerve lesion, a smaller incision, costal resection (Gottschalk et al., 2006), muscle preservation (Benedetti et al., 1998), or intracostal sutures (Cerfolio et al., 2003) should be tested in the long term. Drugs investigated using other surgical models such as non-steroidal anti-inflammatory drugs or steroids (Reuben et al., 2006; Romundstad et al., 2006) could be tested in thoracotomised patients. Drugs acting on the processes of neuropathic pain, such as oral NMDA-R inhibitors or gabapentin/pregabalin, may also be tested over several months following surgery (Sihoe et al., 2006; Solak et al., 2007). Finally, one of the most promising methods for the prevention of chronic post-thoracotomy pain could be perioperative block of the afferent volley by locoregional anesthesia, as suggested by preclinical (Xie et al., 2005) and clinical studies (Sentürk et al., 2002; Tiippana et al., 2003; Lavand'homme et al., 2005; Kairaluoma et al., 2006; Brandsborg et al., 2007).

During the immediate postoperative period, the baseline values of pain scores and morphine consumption reported in this

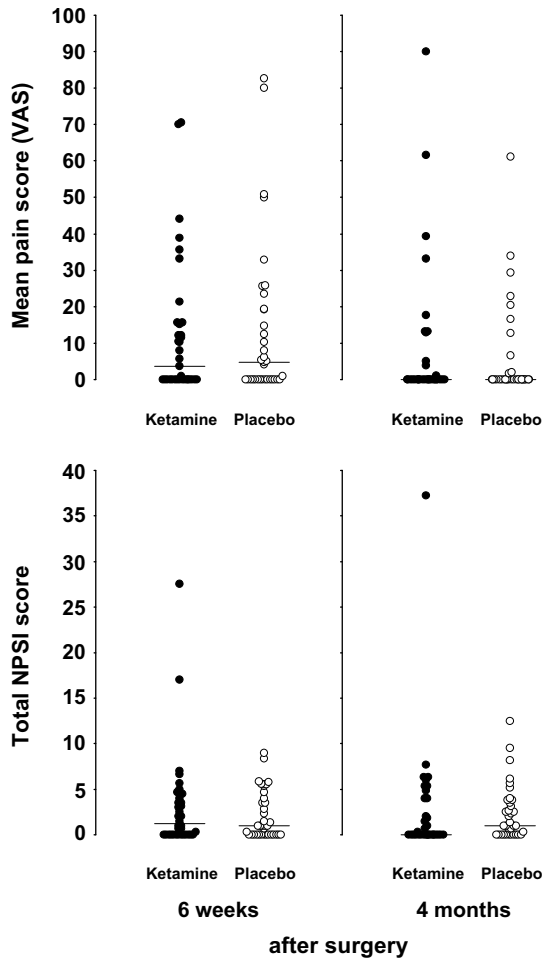

Fig. 3. Scattergrams showing the values of the chronic pain scores following the time of observation and the group of randomisation. The horizontal bars signal the median value for the group. Top: mean pain scores expressed as VAS score out of 100. Bottom: total scores of neuropathic pain assessed by the NPSI questionnaire. Black circles: ketamine; white circles: placebo.

Table 5
Health-related quality of life parameters (based on the SF-36 questionnaire) at the late postoperative observations

Axis	Ketamine (n = 36)	Placebo (n = 37)	p value
Six weeks after surgery			
PF	73.3 ± 22.3	74.4 ± 19.8	0.96
RP	30.6 ± 32.2	23.6 ± 25.6	0.46
BP	64.1 ± 24.5	62.4 ± 23.0	0.69
GH	67.4 ± 17.5	70.3 ± 19.1	0.40
VT	47.5 ± 17.7	47.6 ± 18.0	0.77
SF	78.1 ± 25.6	80.1 ± 24.7	0.82
RE	65.8 ± 19.2	67.7 ± 20.7	0.65
MH	59.3 ± 39.1	65.8 ± 38.1	0.53
	Ketamine (n = 34)	Placebo (n = 35)	
Four months after surgery			
PF	80.1 ± 14.8	75.6 ± 21.8	0.63
RP	40.4 ± 40.8	41.4 ± 35.8	0.86
BP	74.7 ± 25.7	64.1 ± 26.4	0.07
GH	59.3 ± 19.7	62.7 ± 19.4	0.33
VT	51.6 ± 19.4	52.3 ± 20.2	0.72
SF	83.8 ± 23.7	82.1 ± 24.9	0.67
RE	69.2 ± 18.5	68.5 ± 17.6	0.85
MH	68.6 ± 37.6	69.5 ± 31.7	0.82

PF: physical functioning; RP: role function-physical aspect; BP: bodily pain; GH: general health perception; VT: vitality; SF: social functioning; RE: role function-emotional aspect; MH: mental health. Data are expressed as means ± SD.

study did not differ from those of studies using similar anaesthetic and analgesic protocols (Blanloeil et al., 2001; Sentürk et al., 2002; Erolcay and Yuceyar, 2003; Marret et al., 2005; Michelet et al., 2007). An improvement in analgesia during ketamine administration was noted (Table 2), as commonly described for different types of surgery (Bell et al., 2005) including thoracotomy (Michelet et al., 2007). A non-significant reduction in morphine consumption was observed within the ketamine group (19% less than placebo). This is contrary to the statistically significant reduction (25%) noted in a recent study in which postoperative ketamine was compared to placebo after thoracotomy (Michelet et al., 2007). The size of the effect appears to be lower than that reported for other types of surgery (Bell et al., 2005). As the quality of pain relief in the current study was rather poor despite the use of self-administered morphine (still 30–40% of observations with pain on VAS > 3/10, see Table 2), it is likely that the low effect of ketamine on morphine consumption is linked to a low potency of morphine *per se*. Indeed, there is a strong part of mechanical pain after thoracotomy (due to rib cage mobilization), which may be poorly relieved by intravenous analgesia. This is further illustrated by the inability of ketamine to improve functional respiratory parameters after this type of surgery (Michelet et al., 2007).

The conclusion of this study is that the NMDA-R inhibitor ketamine, given in 24-h infusion at antihyperalgesic dose, failed to prevent chronic neuropathic pain after thoracotomy. The consistency of these results for all the studied endpoints means that a larger trial with a similar protocol cannot be justified. Other perioperative preventive treatments or techniques should be tested in this clinical context. Treatments should be given over a longer period, to cover the development of neuropathic processes, and be previously tested in a relevant animal model.

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