Effect of i.v. ketamine in combination with epidural bupivacaine or epidural morphine on postoperative pain and wound tenderness after renal surgery


Summary

We studied 60 patients undergoing operation on the kidney with combined general and epidural anaesthesia, in a double-blind, randomized, controlled study. Patients were allocated to receive a preoperative bolus dose of ketamine 10 mg i.v., followed by i.v. infusion of ketamine 10 mg h⁻¹ for 48 h after operation, or placebo. During the first 24 h after surgery, all patients received 4 ml h⁻¹ of epidural bupivacaine 2.5 mg ml⁻¹. From 24 to 48 h after operation, patients received epidural morphine 0.2 mg h⁻¹ preceded by a bolus dose of 2 mg. In addition, patient-controlled analgesia (PCA) with i.v. morphine (2.5 mg, lockout time 15 min) was offered from 0 to 48 h after operation. Patients who received ketamine felt significantly more sedated at 0–24 h, but not at 24–48 h after operation, compared with patients who received placebo (P=0.002 and P=0.127, respectively). There were no significant differences in pain (VAS) at rest, during mobilization or cough, PCA morphine consumption, sensory block to pinprick, pressure pain detection threshold assessed with an algometer, touch and pain detection thresholds assessed with von Frey hairs, peak flow or side effects other than sedation. The power of detecting a reduction in VAS scores of 20 mm in our study was 80% at the 5% significance level. We conclude that we were unable to demonstrate an (additive) analgesic or opioid sparing effect of ketamine 10 mg h⁻¹ i.v. combined with epidural bupivacaine at 0–24 h, or epidural morphine at 24–48 h after renal surgery. (Br. J. Anaesth. 1998; 81: 707–712).

Keywords: anaesthetic techniques, epidural; anaesthetics i.v., ketamine; anaesthetics local, bupivacaine; analgesics opioid, morphine; pain, postoperative; surgery, urological

Ketamine has been used as an analgesic for more than 30 yr. For many years its mechanism of action was disputed but it is now generally agreed that one mechanism is specific binding to the phencyclidine site of the N-methyl-D-aspartate (NMDA) receptor ion channel.

In experimental studies, the NMDA receptor was found to play a significant role in injury-induced spinal hypersensitiveness.¹ This sensitization of the central nervous system may account for significant postoperative pain.² The development of chronic neuropathic pain has also been related to activation of the NMDA receptor.³⁻⁵ Experimental and clinical studies have demonstrated that block of the NMDA receptor before or during injury may prevent or reduce the development of central sensitization⁶⁻¹⁵ and NMDA receptor block after injury can reduce or abolish central sensitization that has already been established.¹⁶

Previous studies indicate that NMDA receptor antagonists potentiate the effects of other analgesics, such as morphine,¹⁷⁻²⁰ local anaesthetics²¹⁻²⁴ and NSAID.²⁵ The mechanism of this potentiation may include reduced development of tolerance to opioids²⁶ and reduced tachyphylaxis to local anaesthetics.²² As an NMDA receptor antagonist, ketamine may produce additive or synergistic effects with “balanced” treatment of postoperative pain.

The aim of our study was to investigate the effect of low-dose i.v. ketamine in combination with epidural bupivacaine and epidural morphine on pain and wound tenderness after renal surgery.

Patients and methods

We studied 60 patients undergoing elective nephrectomy or operation on pelvic structures (Hynes–Anderson operation), procedures with a similar lateral approach. Informed written consent was obtained from all patients and approval was obtained from the local Ethics Committee and the Danish National Board of Health. Patients were recruited from the Department of Urology, Skejby Sygehus, Aarhus University Hospital, during the period October 1994 to September 1996. Patients with a history of drug or alcohol abuse, chronic pain or daily intake of analgesics, with contraindications to insertion of epidural catheters, and those unable to cooperate, were not included.

The study was double-blind, randomized and placebo-controlled. The study drugs (ketamine 10 mg ml⁻¹) and placebo (isotonic saline) were prepared under sterile conditions by the hospital pharmacy in identical containers, marked with the name of the project, the investigator’s name and consecutive patient numbers.

One hour before surgery, patients received diazepam 5–10 mg orally as premedication. Before

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induction of general anaesthesia, an epidural catheter was inserted between the T8–T9 interspace, and tested with lidocaine 20 mg ml⁻¹ with epinephrine 3 + 2 ml. A bolus dose of 8 ml of bupivacaine 5 mg ml⁻¹ was administered, followed by continuous infusion of 5 ml h⁻¹ of bupivacaine 5 mg ml⁻¹ throughout the operation, using a Pharmacia Deltec pump.

General anaesthesia was induced with fentanyl 0.2 mg, thiopental 3–7 mg kg⁻¹ and midazolam 5 mg. Atracurium 0.5 mg kg⁻¹ was used to facilitate orotracheal intubation, followed by infusion of atracurium 0.5 mg kg⁻¹ h⁻¹ for neuromuscular block. General anaesthesia was maintained with isoflurane up to a maximum of 1% and 66% nitrous oxide in oxygen. After induction of general anaesthesia, patients were allocated randomly to receive a bolus dose of ketamine 10 mg i.v. before surgical incision, followed by continuous i.v. infusion of ketamine 10 mg h⁻¹ or placebo for 48 h after operation, using a Pharmacia Deltec pump. No other analgesics were administered during operation.

Infusion of dopamine 3 µg h⁻¹ was started before surgery and continued throughout operation to optimize renal perfusion. Hypotension during and after operation was treated with i.v. infusion of isotonic sodium chloride, ephedrine 5 mg i.v. or increased doses of dopamine if considered necessary by the anaesthetist. Fluid and blood losses were replaced according to the standard prescriptions of the department. After operation, neuromuscular block was antagonized with glycopyrrolate 0.5 mg and neostigmine 2.5 mg. All patients were observed for at least 5 h after operation in the recovery unit.

POSTOPERATIVE ANALGESIA

For the first 24 h after surgery, patients received a continuous infusion of 4 ml h⁻¹ of epidural bupivacaine 2.5 mg ml⁻¹. From 24 to 48 h after operation they received epidural morphine 0.2 mg h⁻¹ preceded by a bolus dose of 2 mg. In addition, patients were offered patient-controlled analgesia (PCA) with morphine (2.5 mg, lockout time 15 min) for 0–48 h after operation, using a Pharmacia Deltec CADD-PCA ambulatory infusion pump. Except for ketamine–placebo, as described above, no other analgesics were administered.

POSTOPERATIVE RECORDINGS AND PAIN ASSESSMENTS

Pain scores on a visual analogue scale (VAS, 0 mm = no pain, 100 mm = worst pain imaginable) at rest, during mobilization from the supine to the sitting position and during cough were assessed by patients at 4, 6, 8, 22, 24, 26, 28, 30, 32, 46 and 48 h after operation. The number of PCA morphine doses used was recorded at the same times. Levels of sensory block to pinprick bilaterally were assessed at 4, 8 and 22 h after operation.

Pressure pain detection threshold was determined 2 cm caudal to the middle of the surgical incision with a hand-held electronic pressure algometer (Somedic AB, Sweden) before operation and at 6, 22, 30 and 46 h after operation. The stimulation probe has a circular tip of 6 mm (0.28 cm²) and is connected to a pressure transducer built into the gun-shaped handle. The signal from the pressure transducer is amplified in a main unit, and the applied pressure is shown (in kPa) on a digital display. A display consisting of horizontal light bars indicates if the applied pressure is above or below a preset rate (20 kPa s⁻¹ in this study). When the pressure pain detection threshold (defined as the minimal pressure [force] which induces pain) was reached, the subject was instructed to activate a push-button, which freezes the digital display. Three determinations with an interval of 30 s were made at each assessment, and a mean calculated.

Pain sensitivity was assessed before operation, and at 6, 22, 30 and 46 h after operation, with von Frey hairs, consisting of nine monofilaments (numbered 1–9) of variable diameter calibrated to deliver a specific force of 0.5–16 g on the skin. Touch detection threshold and pain detection threshold were assessed by applying von Frey hairs of increasing force to the skin 10 cm distal to the middle of the surgical incision. At the first test the region was marked. Patients were instructed to tell when touch was first detected, and when the stimulus became uncomfortable. If touch or pain detection thresholds exceeded 16 g (hair No. 9), this was registered with the No. 9.8. Each threshold was assessed three times, with an interval of 30 s and a mean calculated.

Peak flow (litre min⁻¹) was determined with a peak flow monitor (Spiropharma, Copenhagen) before operation, and at 6, 22, 30 and 46 h after operation with the patient in the sitting position. Three determinations with an interval of 30 s were made at each assessment and a mean calculated.

Side effects were recorded at 4, 6, 8, 22, 24, 26, 28, 30, 32, 46 and 48 h after operation. Sedation was assessed by patients using a visual analogue scale with the descriptors “fully awake” (0 mm) and “almost sleeping” (100 mm). Dreams were registered as none, pleasant or unpleasant. Nausea was registered as none, light, moderate or severe. The number of vomits (> 100 ml) was registered. Itching was registered as none, light, moderate or severe.

All assessments were made by three authors (S. I., L. N. and T. M. H.), with a maximum of two persons for each patient.

STATISTICAL ANALYSIS

The sample size was based on a power calculation which showed that 24 patients per group were necessary to achieve 80% power to detect a difference of 20 mm (VAS) in pain scores between patients treated with ketamine compared with placebo, with alpha = 0.05 (two-tailed). Based on these values we decided to include 30 patients in each group.

Data are presented as medians, with upper and lower quartiles. Statistical analyses were performed using Fisher’s exact test, the Mann–Whitney rank sum test for unpaired data and non-parametric two-way ANOVA for repeated measurements, where appropriate. If multiple testing was performed, significant P values were corrected with a Bonferroni test for repeated measurements. P < 0.05 was considered statistically significant. Calculations were performed using Statgraphics Plus 7.0 under Windows 95, on a Pentium PC (150/LS-AWARD-PB/16M SIMM).
Results
Of the 60 patients studied, eight were excluded; therefore, there were 24 patients in the ketamine group and 28 in the placebo group. Reasons for exclusions were: displacement of the epidural catheter (two patients); change of operation type (two patients); wish to withdraw from the study (two patients); and inclusion criteria not fulfilled (two patients).

Patient characteristics and operative data are shown in table 1.

POSTOPERATIVE RECORDINGS AND PAIN ASSESSMENTS
There were no significant differences between groups for VAS scores at rest, during mobilization from the supine to the sitting position, or during cough at any time ($P>0.05$) (fig. 1). The number of PCA morphine doses used was not significantly different between groups at 0–24 h after operation (ketamine nine, placebo 12 doses; $P=0.26$) or at 24–48 h after operation (ketamine 2.5, placebo 3.5 doses; $P=0.96$).

The level of sensory block to pinprick was not different between groups ($P=0.21$). The levels were between T4 and L2 in both groups.

There were no significant differences between groups for pressure pain detection thresholds ($P>0.05$) (fig. 2), von Frey hair touch and pain detection thresholds ($P>0.23$) at 0–24 h and 24–48 h after operation ($P=0.96$) for all assessments at any time. The level of sedation was significantly higher in the ketamine group compared with the placebo group at 0–24 h after operation ($P=0.002$) but not at 24–48 h ($P=0.127$) (fig. 3). Two patients in the ketamine group and one in the placebo group experienced psychomimetic side effects; one patient in each group had unpleasant dreams ($P=0.55$). There were no significant differences between groups for nausea ($P>0.15$), number of vomits ($P>0.22$) or itching ($P>0.19$).
Discussion

We found that patients who received ketamine 10 mg h$^{-1}$ i.v. for 48 h after urological surgery felt significantly more sedated at 0–24 h after operation (during epidural analgesia with bupivacaine 10 mg h$^{-1}$), but not at 24–48 h after operation (during epidural analgesia with morphine 0.2 mg h$^{-1}$) compared with patients receiving placebo. There were no significant differences between groups in pain scores, PCA morphine consumption, sensory block to pinprick, pressure pain detection threshold and von Frey hair thresholds at surgical incision, peak flow or side effects. Consequently, we were unable to demonstrate additional analgesic (spinal) effects of low-dose i.v. ketamine in combination with epidural local anaesthetic or epidural morphine, but only mild supra-sensory effects (sedation).

Much of the pharmacological knowledge of the analgesic effect of ketamine is new, although the drug has been used for postoperative analgesia for several years. Only a few randomized, double-blind, placebo-controlled studies have been published.\textsuperscript{23,24,25,27,28} Eight placebo-controlled studies investigated the effect of i.v. or i.m. ketamine on postoperative pain,\textsuperscript{23,25,27,28} seven of which showed an analgesic effect. One of the first studies found that a single dose of ketamine 0.44 mg kg$^{-1}$ i.m. produced analgesia with a mild degree of sedation and dizziness after orthopaedic surgery-laparotomy.\textsuperscript{27} In another study, 60 patients were allocated randomly to receive either i.v. morphine 1 mg h$^{-1}$, ketamine 50 mg h$^{-1}$ or placebo for 6 h after major, non-specified surgery. Morphine produced superior pain relief for the first 3 h, but ketamine was equally effective subsequently, and more effective than placebo.\textsuperscript{28} I.v. ketamine (bolus of 30 mg followed by an i.v. infusion of 1 mg min$^{-1}$ for 8 h) was compared with placebo during postoperative ventilator treatment after major abdominal surgery. The placebo group received significantly more supplementary analgesia than patients receiving ketamine.\textsuperscript{29} Roytblat and colleagues found that the time to first request for morphine was increased and total demand for supplementary postoperative morphine was reduced when a single dose of ketamine 0.15 mg kg$^{-1}$ i.v. was added to a standardized general anaesthetic in patients undergoing cholecystectomy.\textsuperscript{30} Similar results were observed in Caesarean section patients where the time to first demand of morphine was increased and total morphine consumption over 24 h was reduced when general anaesthesia was induced with ketamine 1 mg kg$^{-1}$ compared with induction with thiopental 4 mg kg$^{-1}$.\textsuperscript{31} In a recent study of 20 patients undergoing nephrectomy, a bolus dose of ketamine 0.5 mg kg$^{-1}$ i.v. followed by a continuous infusion of 2 $\mu$g kg$^{-1}$ min$^{-1}$ reduced pain and PCA morphine consumption during the first few postoperative hours compared with placebo. Further, hyperalgesia around the surgical wound was reduced 1, 3 and 7 days after operation in patients receiving ketamine.\textsuperscript{32} Javery and colleagues\textsuperscript{20} showed that addition of ketamine 1 mg ml$^{-1}$ to morphine 1 mg ml$^{-1}$ as i.v. PCA (1 ml with lockout period of 6 min) improved analgesia and reduced side effects compared with morphine 1 mg ml$^{-1}$ alone.\textsuperscript{30} Finally, morphine 1 mg h$^{-1}$ with ketamine 5, 10 or 20 mg h$^{-1}$, or placebo, was given as an i.v. infusion for 24 h after upper abdominal surgery in 40 elderly patients. Ketamine did not significantly improve analgesia, but higher doses increased the incidence of postoperative dreaming.\textsuperscript{33}

Varying doses of ketamine (4–30 mg) have been administered epidurally, but few were investigated in randomized, double-blind, placebo-controlled studies. One study found no improved analgesic effect of epidural ketamine compared with placebo\textsuperscript{34} and another found ketamine to potentiate the analgesic effect of epidural morphine, but to have no analgesic effects on its own.\textsuperscript{19} The combination of epidural ketamine and bupivacaine reduced onset time and increased the level of sensory block,\textsuperscript{34} improved analgesia,\textsuperscript{21} increased time to first analgesia and reduced analgesic consumption\textsuperscript{22} compared with bupivacaine alone, or was found to have no effect on postoperative pain.\textsuperscript{35}

The dose regimen chosen in our study was based on results from previous studies. Thus ketamine 0.15 mg kg$^{-1}$ reduced secondary hyperalgesia caused by burn injury in human volunteers with acceptable side effects.\textsuperscript{7} A single dose of ketamine 0.15 mg kg$^{-1}$ reduced pain and analgesic requirements after cholecystectomy,\textsuperscript{30} and Edwards and colleagues observed unacceptable side effects with doses of i.v. ketamine that were higher than 10 mg h$^{-1}$.\textsuperscript{31}

I.v. and not epidural, administration was chosen in our study because the potential neurotoxic effect of long-term epidural infusion of ketamine has not been evaluated fully and ketamine has a local anaesthetic effect\textsuperscript{36} which could interfere with the interpretation of our study. The postoperative regimen was designed to investigate if i.v. ketamine potentiated either epidural bupivacaine, epidural morphine, or both.

The dose and route of administration (i.v.) used in our study differed from previous combination studies with significant analgesic effects of ketamine. Thus in the studies with epidural local anaesthetic,\textsuperscript{22–24,35} ketamine was administered epidurally in higher doses. Similarly, morphine and ketamine were administered epidurally in the study of Wong and colleagues\textsuperscript{19} and this may explain the different results. Furthermore, the additional analgesic effect of ketamine in the above
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studies could be related to a local anaesthetic effect of ketamine, and not necessarily to block of the NMDA receptor.

The results of our study are in agreement with those of Edwards and colleagues and similar to those of Stubhaug and colleagues where a comparable dose regimen of ketamine resulted in only a modest and short lasting effect on pain and analgesic consumption, and no effect on pressure pain thresholds at the wound site. Reduction of the area of mechanical hyperalgesia around the surgical wound on postoperative days 1, 3 and 7 observed by Stubhaug and colleagues in patients treated with ketamine may reflect reduced sensitization of central nociceptive neurons. However, this did not lead to reduced pain intensity, as measured by VAS, or reduced morphine consumption, and the clinical implication of this finding remains to be evaluated.

We were unable to demonstrate any effects of ketamine on von Frey hair thresholds 10 cm from the surgical incision during epidural infusion with either bupivacaine or morphine. The discrepancy between our findings and those of Stubhaug and colleagues may be because we investigated von Frey hair thresholds at some distance from the surgical wound and not at the area of hyperalgesia surrounding the wound. Thus a potential area of hyperalgesia around the wound in our patients may not have included the area where we performed our measurements.

In summary, an i.v. bolus dose and continuous infusion of ketamine did not reduce postoperative pain but increased side effects in the form of increased sedation during the first 24 h after operation. It is likely that a higher dose of i.v. ketamine would provide increased analgesia but it is not known if this could be achieved without unacceptable side effects.

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