S(+) -Ketamine as an Analgesic Adjunct Reduces Opioid Consumption After Cardiac Surgery

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Accepted for publication May 11, 2004.
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DOI: 10.1213/01.ANE.0000133913.07342.B9

There are no studies evaluating S(+) -ketamine for pain management after sternotomy. In this prospective, randomized, double-blind, placebo-controlled clinical trial, we evaluated the efficacy and feasibility of S(+) -ketamine as an adjunctive analgesic after cardiac surgery. Ninety patients scheduled for elective coronary artery bypass grafting (CABG) were randomized to receive either a 75 μg/kg bolus of S(+) -ketamine followed by a continuous infusion of 1.25 μg · kg⁻¹ · min⁻¹ for 48 h (n = 44) or placebo (normal saline bolus and infusion) (n = 46). From the time of tracheal extubation, patients could access an opioid (oxycodeone) via a patient-controlled analgesia device, and the cumulative oxycodone doses were measured over 48 h. Pain was evaluated on a visual analog scale three times daily. The quality of recovery, patient satisfaction with pain management, and adverse effects were recorded. The cumulative oxycodone consumption during the first 48 postoperative hours was less in the S(+) -ketamine group (103 ± 44 mg) than in the placebo group (125 ± 45 mg; mean difference, 22 mg; 95% confidence interval for the difference, 3–40 mg; P = 0.023). Pain scores did not differ between the groups at rest (P = 0.17) or during a deep breath (P = 0.23). Patient satisfaction was superior in S(+) -ketamine-treated patients: 26 (60%) of 44 in the S(+) -ketamine group compared with 16 (35%) of 46 in the placebo group were very satisfied with the analgesic management (P = 0.032). Nausea and vomiting were the most common adverse events, with similar frequencies in both groups. Four patients in the S(+) -ketamine group developed transient hallucinations during the infusion, versus none in the placebo group. In conclusion, small-dose S(+) -ketamine decreased opioid consumption in CABG patients during the first 48 h after surgery. (Anesth Analg 2004;99:1295–1301)

Pain after cardiac surgery may be intense and require the administration of large doses of opioids (1,2). Pure opioids have a dose-dependent analgesic effect. However, opioid administration is also associated with a number of adverse effects, such as nausea, vomiting, depressed gastrointestinal motility, drowsiness, and, especially with larger doses, respiratory depression (3).

Non-opioid analgesics, such as nonsteroidal antiinflammatory drugs (1,2), ketamine, a recently launched N-methyl-d-aspartate antagonist, has analgesic properties when used in subanesthetic doses. It has been shown to reduce opioid consumption after abdominal and orthopedic surgery (6,7). However, reported psychotomimetic adverse effects have diminished the clinical feasibility of racemic ketamine (8). S(+) -Ketamine, a recently launched S-isomer of ketamine, reportedly enhances analgesia and induces less cognitive impairment than the racemic mixture (9). Although it has a proven efficacy in orofacial and orthopedic surgery (10,11), S(+) -ketamine has not been tested as an analgesic adjunct after cardiac surgery. In this prospective, randomized, and double-blind clinical trial, we evaluated the efficacy, as assessed by cumulative opioid consumption, and the clinical feasibility of small-dose S(+) -ketamine as an adjunctive analgesic when infused for 48 h after coronary artery bypass grafting (CABG).
Methods

This study was approved by the Ethics Committee of Kuopio University Hospital and was conducted in accordance with the latest (October 2000) revision of the Declaration of Helsinki. All patients were informed and gave written consent. Patients scheduled for elective CABG with cardiopulmonary bypass and younger than 70 yr of age were considered eligible for the study, with the exclusion of those with sleep apnea syndrome or those receiving drug therapy for mental problems. Patients with low cardiac output syndrome (cardiac index <2.0 L/min·m−2) after cardiopulmonary bypass or who could not be weaned from mechanical ventilation within 12 h of the end of surgery were also excluded, as were those who underwent a combined cardiac operation including valvular surgery and patients operated on with a beating heart (off-pump technique). Patients who underwent reoperation for bleeding or other reasons were also excluded.

One-hundred-two patients were randomized into the S(+) -ketamine group (n = 51) or placebo group (n = 51). Randomization was performed with a computer program by using random numbers and a balanced design. The code remained blinded until the end of the study. Immediately after anesthesia induction, patients in the S(+) -ketamine group received a 75 µg/kg bolus of S(+) -ketamine (Ketanest-S; Pfizer, Espoo, Finland) in 15 mL of normal saline, whereas the placebo group patients received a 15-mL bolus of normal saline from a syringe with an identical appearance. Bolus dosing (15 min) of either S(+) -ketamine or placebo was followed by continuous infusion of S(+) -ketamine 1.25 µg·kg−1·min−1 (3 mL/h, with varying concentrations according to body weight) or placebo infusion at the same rate (3 mL/h) for 48 h after arrival (Time 0) to the postanesthesia care unit (PACU). The dose estimation of S(+) -ketamine was based on a previous study (12) with racemic ketamine in patients undergoing laparotomy. However, all 3 patients in our pilot study developed delusions or hallucinations during a deep breath by using a 10-cm visual analog scale (VAS), with 0 cm equaling no pain and 10 cm the worst pain imaginable. Overall satisfaction with pain therapy was estimated on a 4-point scale: 1 = very satisfied, 2 = satisfied, 3 = unsatisfied, and 4 = very unsatisfied. Concomitantly with pain assessments, sedation and all adverse effects were registered. Sedation was assessed in the PACU on a 7-point sedation-agitation scale (SAS) from 0 (unarousable) to 6 (combative) (13), whereas in the surgical ward a 10-cm VAS scale was used. All the assessments were accomplished by the attending PACU or surgical ward nurse blinded to group assignment. Success of mobilization was graded by the physiotherapists (blinded to group assignment) in the surgical ward on the second postoperative morning. Mobilization grading consisted of 5 steps, each scored from 0 to 2 points, with 0 points equaling not able to do the step, 1 point equaling a step accomplished with little help, and 2 points equaling success without any help. The 5 steps were 1) moving from the supine to the sitting position, 2) moving to one side of the bed, 3) getting up beside the bed, 4) walking, and 5) lying down on the bed. Physiotherapists also evaluated the pain associated with walking, by using a 10-cm VAS score. At the end of the study, patients were asked if they would choose the same pain control method if they had the operation a second time.

Pulmonary function tests (forced vital capacity, forced expiratory volume in 1 s, and peak expiratory flow rate) were assessed with a portable pulmonary function monitor (Vitalograph Escort; Buckingham, England). The monitor was calibrated before each measurement according to the manufacturer’s recommendations. Each measurement was duplicated, and the best value was recorded. Maximum inspiratory force and maximum expiratory force were measured with a flowmeter (Spira, Helsinki, Finland) by a physiotherapist. The monitor was calibrated before each measurement according to the manufacturer’s recommendations. Each measurement was duplicated, and the best value was recorded. Oxygen consumption (VO₂) and carbon dioxide production (VCO₂) were measured with indirect calorimetry before surgery (canopy mode), before extubation (ventilator mode), and on the first postoperative morning (canopy mode) (Deltatrac; Datex-Ohmeda, Helsinki, Finland) for 20 min by disregarding the first 5 min and averaging values. Samples for arterial blood gas analyses were taken immediately before anesthesia induction, after arrival in the PACU, and once between 10:00 AM and noon on the 2 first postoperative mornings for the PO₂ and PCO₂ analyses. The samples were analyzed immediately (ABL-520; Radiometer, Copenhagen, Denmark).
Before the patient-controlled analgesia (PCA) began and after tracheal extubation, opioid titration was accomplished to control the pain. A PACU nurse administered oxycodone as 2-mg boluses every 10 min until the VAS score at rest was ≤3 or until excessive sedation (SAS score <4) or respiratory depression (respiratory rate ≤8 breaths/min) developed. After opioid titration and repeating the instructions, the patients had access to oxycodone (Oxanest; Leiras, Turku, Finland) with a PCA device (Graseby 3300P; Hoyer, Bremen, Germany) with a standardized protocol: bolus dose, 2 mg; dose duration, 2 min; lockout interval, 13 min (15-min effective lockout time); and no background infusion or upper dose limit. Before tracheal extubation, the nurses in the PACU were allowed to give oxycodone 5 mg IV to facilitate the patient’s comfort. This extra bolus dose of oxycodone was also allowed once an hour as a rescue analgesic if pain relief with PCA was insufficient.

Oxycodone consumption was recorded from the PCA device at the end of the 48-h study period. Per protocol, the primary efficacy variable was cumulative oxycodone consumption (the combined amount administered as opioid titration, via the PCA device, and as rescue doses) at 48 h after surgery.

Cognitive functions after surgery were investigated with the Mini-Mental State Examination (14) and the Delirium Rating Scale (DRS) (15), which were evaluated by study nurses guided by a neuropsychologist. The study patients were also asked whether they had hallucinations or any unreal perceptions during the study period.

The sample size was estimated by using a two-sided P level of 0.05 and a power of 0.80. Assuming a decrease in opioid consumption by 30%, the power analysis indicated that 35 patients had to be included in each group. To allow for a few dropouts, on the basis of our previous study (4), we estimated 51 patients per group as an appropriate sample size.

Patient characteristics and anesthetic and operative variables were compared by using the Student’s t-test for independent samples (continuous variables) or the Mann-Whitney U-test and χ²-test (Pearson) or Fisher’s exact test when appropriate (categorical variables). Cumulative oxycodone consumption between groups was compared with the Student’s t-test for independent samples after tests for homoscedasticity (equality of variances) and normality. Comparison of VAS scores over time was performed with two-way analysis of variance for repeated measurements by using a mixed design. A P value <0.05 was considered statistically significant. Results are given as mean (SD) or number of patients as appropriate. All statistical analyses were performed with SPSS Version 11.01 (SPSS Inc., Chicago, IL).

Results

One-hundred-two patients were recruited and randomized, but 12 of these were excluded (Fig. 1). Therefore, data on 90 patients, 46 in the placebo group and 44 in the S(+-)-ketamine group, were included in the efficacy analysis. Patient characteristics and operative and anesthetic variables, including opioid consumption during surgery, were fairly similar (Table 1).

Cumulative oxycodone consumption during the first 48 postoperative hours was less in the S(+-)-ketamine group (103 ± 44 mg) than in the placebo group (125 ± 45 mg; mean difference, 22 mg; 95% confidence interval for the difference, 3–40 mg; P = 0.023). The time after tracheal extubation to the first dose of oxycodone with PCA was longer in the S(+-)-ketamine group (134 ± 125 min) than in the placebo group (101 ± 197 min; P = 0.013).

Overall satisfaction with analgesia was high in both groups: all patients in the S(+-)-ketamine group and 96% in the placebo group were very satisfied or satisfied. However, significantly more patients in the S(+-)-ketamine group (26 of 44) were very satisfied with the analgesic management, compared with 16 of 46 in the placebo group (P = 0.032). Two patients in the placebo group were unsatisfied with the pain therapy, versus none in the S(+-)-ketamine group. One patient was dissatisfied because of opioid-induced nausea, and the other was dissatisfied because of unsatisfactory pain relief despite an excessive dose of oxycodone (220 mg).

The VAS pain scores during the 48-h study period were comparable both at rest (P = 0.17) and during a deep breath (P = 0.23) (Fig. 2). When asked whether they would choose the same pain management method again, 41 of 44 patients in the S(+-)-ketamine group and 41 of 46 in the placebo group replied affirmatively.

The groups were similar in terms of tracheal extubation time (Table 1), pulmonary function tests (Table 2), mobilization tests, walking exercise with physiotherapists, VO₂, and VCO₂. Postoperative PCO₂ values were higher in the placebo group than in the S(+-)-ketamine group (P = 0.021) and, although slightly increased, were within safe limits in both groups (Table 2).

There were no differences between groups in cognitive function after surgery. The mean value for the Mini-Mental State Examination (best outcome, 30) was 23 ± 2.6 in the S(+-)-ketamine group and 25 ± 2.7 in the placebo group (P = 0.69), and the mean value for DRS (best outcome, 0) was 3.4 ± 0.7 in the S(+-)-ketamine group and 3.1 ± 0.4 in the placebo group (P = 0.10). However, in the DRS evaluation, 2 patients in
the S(+)ketamine group achieved 5 points and 1 patient 6 points, compared with none in the placebo group.

Sedation scores did not differ between groups: SAS scores on the operative day were 3.6 ± 0.1 in the S(+)ketamine group and 3.7 ± 0.1 in the placebo group (P = 0.735). VAS scores on the first postoperative day were 3.3 ± 0.2 in the S(+)ketamine group and 3.4 ± 0.2 in the placebo group (P = 0.115), and on the second postoperative day they were 3.4 ± 0.2 in the S(+)ketamine group and 2.9 ± 0.4 in the placebo group (P = 0.140).

Because 4 (8%) patients in the S(+)ketamine group developed psychotomimetic disturbances (versus none in the placebo group; P = 0.053 between groups), discontinuation of the study drug infusion was considered. Two of these patients were very confused and were withdrawn from the study. The two other patients were offered the possibility to withdraw, but both decided to continue. In addition, all 3 pilot patients with S(+)ketamine as a 150 μg/kg bolus and a 2.5 μg·kg⁻¹·min⁻¹ infusion—a dosage based on previous research (12)—developed hallucinations. Hallucinations disappeared readily after discontinuation of

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**Figure 1.** Flowchart of recruitment and dropouts. PCA = patient-controlled analgesia; Resp. = respiratory.
S-(-)-ketamine in all of the affected patients, and in the remaining study patients the rest of the hospital stay was uneventful. All the patients with psychotomimetic adverse reactions recalled the event after the study period. Altogether, 7 of 54 patients receiving S-(-)-ketamine developed major psychotomimetic adverse effects during S-(-)-ketamine infusion, versus none in the placebo group.

Nausea and vomiting were the most common adverse events, with similar frequencies in the two groups. A few serious complications appeared in both groups during or after the study period (Table 3).

**Discussion**

This study is the first randomized trial showing that S-(-)-ketamine has an opioid-sparing effect after cardiac surgery. The analgesic property of S-(-)-ketamine was also supported by the finding that the time to the first request for an analgesic after surgery was longer in the ketamine group. Satisfaction with the pain management was superior in the ketamine group; almost two thirds of the patients were very satisfied, compared with approximately one third in the placebo group.

S-(-)-Ketamine has not been evaluated as an analgesic after sternotomy, and studies with other types of surgery are sparse. Epidural S-(-)-ketamine in combination with ropivacaine diminished postoperative patient-controlled epidural ropivacaine use and alleviated pain after knee arthroplasty (16). S-(-)-Ketamine for caudal block also appears to be as effective an analgesic as bupivacaine after pediatric hernia repair (17). However, in a trial in arthroscopic knee surgery patients, S-(-)-ketamine given as an IV infusion neither provided an opioid-sparing effect nor enhanced analgesia (18). The most plausible explanation for this negative finding was the shorter duration of postoperative S-(-)-ketamine infusion, the smaller sample size, and the more minor surgery; there is less associated postoperative pain after arthroscopic knee surgery than after sternotomy, as in this study.

The analgesic effect of the racemic mixture of ketamine is well established in patients undergoing noncardiac surgery (6,19–21). However, there are no studies after sternotomy in cardiac surgery patients. Pain after sternotomy is more intense than after minor surgery (1,2,22), and several nociceptive mechanisms may be involved. Therefore, the opioid-sparing effect of non-opioid adjuvants may be less after cardiac surgery. In a recent large-scale study of propacetamol for...

**Table 1. Demographic, Operative, and Anesthetic Data**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo (n = 46)</th>
<th>S-Ketamine (n = 44)</th>
<th>P value</th>
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</thead>
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<tr>
<td>Sex (M/F)</td>
<td>43/3</td>
<td>37/7</td>
<td>0.19</td>
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<tr>
<td>Age (yr)</td>
<td>58 ± 7</td>
<td>59 ± 5</td>
<td>0.31</td>
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<tr>
<td>Height (cm)</td>
<td>173 ± 6</td>
<td>172 ± 8</td>
<td>0.29</td>
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<tr>
<td>Weight (kg)</td>
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<td>85 ± 13</td>
<td>0.43</td>
</tr>
<tr>
<td>NYHA (I/II/III/IV)</td>
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<td>3/17/18/6</td>
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</tr>
<tr>
<td>Duration of CPB (min)</td>
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<td>83 ± 30</td>
<td>0.35</td>
</tr>
<tr>
<td>AO time (min)</td>
<td>80 ± 26</td>
<td>77 ± 28</td>
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</tr>
<tr>
<td>Duration of anesthesia (min)</td>
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<td>194 ± 50</td>
<td>0.86</td>
</tr>
<tr>
<td>Extubation time (min)</td>
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<td>347 ± 91</td>
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<td>Fentanyl dose (µg/kg)</td>
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<td>10 ± 1</td>
<td>0.32</td>
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<tr>
<td>Alfentanil dose (µg/kg)</td>
<td>163 ± 38</td>
<td>170 ± 50</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Values are mean ± sd or number of patients.

NYHA = New York Heart Association classification of severity of coronary heart disease; CPB = cardiopulmonary bypass; AO = aortic occlusion.

**Figure 2.** Visual analog scale (VAS) pain scores at rest and during a deep breath. Values are expressed as mean ± sd. OD-EXT = immediately after extubation and before commencing the patient-controlled analgesia (PCA) on the day of the operation; OD-TITR = after titration of oxycodone until the VAS score was ≤3 on the day of the operation; ODPCA-24H = after having allowed access to the PCA on the day of operation at 12:00 PM; POD1–8H = first postoperative day at 8:00 AM; POD1–16H = first postoperative day at 4:00 PM; POD1–24H = first postoperative day at 12:00 PM; POD2–8H = second postoperative day at 8:00 AM; POD2–16H = second postoperative day at 4:00 PM.

S-(-)-ketamine in all of the affected patients, and in the remaining study patients the rest of the hospital stay was uneventful. All the patients with psychotomimetic adverse reactions recalled the event after the study period. Altogether, 7 of 54 patients receiving ketamine developed major psychotomimetic adverse effects during S(-)-ketamine infusion, versus none in the placebo group.

Nausea and vomiting were the most common adverse events, with similar frequencies in the two groups. A few serious complications appeared in both groups during or after the study period (Table 3).
postoperative patients, opioid-sparing was less (18%) in patients with severe pain compared with patients with moderate pain (37%) (23). In the present trial, there was a difference of 17% in opioid consumption between groups within 48 postoperative hours. Consistent with this, propacetamol, a prodrug of paracetamol (acetaminophen), had an opioid-sparing effect of 13% (4), and the cyclooxygenase (COX)-2 inhibitors parecoxib and valdecoxib reduced opioid consumption by 20% during the first 72 hours after CABG surgery (5). For targeting further reduction in opioid consumption and better pain management after sternotomy, the balanced analgesic technique (combined use of various analgesics and techniques targeting different receptors and mechanisms) may be considered (24). For example, continuous infusion of bupivacaine at the median sternotomy site alleviates pain and reduces opioid consumption after cardiac surgery (25). In this context, further studies are needed to evaluate the role of S(+)-ketamine within multimodal analgesic regimens after cardiac surgery.

The opioid-sparing effect observed in this trial may result not only from the intrinsic analgesic effect of S(+)-ketamine, but also from the attenuated development of acute opioid tolerance and hyperalgesia (26,27). Although both of these mechanisms may be at work, it is noteworthy that our study did not aim to investigate the mechanisms of S(+)-ketamine action. Therefore, the mechanisms of opioid sparing in our patients remain unknown. However, there is evidence from clinical trials that subanesthetic doses of ketamine may effectively alleviate hyperalgesia after surgery (28).

The S (+)-ketamine dosing in this study was based on a study in gynecological laparotomy patients instead of those with cardiac surgery. A limitation of the study is that no dose-finding study was performed before we performed the current efficacy analysis with a single dosing.

Untoward adverse effects, such as hallucinations and other psychological disturbances, have restricted the use of ketamine (9). S(+)-Ketamine has double the analgesic efficacy of the racemate and has a better adverse-effect profile (29). S(+)-Ketamine reportedly produces fewer psychotomimetic disorders than the racemate (9). However, our results with the observed 8% incidence of these disorders conflict with previous reports indicating no psychotomimetic responses (18). The incidence of psychotomimetic adverse effects in this trial is concerning. Our results indicate that S(+)-ketamine should be administered with caution to postoperative cardiac surgery patients and with frequent evaluation for any untoward adverse effects. Further dose-determining studies are warranted to find the optimal infusion rate to achieve a desired analgesic effect with the least incidence of psychotomimetic adverse effects. Cost-effectiveness studies are also needed. In this study, the direct drug costs per patient were $38 more in the S(+)-ketamine group than in the control group.
Besides analgesic and psychotropic influences, S(+)-ketamine has other effects, which may be either beneficial or harmful for cardiac surgery patients. Despite the similar VAS scores between groups, the patients given ketamine were more satisfied with the pain therapy. This may relate to the suggested antidepressant action of ketamine (30). Although untoward cardiovascular effects have been reported with the use of ketamine (31), in our patients there were no tachycardic responses, incidents of pulmonary hypertension, or any other hemodynamic adverse effects after the bolus dosing or at any other phase of S(+)-ketamine administration. Therefore, it seems that, at the dose applied in this study, S(+)-ketamine has a safe hemodynamic profile in patients undergoing CABG surgery.

In conclusion, a small-dose S(+)-ketamine infusion as an adjunct to PCA oxycodone exerts an opioid-sparing effect without untoward hemodynamic sequelae after sternotomy in CABG patients. Although patients given S(+)-ketamine were more satisfied with the pain therapy, a few of them developed psychological disturbances. This should be considered as an indication for further dose-optimizing studies for S(+)-ketamine as an analgesic adjunct to opioids after cardiac surgery.

The authors wish to thank P. Toroi, RN, T. Tuovinen, RN, and the nursing staff of the PACU and cardiac surgical ward of Kuopio University Hospital for their invaluable collaboration in this study.

References


