The Benefits of Intraoperative Small-Dose Ketamine on Postoperative Pain After Anterior Cruciate Ligament Repair

Christophe Menigaux, MD, Dominique Fletcher, MD, Xavier Dupont, MD, Bruno Guignard, MD, Frederic Guirimand, MD, and Marcel Chauvin, MD

Department of Anesthesiology, Hôpital Ambroise Pare, Boulogne-Billancourt, France

In a randomized, double-blinded study with three parallel groups, we assessed the analgesic effect of intraoperative ketamine administration in 45 ASA physical status I or II patients undergoing elective arthroscopic anterior ligament repair under general anesthesia. The patients received either IV ketamine 0.15 mg/kg after the induction of anesthesia and before surgical incision and normal saline at the end of surgery (PRE group); normal saline after the induction of anesthesia and before surgical incision and IV ketamine at the end of surgery (POST group); or normal saline at the beginning and the end of surgery (CONT group). Anesthesia was performed with propofol (2 mg/kg for induction, 60–200 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for maintenance), sufentanil (0.2 μg/kg 10 min after surgical incision, followed by an infusion of 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ stopped 30 min before skin closure), vecuronium (0.1 mg/kg), and 60% N_2O in O_2 via a laryngeal mask airway. Postoperative analgesia was initially provided with IV morphine in the postanesthesia care unit, then with IV patient-controlled analgesia started before discharge from the postanesthesia care unit. Pain scores, morphine consumption, side effects, and degree of knee flexion were recorded over 48 h and during the first and second physiotherapy periods, performed on Days 1 and 2. Patients in the ketamine groups required significantly less morphine than those in the CONT group over 48 h postoperatively (CONT group 67.7 ± 38.3 mg versus PRE group 34.3 ± 23.2 mg and POST group 29.5 ± 21.5 mg; $P <$ 0.01). Better first knee flexion (CONT group 35 ± 10° versus PRE group 46 ± 12° and POST group 47 ± 13°; $P < 0.05$) and lower morphine consumption (CONT group 3.8 ± 1.7 mg versus PRE group 1.2 ± 0.4 mg and POST group 1.4 ± 0.4 mg; $P < 0.05$) were noted at first knee mobilization. No differences were seen between the PRE and POST groups, except for an increase in morphine demand in the PRE versus the POST group ($P < 0.05$) in the second hour postoperatively. **Implications:** We found that intraoperative small-dose ketamine reduced postoperative morphine requirements and improved mobilization 24 h after arthroscopic anterior ligament repair. No differences were observed in the timing of administration. Intraoperative small-dose ketamine may therefore be a useful adjuvant to perioperative analgesic management.

(Anesth Analg 2000;90:129–35)

The *N*-methyl-D-aspartate (NMDA) receptors are activated by C-fiber inputs triggered by surgical tissue trauma via nociceptive transmitter release in the dorsal horn of the spinal cord (1). The activation of these receptors enhances central nervous system sensitization and, therefore, the intensity of perceived postoperative pain (1). It has been proposed that analgesic drugs might more adequately prevent this central sensitization when administered before the tissue trauma. This is the theory behind the concept of preemptive analgesia. The clinical evidence for this concept has been debated (1). Initially, the importance of timing the analgesic administration and the need to compare the same treatment before and after the surgical injury were emphasized (2). Later, many studies were performed with this correct methodology and failed to find any preemptive effect for most analgesics. According to its mechanism of action, explained mainly by a NMDA channel blockade (3), ketamine may be more appropriate for this indication. However, available clinical studies (4–6) did not precisely investigate, according to McQuay's (2) methodology, the importance of timing IV ketamine administration on the quality of postoperative analgesia.

The purpose of our study was to assess the preemptive analgesic effect of IV ketamine. We also compared intraoperative ketamine with a placebo to determine whether the addition of a small dose of ketamine to general anesthesia could provide analgesic benefits after anterior cruciate ligament repair (ACLR).

Accepted for publication August 27, 1999.

Address correspondence and reprint requests to Marcel Chauvin, MD, Department of Anesthesiology, Hôpital Ambroise Pare, 9 Ave. Charles de Gaulle, Boulogne-Billancourt, 92100 France. Address e-mail to marcel.chauvin@apr.ap-hop-paris.fr.

0003-2999/00

Methods

After informed consent and with institutional approval, 45 inpatients, ASA physical status I or II, aged 18–65 yr, and scheduled to undergo elective arthroscopic ACLR under general anesthesia, were enrolled in the study. Exclusion criteria included ASA physical status >II, any type of surgery other than ACLR, surgery performed under regional anesthesia, history of chronic pain, regular medication with analgesics, drug or alcohol abuse, psychiatric disorder, and contraindications to the self-administration of opioids (i.e., unable to understand the patient-controlled analgesia [PCA] device). On the evening before surgery, patients were instructed about the use of a 10-cm visual analog scale (VAS) (0 = no pain to 10 = worst possible pain), a 5-point verbal rating scale (VRS) (0 = no pain; 1 = light pain; 2 = moderate pain; 3 = intense pain; 4 = severe pain), and the PCA system (Graseby 3300 PCAS, Watford, UK). Patients were randomly allocated in a double-blinded fashion to three groups—a control group (CONT), a preoperative ketamine group (PRE), and a postoperative ketamine group (POST)—by using a random number table.

Patients were premedicated with hydroxyzine 100 mg orally, 1–2 h before surgery. Anesthesia was induced with propofol at an initial target concentration of 5 μg/mL (e.g., 2 mg/kg) and vecuronium 0.1 mg/kg to facilitate placement of a laryngeal mask airway. Anesthesia was maintained with a continuous administration of propofol (target concentration 2–6 μg/mL; e.g., 60–200 $\mu g \cdot kg^{-1} \cdot min^{-1}$) and 60% N_2O in O_2 during controlled ventilation. The objective was to maintain arterial pressure and heart rate within 30% of the preoperative value. A bolus of 0.2 μg/kg sufentanil was administered 10 min after surgical incision, followed by a continuous infusion of 0.25 $\mu g \cdot kg^{-1} \cdot h^{-1}$ that was stopped 30 min before skin closure.

Before starting the study, a nurse not involved in the evaluation of the patient prepared two identical syringes of 10 mL containing either isotonic sodium chloride solution or ketamine 0.15 mg/kg diluted in isotonic sodium chloride solution. These syringes were labeled for preincisional and postincisional injections. All patients and personnel involved in patient management and data collection were unaware of the group to which the patient had been assigned. In case of emergency, the anesthesiologist in charge of the patient had ready access to the information about the drugs administered. In the PRE group, the patients received IV ketamine 10 min after the induction of anesthesia but before tourniquet inflation and 10 mL of isotonic sodium chloride solution at the end of surgery after skin closure. In the POST group, the patients received 10 mL of isotonic sodium chloride solution 10 min after the induction of anesthesia but before tourniquet inflation and IV ketamine at the end of surgery. In the CONT group, both injections were of isotonic sodium chloride solution.

After emerging from anesthesia, patients were transferred to the postanesthesia care unit (PACU), where they stayed for at least 3 h, then were discharged to the ward. The time until the first request for analgesic medication by the patient was recorded. In the PACU, the pain was controlled by a titration of IV morphine administered by a nurse. This titration consisted of repeated boluses of 3 mg of morphine every 5 min until the VRS was <2. The titration was stopped in case of a sedation score >3 or a respiratory rate <12 breaths/min. Subsequently, the patients were given access to a PCA device. The PCA device was set to deliver morphine 1 mg as an IV bolus with an interval of 5 min and no background infusion or limits. This regimen of PCA was continued for 48 h on the surgical ward. Acetaminophen, , 1 g every 6 h, was added during the second postoperative day. During physical therapy sessions 24 and 48 h after surgery, patients used IV morphine PCA to provide analgesia.

The pain intensity was assessed by the patients using a VAS and a VRS. Pain was recorded hourly in the PACU for 3 h, then every 4 h in the surgical ward for 48 h by nurses. The physical therapist mobilized the operated knee 24 and 48 h after surgery at levels of motion tolerated by the patient up to 90° maximal knee flexion. First mobilizations were passive, and each session lasted 20 min. At the end of each session, patients performed active knee flexion. Pain intensity (VRS), anxiety (scale 0–3: 0 = no anxiety; 1 = light anxiety; 2 = moderate anxiety; 3 = intense anxiety), degree of first knee flexion, maximal degree of knee flexion tolerated by each patient, and morphine PCA consumption during these mobilizations were recorded by the physical therapist.

Side effects (nausea, vomiting, pruritus, dysphoria [including hallucinations and dreams], and diplopia), if present, were noted. Difficulty urinating or urinary retention was recorded every 3 h. Sedation was monitored using the following 4-point rating scale: 0 = patient fully awake; 1 = patient somnolent and responsive to verbal commands; 2 = patient somnolent and responsive to tactile stimulation; 3 = patient asleep and responsive to painful stimulation. In the PACU, respiratory depression was defined as persistent sedation, respiratory rate <10 breaths/min, and hypoxemia with capillary oxygen saturation <90%; in the surgical ward, it was defined as a sedation score >1 and a respiratory rate <10 breaths/min.

Before the study, the sample size was determined. According to a previous study (7) and our experience, we anticipated the mean PCA morphine use over 48 h to be 80 mg. The estimated sample size was 15 patients per group to detect a difference of at least 30% in morphine consumption with mean (± SD) difference between groups of 1, a power of 80%, and $\alpha = 0.05$. All

Table 1. Patient Characteristics and Intraoperative Data

	PRE	POST	CONT
Age (yr)	26 ± 6	26 ± 6	28 ± 7
Weight (kg)	72 ± 17	74 ± 10	71 ± 11
Gender (M/F)	10/5	9/6	11/4
Length of surgery (min)	125 ± 44	113 ± 36	121 ± 33
Total amount of propofol administered (mg/kg)	12.0 ± 2.8	11.5 ± 3.1	12.6 ± 2.9
Total amount of sufentanil administered (μg/kg)	0.6 ± 0.1	0.5 ± 0.1	0.6 ± 0.1

statistical analyses were performed using SPSS 6.1 for Windows statistical package. Age, weight, length of surgery, total amount of intraoperative propofol and sufentanil, time from laryngeal mask removal to first analgesic request, and cumulative and hourly doses of morphine over 48 h and during physical therapy were compared using one-tailed Student's *t*-tests. The VAS scores at rest and on movement during knee manipulations were analyzed by using two-way repeated-measures analysis of variance and *post hoc* comparisons at various points in time using Bonferroni's type I error rate correction for multiple tests of significance (i.e., α per number of tests). Anxiety and VRS scores at knee mobilization sessions were analyzed by using the Mann-Whitney *U*-test. The χ^2 test was used to compare frequency of side effects and sex distribution. $P <$ 0.05 was considered statistically significant. Data are expressed as mean ± SD.

Results

Forty-five patients, 15 per group, were enrolled in the study. There was no exclusion. The three groups were comparable with respect to demographic data, duration of surgery, and intraoperative doses of propofol and sufentanil (Table 1). All patients underwent ACLR performed by the same surgeon.

The VAS pain scores at rest were not significantly different among the groups (Fig. 1). The time from laryngeal mask airway removal and the first request for analgesics in the PACU was longer in both ketamine-treated groups compared with the control group (27 ± 23, 29 ± 22, and 10 ± 7 min for the PRE, POST, and CONT groups, respectively; $P < 0.05$) (Table 2).

Cumulative morphine consumption at 24 and 48 h was greater in the CONT group than in the PRE and POST groups ($P < 0.01$); there were no differences between the PRE and POST groups (Table 2). Incremental morphine consumption by patients on Postoperative Days 1 and 2 was less in the POST group than in the CONT group for all studied periods (Fig. 2), with a significant difference in the first 3 h and at 19–24 h ($P < 0.01$). Morphine consumption was less in the first hour ($P < 0.05$) and similar in the second hour in the PRE group compared with the CONT group.

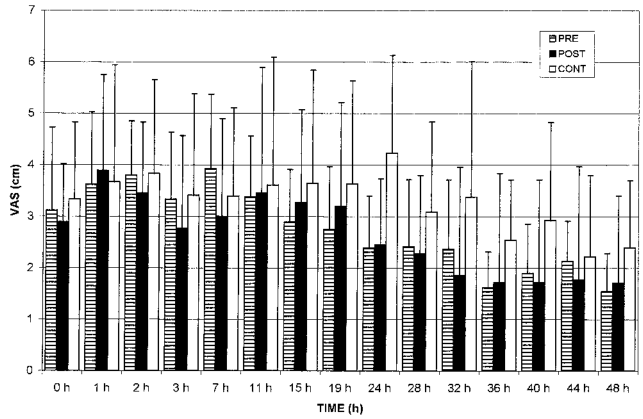

Figure 1. Visual analog scale (VAS) pain scores (0–10 cm) in the three groups during 48 h postoperatively. Values are mean ± SD.

The PRE group then followed the same time course in morphine use as the POST group, with a significant decrease at 19–24 h ($P < 0.05$).

The degree of first and maximal knee flexion, pain perception, anxiety, and morphine consumption during the physiotherapy sessions at 24 and 48 h are presented in Table 3. Compared with the CONT group, significantly better first knee flexion and lower morphine consumption were noted in the two ketamine groups during the first session at 24 h. Anxiety, pain scores, and the degree of maximal knee flexion were comparable in the three groups during this session. During the second physical therapy session, no intergroup differences were observed. Knee flexion was better and VRS scores were lower at 48 h than at 24 h.

Three cases of urinary retention were observed (one in each group). Nausea and vomiting requiring treatment occurred with no significant differences among groups (two, one, and three patients in the PRE, POST, and CONT groups, respectively). No patient in any group reported sedation, dysphoria, hallucinations, pruritus, or diplopia. No case of respiratory depression occurred during the study.

Discussion

Our results demonstrate that a single small dose of ketamine administered intraoperatively delays the

Table 2. Cumulative Morphine Consumption and Time from Laryngeal Mask Airway Removal and First Morphine Request

	PRE	POST	CONT
Morphine consumption (mg)			
24 h	28.2 ± 18.4*	24.2 ± 17.8*	49.7 ± 24.1
48 h	34.3 ± 23.2*	29.5 ± 21.5*	67.7 ± 38.3
First morphine demand (min)	27 ± 23†	30 ± 22†	10 ± 7

* $P < 0.01$ PRE and POST groups versus the CONT group.
† $P < 0.05$ PRE and POST groups versus the CONT group.

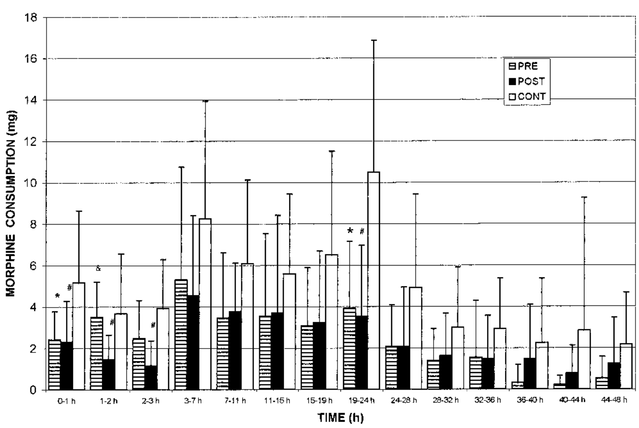

Figure 2. Incremental postoperative morphine consumption in the three groups during 48 h postoperatively. Values are mean ± SD. *$P < 0.05$ PRE versus CONT. #$P < 0.01$ POST versus CONT. &$P <$ PRE versus POST.

first request for analgesic, produces a significant 50% morphine-sparing effect during the first 48 hours after knee surgery performed under arthroscopy, and facilitates knee mobilization at 24 hours. However, this delayed beneficial effect was not related to the timing of intraoperative ketamine administration.

We chose ACLR as a clinical model in which to investigate the analgesic effect of intraoperative ketamine because, despite arthroscopic technique, this surgery is painful postoperatively, especially on movement (7–9), and may require opioids to provide adequate postoperative analgesia (7,8). We chose a small dose of ketamine (0.15 mg/kg) that had been proven effective after subcostal incision for open cholecystectomy (4). The small dose had the clear advantage of avoiding side effects. We used balanced anesthesia, combining an opioid and propofol, during surgery. To limit possible confusion related to the preemptive analgesic effect of the opioid, we delayed the first administration of intraoperative sufentanil, although the preemptive analgesic effect of an intraoperative opioid is controversial (1,2).

We observed that the analgesic effect of ketamine is not dependent on the timing of administration. By contrast, immediate morphine consumption was lower when ketamine was injected at the end of surgery. This result is likely related to a pharmacological action of the drug. Our study is the first that precisely compared the effect of the same dose of peroperative IV ketamine administered either before or after surgery. Fu et al. (6) compared preemptive administration of systemic ketamine with post-wound closure administration of ketamine in patients undergoing abdominal procedures and concluded that there was a preemptive analgesic effect. However, in that study, patients in the preemptive group received more ketamine, because they received 0.5 mg/kg at the time of anesthetic induction, followed by an infusion of 10 $\mu g \cdot kg^{-1} \cdot min^{-1}$ during surgery, compared with only a 0.5-mg/kg bolus dose in patients in the post-wound closure group, which suggests that the benefit of preadministration could be due only to the difference in dosage. Moreover, because of additional differences in the administration of ketamine in the preemptive group compared with the post-wound group, the study by Fu et al. (6) cannot precisely evaluate the role of timing of administration. In addition, the fact that these authors did not use any opioid during surgery may have sensitized their study. Roytblat et al. (4) and Tverskoy et al. (5) have demonstrated the benefit of an intraoperative ketamine administration in reducing postoperative pain or wound hyperalgesia and postoperative morphine requirements, but they did not investigate the influence of presurgical versus postsurgical ketamine administration. Results concerning the preemptive analgesic effect of epidural ketamine are conflicting. They were positive in one study combining morphine and ketamine (10) and negative in another using ketamine alone (11). In volunteers, ketamine reduced capsaicin-evoked pain, allodynia, and hyperalgesia by approximately the same degree whether given before or after the capsaicin (12). Finally, in an animal study (13), an NMDA antagonist was effective in reducing central sensitization when administered either before or after the nociceptive inputs. According to these data, it is conceivable that the timing of administration for the expression of NMDA receptor antagonist-induced analgesia is not decisive. These findings support the belief that prolonged postoperative pain stimuli resulting from the inflammatory reaction to damaged tissue are more determinant than short-lasting intraoperative stimuli in producing hypersensitivity in the spinal cord (1). This is likely the main explanation of the insufficient

Table 3. Knee Flexion, Pain Scores, Anxiety, and Morphine Consumption During Physiotherapy

	Day 1			Day 2		
	PRE	POST	CONT	PRE	POST	CONT
First flexion (°)	46 ± 12*†	45 ± 14*†	37 ± 11†	65 ± 12	60 ± 15	63 ± 18
Maximal flexion (°)	66 ± 7†	67 ± 15†	62 ± 11†	83 ± 7	83 ± 10	81 ± 11
VRS	2.4 ± 0.6†	2.3 ± 0.4†	2.9 ± 0.4†	1.8 ± 0.7	1.9 ± 0.9	1.8 ± 0.5
Anxiety	2.4 ± 0.8	1.6 ± 0.7	2.5 ± 1.0	1.6 ± 0.7	1.6 ± 0.7	2.3 ± 1.4
Morphine use (mg)	1.2 ± 0.4*†	1.4 ± 0.7*†	3.8 ± 1.7†	0.4 ± 0.5	0.4 ± 0.5	0.6 ± 0.7

Values are mean ± SD.
VRS = Verbal rating scale.
* $P < 0.05$ PRE and POST groups versus the CONT group.
† $P < 0.05$ Day 1 versus Day 2 in each group.

preemptive analgesic effect of a single dose of an analgesic administered before surgery.

Compared with a placebo, the intraoperative administration of a small dose of ketamine offered significant analgesia during the 48 hours of follow-up. Although the pain scores at rest were not modified, the 50% morphine-sparing effect observed at 48 hours reflected the analgesic effect of ketamine. This level of morphine sparing is comparable to that observed in other studies using small ketamine doses either peroperatively (4–6) or postoperatively (14,15). Ilkjaer et al. (16) failed to demonstrate the analgesic effect of a ketamine infusion after renal surgery, but IV ketamine was combined with epidural bupivacaine on Day 1 and with epidural morphine on Day 2—analgesic regimens that were already very effective alone. We did not observe any change in the incidence of morphine-related side effects, but this is probably due to the small number of patients in each group. However, this reduction in morphine consumption is certainly clinically relevant.

No benefit of ketamine administration on pain scores at rest was observed, probably because all patients used the PCA correctly to obtain an adequate and comparable analgesia. However, significant pain relief on movement was obtained in both ketamine-treated groups during the first physical therapy session. This is reflected by the increased amplitude of the first passive knee flexion and lower PCA morphine requirements during this session. No previous study has evaluated the analgesic effect of ketamine during movement after orthopedic surgery. All studies demonstrating the analgesic effect of the co-administration of small-dose ketamine during pain-provoking movement were performed in patients undergoing visceral or thoracic surgery (5,10,15).

We observed this action of ketamine on morphine requirement and movement amplitude during the first physical therapy session, which was beyond the pharmacological actions of ketamine. This benefit did not persist at 48 hours, and this is probably explained by the limitation in possible maximal knee flexion allowed at that time by the surgeon (i.e., 90°). The lower pain levels observed during the second physical therapy session are in line with this hypothesis. We did not evaluate the mobility of the operated knee after 48 hours and thus may have missed the delayed beneficial effect. Roytblatt et al. (4) found pain relief after the administration of ketamine 0.15 mg/kg mainly during six hours; however, a more prolonged action of ketamine was reported in other studies. Tverskoy et al. (5) found a decrease in wound hyperalgesia 48 hours after anesthesia using ketamine. An infusion of ketamine for three days after nephrectomy reduced the area of punctuate mechanical hyperalgesia surrounding the surgical incision during the seven days of the study (15). Fu et al. (6) observed a decrease in morphine requirement induced by preemptive ketamine during the two days of their study. A reduction in morphine consumption was still present 24 hours after an induction of anesthesia with ketamine for elective cesarean section (17). Together, these results may specifically reflect the persistent effect of ketamine on central nervous system (CNS) sensitization to pain caused by increased nociceptive input during and after surgery, regardless of the regimen of administration, either as a single injection or a continuous infusion. The long-lasting effect of ketamine on central sensitization allows its administration in only a single dose, as in the present study, or in a short-term infusion.

Ketamine has analgesic properties that are mediated by a number of mechanisms (3). NMDA receptor non-competitive antagonism accounts for most of its analgesic effects through a use-dependent channel blockade (3). In experimental pain research, NMDA receptor antagonists reduced wind-up and central sensitization (18), and the receptors for NMDA are thought to play a pivotal role in CNS nociceptive sensitization, whereas morphine abolished wind-up only at very large doses (18). In experimental studies, NMDA antagonists reduced responses to compression of inflamed joints (19), which suggests that NMDA receptors are involved in this inflammatory model. This long-term effect on cellular sensitization may explain the extended analgesic action that we observed and the preventive effect on the development of hyperexcitability, even if ketamine treatment takes place after surgery. Another hypothesis to explain the analgesic effect of small doses of ketamine may be the synergistic or additive interaction among opioids, which elicits activation of the NMDA receptors (20) and NMDA antagonists. A potentiation between the effects of intrathecal morphine and an NMDA antagonist on wind-up of C fiber-evoked responses of spinal dorsal horn neurons has been reported (18). In a clinical study, Wong et al. (21) demonstrated that ketamine coadministered with epidural morphine potentiates morphine's analgesic effect but has no analgesic effect on its own in patients undergoing major joint replacement. In another study, an additive interaction for the analgesic effects of systemic ketamine and alfentanil was reported after the administration of intradermal capsaicin (22). Furthermore, NMDA antagonists seem to have the additional advantage of attenuating analgesic tolerance to opioids (20). These results suggest the possibility of adding small-dose ketamine to morphine administered either IV or epidurally.

Early and intensive physiotherapy avoids the detrimental effects of immobilization and accelerates functional recovery after knee surgery. An active, supervised rehabilitation program based on kinesiologic and biomechanical factors allows rapid restoration of sporting activity in athletes after ACLR (23). The same results, highlighting the importance of instituting an early intensive rehabilitation, were reported after arthroscopic meniscectomy in workers returning to a physically demanding job (24). However, few studies have assessed the influence of postoperative pain on knee rehabilitation after ACLR. In a study examining analgesic consumption and the intensity of pain and its effect on patients' activity after arthroscopic ACLR over five postoperative days, Brown et al. (8) found that VAS scores for attempting straight leg raises were significantly higher for patients unable to successfully perform that activity than for patients who were able to perform it. Furthermore, effective pain control during movement is a factor in better and faster postoperative knee rehabilitation, earlier ambulation, and shorter duration of hospital stay (25), although these benefits do not affect outcome at three months. Techniques using regional analgesia (peripheral nerve block or epidural analgesia) are especially effective in blocking provoked pain, but they require technical expertise, may have significant side effects, and may be indicated in invasive surgery, e.g., total knee arthroplasty (25). Systemic analgesics in a multimodal approach are more appropriate to arthroscopic ACLR (9). In this analgesic regimen, our results suggest that ketamine may be a useful component.

In conclusion, our study shows that a small dose of intraoperative ketamine can significantly enhance postoperative analgesia after ACLR under arthroscopy without any side effects. This is probably due to the action of ketamine on CNS sensitization. This effect is not dependent on the timing of ketamine administration during surgery.

References

1. Woolf CJ, Chong MS. Preemptive analgesia: treating postoperative pain by preventing the establishment of central sensitization. Anesth Analg 1993;77:362–79.
2. McQuay HJ. Pre-emptive analgesia. Br J Anaesth 1992;69:1–3.
3. Kohrs R, Durieux ME. Ketamine: teaching an old drug new tricks. Anesth Analg 1998;87:1186–93.
4. Royblat L, Korotkoruchko A, Katz J, et al. Postoperative pain: the effect of low-dose ketamine in addition to general anesthesia. Anesth Analg 1993;77:1161–5.
5. Tverskoy M, Oz Y, Isakson A, et al. Preemptive effect of fentanyl and ketamine on postoperative pain and wound hyperalgesia. Anesth Analg 1994;78:205–9.
6. Fu ES, Miguel R, Scharf JE. Preemptive ketamine decreases postoperative narcotic requirements in patients undergoing abdominal surgery. Anesth Analg 1997;84:1086–90.
7. Kao JT, Giangarra CE, Singer G, Martin S. A comparison of outpatient and inpatient anterior cruciate ligament reconstruction surgery. Arthroscopy 1995;11:151–6.
8. Brown DW, Curry CM, Ruterbories LM, et al. Evaluation of pain after arthroscopically assisted anterior cruciate ligament reconstruction. Am J Sports Med 1997;25:182–6.
9. Reuben SS, Steinberg RB, Cohen MA, et al. Intraarticular morphine in the multimodal analgesic management of postoperative pain after ambulatory anterior cruciate ligament repair. Anesth Analg 1998;86:374–8.
10. Choe H, Choi YS, Kim YH, et al. Epidural morphine plus ketamine for upper abdominal surgery: improved analgesia from preincisional versus postincisional administration. Anesth Analg 1997;84:560–3.
11. Kucuk N, Kizilkaya M, Tokdemir M. Preoperative epidural ketamine does not have a postoperative opioid sparing effect. Anesth Analg 1998;87:103–6.
12. Park KM, Max MB, Robinovitz E, et al. Effects of ketamine, alfentanil, or placebo on pain, pinprick hyperalgesia, and allodynia produced by intradermal capsaicin in human subjects. Pain 1995;63:163–72.
13. Woolf CJ, Thompson SWN. The induction and maintenance of central sensitization is dependent on N-methyl-D-aspartic acid receptor activation: implications for the treatment of post-injury pain hypersensitivity states. Pain 1991;44:293–9.
14. Javery KB, Ussery TW, Steger HG, Colclough GW. Comparison of morphine and morphine with ketamine for postoperative analgesia. Can J Anaesth 1996;43:212–5.
15. Stubhaug A, Breivik H, Eide PK, et al. Mapping of punctuate hyperalgesia around a surgical incision demonstrates that ketamine is a powerful suppressor of central sensitization to pain following surgery. Acta Anaesthesiol Scan 1997;41:1124–32.
16. Ilkjaer S, Nikolajsen L, Hansen TM, et al. Effect of i.v. ketamine in combination with epidural bupivacaine or epidural morphine on postoperative pain and wound tenderness after renal surgery. Br J Anaesth 1998;81:707–12.
17. Kee WDN, Khaw KS, Ma ML, et al. Postoperative analgesic requirement after cesarean section: a comparison of anesthetic induction with ketamine or thiopental. Anesth Analg 1997;85:1294–8.
18. Chapman V, Dickenson AH. The combination of NMDA antagonism and morphine produces profound antinociception in the rat dorsal horn. Brain Res 1992;573:321–3.
19. Neugebauer V, Lücke T, Schaible HG. N-methyl-D-aspartate (NMDA) and non-NMDA receptor antagonists block the hyperexcitability of dorsal horn neurons during development of acute arthritis in rat's knee joint. J Neurophysiol 1993;70:1365–77.

20. Mao J, Price DD, Mayer DJ. Mechanisms of hyperalgesia and morphine tolerance: a current view of their possible interactions. Pain 1995;62:259–74.
21. Wong CS, Liaw WJ, Tung CS, et al. Ketamine potentiates analgesic effect of morphine in postoperative epidural pain control. Reg Anesth 1996;21:534–41.
22. Sethna NF, Liu M, Gracely R, et al. Analgesic and cognitive effects of intravenous ketamine-alfentanil combinations versus either drug alone after intradermal capsaicin in normal subjects. Anesth Analg 1998;86:1250–6.
23. Lutz GE, Stuart MJ, Sim FH. Rehabilitative techniques for athletes after reconstruction of the anterior cruciate ligament. Mayo Clin Proc 1990;65:1322–9.
24. Moffet H, Richards CL, Malouin F, et al. Early and intensive physiotherapy accelerates recovery postarthroscopic meniscectomy: results of a randomized controlled study. Arch Phys Med Rehabil 1994;75:415–26.
25. Singelyn FJ, Deyaert M, Joris D, et al. Effects of intravenous patient-controlled analgesia with morphine, continuous epidural analgesia, and continuous three-in-one block on postoperative pain and knee rehabilitation after unilateral total knee arthroplasty. Anesth Analg 1998;87:88–92.