Does Intraoperative Ketamine Attenuate Inflammatory Reactivity Following Surgery? A Systematic Review and Meta-Analysis

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BACKGROUND: Reports regarding the ability of the anesthetic drug ketamine to attenuate the inflammatory response to surgery are conflicting. In this systematic review we examined the effect of perioperative ketamine administration on postoperative inflammation as assessed by concentrations of the biomarker interleukin-6 (IL-6).

METHODS: This study was based on a systematic search in PubMed, Scopus, Web of Knowledge, and the Cochrane Library. English written randomized controlled trials conducted in humans were eligible. To be included in the analysis, outcome had to relate to inflammation or immune response. Each study was reviewed independently by 2 assessors. Data were analyzed according to the GRADE’s approach and reported in compliance with the PRISMA recommendations.

RESULTS: Fourteen studies were eligible for evaluation (684 patients). Surgery was performed under general anesthesia, and ketamine was given before or during the surgery in varied doses. Eight studies involved cardiopulmonary bypass operations, 4 were for abdominal surgery, 1 thoracic surgery, and 1 cataract surgery. Three studies were deemed of low quality. Nine studies measured IL-6 concentrations within the first 6 hours postoperatively; but in 3 studies, other potent anti-inflammatory drugs were used as premedication or during the operation; thus 6 studies (n = 331) were included in the meta-analysis. Using postoperative IL-6 concentrations as an outcome, ketamine had an anti-inflammatory effect; the meta-analysis showed a mean preoperative-postoperative IL-6 concentration difference (95% confidence interval) of –71 (–101 to –41) pg/mL.

CONCLUSIONS: It can be concluded that intraoperative administration of ketamine significantly inhibits the early postoperative IL-6 inflammatory response. Future studies should further examine the anti-inflammatory effect of ketamine during major surgery, determine whether ketamine treatment alters functional outcomes, elucidate the mechanisms of its anti-inflammatory effect, and suggest an appropriate dosing regimen. (Anesth Analg 2012;115:934–43)

Major surgery invariably evokes the inflammatory response. It has been shown that the extent of systemic inflammatory response in cardiac surgery is associated with the outcome of the intervention.1–3 For instance, increased serum concentration of interleukin-6 (IL-6, a major proinflammatory cytokine) has been associated with postoperative left ventricular wall motion abnormalities and myocardial ischemic episodes,3 perioperative complications,3 and postoperative hyperdynamic instability.1 IL-6 concentrations were correlated with postoperative morbidity and mortality in children after an open-heart surgery,4 as well as with the severity of adult respiratory distress syndrome.5 It has become increasingly appreciated that in the perioperative period, circulating concentrations of cytokines may play an important role in surgery outcome and therefore should be controlled. Indeed, several tactics have been used by clinicians to curb perioperative cytokine response.6

Strategies used in the past to reduce the systemic cytokine response include treatment with glucocorticoids or with the serine protease inhibitor aprotinin.2,6 Another strategy is to use anesthetic or subanesthetic doses of general anesthetics or opioids with potential anti-inflammatory effects.7–12 The results of multiple studies on the systemic anti-inflammatory effects of fentanyl7–9 or morphine10 are conflicting, and single studies on sevoflurane11 or propofol12 indicate anti-inflammatory effects at anesthetic doses of these drugs. Notably, local anesthetics (LA) are the most widely studied anesthetic drugs with clinically relevant endpoints. Hollmann and Durieux13
reviewed the anti-inflammatory effects of LA, and Herroeder et al.\textsuperscript{14} provided evidence that the frequently shown beneficial effects of LA on gastrointestinal recovery after surgery are most likely due to a potent modulatory effect of the proinflammatory response.

Among the general anesthetics, ketamine is the most widely studied in the search for strategies to modulate systemic perioperative cytokine response. Ketamine is a potent anesthetic and analgesic drug. When administered IV during anesthesia in adults, ketamine decreased postoperative pain intensity for up to 48 hours, decreased cumulative 24-hour morphine consumption, and delayed the time to first request of rescue analgesic.\textsuperscript{15} On the basis of current recommendations for ketamine, there is level I evidence for an opioid-sparing effect and level II evidence for the anti-inflammatory effects of ketamine in surgical patients in the early postoperative period based on randomized controlled trials (RCT) in which ketamine was used as part of the early postoperative period. Doses ranged from a small supplemental single bolus dose and up to full ketamine anesthetic doses, either with racemic drug or the pharmacologically more active S-(+)-ketamine. Ketamine has been found to act as an immune modulator. Furthermore, it has been argued that ketamine is a unique, specific anti-inflammatory drug,\textsuperscript{16} which inhibits the systemic response without affecting local healing processes.

It has been suggested that ketamine’s anti-inflammatory activity might be mediated by suppression of microglia activation, as demonstrated by inhibition of extracellular signal-regulated kinase 1/2 phosphorylation in primary cultured microglia,\textsuperscript{17} or by inhibition of l-arginine transport. L-arginine is a unique, specific anti-inflammatory drug,\textsuperscript{18} which inhibits the systemic response without affecting local healing processes.

The aim of this systematic review was to evaluate the anti-inflammatory effect of ketamine in surgical patients in the early postoperative period based on randomized controlled trials (RCT) in which ketamine was used as part of the intervention. The effect of ketamine on systemic exposure of the cytokine IL-6 was of special interest because its plasma concentration serves as a useful and reliable biomarker of systemic inflammation.\textsuperscript{19}

**METHODS**

A systematic search was performed in PubMed, Scopus, Embase, Web of Science, and the Cochrane Central Register of Controlled Trials (CENTRAL) up to October 13, 2011. In addition the reference lists of the retrieved full articles were searched.

The following search strategy combining free text and MeSH terms (ME) was set up for PubMed:


A similar search strategy was set up for CENTRAL, Scopus, and Web of Science, with search terms adapted to specific terminology and indexing characteristics. In the updating search March–October 2011 Embase was used instead of Scopus. A detailed account of the searches can be obtained from O. Dale.

Inclusion criteria included the following: English written RCT conducted in humans were eligible. Ketamine had to be part of the intervention, and study outcomes had to relate to inflammation/immune modulation. If the primary outcome was not a clinical measure, any surrogate outcomes had to be measured directly in a biological sample (in vivo), or resulting from manipulation of such a sample (ex vivo). If eligibility could not be determined from the title of the study or its abstract, the full paper was retrieved. During the search process, several relevant publications in Chinese were identified. These were preliminarily reviewed by one of the authors (Y.L.) with native knowledge of Chinese.

The following were summarized in a data extraction form: publication details, study design and limitations, patient population details, settings, interventions, validity of methods for assessing outcomes, results, internal and external validity, and narrative summary of the main findings. Each study was reviewed and rated independently by 2 assessors (O.D. and Y.S.). The internal validity of each RCT was assessed using a checklist adapted from the criteria recommended in the National Health Service Centre for Reviews and Dissemination guidance document,\textsuperscript{22} as described earlier.\textsuperscript{23} Data were analyzed in accordance with the GRADE’s approach,\textsuperscript{24} which includes reporting of an evidence profile for the outcome. This profile consists of the number and type of eligible studies, number of participants,
study limitations, consistency, directness, precision, publication bias, and factors that might increase quality of evidence. On this basis a recommendation was given. Finally, the process was reported in accordance with the PRISMA requirements (www.prisma-statement.org/), although the review protocol was not registered as recommended.

On the basis of the evaluation process, we conducted a meta-analysis on the most consistently reported outcome, plasma concentrations of IL-6 within the first 6 postoperative hours. Pre- to postoperative changes in plasma or serum IL-6 concentrations were extracted for each randomized group within each study. The precise data for postoperative IL-6 concentration were not reported by Zeyneloglu et al.,25 Bartoc et al.,26 and Choe et al.27 but were collected by consulting the authors by e-mail. Differences between groups (ketamine vs control treated) were then pooled using a random effects meta-analysis model according to the DerSimonian–Laird method.28 Heterogeneity in mean differences was assessed using the I-squared statistic29 and a χ² test of goodness of fit. Publication bias in the meta-analysis was assessed visually using a funnel plot.30

RESULTS

Ketamine had an anti-inflammatory effect based on the 6 studies included in the meta-analysis (Table 1, Figs. 1 and 2) when using postoperative plasma/serum IL-6 as an outcome. The overall mean (95% confidence interval [CI]) difference was −71 (−101 to −41) pg/mL (P < 0.001). No dose response was observed. The degree of heterogeneity was high when all studies were pooled (I-squared = 91.1%), but low for the CPB studies (I-squared = 0.0%). Using Egger’s funnel plot,30 we observed no sign of publication bias. Including the studies in which a potent anti-inflammatory drug was given25,29,32 in the meta-analysis (results not shown) did not abolish the major finding, although the mean effect estimate (95% CI) was reduced to −50 (−75 to −25) pg/mL.

In total, the search for relevant studies yielded 1187 + 136 (original + additional search, respectively) records as follows: PubMed (148 + 28), Scopus/Embase (925 + 82), CENTRAL (0), and Web of Science (114 + 26) (Fig. 1). No additional records were identified through other sources, and 1038 + 113 records remained after removing duplicates. Removing 10 records (articles written in non-English languages—Chinese [6], German [2], Spanish [1], and Japanese [1]), left 1136 records for screening. A total of 1083 + 13 records were removed on the basis of their titles or after reading the abstract when deemed necessary. Forty full-text articles were retrieved, and 26 were not rated eligible for further analysis.

Since one of the authors (Y.L.) is native Chinese, and since 5 of the Chinese publications were relevant to the aim of this review, these publications underwent a separate evaluation (was not included in the primary evaluation, but as a supplement), as described under Methods.

The 14 studies eligible for evaluation included 684 patients. In all (except for 2 studies including 3 groups26,33), 2 groups were compared. Ten studies were double-blind, 2 single-blind24,35 (one did not report this originally,35 but confirmed single-blinding upon request), and 2 of the studies were open.25,33 Three studies31,34,36 reported patient flow according to CONSORT agreement. All but 2 studies25,32 were conducted in adults. In 7 studies, CPB was used; in another, cardiac surgery was conducted off-pump27; 4 studies included major abdominal operations35,37,38; 1 thoracic surgery36; and in 1,33 cataract surgery was performed. All patients underwent surgery under general anesthesia, except one group in Tu et al.’s study,33 and a varying number of patients who received epidural anesthesia in the control and interventions groups in D’Alonzo et al.’s study.36 Total subject numbers varied from 24 to 142 patients, with the sample size justified in 6 studies,25–27,31,34,36 One of the studies had a clinical primary outcome (neurodevelopment),32 12 measured surrogate outcomes such as markers of inflammations directly in blood samples, and 2 measured similar outcome in “stimulated” blood samples (ex vivo).35,39 All studies (except for Akhlagh et al.40 and Zilberstein et al.39) measured IL-6. Samples were drawn at a myriad of different time points, from 4 hours to 8 days. All studies (but 224,40) used racemic ketamine. The intervention varied from an anesthesia based entirely on (S)-ketamine (single dose of 2 to 4 mg/kg followed by 2 to 4 mg/kg/h),25 ropivacaine (2–4 mg/kg/h),25,32 racemic ketamine single dose (1 to 2 mg/kg) followed by infusion (1.5 to 3.5 mg/kg/h),25 low dose (150 mg/kg/h),25 low dose (5–75 mg/kg/h),40 or low (0.15 to 0.5 mg/kg) single doses. In Tu et al.’s study33 one group received ketamine 1 mg/kg infused over the duration of surgery. In all studies, ketamine was given at induction of anesthesia, except Bhutta et al.,32 in which ketamine was administered just before CPB.

Of the 14 eligible studies, 2 were deemed high quality (+ +)26,34 9 were of medium quality (+)25,27,31,32,35,38–41 and 3 were of low (−) quality and therefore excluded from the qualitative analysis: Mostafa et al.37 because of lack of preoperative sampling, Tu et al.33 because of large losses to follow-up, and D’Alonzo et al.36 primarily because of heterogeneity of study groups, and also lack of control of preoperative use of nonsteroidal anti-inflammatory drugs. One study reported regular use of nonsteroidal anti-inflammatory drugs before the operation that was similar in the study groups.26 Thus, 11 studies were included in the qualitative analysis. Of these, drugs with significant anti-inflammatory effects (methyl prednisolone, dexamethasone, and ibuprofen) were administered as premedication or during the operations in 3 studies25,31,32, respectively; this fact may cancel the effects of ketamine on inflammatory biomarkers. Three of the studies used questionable statistics, such as failing to consider the fact that repeated measures were conducted, or not compensating for multiple comparisons.38,40,41 Primary endpoints were stated clearly in 2 studies,25,34,36 but could be anticipated in 4 studies.25–27,31 The primary endpoints chosen in the included studies were all different, and only Welters et al.34 and D’Alonzo et al.36 reported their primary endpoint in a precise manner.

Five of the studies (Table 1) reported that racemic or (S)-ketamine significantly reduced the inflammatory response after surgery,26,34,35,38,41 as measured by plasma/serum IL-6 concentrations (Table 1). Effect size was larger and lasted for a longer time period in early studies38,41 in comparison with the later studies by Bartoc et al. and
<table>
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<tr>
<td>Bartoc et al., 2006</td>
<td>Elective cardiac surgery (CABG, valve replacements, and combinations) with CPB (32 C), meeting at least 1 of following criteria: age &gt;70 years, recent (&lt;14 days) MI, elevated creatinine (&gt;1.3 mg/dL), previous stroke, previous cardiac surgery. Anesthesia at the discretion of the anesthetist. Preoperative NSAIDs equal in study groups. Sample size: 30 (15 pair ketamine groups).</td>
<td>Racemic ketamine 0.25 mg/kg. Racemic ketamine 0.5 mg/kg at induction as an adjuvant to anesthetic procedure. Controls received saline. ANOVA followed by Tukey test for pairwise comparison of means or Dunnet for between ketamine groups. Quantikine IL-6; R+D Systems. Sampling until POD 1.</td>
<td>Primary outcome: difference between ketamine groups in IL-6 on POD 1 (in vivo). Secondary outcome: differences between ketamine groups and placebo any time. Also CRP, IL 8 and 10. Data also at ICU arrival.</td>
<td>Primary outcome: no statistically significant difference between ketamine groups in IL-6 on POD 1. Secondary outcome: ketamine lowered IL6 in comparison with placebo upon arrival at the ICU and POD1, while IL-10 was lower for ketamine POD 1. No changes observed for IL8. CRP lower in the 0.5 mg/kg group POD1. Written to author for data: IL-6 pg/L, at ICU, mean (SD): Control: 152 (114). Ketamine (0.25): 59 (53). Ketamine (0.5): 53 (38). MAP and SVT higher for ketamine.</td>
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<td>Welters et al., 2011</td>
<td>Elective CABG with CPB (tp not given). Exclusions: CK &gt;170 U/L, repeat cardiac surgery and combined operations, hepatic (ASAT/ALAT &gt;150 U/L) and renal (creatinine &gt;132 µM) disease, immunosuppressive medications, immunodeficiency syndromes, neurologic or psychiatric disease. Pats with CRP &gt;16 mg/L, IL-6 &gt;24 pg/mL in the morning were excluded. Anesthesia well controlled. CPB 32</td>
<td>S-ketamine-based anesthesia (1–3 mg/kg, 2–4 mg/kg/h). Control: sufentanil based (0.25–1 µg/kg, 0.5–2 µg/kg/h). Randomization: computer generated. Normal distribution checked. Repeated-measures ANOVA with Greenhouse–Geisser–Epsilon adjustment, otherwise Mann–Whitney. Categorical by chi-square. Cytosets, Biosource BD OptEIA, BD Biosciences Sampling for 24 hours.</td>
<td>Primary outcome: IL-6 6 hours after aortic unclamping in vivo. Secondary: IL-8, 10. TNF-α, TNF-Receptor 1, sFAS (proapoptotic protein soluble FAS), CRP.</td>
<td>Primary outcome: IL-6 pg/L, mean (SD): Ketamine: 56.8 (46.3). Sufentanil: 172.6 (149.9). P &lt; 0.01 Secondary: IL-8 also decreased at 6 hours. IL-10 increased at 1 hour. No changes for TNF-α, TNF-R1, sFAS, CRP.</td>
</tr>
<tr>
<td>Beilin et al., 2007</td>
<td>Patients undergoing abdominal surgery (hysterectomy and gastroplasty). Other inclusion/exclusion criteria not given. Sample size: not estimated 36 pats randomized, 17 to ketamine, 19 to isotonic saline (control).</td>
<td>0.15 mg/kg racemic ketamine 5 minutes before induction as an adjuvant to anesthetic procedure. Controls: isotonic saline. Repeated-measures ANOVA (for time period before Student t test post hoc. ELISA kits: R+D Systems, Biosource International, Pharmingen. Sampling for 72 hours.</td>
<td>Primary outcome. Not given. IL- beta, IL-2, IL-6, TNF-alpha, mitogen response, NKCC, ex vivo.</td>
<td>Outcome (all-over): IL-6 pg/L, mean (SEM). 4 hours postoperative. Ketamine: 68.3 (10.6). Placebo: 114.4 (16.7). P &lt; 0.05 Moderate effect of ketamine, lower IL-6 TNF-alpha (small) at 4 hours. IL-2 was maintained (and not reduced as for controls) in study period.</td>
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**Table 1. (Continued)**

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<tr>
<th>Study/design</th>
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<tr>
<td>Cho et al., 2009&lt;sup&gt;27&lt;/sup&gt;</td>
<td>Patients undergoing elective, multivessel OPCAB. Exclusion criteria: age &gt; 75 years, recent (&gt; 14 days) myocardial infarction, unstable angina with elevated creatine kinase-MB (CK-MB), elevated serum creatinine (&gt; 1.3 mg/dL) before operation, EF &lt; 40%, previous cardiac surgery, previous stroke or pulmonary disease, and history of treatment with steroid or nonsteroidal anti-inflammatory drugs within a month (normotremia). Anesthesia well controlled (sufentanil-sevoflurane based). One surgeon. Sample size not estimated. (CRP POD 1?) 50 patients randomized, 2 × 25 computer-generated randomization.</td>
<td>0.5 mg/kg racemic ketamine at induction as an adjuvant to anesthetic procedure. Controls received saline. t test and repeated-measures ANOVA; post hoc Dunnett test. Wilcoxon rank sum (between groups), Friedman test (within group) further investigated by Mann–Whitney with Bonferroni. Between the groups: ×2 test or by Fisher exact test. CRP: institutional lab. Quantikine high-sensitivity immunoassay; R + D Systems. Sampling to POD 2</td>
<td>Primary outcome: not given, but according to sample size CRP POD 1.</td>
<td>No specific data given. No difference between groups. CRP and IL-6 increased postoperative maximum at 2 days (about 15 mg/dL) and 4 hours (about 300 pg/mL), respectively. TNF-alfa stable. Written to author for data. IL-6 (pg/mL) 4-hour postanastomoses: mean (SD): Ketamine: 163. Control: 95 (82).</td>
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<tr>
<td>Roytblat et al., 1996&lt;sup&gt;30&lt;/sup&gt;</td>
<td>ASA 1–2 women, undergoing elective abdominal hysterectomy. Pain Clin Double blind. Single-center study. Consort not reported.</td>
<td>Ketamine 0.15 mg/kg before incision. Controls saline. Anesthesia based on isoflurane and fentanyl (5 μg/kg). Two way ANOVA followed by multiple comparisons. IL-6 immunoassay kit, Biosource International. Sampling preoperative, uterus mobilization, 4, 24, 48, and 72 hours.</td>
<td>Primary outcome: not given, but 4-hour IL-6 is accurately reported. Circulatory variables.</td>
<td>IL-6 at 4-hour pg/mL, mean (SD). Ketamine: 9.3 (12.6). Control: 45.8 (9.5). All over: IL-6 increased at 4, and 24 h for both groups, control also at 48 hr. Controls higher than ketamine group at these time points. Control group had higher mean arterial blood pressure and heart rate than the ketamine group.</td>
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<tr>
<td>Roytblat et al., 1998&lt;sup&gt;41&lt;/sup&gt;</td>
<td>Elective CABG points with EF &gt; 0.4. Uncontrolled systemic disease (hypertension, diabetes, renal failure) and requirement for aortic balloon pump lead to exclusion. Aspirin and NSAIDs stopped 10 days before surgery. Standard operative/anesthetic (high-dose fentanyl) procedures. Anesthesia well controlled. Two surgeons only. CPB: 32C. Sample size: not estimated.</td>
<td>0.25 mg/kg racemic ketamine at induction as an adjuvant to anesthetic procedure. Controls received saline. Randomization: not described. Two-way ANOVA with multiple post hoc testing. Quantikine IL-6; R + D Systems. Sampling for 8 days.</td>
<td>Primary outcome: No. Reported. Differences in IL-6 serum concentration post-CPB, 4, 24, 48, and days 3–8 (in vivo). And at 4 hours.</td>
<td>Statistically significant lower IL-6 concentration at all measuring points until return to baseline at day 8. Precise figures not given (only graphic). IL-6 pg/L, mean (SD) 4 hours after CPB: Ketamine: 70 (38). Control: 200 (44).</td>
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**Table 1.** Study/design

- Cho et al., 2009: Effect of low-dose ketamine on inflammatory response in off-pump coronary artery bypass graft surgery. *BJA*
- Roytblat et al., 1996: Preoperative low-dose ketamine reduces serum interleukin-6 response after abdominal hysterectomy. *Pain Clin*
- Roytblat et al., 1998: Ketamine attenuates the interleukin-6 response after cardiopulmonary bypass. *Anesth Analg*

**Participants**

- Patients undergoing elective, multivessel OPCAB.
- ASA 1–2 women, undergoing elective abdominal hysterectomy.
- Elective CABG points with EF > 0.4.

**Intervention/statistics lab analysis**

- 0.5 mg/kg racemic ketamine at induction as an adjuvant to anesthetic procedure.
- Ketamine 0.15 mg/kg before incision.
- 0.25 mg/kg racemic ketamine at induction as an adjuvant to anesthetic procedure.

**Outcome measures**

- Primary outcome: not given, but according to sample size CRP POD 1.
- Primary outcome: not given, but 4-hour IL-6 is accurately reported.
- Primary outcome: No. Reported.

**Outcomes**

- No specific data given. No difference between groups. CRP and IL-6 increased postoperative maximum at 2 days (about 15 mg/dL) and 4 hours (about 300 pg/mL), respectively. TNF-alfa stable. Written to author for data. IL-6 (pg/mL) 4-hour postanastomoses: mean (SD): Ketamine: 163. Control: 95 (82).
- IL-6 at 4-hour pg/mL, mean (SD). Ketamine: 9.3 (12.6). Control: 45.8 (9.5). All over: IL-6 increased at 4, and 24 h for both groups, control also at 48 hr. Controls higher than ketamine group at these time points. Control group had higher mean arterial blood pressure and heart rate than the ketamine group.

**CABG** = coronary artery by-pass graft; **CPB** = cardiopulmonary bypass; **EF** = ejection fraction; **MAP** = mean arterial blood pressure; **OPCAB** = off-pump coronary artery bypass; **SVT** = systemic vascular resistance; **ASA** = American Society of Anesthesiologists physical classification system; **Tp** = temperature; **ALAT (ALT)** = alanine amino transferase; **ASAT (AST)** = aspartate amino transferase; **CK** = creatine kinase; **CRP** = C-reactive protein; **IL** = interleukin; **TNF** = tumor necrosis factor; **ANOVA** = analysis of variance; **ITT** = intention to treat; **SEM** = standard error of the mean; **POD 1** = postoperative day; **CPB** = cardiopulmonary bypass; **MI** = myocardial infarction; **NSAIDs** = nonsteroidal anti-inflammatory steroids; **ICU** = intensive care unit; **NKCC** = natural killer cell cytotoxicity.
Welters et al., 26,34 all conducted in patients undergoing CPB. The study of off-pump cardiac surgery patients did not show ketamine’s effect. 27 Moreover, effect size was smaller and duration was shorter in patients undergoing major abdominal surgery. 35,38

Overall, plasma/serum C-reactive protein, IL-8, or TNF-α concentrations either did not show differences or decreased in a fashion similar to IL-6 in ketamine-treated patients, 26,34,35,40 while IL-10 concentrations increased in the 2 high-quality studies. 26,34 Zilberstein et al. have reported that the addition of low-dose ketamine to general anesthesia attenuated postoperative neutrophil activation up to 6 days after CPB. 39

Among the 5 papers in Chinese, 1 was excluded because it could not be asserted whether it was an RCT, 42 and another because the reported baseline IL-6 concentrations deviated significantly from all other studies. 43 Two of the remaining studies included abdominal operations 44,45 and

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**Figure 1.** PRISMA 2009 flow diagram.

**Figure 2.** Forest plot of early postoperative IL-6 serum/plasma concentrations. The designation of the abscissa is in pg/mL.

<table>
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<tr>
<th>Study</th>
<th>Mean difference (66% CI)</th>
<th>Weight</th>
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<tr>
<td>Raynal et al 1999</td>
<td>-24.50 (-43.60, -25.17)</td>
<td>20.33</td>
</tr>
<tr>
<td>Raynal et al 2004</td>
<td>-130.60 (-160.45, -90.85)</td>
<td>17.00</td>
</tr>
<tr>
<td>Bartac C et al 2006</td>
<td>-65.97 (-152.10, -19.82)</td>
<td>11.82</td>
</tr>
<tr>
<td>Belin B et al 2007</td>
<td>-48.10 (-84.87, -7.33)</td>
<td>15.29</td>
</tr>
<tr>
<td>Cho et al 2008</td>
<td>-39.00 (-41.48, -16.52)</td>
<td>20.01</td>
</tr>
<tr>
<td>Welters et al 2011</td>
<td>-114.00 (-151.51, -76.50)</td>
<td>15.95</td>
</tr>
<tr>
<td>Overall (I² = 91.1%, p = 0.009)</td>
<td>-71.06 (-100.57, -41.44)</td>
<td>100.00</td>
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**NOTE:** Weights are from random-effects analysis.
1, acute burn patients given analgesia. Neither of the abdominal studies showed an effect of ketamine on plasma IL-6, while the latter supported the findings of the meta-analysis (−120 [−156 to −84]) pg/mL (95% CI for the difference). It should be noted that the ketamine intervention started after the trauma (burn); thus this study had starting IL-6 concentrations of about 120 pg/mL, which increased over 48 hours in the control group but decreased in the ketamine-exposed groups.

The overall evidence profile as rated according to the GRADE recommendation for intraoperative ketamine on the postoperative IL-6 response was considered high.

**DISCUSSION**

This systematic review substantiates the notion that intraoperative ketamine has an anti-inflammatory effect, as indicated by the meta-analysis showing a considerable reduction in circulating concentrations of the proinflammatory cytokine IL-6 during the first 6 hours after surgery.

IL-6 concentration in the first 6 postoperative hours was chosen as a representative outcome for the inflammatory response for several reasons. First, IL-6 was the most consistently reported inflammation biomarker in the studies included in this review, and most studies provided data in the early postoperative phase. Second, it has a proinflammatory action, and ketamine has been suggested to act as an anti-inflammatory drug. Third, any action of ketamine given intraoperatively should last into the early postoperative phase to have any potential clinical relevance, and possibly even be more prominent at this stage than later. Numerous studies have indicated the importance of IL-6 as a reliable and particularly sensitive biomarker of inflammatory activation and a predictor of subsequent organ dysfunction and death. For example, higher plasma/serum concentrations of IL-6 have been associated with increased risk for major cardiopulmonary complications after general thoracic surgery, postoperative morbidity after cardiac surgery, postoperative complications, cognitive dysfunction after coronary artery surgery, increased risk of coronary heart disease, adverse postoperative outcome (mortality and complications) in elderly patients undergoing hip fracture surgery, and poor outcome and death after stroke.

The overall effect size of ketamine on IL-6 was large even when including, in a separate meta-analysis, the 3 studies using potent anti-inflammatory drugs in the perioperative period. This was especially true for surgeries with CPB in which ketamine reduced IL-6 concentrations to about one third of those of the control group. This effect size was of the same magnitude (or larger) as reported for pretreatment with methylprednisolone (30 mg/kg) in which IL-6 was measured at declamping of the aorta during CPB surgery or 60 minutes later. The effect of methylprednisolone in the former study, however, was short-lived and did not last beyond 1 hour after termination of the extracorporeal circulation.

According to the GRADE approach the evidence level is rated high because it is based upon RCTs. Studies with questionable quality did not enter the qualitative analysis, while studies that included potent anti-inflammatory drugs did not enter the quantitative analysis. The meta-analysis showed consistent data for the chosen endpoint. The data, however, were inconsistent with regard to the duration of action of intraoperative ketamine. There are no signs of publication bias. Perhaps the weakest of the GRADE evidence elements is related to directness, because IL-6 may be a "narrow" or rather indirect measure of inflammation and its clinical consequences.

According to GRADE, a dose–response association would strengthen the evidence. In the present review neither a more pronounced effect nor a longer duration of action was seen, although the doses ranged from a single subanesthetic dose up to doses required for full ketamine-based anesthesia. This lack of dose response is difficult to understand, but the studies all have in common the fact that a bolus dose of at least 0.15 mg/kg ketamine was given before the surgical intervention. If this bolus dose is at the top of the dose-response curve for ketamine’s anti-inflammatory effect, higher bolus doses or infusion may be futile. However, the study of Welters comparing ketamine anesthesia with sufentanil-based anesthesia presents important evidence that ketamine itself has an anti-inflammatory effect.

Although not derived from the meta-analysis, it is noteworthy that the duration of action of intraoperative ketamine differed substantially among studies. Duration of up to 6 hours postoperatively was documented in the present review. Furthermore, some of the studies reported duration of action of up to 24 hours, or even up to 8 days. Although there are statistical concerns with the last 3 studies, the findings are corroborated by other reports (not included in this review), showing long-term effects (5 to 7 days) after short-duration infusions (4 hours or less) of ketamine in both depression and pain relief in patients with critical limb ischemia.

Most of the studies included other measures of inflammation in addition to IL-6. Among these were C-reactive protein, IL-8, IL-10, and TNFα. Only the data for IL-10 were consistent, showing that ketamine increased the concentrations of this anti-inflammatory cytokine, providing further evidence to the main observation of this review, i.e., that ketamine plays an anti-inflammatory role. Moreover, since the most consistent finding was related to IL-6, this review lends credibility to the suggestion that ketamine primarily acts as an anti-inflammatory drug.

Several potentially interesting studies written in Chinese were identified. Since one of the authors (Y.L.) is a native Chinese, it was decided to do a preliminary evaluation of these studies in addition to the primary papers written in English. These studies for reasons stated above added little. However, the study comparing the effect of ketamine on IL-6, as a part of the acute pain control regimen in burn patients, attracted attention, since evidence suggests a role for inflammation as an inducer of microglial-mediated hyperalgesia. Interestingly, the effect size reported by Xia et al. for IL-6 was of the same magnitude as that after CPB. The study also indicated that ketamine may potentially reduce the inflammatory response even when given after a trauma, at a time when biomarkers such as IL-6 are already increased.

Various studies, including clinical and preclinical research, in vivo and in vitro, have shown that in addition to

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its anesthetic activity, ketamine has an anti-inflammatory effect (for a recent review, see Loix et al.17). The mechanisms by which ketamine produces its anti-inflammatory actions needs to be elucidated. The acute analgesic effects of ketamine are generally believed to be mediated through the blockade of phencyclidine binding site of N-methyl-D-aspartate (NMDA) receptors of the nociceptive neurons; this mechanism could also partly account for the anti-inflammatory effects of ketamine. However, ketamine has also been reported to interact with opioid, monoamine, cholinergic, purinergic, and adenosine receptor systems. The functional anti-inflammatory effects of ketamine without affecting local healing processes (blunting neutrophil activation but sparing endothelial production of cytokines) shares similarities to those of LAs,13 which is considered to be due to their effect on G-protein-coupled-receptor signaling, specifically Gq downregulation.60 Because ketamine also has local anesthetic effects,60 it remains speculative as to whether they share a common anti-inflammatory mechanism.

Moreover, numerous mechanisms in addition to those discussed above have been shown to mediate the anti-inflammatory effects of ketamine. A nonexhaustive list of proposed mechanisms include inhibition of transcription factors nuclear factor-κB and activator protein 1,61 inhibition of proinflammatory cytokine production (IL-6 and TNFα),62-64 inhibition of neutrophil functions,65 the release of adenosine,66 the blockade of large-conductance KCa channels on microglia (BK channels),19 or the inhibition of nitric oxide production in macrophages.67 Ketamine has been shown to downregulate the proinflammatory enzymes cyclooxygenase 2 and inducible nitric oxide synthase, while preserving expression of the anti-inflammatory enzyme heme-oxygenase-1.68 This review does not shed light on the mechanisms of the anti-inflammatory action of ketamine in the perioperative period. Whether it is mediated by NMDA or non-NMDA mechanisms remains to be elucidated, but the finding of this review should certainly stimulate basic researchers to clarify these aspects.

In this systematic search, no studies examining any clinical outcome were found. Although there are some indications that IL-6 is associated with a clinical outcome,1-5,31-54,69 the bulk of evidence seems weak. Therefore, clinical outcome studies are warranted, and the evidence presented in this review suggests that subanesthetic single doses should be examined first. It is also intriguing to examine whether the anti-inflammatory effect of ketamine may have an impact on postoperative pain management.

DISCLOSURES

Name: Ola Dale, MD, PhD.
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