

A randomised, controlled study of peri-operative low dose s(+)-ketamine in combination with postoperative patient-controlled s(+)-ketamine and morphine after radical prostatectomy*

D. G. Snijdelaar,¹ H. B. Cornelisse,² R. L. Schmid³ and J. Katz⁴

¹ Consultant Anaesthetist and ² Resident in Anaesthesia, Department of Anesthesiology/Pain Centre, University Medical Centre Nijmegen, PO Box 9101, 6500 HB Nijmegen, The Netherlands

³ Consultant Anaesthetist, Department of Anesthesiology, Klinik Links vom Rhein, Cologne, Germany

⁴ Professor and Canada Research Chair, Department of Psychology and School of Kinesiology and Health Science, York University, Toronto, ON, Canada, Senior Scientist, Department of Anesthesia and Pain Management, Toronto General Hospital and Mount Sinai Hospital, Toronto, ON, Canada and Professor, Departments of Anesthesia and Public Health Sciences, University of Toronto, Toronto, ON, Canada

Summary

In a randomised, double-blind prospective study we compared the effects on postoperative pain and analgesic consumption of intra-operative s(+)-ketamine (100 $\mu\text{g.kg}^{-1}$ bolus and a continuous infusion of 2 $\mu\text{g.kg}^{-1}.\text{min}^{-1}$) followed by postoperative patient-controlled analgesia with morphine (1 mg per bolus) plus s(+)-ketamine (0.5 mg per bolus), or intra-operative saline followed by postoperative patient-controlled analgesia morphine (1 mg per bolus) alone. A total of 28 male patients undergoing radical prostatectomy were studied. Morphine consumption, pain scores, pressure algometry and adverse effects were recorded for 48 h after surgery. Cumulative morphine consumption was significantly lower in the ketamine/morphine group (47.9 ± 26.2 mg) than in the saline/morphine group (73.4 ± 34.8 mg; $p = 0.049$). Pain scores at rest were significantly lower in the ketamine/morphine group across the 48-h study period ($p = 0.01$). No significant differences were found in pressure algometry measurements or the occurrence of adverse effects.

Keywords Ketamine. Receptors'; N-methyl-D-aspartate. Analgesia'; patient-controlled. Pain: postoperative.

Correspondence to: D. G. Snijdelaar

E-mail: d.snijdelaar@anes.umcn.nl

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There is a large body of evidence indicating that noxious stimulation and frank injury may have profound effects on the central neural processes involved in pain transmission, including the establishment of central sensitisation and the transition of acute, time-limited pain to chronic, pathological pain [1, 2]. It is now well established that the N-methyl-D-aspartate (NMDA) receptor-ion channel complex plays a critical role in the development of central sensitisation [3, 4]. This has led to renewed interest in the pain-relieving properties of clinically

available NMDA receptor antagonists such as ketamine [5] for use in humans undergoing major surgery.

More recently, NMDA receptor activation has also been linked to the development of acute opioid tolerance and opioid-induced hyperalgesia [6, 7]. Furthermore it is now recognised that the process of central sensitisation is induced not only during surgery but also postoperatively by inflammatory injuries [8, 9]. In the clinical setting this suggests that for optimal effect, NMDA receptor antagonists need to be administered before induction of

anaesthesia (before the opioids are given) and continued during surgery and well into the postoperative period. To evaluate this possibility we compared the effects of intra-operative low dose s(+)-ketamine vs. saline given intravenously (started before induction of anaesthesia) followed by intravenous postoperative patient-controlled low dose s(+)-ketamine plus morphine, vs. morphine alone, on postoperative pain and analgesic consumption after radical prostatectomy.

Methods

Approval to carry out the study was obtained from the institutional ethics committee at the University Medical Centre, Nijmegen. Eligible patients were men scheduled for radical retropubic prostatectomy. Inclusion criteria were ability to speak Dutch, 18–75 years of age, ASA class 1–3, stable or no significant central nervous system, respiratory, cardiac, hepatic, renal or endocrine dysfunction and/or any significant sequelae, no history of significant psychopathology, chronic pain or chronic use of opioid or non-opioid analgesics, no previous allergies or adverse reactions to opioid analgesics, no ingestion of antitussive medication (dextromethorphan) within 48 h of surgery, no history of alcohol or drug dependency or abuse, and body weight 60–100 kg with a body mass index $\leq 30 \text{ kg.m}^{-2}$.

All patients were told about the study and screened for suitability and interest during the visit to the Preoperative Assessment Clinic approximately 2–4 weeks before surgery. At that time patients were informed about the nature and purpose of the study and were sent home with a consent form describing the study purpose, procedures and risks. One week later, the patient was telephoned at home to answer any questions and to obtain verbal informed consent. On the day before surgery, after admission to the hospital, patients who had verbally consented were visited on the ward to obtain written, informed consent. Patients were then introduced to the Visual Analogue Scale (VAS), the patient-controlled analgesia (PCA) pump, and pressure algometry. A baseline VAS pain score was taken with the patient in a resting position. On the day before surgery, patients were randomly assigned to one of two groups: ketamine/morphine or saline/morphine. Two syringes were prepared for each patient; one contained either 50 ml s(+)-ketamine 1 mg.ml^{-1} or saline for intra-operative administration and the other 50 ml s(+)-ketamine 1 mg.ml^{-1} plus morphine 2 mg.ml^{-1} or morphine 2 mg.ml^{-1} alone for postoperative use in the PCA pump. Study syringes were prepared and dispensed by the Pharmacy of the University Medical Centre Nijmegen on the basis of a predetermined randomisation schedule

(using the random function of Microsoft EXCEL 97). The syringes were coded and prepared in a blinded fashion for each patient and retained by the pharmacy department.

Premedication consisted of oral midazolam 7.5 mg (administered 45–60 min before the expected time of induction of general anaesthesia). An additional 2 mg midazolam was given intravenously after insertion of a venous line. Five minutes before induction with propofol (2 mg.kg^{-1}) and fentanyl ($2 \mu\text{g.kg}^{-1}$), patients received a bolus injection of 0.1 ml.kg^{-1} s(+)-ketamine (ketamine/morphine group) or saline (saline/morphine group), followed by a continuous infusion of $0.002 \text{ ml.kg}^{-1}.\text{min}^{-1}$ of the same agent. For patients in the ketamine/morphine group, this amounted to a bolus dose of $100 \mu\text{g.kg}^{-1}$ s(+)-ketamine and a continuous infusion of $2 \mu\text{g.kg}^{-1}.\text{min}^{-1}$ s(+)-ketamine. After induction, 0.6 mg.kg^{-1} rocuronium was given to facilitate tracheal intubation. Anaesthesia was maintained with isoflurane in $\text{N}_2\text{O/O}_2$ (60%/40%) aiming at an end expiratory concentration of isoflurane of 0.7%. Further rocuronium $0.1\text{--}0.2 \text{ mg.kg}^{-1}$ was given when necessary. Morphine in a dose of $50 \mu\text{g.kg}^{-1}$ was given when there were signs of inadequate analgesia (increase in blood pressure or heart rate above 10% of baseline value). The continuous infusion of s(+)-ketamine (ketamine/morphine group) or saline (saline/morphine group) was stopped at skin closure. At the conclusion of surgery, neuromuscular blockade was reversed (when necessary) with neostigmine (0.05 mg.kg^{-1}) and atropine ($0.01\text{--}0.02 \text{ mg.kg}^{-1}$).

Immediately on arrival in the Post Anaesthesia Care Unit the PCA pump (SIMS Graseby 3300 PCA Pump, Watford, Herts, UK), loaded with the coded syringes, was attached to the patient's intravenous cannula. The PCA system was programmed to deliver a bolus of 0.5 ml, corresponding to a bolus dose of $0.5 \text{ mg s(+)-ketamine}$ plus 1 mg of morphine for the ketamine/morphine group and 1 mg morphine for the saline/morphine group. The lock-out time was set at 5 min. No background infusion was delivered. If the patient complained of pain in the Post Anaesthesia Care Unit but was too drowsy to use the PCA pump, the attending nurse was permitted to push the PCA pump button. PCA was continued until the end of the study, 48 h after surgery. No other analgesics were administered during the study period. When required, bladder spasm pain was treated with 5 mg oxybutynin three times daily. After transfer to the ward, pain management was supervised by the researchers and the Acute Pain Service. If a patient required intravenous analgesia beyond the 48-h study period, the study syringes were removed and the patient was treated according to the hospital's Acute Pain Service protocol for managing pain. Nausea and vomiting were treated with ondansetron 4 mg given intravenously.

Pain was assessed with patients at rest (VAS-R) at 1, 2, 3, 4, 8, 12, 18, 24, 30, 36, 42 and 48 h after surgery. The VAS pain scale consists of a 10-cm horizontal line with the two endpoints labelled 'no pain' and 'worst possible pain'. Pain was also assessed after standard mobilisation (VAS-M) at 24 and 48 h by asking patients to perform two maximal inspirations before rating their pain. Sensitivity to mechanical pressure around the surgical wound was assessed using a Pressure Threshold Meter (Pain Diagnostics and Thermography Inc., Great Neck, NY), a force gauge with a rubber tip (1 cm² in diameter) and a 10-kg range in 0.1-kg divisions. The pain perception threshold was determined by applying pressure and recording in kg.cm⁻² the level at which the patient first reported pain. The patient then rated, on a 10-cm VAS, the intensity of the pain at this threshold. After surgery, pain perception thresholds were obtained 5 cm from the left and right edges of the surgical wound (halfway between umbilicus and pubic symphysis) at 24 and 48 h after surgery.

Subjective reports of dreams (0 = none, 1 = pleasant, 2 = unpleasant, 3 = nightmare), hallucinations (0 = no, 1 = yes) and other adverse effects were documented for all patients at 24 and 48 h after surgery. The latter effects included drowsiness, dizziness, confusion and feelings of unreality (0 = none, 1 = mild, 2 = moderate, 3 = severe). Postoperative sedation was assessed at 1, 2, 3, 4, 8, 12, 18, 24, 30, 36, 42 and 48 h after surgery using a 5-point modified sedation scale (0 = alert and orientated, 1 = awake but drowsy, 2 = sleeping but arousable by verbal commands, 3 = sleeping but arousable by tactile stimuli, and 4 = comatose) [10]. Postoperative nausea and vomiting were assessed at 1, 2, 3, 4, 8, 12, 18, 24, 30, 36, 42 and 48 h after surgery. Nausea was measured using a 10-cm horizontal VAS with endpoints labelled 'no nausea' and 'extreme nausea'. Vomiting was assessed as present or absent. Postoperative pruritus was assessed at 1, 2, 3, 4, 8, 12, 18, 24, 30, 36, 42 and 48 h after surgery using a 10-cm horizontal VAS with endpoints labelled 'no itching' and 'extreme itching'.

Before the start of the study we estimated that a total sample size of 22 patients would be required (11 per group). This was based on a type-I error rate of 0.05 and power of 0.90, using 48-h mean cumulative morphine consumption used by patients in the study by Adriaenssens *et al.* [11], with ability to detect a mean difference of ~27 mg (27 mg vs. 54 mg) with a standard deviation of 20 mg. Based on an anticipated attrition rate of 20–25% due to prerandomisation drop-outs, complications, adverse effects, protocol violations, and withdrawals, a total of 28 patients were recruited. Data were analysed using the Statistical Package for the Social Sciences (SPSS for WINDOWS, release 10.0, Chicago, IL). Clinical

variables and cumulative morphine consumption were compared using independent *t*-tests for continuous data and Fisher's exact test for categorical data. The primary outcome measure, cumulative morphine consumption at 48 h after surgery, was compared by independent samples *t*-test. The VAS-R pain scores at set intervals (see above) and PCA morphine consumption between these intervals were each analysed by two-way repeated measures ANOVA using group as the independent samples factor and time as the repeated measures factor. Area under the curve was also computed for the two groups for morphine consumption and VAS-R pain scores and compared between the groups by independent samples *t*-test [12]. Visual analogue pain scores on movement (VAS-M), pressure pain threshold and magnitude of side-effects were analysed by Mann-Whitney *U*-test, and incidence of adverse effects by Chi-squared test. Statistical significance was set at *p* < 0.05. No intent-to-treat analysis was planned; only a per protocol analysis was performed.

Results

Of the 28 patients enrolled in the study, three were excluded: one in the ketamine/morphine group because of protocol violation on the first postoperative day (he was given a sedative by the attending urologist) and two in the saline/morphine group (one because of surgery lasting > 6 h with the need for postoperative ventilation, and another because of development of a large wound haematoma on the first postoperative day). Baseline characteristics and clinical variables are shown in Table 1. Although mean end-expiratory isoflurane concentration

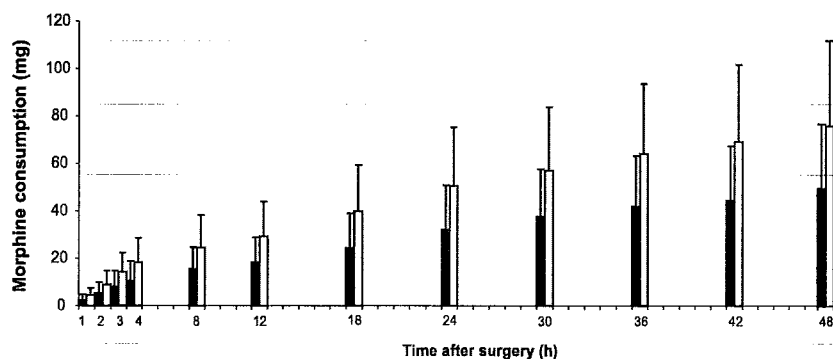
Table 1 Baseline and pre- and intra-operative data in patients receiving ketamine/morphine or saline/morphine. Values are as mean (SD).

	Ketamine/ morphine (<i>n</i> = 13)	Saline/ morphine (<i>n</i> = 12)
Age; years	60.1 (4.7)	61.7 (4.7)
Weight; kg	83.1 (13.6)	79.9 (12.2)
Height; cm	179 (5.8)	180 (8.3)
Preoperative VAS* for pain; cm	0.0 (0.0)	0.0 (0.0)
Total intra-operative morphine; mg	8.5 (6.3)	10.0 (6.1)
Mean end-expiratory isoflurane concentration; %	0.65 (0.07)†	0.71 (0.04)†
Blood loss; ml	1472 (752)	1518 (856)
Duration of surgery; min	148 (23)	158 (25)

*VAS; visual analogue scale.

†*p* = 0.009.

Figure 1 Cumulative PCA-morphine consumption in patients receiving ketamine/morphine (solid) or saline/morphine (clear). Values are mean (SD). Overall consumption was less in the ketamine/morphine group than in the saline/morphine group ($p = 0.049$).



differed significantly between the groups this was not considered clinically significant.

Mean (SD) total cumulative morphine consumption was significantly lower ($p = 0.049$) in the ketamine/morphine group ($47.9 \text{ mg} \pm 26.2 \text{ mg}$) compared with the saline/morphine group ($73.4 \text{ mg} \pm 34.8 \text{ mg}$) at the end of the study, 48 h after surgery; cumulative consumption over time is shown in Fig. 1. Results of the ANOVA indicated that over the 48-h study period patients in the ketamine/morphine group consistently self-administered significantly less morphine ($p = 0.049$) than those in the saline/morphine group and consistent with this, the area under the curve for morphine in the ketamine/morphine group was also less ($p = 0.037$). Pain scores at rest analysed by ANOVA and by comparison of area under the curve also revealed significant differences between the groups (Table 2). Significant differences were not found for VAS-M pain scores (Table 2), nor for the number of patients needing oxybutynin for bladder spasm pain or pressure pain thresholds at 24 or 48 h after surgery (Table 3).

No significant differences were found in the incidence or extent of morphine or s(+)-ketamine-related side-effects. No hallucinations were reported at any time point. One patient in each group reported 'pleasant' dreams at 24 h, but no dreams were reported at 48 h. All other side-effects are presented in Table 4.

Discussion

The results of this study show that low-dose s(+)-ketamine given during and after radical prostatectomy reduces PCA morphine consumption by 34% at 48 h after surgery and lower pain scores at rest compared with a standard treatment control group that did not receive s(+)-ketamine.

Ketamine belongs to the group of non-competitive NMDA receptor antagonists that bind to the phenylcyclo-lidine recognition site in the NMDA receptor-operated ion channel [13]. Although there is evidence for the

Table 2 Postoperative pain scores at rest (VAS-R) and after standard mobilisation (VAS-M) in patients receiving ketamine/morphine or saline/morphine. Data are mean (SD [range]).

	Ketamine/ morphine (n = 13)	Saline/ morphine (n = 12)	p-value
VAS-R; cm			
1 h	3.3 (1.6 [0.9–6.1])	4.9 (1.5 [2.7–8.4])	0.01*
2 h	2.4 (1.8 [0–5.8])	4.2 (1.8 [0.8–6.9])	
3 h	1.7 (1.2 [0–3.8])	3.3 (1.4 [1.3–6.1])	
4 h	1.4 (1.2 [0–2.9])	2.9 (1.6 [0.8–5.5])	
8 h	1.8 (1.4 [0–4.9])	2.2 (1.3 [0–4.0])	
12 h	1.2 (1.2 [0–4.0])	2.1 (1.5 [0–5.0])	
18 h	1.5 (1.4 [0–4.8])	2.8 (1.2 [1.3–4.8])	
24 h	1.2 (1.0 [0–3.1])	2.0 (1.4 [0–5.4])	
30 h	1.6 (2.2 [0–8.6])	1.8 (2.0 [0–6.8])	
36 h	0.6 (0.8 [0–2.0])	1.5 (1.4 [0–5.0])	0.049
42 h	1.1 (1.9 [0–5.0])	1.4 (1.3 [0–4.0])	
48 h	0.8 (0.8 [0–2.5])	0.9 (0.8 [0–2.1])	
Area under the curve†	61.2 (29.2 [7.9–109])	92.4 (44.9 [42.2–204.8])	
VAS-M; cm			
24 h	2.7 (2.5 [0.0–7.3])	2.8 (2.6 [0.0–9.0])	NS
48 h	1.1 (1.2 [0–3.7])	0.5 (0.4 [0–1.1])	NS

*For ANOVA across whole 48-h study period.

†Area under the curve for VAS-R 1–48 h.

interaction of ketamine with opioid receptors, monoam-nergic receptors, nicotinic and muscarinic cholinergic receptors, Ca^{2+} channels, GABA receptors and Na^+ channels [14, 15], ketamine has the highest affinity for the NMDA receptor. Ketamine is a racemic mixture of two enantiomers, s(+) and r(–) ketamine. S(+)-ketamine shows an affinity for the NMDA receptor that is four times higher than that of r(–)-ketamine [16]. In a study of healthy volunteers, ketamine isomers induced less fatigue and cognitive impairment than equianalgesic low-dose racemic ketamine. In addition, s(+)-ketamine produced less of a decline in concentration capacity and primary memory [17]. Because of its higher potency (about twice that of racemic ketamine) and more favourable

Table 3 Need for oxybutynin for bladder spasm pain, and pressure pain thresholds (PPT) at 24 and 48 h after surgery, in patients receiving ketamine/morphine or saline/morphine. Values are number (proportion) or mean (SD [range]). No significant differences between groups.

	Ketamine/morphine (n = 13)	Saline/morphine (n = 12)
Oxybutynin required		
24 h	1 (8%)	0
48 h	1 (8%)	1 (8%)
PPT; kg.cm ⁻²		
24 h	1.7 (1.2 [0-6.0])	1.2 (0.6 [0.1-2.2])
48 h	1.9 (0.7 [0.5-3.2])	2.0 (0.9 [0.2-4.7])
VAS* at PPT; cm		
24 h	4.9 (1.8 [2.2-7.7])	3.9 (2.3 [0.4-8.0])
48 h	4.6 (2.4 [0.3-8.6])	4.2 (2.6 [0.1-8.9])

*VAS; visual analogue scale.

Table 4 Adverse effects in patients receiving ketamine/morphine or saline/morphine. Values are number or mean (SD [range]). No significant differences between groups.

	Ketamine/morphine (n = 13)	Saline/morphine (n = 12)
Drowsiness*		
24 h	1/4/7/1	1/4/6/1
48 h	4/5/3/1	5/6/1/0
Dizziness*		
24 h	10/2/1/0	12/0/0/0
48 h	8/4/1/0	9/3/0/0
Confusion*		
24 h	11/1/1/0	10/1/1/0
48 h	13/0/0/0	11/1/0/0
Feelings of unreality*		
24 h	12/1/0/0	10/2/0/0
48 h	11/2/0/0	12/0/0/0
Sedation†		
24 h	13/0/0/0/0	11/1/0/0/0
48 h	12/0/1/0/0	12/0/0/0/0
Nausea VAS; cm		
24 h	1.1 (2.1 [0-6.9])	0.4 (0.6 [0-2.0])
48 h	0.1 (0.4 [0-1.4])	0.4 (1.0 [0-3.6])
Vomiting; Y/N		
24 h	0/13	1/11
48 h	0/13	1/11
Pruritus VAS; cm		
24 h	0 (0 [0-0.1])	0 (0 [0-0.1])
48 h	0.1 (0.3 [0-1.2])	0.1 (0.3 [0-1.0])

*None/mild/moderate/severe

†Alert and orientated/awake but drowsy/sleeping but rousable by verbal commands/sleeping but rousable by tactile stimuli/comatose.

adverse-effects profile, s(+)-ketamine is an attractive alternative to the racemate for peri-operative use in humans.

For low-dose ketamine to be an effective (co)analgesic and morphine-sparing agent in the surgical patient, two recently evolved concepts are of major importance. First,

it has been shown that opioids activate not only antinociceptive systems but also pronociceptive systems, causing acute opioid tolerance and opioid-induced hyperalgesia [6, 7]. These phenomena seem to stem from a common NMDA receptor-dependent mechanism; use of μ -opioid receptor agonists causes a sustained increase in NMDA-activated currents by activating intracellular protein kinase C. In turn, protein kinase C potentiates the NMDA response by reducing the voltage-dependent Mg^{2+} block of NMDA-receptor channels [18]. In rats, pretreatment with ketamine (before opioid administration) and subsequent repeated ketamine injections prevented opioid-induced hyperalgesia and acute tolerance to opioids [19]. Second, it is now recognised that central sensitisation is not only induced during surgery by incisional injury but also postoperatively by inflammatory injuries [8, 9]. This means that efforts to prevent the development of central sensitisation must be continued well into the postoperative period and should not be limited to the duration of the surgical procedure. The practical consequences of both of these concepts are that ketamine should be administered before induction of anaesthesia (especially before the opioids are given) and continued during surgery and into the postoperative period. As suggested by the results of the present study, this leads to lower postoperative morphine consumption and also to lower postoperative pain scores. Further study is required to ascertain the practical importance, in the clinical setting, of the need to give ketamine before the opioids, by comparing the administration of ketamine before and after the opioids.

We did not find significant differences in the sensitivity to mechanical pressure applied around the surgical wound. Tverskoy *et al.* [20] used pressure algometry on the wound to show that the use of a rather high dose of racemic ketamine (bolus dose of 2 mg.kg⁻¹ during induction followed by a continuous infusion of 20 μ g.kg⁻¹.min⁻¹ until the end of surgery) decreased wound sensitivity in patients after abdominal hysterectomy. Kopert *et al.* [21] used von Frey filaments to show that a mean dose of 0.4 mg.kg⁻¹ of s(+)-ketamine (administered over 20 min) was capable of inhibiting the development of secondary hyperalgesia in experimentally electrically induced pain. The use of higher doses of s(+)-ketamine might have yielded more significant differences in sensitivity to mechanical pressure around the surgical wound in the present study.

To date only one other published study has described the use of intravenously given low-dose s(+)-ketamine in the surgical patient. In contrast to the results of the present study, Jaksch *et al.* [22] did not find evidence for improved postoperative analgesia when s(+)-ketamine was used in patients undergoing arthroscopic anterior

cruciate ligament repair. There are three obvious differences between our study and that of Jaksch *et al.*: starting the s(+)-ketamine after opioids were given; discontinuation of s(+)-ketamine 2 h after surgery; and the type of surgery. As discussed, the first differences can possibly lead to a reduced effectiveness of low-dose s(+)-ketamine. Most importantly, the study by Jaksch *et al.* examined the effect of peri-operative s(+)-ketamine on later postoperative pain since they stopped the ketamine infusion 2 h after surgery but continued to look for effects over the following 5 days. In contrast, we examined the effect on postoperative use of morphine and postoperative pain of starting a low dose of s(+)-ketamine before induction with continuation during surgery and for 48 h thereafter. Another difference between studies concerns the patient populations and surgical procedures. Compared with the major surgery (radical prostatectomy) in the present study, the arthroscopic knee surgery used in the study of Jaksch *et al.* is a relatively minor type of surgery. It is clear that arthroscopic surgery causes less tissue trauma, which may lead to a lower postoperative pain intensity. Finally, patients in the study by Jaksch *et al.* were substantially younger (30 (8) years and 33 (7) years) than the patients in the present study (60 (4.7) years and 61.2 (4.7) years). This raises the possibility that the opioid-sparing effects of s(+)-ketamine may be age related; however, further research is required to evaluate this possibility.

There are several limitations to the present study. The first concerns the relatively small number of patients studied. This might explain why, despite the 34% reduction in 48-h morphine consumption in the ketamine/morphine group, no differences in morphine related side-effects were found. Second, patients in this study were only followed up to 48 h after surgery. The study cannot address the question of whether peri-operative s(+)-ketamine influences pain and analgesic consumption in the longer term. Third, although we did not find differences in psychomimetic side-effects, a larger study is needed to assess this properly. A larger study is also needed to assess whether the favourable postoperative effects of s(+)-ketamine make a difference in clinical outcomes such as time to ambulation, resumption of dietary intake and discharge from hospital.

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