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Analgesic efficacy of intravenous perfusion of lidocaine, ketamine or a combination after laparotomy in a placebo-controlled, randomized, double-blind prospective study

THESE

préparée sous la direction du Professeur Christian Kern
(avec la collaboration des Professeurs Isabelle Decosterd et Jean-Patrice Gardaz)

et présentée à la Faculté de biologie et de médecine de l'Université de Lausanne pour l'obtention du grade de

DOCTEUR EN MEDECINE

par

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Analgesic efficacy of intravenous perfusion of lidocaine, ketamine or a combination after laparotomy in a placebocontrolled, randomized, double-blind prospective study

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Madame le Professeur Stephanie Clarke
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SUMMARY

In acute postoperative pain management intravenous lidocaine and/or ketamine have been advocated because of their morphine-sparing effect.

The goal of this prospective, randomised, double-blind study was to assess morphine consumption with different regimens of intravenous infusion of lidocaine, ketamine or both during 48 hours following laparotomy. Patients were randomised into four groups. Group L, K, and KL received intravenous lidocaine, ketamine or a combination, respectively, before incision and during 48 hours postoperatively. The control group (C) received a similar volume of saline bolus and infusion. Postoperative analgesia included morphine delivered by a patient-controlled analgesia device. Primary outcome was the cumulative morphine consumption and pain, sedation scores, pressure algometry and side effects were our secondary outcomes. Cognition and psychomotor performance were also tested.

Out of 57 eligible patients, 44 completed the study. Lidocaine reduced the cumulative morphine consumption compared with the control group (mean 0.456 mg.kg-1 +/- 0.244 (SD) versus 0.705 +/- 0.442, respectively, $P < 0.001$). Pain scores during movement were statistically lower in all three treatment groups. Psychometric tests showed that the lidocaine group expressed more depressed feelings and sadness compared to the control group.

Lidocaine administration had a morphine-sparing effect with a 36% reduction of morphine consumption while ketamine alone or combined with lidocaine did not. As a whole, our results suggest that intravenous lidocaine may offer advantages for postoperative analgesia. We propose lidocaine as a new alternative for pain control that needs to be studied further in future multicentric studies.

INTRODUCTION

Optimal postoperative pain management facilitates rehabilitation immediately after abdominal surgery. Multiple studies have demonstrated that successful postoperative analgesia also reduces perioperative complications and improves patient comfort, thereby providing many benefits for the patient [1-3]. In addition, improved pain control during the perioperative period is one possible measure for the prevention of chronic postsurgical pain [4].

Opioids are frequently used for pain relief. Unfortunately, the vast interpatient variability to reach an optimal therapeutic level along with a host of adverse effects including nausea, vomiting, sedation, decreased intestinal motility and acute tolerance, limits its use in the postoperative period.

Multimodal postoperative analgesia is a current trend in acute postoperative pain management. Different options are available including regional techniques such as epidural analgesia, peripheral nerve blocks, wound and intracavity infiltration. Other analgesic adjuncts are of increasing interest like N-methyl-D-aspartate (NMDA) receptor antagonists (e.g., ketamine), anticonvulsants (e.g., gabapentine) and intravenous infusion of local anaesthetics [1-3].

Intravenous infusion of lidocaine (L) or ketamine (K) has recently been advocated for perioperative pain management [5-7]. Lidocaine acts mainly as a voltage-gated sodium channel blocker and shares analgesic, antihyperalgesic [8], antiallodynic effects as well as anti-inflammatory properties [9]. In recent studies, the use of intravenous lidocaine was shown to reduce morphine consumption, improve both pain control and bowel function after abdominal surgery [8,10,11].

Ketamine is an N-methyl-D-aspartate (NMDA) antagonist although it also has other mechanisms of action. NMDA receptors play an important role in synaptic plasticity and multiple experimental pain models have shown that blockade of the NMDA receptor reduces central sensitization induced by tissue injury [12,13]. Ketamine also reverses opioid-induced hyperalgesia and could thus reduce acute tolerance to opioids and delayed hyperalgesia [7,14]. Interestingly, several studies have demonstrated that ketamine at a low dose (in order to avoid psychomimetic side effects) decreases both pain and morphine

consumption during the postoperative period [7,15].

The aim of the present study was to evaluate the benefit of lidocaine and ketamine in the perioperative period of abdominal surgery. We conducted a placebo-controlled, randomised, double-blind prospective study and recorded morphine consumption that was our primary outcome. Pain scores at rest and during movement, sedation scores, pressure algometry, side effects and psychomimetic effects after systemic infusion of ketamine and lidocaine alone and combined were also measured.

METHODS

The study was conducted between January 2006 and February 2007 at the Lausanne University Hospital Centre, a tertiary-care teaching hospital in Switzerland. Adult patients (age 20 to 75 years) scheduled to undergo abdominal surgery by laparotomy were randomly assigned to a treatment or the control group. Exclusion criteria included laparoscopy, history of chronic pain, opioid self-administration, psychiatric disorders, difficulties with communication, renal or hepatic dysfunction and an ASA physical status > III.

The study was approved by our hospital's Institutional Ethics Committee. After patients had signed a written informed consent, they were randomised according to a double-blind design to one of four groups. Our hospital's central pharmacy was in charge of randomly assigning a treatment to each patient. A box containing the drug labelled with only the patient's name but no indication of the treatment was delivered to the investigators. In parallel, a rescue envelope with treatment specifics was sent to the postoperative care unit (PACU) and kept in a safe box. Table 1 summarises the four different regimens. Lidocaine (L) group received an IV bolus of lidocaine (1.5 $mg.kg^{-1}$) at anaesthesia induction time (AI), followed by a continuous infusion of 2 $mg.kg^{-1}.h^{-1}$ intraoperative (IO) and 1.33 $mg.kg^{-1}.h^{-1}$ for 48 h postoperative (PO). Ketamine (K) group received a bolus of ketamine (0.5 $mg.kg^{-1}$) at AI, then 0.25 $mg.kg^{-1}.h^{-1}$ IO followed by 0.1 $mg.kg^{-1}.h^{-1}$ for the first 24 h PO, then 0.05 $mg.kg^{-1}.h^{-1}$ for the next 24 h. Ketamine-lidocaine (KL) group received at AI a bolus injection of 1.5 $mg.kg^{-1}$ of lidocaine and 0.5 $mg.kg^{-1}$ of ketamine, a continuous infusion of 1.3 $mg.kg^{-1}.h^{-1}$ of lidocaine and 0.17 $mg.kg^{-1}.h^{-1}$ of ketamine was delivered IO followed by 0.9 $mg.kg^{-1}$ of lidocaine with 0.08 $mg.kg^{-1}.h^{-1}$ of ketamine during 48 h PO, the dose of ketamine being reduced to 0.04 $mg.kg^{-1}.h^{-1}$ after the first 24 hours. The control group (C) received an equal volume of saline 0.9 % from AI to 48 h. The rate of infusion was similar for the four groups according to the patient's weight.

Ex-vivo studies were performed by our central pharmacy before the start of our study to establish the compatibility of the mixture of ketamine and lidocaine since this is a non standard formulation.

The day before surgery, patients were instructed on the use of the patient-controlled analgesia device

(PCA, Abbott Lifecare® 4200, Abbott AG, Baar/Zug, Switzerland) as well as the visual analogue scale (VAS) for pain. Psychometric tests, a modified Mini-Mental State Examination [16] and pressure algometry test [17] were explained and administered preoperatively.

The day of the surgery, patients were premedicated one hour before surgery with oral midazolam 7.5 mg. Anaesthesia was induced with fentanyl 3 $mcg.kg^{-1}$, propofol 2 $mg.kg^{-1}$, vecuronium 0.1 $mg.kg^{-1}$ and maintained by boluses of fentanyl and inhaled sevoflurane. Maintenance of anaesthesia was left to the discretion of the respective anaesthesiologist in charge. Ventilation and hemodynamic were adapted to obtain optimal conditions. Fentanyl consumption and awakening time were recorded. Immediately after orotracheal intubation and before surgical incision, a bolus of either L, K, KL or NaCl 0.9% according to the randomisation was administered and the infusion prepared by our pharmacy started.

All patients received 1 g of intravenous (IV) paracetamol 30 minutes before the end of the surgical procedure. In the PACU, pain was controlled by titration of IV morphine. Boluses of 2 mg were administrated by the nurse until the VAS pain score was < 3/10 cm. Thereafter, postoperative analgesia consisted of IV morphine delivered by PCA (1 $mg.ml^{-1}$ morphine and 0.03 $mg.ml^{-1}$ droperidol), IV paracetamol (1 g/6 h) and the regimen of the study according to the assigned group. The parameters of the PCA were morphine 1 mg bolus with a minimum interval of 7 minutes and a maximum dose of 24 mg/4 hours. PCA was started in the PACU as soon as VAS was < 3 and compatible with an awakening state (sedation score < 2). Time to the first PCA request was defined as the time between the arrival in the PACU and the patient's first self-administration of morphine. After 2 hours in the PACU, the patients were transferred to the surgical department where a regimen of morphine PCA was continued for a total of 48 hours, together with IV paracetamol.

The primary outcome of the study was the cumulative morphine consumption over 48 hours postoperatively. Morphine consumption was recorded at 30, 60, 120 minutes and at 4, 12, 24, 36, 48 hours using the PCA software.

Predefined secondary outcomes were pain scores (0-10 cm VAS) at rest and during coughing and/or movement, sedation scores (simplified Ramsay score with 4 levels; 0: awake, 1: sleepy, 2: easily roused, 3: difficult to rouse), mechanical hyperalgesia using pressure algometry (Somedic Sales AB, Hörby, Sweden, in kPa) and occurrence of side effects (sedation, nausea, vomiting, itching, nightmares). Pressure algometry was recorded in the proximity of the incision. A five-point Lickert scale from 0 ("not at all") to 4 ("extremely") was used to rate the following mood states: anxious, happy, relaxed, drowsy, tired, clumsy, alert, energetic, sad and depressed [18]. Cognition was assessed using a modified Mini-Mental State Examination (MMSE) [16,19] and psychomotor performance was tested using the Choice Reaction Time test [20]. The time of the first bowel movement after surgery was recorded for each patient.

Statistical analysis

We designed the study and sample size (11 patients per group) so as to detect a 30% (with a SD being ± 20%) reduction in morphine requirement with a power of 80% and a type I error of 5%. All data are expressed as a mean ± SD. The Chi-square test was used to assess differences between groups for categorical variables. A two-way analysis of variance for repeated measures on one way (time) was used for assessing group and time effects as well as interactions for the total consumption of morphine during 48 hours. A $p < 0.05$ with control group was considered statistically significant. A post hoc t-test with Bonferroni correction was used since we compared each experimental group (K; L; KL) with control group (C). The statistical analysis was performed using the JMP 7 statistical package (SAS Institute Inc, Cary, NC).

RESULTS

Out of a total of 57 eligible patients, 52 were included and 44 (n = 11 in each group) completed the study. Exclusion criteria and patient withdrawal are explained in Figure 1.

As to demographics, the four groups were comparable with regard to age, sex, weight, height and ASA status (Table 2).

The duration of the surgical procedures (expressed in minutes) was not different between the four groups (L: 157.5 ± 46.8, K: 177.0 ± 46.0, KL: 173.5 ± 82.0, C: 174.7 ± 84.9, p = 0.90).

Surgical procedures were comparable across the four groups (p = 0.63, Table S1). There was no perioperative mortality (< 30 days) and the duration of hospitalisation (days ± SD) was not statistically different between the four groups (K: 9.0 ± 3.3, L: 8.3 ± 5.3, KL: 8.2 ± 4.1, C: 8.3 ± 3.7, p = 0.96). None of the study patients had complications requiring admission to the intensive care unit.

Intraoperative fentanyl consumption was significantly lower in the KL group than in the control group: 143.4 ± 35.4 $mcg.h^{-1}$ vs. 212.4 ± 43.8 $mcg.h^{-1}$, respectively (p = 0.02).

Total cumulative morphine consumption (mean expressed in $mg.kg^{-1}$ ± SD) during the 48 h observation period was significantly lower in the lidocaine group compared with the control group (0.456 ± 0.244 versus 0.705 ± 0.442, respectively, p < 0.0001, Figure 2). There was no statistically significant difference between K, KL and the control group (p = 0.48 and 0.43, respectively).

From two hours to 48 hours postoperatively, VAS at rest was < 3/10 cm (Figure 3). No statistical difference was noted for the three groups compared to the control group during any of the observed periods (L: p = 0.17, K: p = 0.89, KL: p = 0.08). During movement "dynamic" VAS (Figure 4) was statistically different for all groups compared to the control group during the 48 hours of observation time (L: p = 0.004, K: p = 0.046, KL: p = 0.006).

No significant differences were found in the mean time (minutes ± SD) to the first morphine administration by PCA among groups (L: 97.3 ± 63.5, K: 208.8 ± 356.7, KL: 78.2 ± 80.9, C: 105.5 ± 68.5, p = 0.37).

A trend towards higher threshold values for the algometry pressure test (Table 3) was noted in the groups L, K and KL versus the control group at 24 hours ($p = 0.07$).

With regard to psychometric tests at 48 h, patients in the lidocaine group expressed more depressed feelings and sadness according to the five-point Lickert scale compared to the control group (1.0 ± 1.4 vs. 0.2 ± 0.4, $p = 0.01$ and 1.1 ± 1.4 vs. 0.2 ± 0.4, respectively, $p = 0.01$). None of the other Lickert scale measures (anxiousness, happiness, relaxed sensation, drowsiness, tiredness, clumsiness, alertness and energetic state) showed a statistically significant difference across groups. The results of the modified Mini-Mental State Examination (MMSE) did not demonstrate any difference at the various points measured (preoperatively, 4, 24 and 48 hours postoperatively).

The results of the coordination Choice Reaction Time test were not different among the four groups for the coordination time variable (Figure 5A), but number of errors was statistically lower in the K group versus the control group during the 48-hour observation period ($p = 0.02$, Figure 5B).

Time to awakening from anaesthesia did not differ among the four groups. Mean times were between 5.2 and 8.5 minutes ($p = 0.36$). No delayed awakening was observed. Sedation was significantly increased in the ketamine group at 15 and 30 minutes after arrival to the PACU, but did not increase thereafter (Table 4). The incidence of postoperative nausea, vomiting and nightmares was also similar among groups ($p = 0.58$ and 0.88, respectively, Table S2).

Postoperative recovery of bowel function (mean in hours ± SD) was not significantly accelerated in any group (L: 57.0 ± 28.5, K: 40.0 ± 13.8, KL: 45.3 ± 8.0, C: 44.0 ± 9.7, $p = 0.39$).

DISCUSSION

The present study demonstrates that administration of preincisional and perioperative intravenous lidocaine during 48 hours associated with postoperative morphine PCA provides superior analgesia. This was confirmed by total cumulative morphine consumption over a 48-hour period that was lower in the lidocaine group when compared to patients receiving only morphine by PCA.

Intravenous lidocaine showed a postoperative opioid-sparing effect (primary outcome) as well as improved pain scores with more improvement during movement than at rest.

Pain is a complex and multifactorial phenomenon [21] and requires multimodal therapy [1-3] that has been proven to be more effective and with reduced analgesic-related side effects in the management of postoperative pain than with a single analgesic [1,3].

Non-opioid strategies of pain control during the perioperative period have recently emerged [21]. The goal to reduce morphine consumption has several benefits for the patient, including reduced opioid side effects, less nausea and a more rapid recovery of bowel function. In addition, recent data suggest that extensive use of opioids is associated with hyperalgesia and allodynia [22].

Some studies have evaluated the analgesic efficacy of ketamine [6,15] and systemic local anaesthetics like lidocaine [5,23,24] but few have evaluated the combination of the two medications. Many trials describe a decrease in analgesia requirement after lidocaine infusion in the postoperative period [23] and other clinical studies with patients undergoing major abdominal surgery have also shown a morphine-sparing effect of intravenous lidocaine [25]. Reducing postoperative pain, especially during movement, is important in facilitating a timely acute rehabilitation program [26].

Local anaesthetics appear to reduce inflammation [27] and suppress C-fiber activity [28] making them potential analgesia drugs for postoperative pain. The anti-inflammatory properties of lidocaine are involved in blocking neutrophil accumulation at the injury site [5] and in reducing the release of inflammatory mediators [29] but the main therapeutic effect is attributed to a central antihyperalgesic effect [30].

As to adverse effects of lidocaine, more sadness and depression were described by the patients in our study at 48 hours. However, we did not observe any coordination trouble of clinical relevance when using the coordination test during the 48 hours postoperatively.

Ketamine is a phencyclidine derivative formulated as a racemic mixture that binds noncompetitively to the phencyclidine binding site of NMDA receptors and also modifies them by allosteric mechanisms [6]. This NMDA receptor antagonist has a significant opioid-sparing effect. The addition of a small intravenous dose of ketamine to local anaesthetics, opioids or other analgesic agents results in superior analgesia with significant morphine sparing and less sedation [31,32]. It has been shown to be particularly useful as an adjunct for patients receiving chronic opioids, patients in whom pain is poorly controlled in spite of high-dose opioid therapy. The adverse effects of ketamine, like psychomimetic effects, often limit the value of its use. The optimal dosing and the duration of administration [33] remain unclear but adverse effects are not significantly increased with small doses of ketamine. Low-dose ketamine has been defined as a bolus of < 1 $mg.kg^{-1}$ IV and an infusion rate $<= 1.2$ $mg.kg^{-1}.h^{-1}$ [34]. A review of randomised trials [15] showed that a wide range of ketamine regimens was used. In sixteen out of 53 trials, cumulative morphine consumption was significantly reduced with concomitant prophylactic intravenous ketamine (median dosage 0.4 $mg.kg^{-1}$). That review concluded that the role of ketamine as a component of perioperative analgesia remains unclear [15].

In contrast to the lidocaine group, we did not observe a benefit of analgesia when administering ketamine or ketamine with lidocaine. On the other hand, we did not observe psychomimetic disorders in the K or KL group as we did in the L group.

In our study, we were unable to confirm an improvement in postoperative bowel function [10] or a shortened hospital stay [26,35] as has been demonstrated in other studies. This can be explained by the low number of patients recruited, sufficient to notice a difference in our primary outcome morphine consumption (initial sample calculated) but inadequate to discriminate other effects (other secondary outcomes recorded). Indeed, patient recruitment was laborious because of the increasing incidence of

laparoscopy in our institution that was an exclusion criterion and we suggest that additional studies must be conducted with another surgery type in order to investigate the potential of lidocaine on other outcomes. In addition, due to the wide range of lidocaine and ketamine infusion protocols (including dosing and duration of infusion) used in different studies, this too may have contributed to the difference in results. We are conscious of the fact that our study implies a low number of patients but we hope that our results can motivate conduct of others studies to confirm the interesting effect of lidocaine on pain control and optimise the best regimen for lidocaine infusion, including dosing and duration.

In conclusion, our study confirmed a beneficial effect of lidocaine administration during the first 48 hours postoperatively in combination with morphine PCA to control pain after laparotomy. We therefore suggest that lidocaine may be an interesting alternative for pain control for the growing number of patients not suited for neuraxial anaesthesia who may benefit from the opioid-sparing effect of lidocaine.

No external funding and no competing interests declared.

TABLES

Table 1 Regimens of intravenous lidocaine, ketamine, association of ketamine and lidocaine, control group.

	Lidocaine (n=11)	**Ketamine (n=11)**	**Ketamine-lidocaine (n=11)**	**Control (n=11)**
Bolus after induction; $mg.kg^{-1}$	1.5	0.5	L* 1.5 K† 0.5	Equal bolus volume of NaCl 0.9%
Intraoperative infusion; $mg.kg^{-1}.h^{-1}$	2.0	0.25	L* 1.3 K† 0.17	Equal infusion volume of NaCl 0.9%
Postoperative infusion 0-24h; $mg.kg^{-1}.h^{-1}$	1.33	0.1	L* 0.9 K† 0.08	Equal infusion volume of NaCl 0.9%
Postoperative infusion 24-48h; $mg.kg^{-1}.h^{-1}$	1.33	0.05	L* 0.9 K† 0.04	Equal infusion volume of NaCl 0.9%

*L: lidocaine; † K: ketamine

Table 2 Demographic data of patients receiving lidocaine, ketamine, ketamine and lidocaine or saline. Values are expressed as mean ± SD.

	Lidocaine group (n=11)	**Ketamine group (n=11)**	**Ketamine-lidocaine group (n=11)**	**Control group (n=11)**	**p value**
Male/Female	10/1	11/0	10/1	11/0	0.55
Age (years)	60.8 ± 8.4	60.1 ± 9.1	61.6 ± 5.8	58.6 ± 9.7	0.85
Weight (kg)	77.3 ± 11.8	74.4 ±10.2	80.4 ± 12.0	81.0 ± 12.5	0.63
Height (cm)	174 ± 5.6	172 ± 7.9	173 ± 7.3	174 ± 9.1	0.87
ASA I/II/III	0/10/1	0/10/1	1/9/1	0/11/0	0.64

Table 3 Pressure algometry before and after laparotomy in the four groups. Values are expressed in kPa as mean ± SD.

	Lidocaine group (n=11)	**Ketamine group (n=11)**	**Ketamine-lidocaine group (n=11)**	**Control group (n=11)**	**p value**
Before surgery	779.3 ± 341.0	675.8 ± 300.3	747.8 ± 304.6	717.0 ± 342.3	0.89
1h	475.6 ± 196.5	401.3 ± 272.3	556.1 ± 361.7	297.0 ± 165.5	0.13
2h	463.5 ± 177.8	431.8 ± 265.9	549.3 ± 424.9	337.7 ± 188.6	0.37
4h	390.6 ± 143.5	430.2 ± 259.8	550.2 ± 473.2	305.9 ± 155.3	0.27
24h	281.4 ± 75.7	293.5 ± 119.1	375.8 ± 200.5	225.9 ± 81.1	0.07
48h	323.8 ± 153.9	298.0 ± 150.6	427.4 ± 192.1	333.8 ± 184.1	0.35

Table 4 Sedation score after surgery in the four groups. Values are expressed as mean ± SD. The sedation score used is the simplified Ramsay score with 4 levels (0: awake, 1: sleepy, 2: easily roused, 3: difficult to rouse).

	Lidocaine group (n=11)	**Ketamine group (n=11)**	**Ketamine-lidocaine group (n=11)**	**Control group (n=11)**	**p value**
15'	0.9 ± 0.7	1.4 ± 1.0*	1.4 ± 1.0	0.4 ± 0.7	0.04*
30'	0.6 ± 0.7	1.3 ± 0.9*	0.6 ± 0.7	0.3 ± 0.5	0.02*
60'	0.5 ± 0.7	1.0 ± 0.8	0.4 ± 0.7	0.3 ± 0.5	0.14
2h	0.5 ± 0.7	0.5 ± 0.7	0.3 ± 0.6	0.1 ± 0.3	0.38
4h	0.4 ± 0.5	0.4 ± 0.8	0.4 ± 0.7	0.2 ± 0.4	0.70
24h	0.0 ± 0.0	0.1 ± 0.3	0.3 ± 0.5	0.1 ± 0.3	0.25
48h	0.1 ± 0.3	0.2 ± 0.4	0.1 ± 0.3	0.1 ± 0.3	0.38

* $p < 0.05$

FIGURES

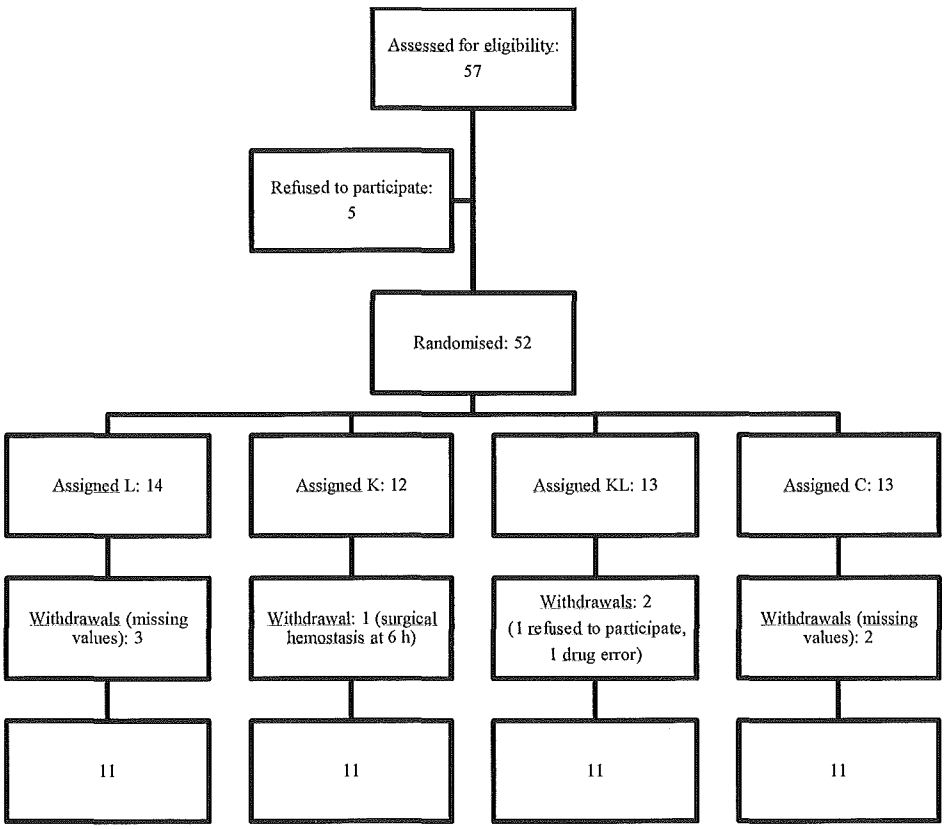

Figure 1 Flow diagram

L: lidocaine group, K: ketamine group, KL: ketamine-lidocaine group, C: control group

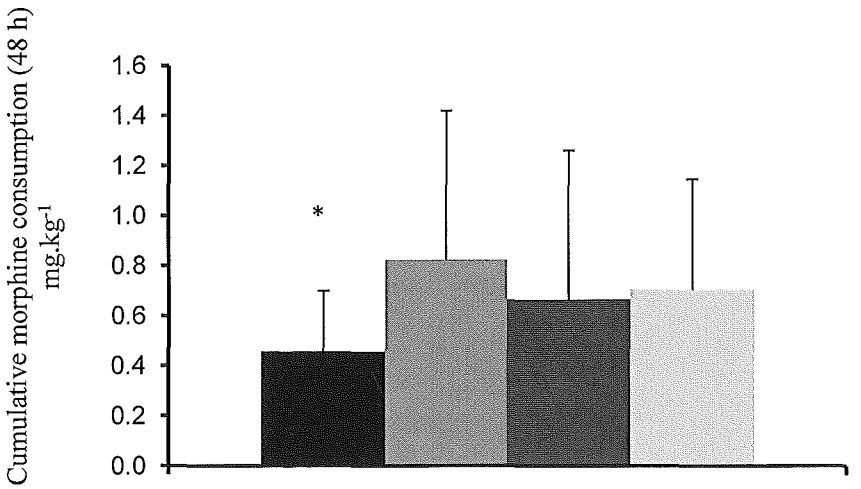

Figure 2 Cumulative morphine consumption ($mg.kg^{-1}$) over 48 hours in patients receiving lidocaine (■) (0.456 ± 0.244, *p < 0.0001) or ketamine (■) (0.823 ± 0.597) or ketamine-lidocaine (■) (0.665 ± 0.595) or saline (■) (0.705 ± 0.442).Values ($mg.kg^{-1}$) are expressed as mean ± SD.

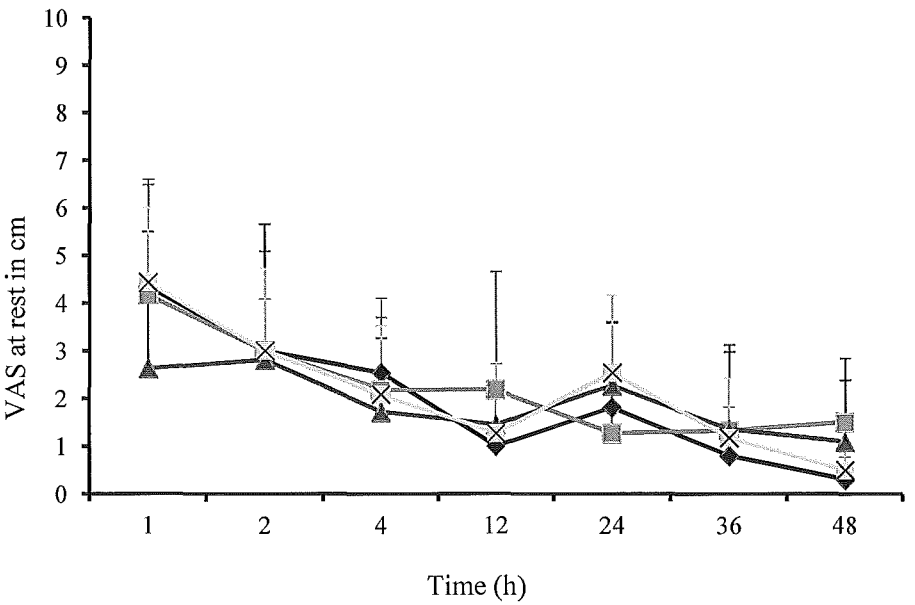

Figure 3 Pain score (VAS: visual analogue score) at rest after laparotomy in patients receiving lidocaine (♦), ketamine (■), ketamine-lidocaine (▲) or saline (×). Data are expressed as mean ± SD. No statistical differences among groups.

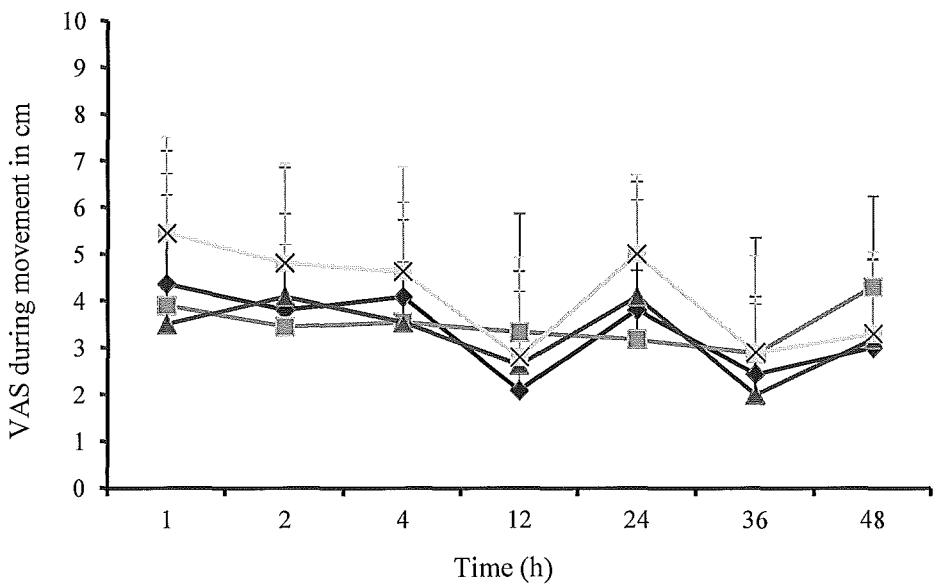

Figure 4 Pain score (VAS: visual analogue score) during movement after surgery in patients receiving lidocaine (♦) ($p < 0.005$), ketamine (■) ($p < 0.05$), ketamine-lidocaine (▲) ($p < 0.01$) or saline (×). Data are expressed as mean ± SD.

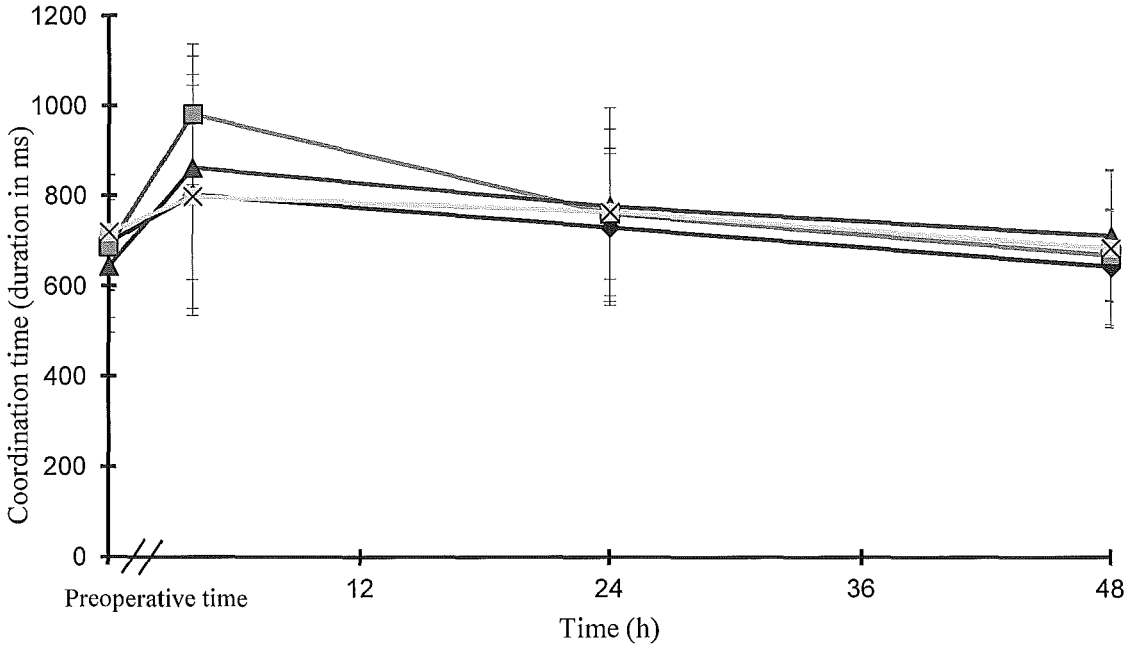

Figure 5A Coordination time test in patients receiving lidocaine (♦), ketamine (■), ketamine-lidocaine (▲) or saline (⊠). No statistically significant difference was observed compared with the control group.

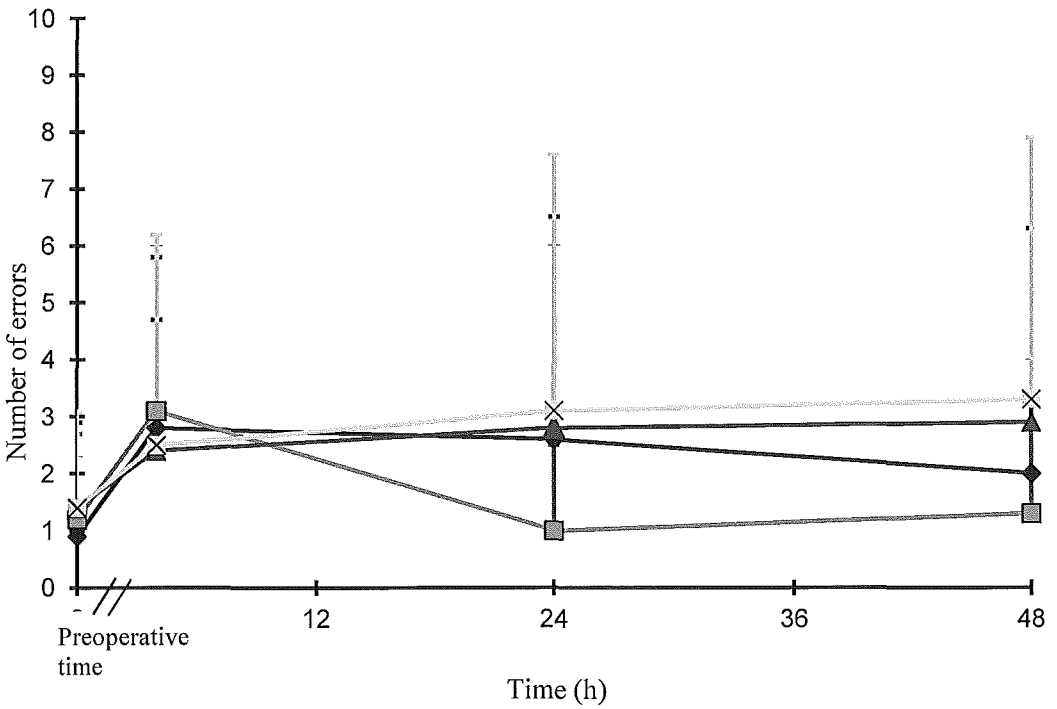

Figure 5B Coordination test: number of errors in patients receiving lidocaine (♦), ketamine (■), ketamine-lidocaine (▲) or saline (×). The number of errors was statistically lower in the ketamine group versus the control group over the 48 hours observed ($p = 0.02$).

Supplemental data

Table S1 Surgical procedures: distribution of surgical procedures among the different groups is equal, p= 0.63.

	Lidocaine group (n=11)	**Ketamine group (n=11)**	**Ketamine-Lidocaine group (n=11)**	**Saline group (n=11)**	**Total**
Prostatic surgery	8	7	8	9	32
Colorectal surgery	2	2	1	0	5
Gastric surgery	1	0	0	1	2
Renal surgery	0	1	1	0	2
Pancreatic surgery	0	1	0	0	1
Retroperitoneal surgery	0	0	0	1	1
Bladder surgery	0	0	1	0	1
Total	11	11	11	11	44

Table S2 Incidence of side effects: results are expressed as number of patients with side effects during 48 hours (n = 11 in each group).

L: lidocaine group, K: ketamine group, KL: ketamine-lidocaine group, C: control group

	Patients with nausea-vomiting				Patients with nightmares				Patients with pruritus			
	L	**K**	**KL**	**C**	**L**	**K**	**KL**	**C**	**L**	**K**	**KL**	**C**
0-48 h	5	5	2	3	2	1	2	1	3	5	7	1
p	0.58				0.88				0.17			

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