

ORIGINAL ARTICLE

Intraoperative Ketamine versus Micro-Dose Morphine Infusion during Thoracolumbar Laminectomy: Pain Trajectory and C-Reactive Protein Response in a Randomized Trial

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ABSTRACT

Background. Pain after spine surgery is often poorly controlled, and whether intraoperative ketamine also attenuates the early inflammatory response is uncertain.

Objective. To compare intraoperative ketamine with a micro-dose morphine infusion for early postoperative pain and high-sensitivity C-reactive protein (hs-CRP) after thoracolumbar laminectomy, in a corrected re-analysis of a published trial.

Methods. In this double-blind randomized trial at Dr. Moewardi Regional General Hospital, Surakarta, Indonesia, 24 adults undergoing elective thoracolumbar decompressive laminectomy received ketamine 10 µg/kg/min or morphine 10 µg/kg/h (n=12 each) from intubation to skin closure. Outcomes were visual analog scale (VAS) pain at 6 and 12 hours and hs-CRP before and 6 hours after surgery, analyzed with 95% confidence intervals (CI) and baseline-adjusted analysis of covariance.

Results. At 6 hours, VAS was lower with ketamine (2.33 vs 3.83; difference -1.50, 95% CI -2.28 to -0.72; Holm-adjusted p=0.001) but not at 12 hours (5.25 vs 5.67; -0.42, -1.32 to 0.49; p=0.660), when 20 of 24 patients (83.3%) scored above 4. hs-CRP rose in every patient; adjusted for baseline, the 6-hour value was 1.28 mg/L lower with ketamine (95% CI 0.53 to 2.03; Holm-adjusted p=0.006), an effect not explained by the imbalance in duration of surgery. Rescue analgesia did not differ (2/12 vs 3/12; p=1.000).

Conclusion. Compared with a micro-dose morphine infusion, intraoperative ketamine improved analgesia for the first postoperative hours and attenuated the early hs-CRP rise, but neither regimen controlled pain at 12 hours; analgesia must extend beyond the operating room.

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1. Introduction

Decompressive laminectomy ranks among the most common spinal operations. Early recovery afterward depends largely on pain control. Current cohorts show that this control is still inadequate. Among 1,294 patients having elective spine surgery, 56.9% reported a mean pain score above 4 in the first 24 hours, and poor control independently predicted failure to reach a clinically important improvement in long-term patient-reported outcomes (odds ratio 2.35).¹ In a population-based Chinese cohort of 26,193 surgical patients, 48.7% had moderate-to-severe pain on the first day after surgery, and the prevalence exceeded 40% after spinal fusion.² Poorly controlled acute pain has lasting consequences. At 3 months after spinal surgery, chronic postsurgical pain affects 28.9–42.9% of adults³ and 24.2% of young patients who had scoliosis fusion.⁴ Persistent opioid use follows major spine surgery in 46.3% of patients⁵ and occurs even in 9% of those who were opioid-naïve before the operation.⁶ High in-hospital opioid trajectories raise the odds of opioid use at 6 months almost fourfold.⁷ Greater acute pain also predicts failure to reach a clinically important functional gain after lumbar fusion.⁸

Two biological processes start in the operating room. Nociceptive input from dissected muscle, removed lamina and retracted nerve roots activates N-methyl-D-aspartate (NMDA) receptors in the dorsal horn, which initiates central sensitization. At the same time, tissue injury releases damage-associated molecular patterns. These drive the release of interleukin-6 (IL-6) and the hepatic acute-phase response that is measured as C-reactive protein (CRP). Experimental studies link the two through glial and macrophage signaling. Morphine activates Toll-like receptor 4 (TLR4) and downstream cytokine production in microglia and macrophages.⁹ In microglia, HMGB1-TLR4 signaling produces opioid-induced hyperalgesia by way of NMDA-receptor phosphorylation,¹⁰ and repeated morphine aggravates post-injury allodynia alongside spinal microgliosis.¹¹ Ketamine and its S-enantiomer, by contrast, suppress spinal glial activation, mitogen-activated protein kinase (MAPK) signaling and pro-inflammatory macrophage polarization in rodent models.^{12–14} Such findings make ketamine an attractive candidate for dampening both pain and inflammation. Caution is needed, because these findings come from animal and cell systems at exposures that do not translate directly to a 2-hour intraoperative infusion.

In spine surgery, clinical evidence for the analgesic effect of ketamine is firmer than that for an anti-inflammatory effect. One meta-analysis of 28 randomized trials reported that perioperative ketamine cut 24-hour opioid consumption by about 18 mg morphine equivalents, although certainty was low.¹⁵ Another, covering 30 trials, found lower pain scores 12–48 hours after surgery.¹⁶ The inflammatory data are mixed. Esketamine lowered IL-6 and tumor necrosis factor- α (TNF- α) after laminectomy for lumbar stenosis¹⁷ and lowered IL-6 and CRP relative to remifentanyl,¹⁸ but two colorectal trials found no effect on IL-6 or CRP.^{19,20} In a meta-analysis of 14 trials, eight in cardiopulmonary bypass surgery, ketamine reduced the early rise in IL-6.²¹ CRP kinetics complicate interpretation. After lumbar surgery the marker peaks about 3 days after the operation,^{22,23} and operating time, number of fused levels and blood loss predict the size of that peak.²² A sample drawn 6 hours after surgery therefore captures only the rising limb of the response.²⁴

Indonesian data are sparse. A pilot trial in Jakarta measured IL-6 and pain at 6 and 12 hours after lumbar decompression in eight patients.²⁵ Low-dose ketamine has also been studied for postoperative sedation in an Indonesian intensive care unit.²⁶ No Indonesian randomized trial of intraoperative ketamine in spine surgery with an inflammatory end point was identified. Trials from Thailand and Malaysia have tested regional blocks, nefopam and ketamine-containing analgesia after spinal and abdominal surgery,^{27–30} and in our judgment their results transfer more directly to Indonesian public hospitals than do trials from high-income settings. At the study hospital, a continuous micro-dose morphine background infusion was established intraoperative practice, so it was the natural comparator for a ketamine regimen.

The objective was to compare an intraoperative ketamine infusion (10 $\mu\text{g/kg/min}$) with a micro-dose morphine infusion (10 $\mu\text{g/kg/h}$). Outcomes were pain at 6 and 12 hours and the high-sensitivity CRP (hs-CRP) response 6 hours after thoracolumbar decompressive laminectomy at Dr. Moewardi Regional General Hospital, Surakarta, Indonesia. We report effect sizes with confidence intervals and adjust the inflammatory outcome for its baseline. We also quantify which conclusions are robust to covariates that were not recorded jointly with the outcomes. The hypothesis was that ketamine would lower 6-hour pain and attenuate the early hs-CRP rise.

2. Methods

2.1. Study design and reporting

This trial was prospective, single-center, parallel-group and double-blind, with randomized 1:1 allocation. It is reported according to the Consolidated Standards of Reporting Trials (CONSORT) 2010 statement, and the completed checklist is in Supplementary File 2. The present article supersedes an earlier report of the same trial.³⁰ All analyses were recomputed from the trial's statistical output. The main corrections involve the basis of the sample-size calculation, the test used for the change in hs-CRP, the description of eligibility, the definition of the rescue-analgesia window and the presentation of the figures. No outcome was added or removed. The threshold-based pain proportions and the sensitivity analyses are post hoc and are labeled as such.

The allocation sequence was generated by an independent biostatistician using a computer-based random-number algorithm. It was concealed in sequentially numbered, sealed, opaque envelopes, which a research team member not involved in patient care opened after enrollment. An anesthesiology resident with no other role in the trial prepared the infusions. These were made up in identical 50-mL syringes, diluted with normal saline to the same volume and appearance, and labeled only with the study identifier and randomization number. The same resident set and started the infusion pumps. Patients, attending anesthesiologists, surgeons, post-anesthesia care unit (PACU) and ward nurses, and outcome assessors did not know the allocation. The code was broken only once data collection and the initial analysis were complete. Blinding success was not formally assessed, and the clinical teams reported no instance of apparent unblinding.

2.2. Setting

The trial took place in the Central Surgical Installation of Dr. Moewardi Regional General Hospital, a regional public referral hospital in Surakarta, Central Java, Indonesia, between April and May 2025.

2.3. Participants and eligibility

Adults scheduled for elective thoracolumbar decompressive laminectomy under general anesthesia were screened at the preoperative anesthesia assessment. Eligible patients had American Society of Anesthesiologists (ASA) physical status I or II, could understand and use the visual analog scale (VAS), and gave written consent. Exclusion criteria were as follows: a history of hypersensitivity or contraindication to ketamine or morphine; severe cardiovascular (atherosclerotic disease, acute coronary syndrome, chronic hypertension), renal (end-stage chronic kidney disease), neurological (stroke), hepatic (cirrhosis), respiratory (pneumonia, tuberculosis), endocrine (metabolic syndrome, type 2 diabetes) or immune (AIDS, severe autoimmune) disease; cancer diagnosed within the previous 3 years, or current chemotherapy or radiotherapy; chronic pain requiring regular opioids; pregnancy or lactation; and cognitive or communication barriers that precluded reliable use of the VAS. Withdrawal was planned after a hypersensitivity reaction to a study drug, a major intraoperative cardiorespiratory event or need for non-protocol analgesia, severe psychotomimetic effects requiring treatment, or withdrawal of consent. No participant met any withdrawal criterion. The number of patients screened and the reasons for non-enrollment were not recorded.

2.4. Sample size

The calculation assumed a standard deviation (SD) of 1 VAS point, a minimal clinically important difference of 1 point, 80% power and α of 0.05. It used a one-sided critical value ($Z_{\alpha} = 1.64$), which gives 12.3 patients per arm, rounded to 12. Under the same assumptions, a two-sided calculation requires 16 (normal approximation) to 17 (t distribution) patients per arm. With 12 per arm, the trial had 65% power for a two-sided test of the planned difference (77% one-sided). Its minimum detectable standardized difference at 80% power was 1.20. For this reason, results are reported with confidence intervals, and the precision achieved is shown explicitly.

2.5. Variables and operational definitions

No sedative premedication was given. Standard ASA monitoring was applied, and anesthesia was induced with fentanyl 2 µg/kg, propofol 1–2.5 mg/kg and atracurium 0.5 mg/kg. It was maintained with sevoflurane in an air-oxygen mixture, titrated to hemodynamic targets. The blinded infusion began after tracheal intubation: ketamine 10 µg/kg/min (0.6 mg/kg/h) or morphine 10 µg/kg/h, with no loading dose in either arm. The ketamine rate falls within the sub-anesthetic range used for intraoperative analgesia. The morphine regimen mirrored the hospital's practice of a continuous low-level opioid background infusion, and it was not meant to serve as the sole analgesic. Infusions continued until the end of skin closure. Given the duration of surgery, the infused dose averaged approximately 1.33 mg/kg of ketamine or 26 µg/kg of morphine (Table 1). At the start of skin closure, all patients received intravenous paracetamol 1 g. After reversal of neuromuscular block and extubation, they were taken to the PACU and then to the ward.

The prespecified primary outcomes were the VAS score at 6 and 12 hours and the hs-CRP response. The prespecified key biological outcome was the change in hs-CRP from baseline. In this analysis, the treatment effect on that outcome was estimated mainly by analysis of covariance (ANCOVA) of the 6-hour value, adjusted for baseline. This approach estimates the same contrast as the change score. It is also more precise and unbiased under chance baseline imbalance,³¹ and the change-score estimate is reported alongside it. The secondary outcome was intravenous tramadol rescue analgesia, given on patient request or for a VAS score above 4. The window ran from the end of surgery until the 12-hour assessment, which closed the observation period. Because VAS was assessed at 6 and 12 hours, a score-triggered rescue within the window could occur only at the 6-hour assessment. Post hoc, we derived the proportions of patients with VAS ≥4 (moderate or worse pain), VAS >4 (the rescue threshold) and VAS ≥7 (severe pain) at each time point. Age, sex, body mass index (BMI), ASA status and duration of surgery were recorded at baseline. Adverse events were not systematically recorded.

2.6. Data sources and measurement

Pain intensity was measured on a 10-cm VAS anchored at 0 (no pain at all) and 10 (worst pain imaginable). The reverse side of the scale carries the corresponding numbers, and scores were recorded as whole numbers. A trained research nurse, blinded to allocation, recorded the score 6 and 12 hours after the end of surgery. Venous blood for hs-CRP was drawn 12 hours before surgery and 6 hours after surgery. Samples were analyzed in the central hospital laboratory with a standardized immunoturbidimetric assay, and results are reported in mg/L. The 6-hour sample was chosen to capture the early rise of the acute-phase response, which after lumbar surgery peaks about the third postoperative day.^{22,23}

2.7. Statistical analysis

Data source. The original analysis was run in IBM SPSS Statistics, version 25. This re-analysis used the SPSS output generated from the trial database. For every variable, overall and by arm, it contained the number of observations, mean, SD (to three to five decimals), minimum and maximum. It also held the Shapiro–Wilk and Kolmogorov–Smirnov statistics; the Mann–Whitney U, Wilcoxon W and Z statistics with asymptotic and exact p

values; the Wilcoxon signed-rank statistic for the pooled hs-CRP change; chi-square and Fisher exact tests; and Levene and t tests with 95% confidence intervals (CI). Patient-level records were not used.

Identification of pain distributions. VAS scores were whole numbers on a bounded scale, with 12 patients per arm. The set of distributions compatible with the reported statistics was therefore finite. We enumerated exhaustively all integer distributions on the observed range that matched the reported number of observations, mean, SD (to three decimals), minimum and maximum. Those whose Shapiro–Wilk W and p values (to three decimals) matched the reported values were retained, and exactly one distribution remained for each arm and time point. These distributions reproduced the reported Mann–Whitney U and Z statistics and the pooled Shapiro–Wilk statistics exactly. They were then used to compute medians, interquartile ranges (IQR), Hodges–Lehmann shifts, exact permutation p values and threshold proportions. The pairing of 6-hour and 12-hour scores within patients was constrained by the reported change scores. It admitted two configurations in the ketamine arm and one in the morphine arm. Analyses that depend on pairing used the change-score SDs, which are identical for every admissible pairing.

Estimation. Between-arm mean differences (ketamine minus morphine) were estimated with Welch 95% CI and standardized as Hedges g, with CI from the noncentral t distribution. Rank-based effects were summarized by the rank-biserial correlation and the Hodges–Lehmann shift with a Moses 95% CI (critical U=37 for 12 versus 12), and they were tested with exact permutation tests that respect ties. For hs-CRP, the within-arm covariance between baseline and 6-hour values was derived from the SDs of the baseline, 6-hour and change values: $\text{cov} = (\text{SD}_{\text{pre}}^2 + \text{SD}_{\text{post}}^2 - \text{SD}_{\text{change}}^2)/2$. These covariances and the arm means are the sufficient statistics for ANCOVA. The analysis was therefore computed exactly, with a test of the homogeneity of regression slopes, and its sensitivity to rounding was checked by repeating it with the two-decimal SDs printed in the earlier report. Baseline hs-CRP was skewed, and a log-scale analysis was not possible without patient-level data, so rank-based tests are reported alongside. The ratio of mean increases was estimated with a Fieller CI. The 6-to-12-hour pain trajectory was also described by ANCOVA of the 12-hour score on the 6-hour score. Because the 6-hour score is measured after randomization, this contrast is descriptive and not a randomized comparison. Proportions are reported with Wilson 95% CI, risk differences with Newcombe hybrid-score CI, and odds ratios by conditional maximum likelihood with exact CI and Fisher exact tests. Baseline balance is described by standardized mean differences (Hedges g), not by significance tests. The four primary comparisons (VAS at 6 and 12 hours, unadjusted 6-hour hs-CRP and ANCOVA-adjusted 6-hour hs-CRP) were adjusted for multiplicity with the Holm procedure. Post hoc, threshold proportions were compared descriptively with published spine-surgery cohorts.

Sensitivity analyses over unrecorded quantities. The joint distributions of duration of surgery, age and BMI with the outcomes, and of pain with hs-CRP, were not recorded. Three analyses quantified what the data can support without them. First, a tipping-point analysis computed duration-adjusted treatment effects for every value from –1 to 1 of a common within-arm correlation (ρ) between duration and the outcome. Second, we considered models

adjusting for duration alone or for age, BMI and duration (and for baseline in models of 6-hour hs-CRP). For each model, 40,000 within-arm correlation matrices were sampled independently for each arm with a partial-correlation (C-vine) parameterization, which spans every positive-definite correlation matrix. The adjusted effect, its p value and its sign were computed for each matrix. Hill-climbing from 40 random starts in each direction searched for the extreme adjusted effects among non-degenerate matrices (smallest eigenvalue ≥ 0.05). Third, the attainable pooled correlation between 6-hour VAS and the hs-CRP change across all 24 patients was computed over every admissible pair of within-arm correlations. An association was regarded as identified only if its entire attainable range lay on one side of the null. The share of sampled matrices meeting a criterion depends on the sampling measure. Robustness was therefore judged from the attainable ranges, and the shares are given as secondary description. All adjustment models assumed linear, additive covariate effects common to both arms.

Software and conventions. Analyses were run in Python 3.13 with SciPy 1.18, statsmodels 0.15 and NumPy 2.4. Figures were drawn with Matplotlib 3.10. All tests were two-sided with $\alpha = 0.05$, and p values are reported to three decimals.

2.8. Ethics

The CMHC Research Center Ethics Committee, Indonesia, approved the protocol in 2024 (Approval No. 2024/8333), before enrollment began. Each participant received a verbal and written explanation of the study's aims, procedures, risks and benefits. Written informed consent was obtained before randomization. The trial followed the Declaration of Helsinki.

3. Results

3.1. Participants and baseline characteristics

Twenty-four patients were randomized, 12 to each arm. All received the allocated infusion, none withdrew or was lost to follow-up, and all were analyzed as randomized. Table 1 lists the baseline characteristics. Mean age was 48.25 years in the ketamine arm and 46.00 years in the morphine arm (Hedges g 0.23), and each arm included seven men and five women. Mean BMI was 22.58 and 23.96 kg/m², respectively (Hedges g -0.34). Operations were shorter in the ketamine arm by a mean of 23.58 minutes (95% CI -50.31 to 3.15; Hedges g -0.72). Baseline hs-CRP was low and similar in the two arms (0.85 and 1.05 mg/L; Hedges g -0.26).

Table 1. Baseline characteristics of the randomized participants.

Characteristic	Ketamine (n=12)	Morphine (n=12)	Difference, K-M (95% CI)	Hedges g
Age, years	48.25 ± 10.31 (32–67)	46.00 ± 8.43 (28–60)	2.25 (-5.73 to 10.23)	0.23
Male sex, n (%)	7 (58.3)	7 (58.3)	0.0 pp (-34.6 to 34.6)	0.00
Body mass index, kg/m ²	22.58 ± 4.29 (17.50–29.70)	23.96 ± 3.59 (18.60–29.80)	-1.38 (-4.73 to 1.96)	-0.34
ASA physical status I–II, n (%)	12 (100)	12 (100)	—	—
Duration of surgery, min	133.17 ± 31.14 (90–187)	156.75 ± 31.98 (90–200)	-23.58 (-50.31 to 3.15)	-0.72
hs-CRP before surgery, mg/L	0.85 ± 0.83 (0.10–3.10)	1.05 ± 0.72 (0.20–2.50)	-0.21 (-0.86 to 0.45)	-0.26
Approximate infused dose per kg*	ketamine ≈ 1.33 mg/kg (0.90–1.87)	morphine ≈ 26 µg/kg (15–33)	—	—

Notes: Values are mean ± SD (range) unless stated otherwise. K–M, ketamine minus morphine; Hedges g, standardized mean difference (bias-corrected difference divided by the pooled SD); pp, percentage points; hs-CRP, high-sensitivity C-reactive protein. *Infusion rate multiplied by the mean (range) duration of surgery, which approximates the infusion period from intubation to skin closure.

3.2. Postoperative pain

Table 2 summarizes the pain scores, and Figure 1 shows their full distributions. At 6 hours, pain was lower in the ketamine arm (mean 2.33 ± 0.78; median 2.0 [IQR 2.00–3.00]) than in the morphine arm (3.83 ± 1.03; median 3.5 [3.00–4.75]). The mean difference was -1.50 points (95%

CI -2.28 to -0.72), the Hodges–Lehmann shift was -1.0 (-2.0 to -1.0), and Hedges g was -1.59 (-2.48 to -0.67). The exact p value was <0.001. The Holm-adjusted p value was 0.001. Seven of the 12 ketamine patients scored 2, and only one scored 4, whereas half of the morphine patients scored 4 or more.

Table 2. Postoperative pain (visual analog scale, 0–10).

Outcome	Ketamine (n=12)	Morphine (n=12)	Mean difference, K-M (95% CI)	Hodges–Lehmann shift (95% CI)	Hedges g (95% CI)	r (rank-biserial)	Exact p	Holm p
VASat 6 h	2.33 ± 0.78 2.0 [2.00–3.00]	3.83 ± 1.03 3.5 [3.00–4.75]	-1.50 (-2.28 to -0.72)	-1.0 (-2.0 to -1.0)	-1.59 (-2.48 to -0.67)	-0.77	<0.001	0.001
VASat 12 h	5.25 ± 0.87 5.5 [4.25–6.00]	5.67 ± 1.23 5.0 [5.00–6.00]	-0.42 (-1.32 to 0.49)	0.0 (-1.0 to 1.0)	-0.38 (-1.15 to 0.41)	-0.10	0.660	0.660
Change, 6 h to 12 h	2.92 ± 0.90 3.0 [2.00–4.00]	1.83 ± 0.83 2.0 [1.00–2.00]	1.08 (0.35 to 1.82)	1.0 (0.0 to 2.0)	1.20 (0.34 to 2.04)	0.62	0.006	—
VASat 12 h adjusted for 6 h†	—	—	0.67 (-0.28 to 1.63)	—	partial η^2 0.09	—	0.156	—

Notes: Arm values are mean ± SD and, on the second line, median [interquartile range]; the distributions are those uniquely implied by the trial's reported statistics (Figure 2). Mean differences with Welch 95% CI; Hedges g with noncentral-t 95% CI; exact permutation p (Mann–Whitney, ties respected); Holm adjustment across the four primary comparisons. Negative values favor ketamine. The Hodges–Lehmann point estimate can coincide with a confidence limit because the scores are integers. Differences are calculated from unrounded values. †Descriptive trajectory model (ANCOVA of the 12-h score on the 6-h score); because the 6-h score is measured after randomization, this contrast is not a randomized comparison.

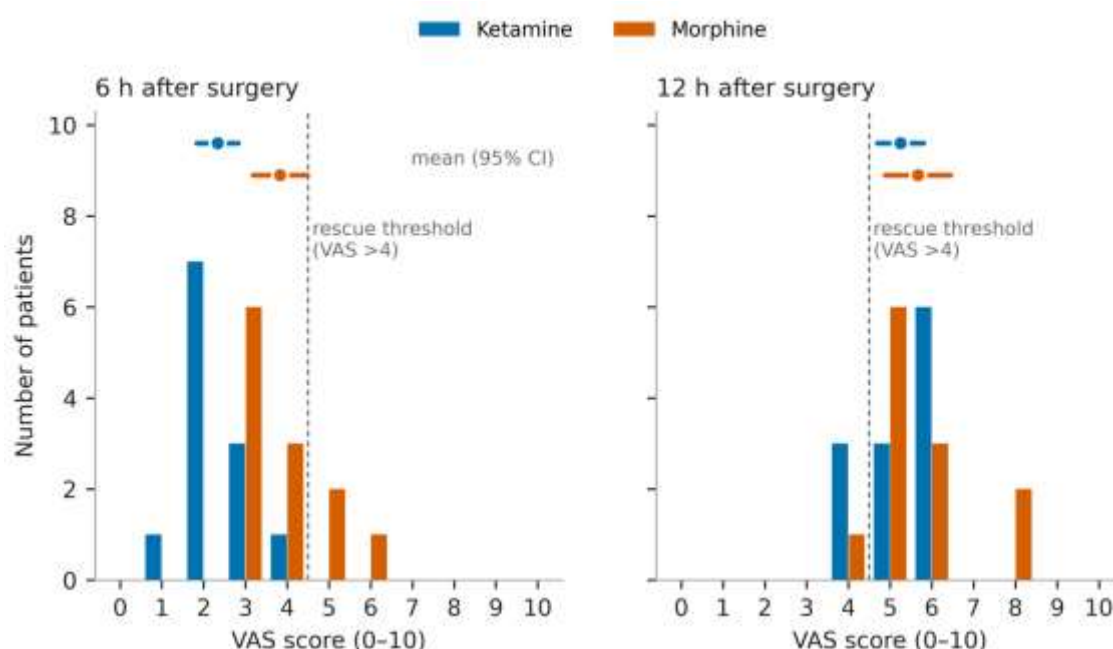


Figure 1. Distribution of pain scores (visual analog scale, 0–10) at 6 h and 12 h after surgery. Bars show the number of patients at each score in the ketamine (blue) and morphine (orange) arms; these distributions are uniquely implied by the trial's reported statistics. Points with horizontal bars show the arm mean and t-based 95% confidence interval. The dashed line marks the rescue threshold (VAS >4).

At 12 hours the difference was small and imprecise: 5.25 ± 0.87 with ketamine and 5.67 ± 1.23 with morphine (mean difference -0.42 , 95% CI -1.32 to 0.49 ; Hedges g -0.38 , -1.15 to 0.41 ; exact $p=0.660$). Pain rose in every patient between 6 and 12 hours, by at least 2 points with ketamine and at least 1 point with morphine. The rise was larger with ketamine (2.92 ± 0.90 vs 1.83 ± 0.83 ; difference 1.08 , 95% CI 0.35 to 1.82 ; exact $p=0.006$) (Figure 3). Within each arm,

the correlation between the 6-hour and 12-hour scores was 0.40 with ketamine and 0.74 with morphine. Conditional on the 6-hour score, 12-hour pain did not differ significantly between arms (0.67 , 95% CI -0.28 to 1.63 ; $p=0.156$). The steeper rise with ketamine therefore reflected the loss of an early advantage. It was not a rebound above the level seen with morphine.

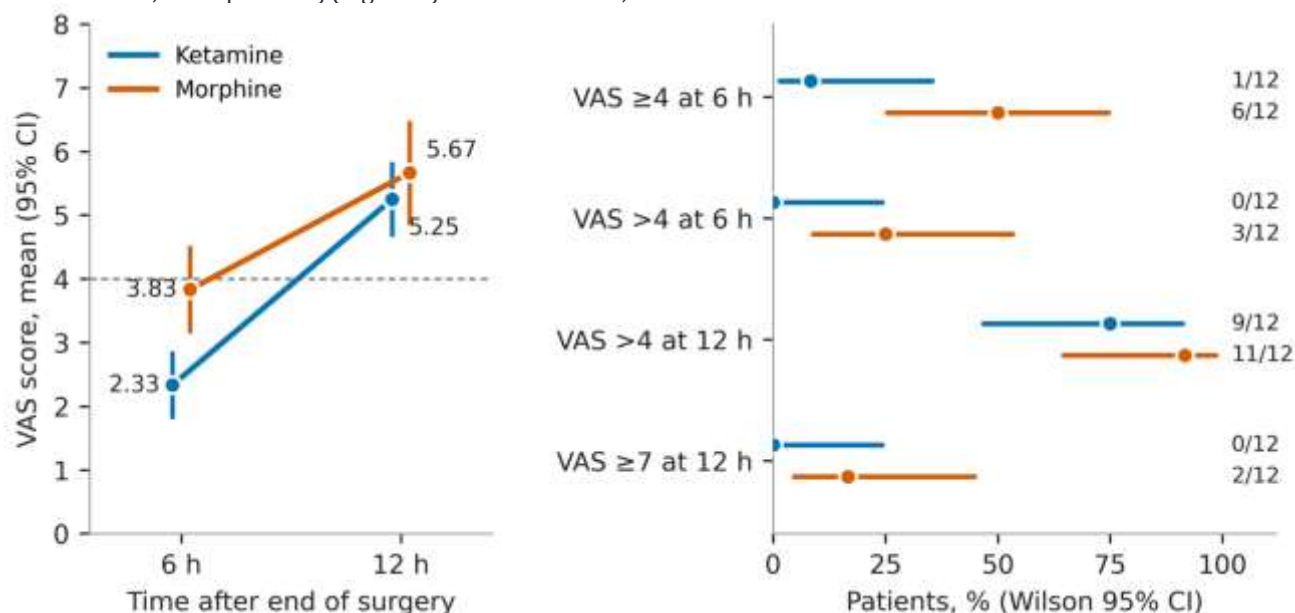


Figure 2. Pain trajectory and pain-threshold proportions. Left: mean VAS with 95% confidence intervals at 6 h and 12 h after surgery; the dashed line marks VAS 4. Right: percentage of patients at or above each threshold, with Wilson 95% confidence intervals and counts.

3.3. Pain thresholds and rescue analgesia

Table 3 and Figure 3 present the pain-threshold proportions and rescue analgesia. At 6 hours, one ketamine patient (8.3%) and six morphine patients (50.0%) had VAS ≥ 4 (risk difference -41.7 percentage points, 95% CI -67.2 to -5.1 ; Fisher $p=0.069$). No ketamine patient exceeded the rescue threshold, but three morphine patients (25.0%) did. At 12 hours, VAS exceeded 4 in 9 of 12 ketamine patients

(75.0%) and 11 of 12 morphine patients (91.7%). Across both arms, 20 of 24 patients (83.3%; 95% CI 64.1–93.3%) were above this level, and two morphine patients reported severe pain (VAS ≥ 7). Before the 12-hour assessment, two ketamine patients (16.7%) and three morphine patients (25.0%) received rescue tramadol (risk difference -8.3 percentage points, 95% CI -39.0 to 24.1 ; odds ratio 0.61, 0.04–6.70; Fisher $p=1.000$). In the morphine arm, rescue use corresponded to the three patients whose 6-hour score

exceeded 4. No ketamine patient exceeded 4 at 6 hours, so both rescues in that arm were given on request. About 370

patients per arm would be needed to detect the observed difference in rescue use (Cohen h 0.21).

Table 3. Pain-threshold proportions and rescue analgesia.

Outcome	Ketamine, n/N (%) [95% CI]	Morphine, n/N (%) [95% CI]	Total, n/N (%)	Risk difference, pp (95% CI)	Odds ratio (95% CI)	Fisher p
Rescue tramadol, end of surgery to 12-h assessment	2/12 (16.7) [4.7–44.8]	3/12 (25.0) [8.9–53.2]	5/24 (20.8)	–8.3 (–39.0 to 24.1)	0.61 (0.04–6.70)	1.000
VAS $\geq$ 4 at 6 h (moderate or worse)	1/12 (8.3) [1.5–35.4]	6/12 (50.0) [25.4–74.6]	7/24 (29.2)	–41.7 (–67.2 to –5.1)	0.10 (0.00–1.13)	0.069
VAS $\geq$ 4 at 6 h (rescue threshold)	0/12 (0.0) [0.0–24.2]	3/12 (25.0) [8.9–53.2]	3/24 (12.5)	–25.0 (–53.2 to 4.1)	not estimable (exact CI 0–2.29)	0.217
VAS $\geq$ 4 at 12 h (rescue threshold)	9/12 (75.0) [46.8–91.1]	11/12 (91.7) [64.6–98.5]	20/24 (83.3)	–16.7 (–45.7 to 14.8)	0.29 (0.00–4.31)	0.590
VAS $\geq$ 7 at 12 h (severe)	0/12 (0.0) [0.0–24.2]	2/12 (16.7) [4.7–44.8]	2/24 (8.3)	–16.7 (–44.8 to 10.4)	not estimable (exact CI 0–5.25)	0.478

Notes: Wilson 95% CI for proportions; Newcombe hybrid-score CI for risk differences; conditional maximum-likelihood odds ratio with exact CI (not estimable when a cell is zero). The Newcombe interval and the Fisher test are different methods and can disagree for small counts. The rescue window closed at the 12-h assessment; because VAS was assessed at 6 h and 12 h, a score-triggered rescue (VAS $\geq$ 4) could occur within the window only at the 6-h assessment, and rescue was otherwise given on patient request. pp, percentage points.

3.4. hs-CRP response

Table 4 and Figure 3 give the hs-CRP results. hs-CRP rose in every patient (24/24; 95% CI 86.2–100%; exact Wilcoxon $p=1.2 \times 10^{-7}$), from a pooled mean of 0.95 ± 0.76 to 3.10 ± 1.81 mg/L. The smallest individual increases were 0.21 mg/L in the ketamine arm and 1.20 mg/L in the morphine arm. Six hours after surgery, hs-CRP was 2.28 ± 1.64 mg/L with ketamine and 3.93 ± 1.63 mg/L with

morphine (difference -1.65 , 95% CI -3.03 to -0.27 ; Hedges g -0.98 ; exact Mann-Whitney $p=0.014$). The mean increase was 1.43 ± 1.04 mg/L with ketamine and 2.88 ± 1.06 mg/L with morphine (difference -1.44 , 95% CI -2.34 to -0.55 ; t -test $p=0.003$). The rise with ketamine was thus 50.3% smaller (95% CI 22.6–72.8%). The 6-hour mean was 2.69 times the baseline mean with ketamine and 3.73 times with morphine.

Table 4. High-sensitivity C-reactive protein (hs-CRP, mg/L).

hs-CRP	Ketamine (n=12)	Morphine (n=12)	Mean difference, K–M (95% CI)	t-test p	Hedges g (95% CI)	U	Exact Mann-Whitney p	Holm p
Before surgery	0.85 ± 0.83	1.05 ± 0.72	-0.21 (-0.86 to 0.45)	0.521	-0.26 (-1.03 to 0.52)	57	0.410	—
6 h after surgery	2.28 ± 1.64	3.93 ± 1.63	-1.65 (-3.03 to -0.27)	0.022	-0.98 (-1.79 to -0.14)	30	0.014	0.029
Change from baseline	1.43 ± 1.04	2.88 ± 1.06	-1.44 (-2.34 to -0.55)	0.003	-1.32 (-2.18 to -0.45)	22	0.003	—
6 h, adjusted for baseline (ANCOVA; primary)	—	—	-1.28 (-2.03 to -0.53)	0.002	partial η^2 0.38	—	—	0.006

Notes: Values are mean $\pm$ SD. ANCOVA computed from the arm means, SDs and within-arm baseline–6-h covariances ($r = 0.84$ ketamine, 0.87 morphine); common slope 1.80; homogeneity of slopes $p = 0.508$. Ratio of mean increases, ketamine/morphine: 0.50 (Fieller 95% CI 0.27–0.77), i.e. a 50.3% smaller rise (95% CI 22.6–72.8%); ratio of 6-h to baseline means 2.69 (ketamine) and 3.73 (morphine). Pooled means: 0.95 ± 0.76 mg/L before and 3.10 ± 1.81 mg/L 6 h after surgery. hs-CRP rose in all 24 patients (exact Wilcoxon $p = 1.2 \times 10^{-7}$). Levene test for the change: $F = 0.030$, $p = 0.864$. Holm adjustment across the four primary comparisons (two of which estimate the same hs-CRP contrast; a conservative choice). Differences are calculated from unrounded values.

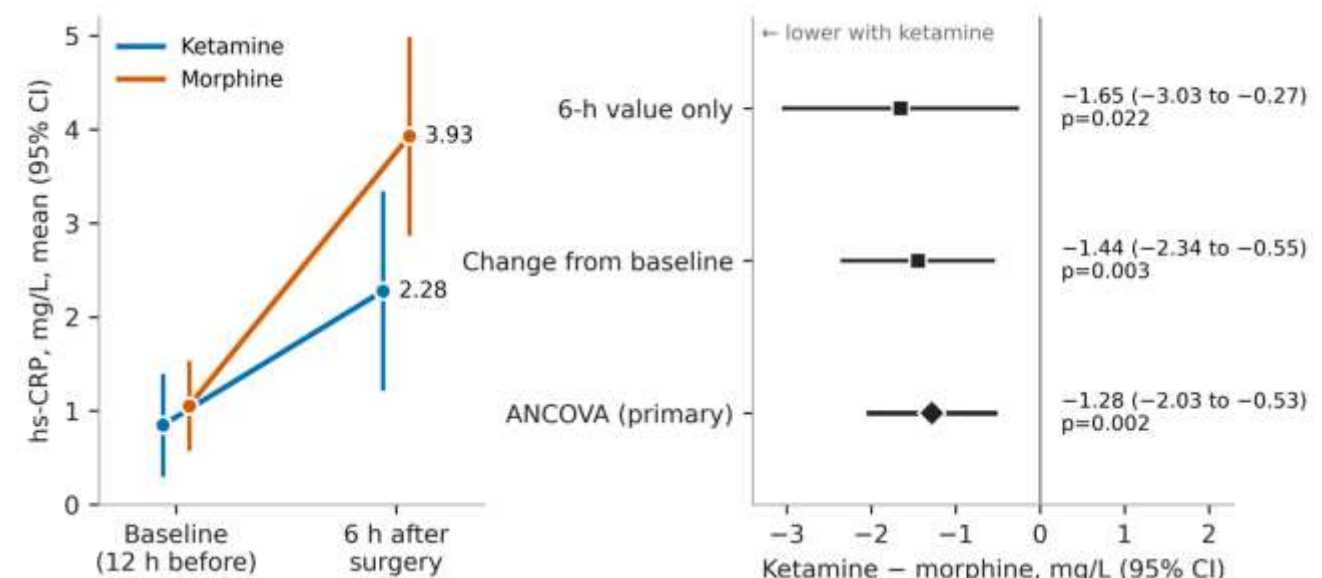


Figure 3. High-sensitivity C-reactive protein (hs-CRP) before and 6 h after surgery. Left: arm means with 95% confidence intervals. Right: ketamine-minus-morphine difference estimated from the 6-h value alone, from the change from baseline, and from analysis of covariance (ANCOVA) adjusting for baseline, with 95% confidence intervals and p values.

Within each arm, baseline and 6-hour values were strongly correlated ($r=0.84$ with ketamine and 0.87 with morphine). The common regression slope was 1.80 (homogeneity of slopes $p=0.508$), and baseline hs-CRP accounted for 73% of the within-arm variance of the 6-

hour value. After adjustment for baseline, the 6-hour hs-CRP was 1.28 mg/L lower with ketamine (95% CI -2.03 to -0.53 ; $p=0.002$; partial η^2 0.38). Using the two-decimal SDs of the earlier report left the estimate unchanged (-1.28 mg/L, 95% CI -2.02 to -0.54). The variances of the change

were similar in the two arms (Levene $F=0.030$, $p=0.864$). Holm adjustment was applied across the four primary comparisons. The 6-hour pain difference ($p=0.001$), the baseline-adjusted hs-CRP difference ($p=0.006$) and the unadjusted 6-hour hs-CRP difference ($p=0.029$) remained significant. The 12-hour pain difference did not ($p=0.660$).

3.5. Standardized effects

Figure 4 shows the standardized differences side by side. The largest effects were for 6-hour pain (Hedges g -1.59 , 95% CI -2.48 to -0.67) and the hs-CRP rise (-1.32 , -2.18 to -0.45). The 12-hour pain difference (-0.38 , -1.15 to 0.41) was small and imprecise. Among the baseline characteristics, only duration of surgery (Hedges g -0.72 , -1.51 to 0.09) came close to the size of the outcome effects.

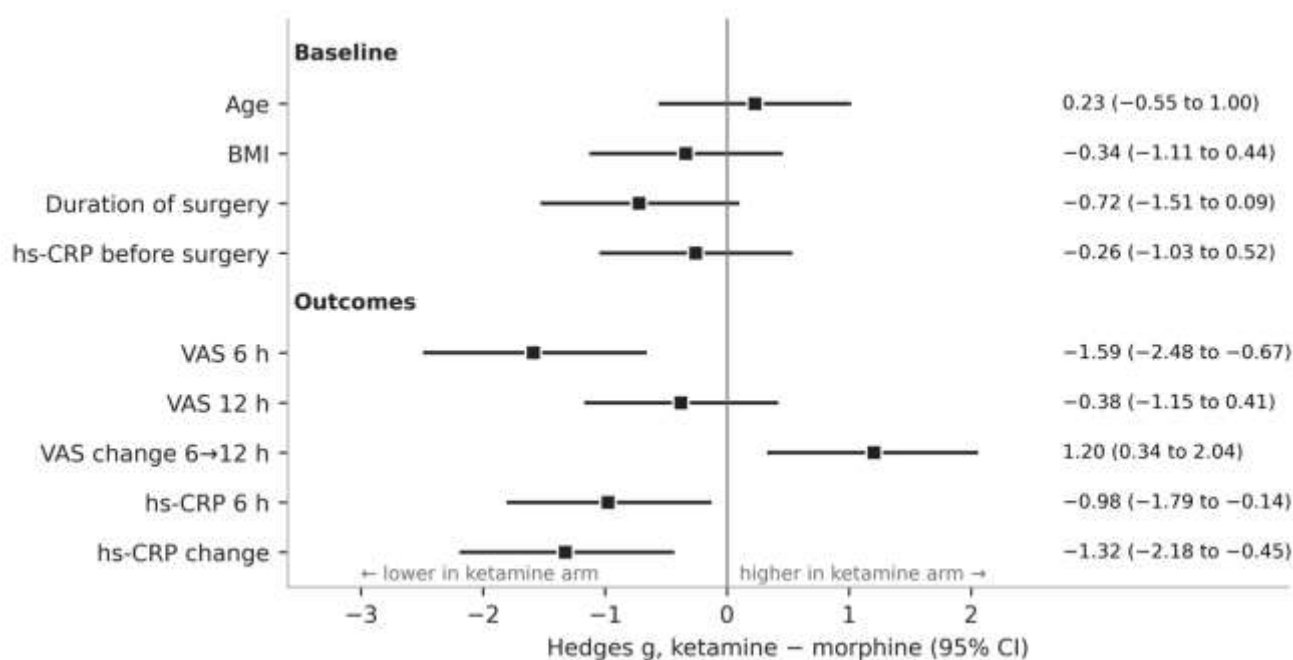


Figure 4. Standardized differences (Hedges g , ketamine minus morphine, with 95% confidence intervals) for baseline characteristics and outcomes. Negative values indicate lower values in the ketamine arm.

3.6. Sensitivity to confounding by unrecorded covariate structures

Duration of surgery was the largest baseline imbalance, so we examined its potential confounding across every possible within-arm correlation with the outcome (Table 5, Figure 5). For every correlation from -1 to 1 , the duration-adjusted hs-CRP rise stayed lower with ketamine (adjusted difference -2.23 to -0.66 mg/L) and was statistically

significant throughout. The same held for 6-hour pain (-2.18 to -0.82 points). The unadjusted 6-hour hs-CRP difference lost significance when the correlation lay between 0.11 and 0.95 , which is why the baseline-adjusted analysis is not affected in the same way (baseline hs-CRP is strongly correlated with the 6-hour value, $r=0.84$ – 0.87). For 12-hour pain, the estimate crossed zero at a correlation of 0.53 , and it was significant only under strong correlations (below -0.54 or above 0.95).

Table 5. Tipping-point analysis for confounding by duration of surgery.

Outcome	Unadjusted K–M	Adjusted K–M over ρ from -1 to 1	Share of ρ range with $p<0.05$	ρ where p crosses 0.05	ρ where the estimate crosses 0
hs-CRP change, mg/L	-1.44	-2.23 to -0.66	100%	never	never
hs-CRP at 6 h (not baseline-adjusted), mg/L	-1.65	-2.87 to -0.43	58%	0.11 and 0.95	never
VAS at 6 h	-1.50	-2.18 to -0.82	100%	never	never
VAS at 12 h	-0.42	-1.20 to 0.37	25%	-0.54 and 0.95	0.53

Notes: ρ is the within-arm correlation between duration of surgery and the outcome, assumed equal in the two arms; it was not recorded. The adjusted difference is the treatment coefficient of a linear model with duration as covariate, computed from the arm means and SDs for each p .

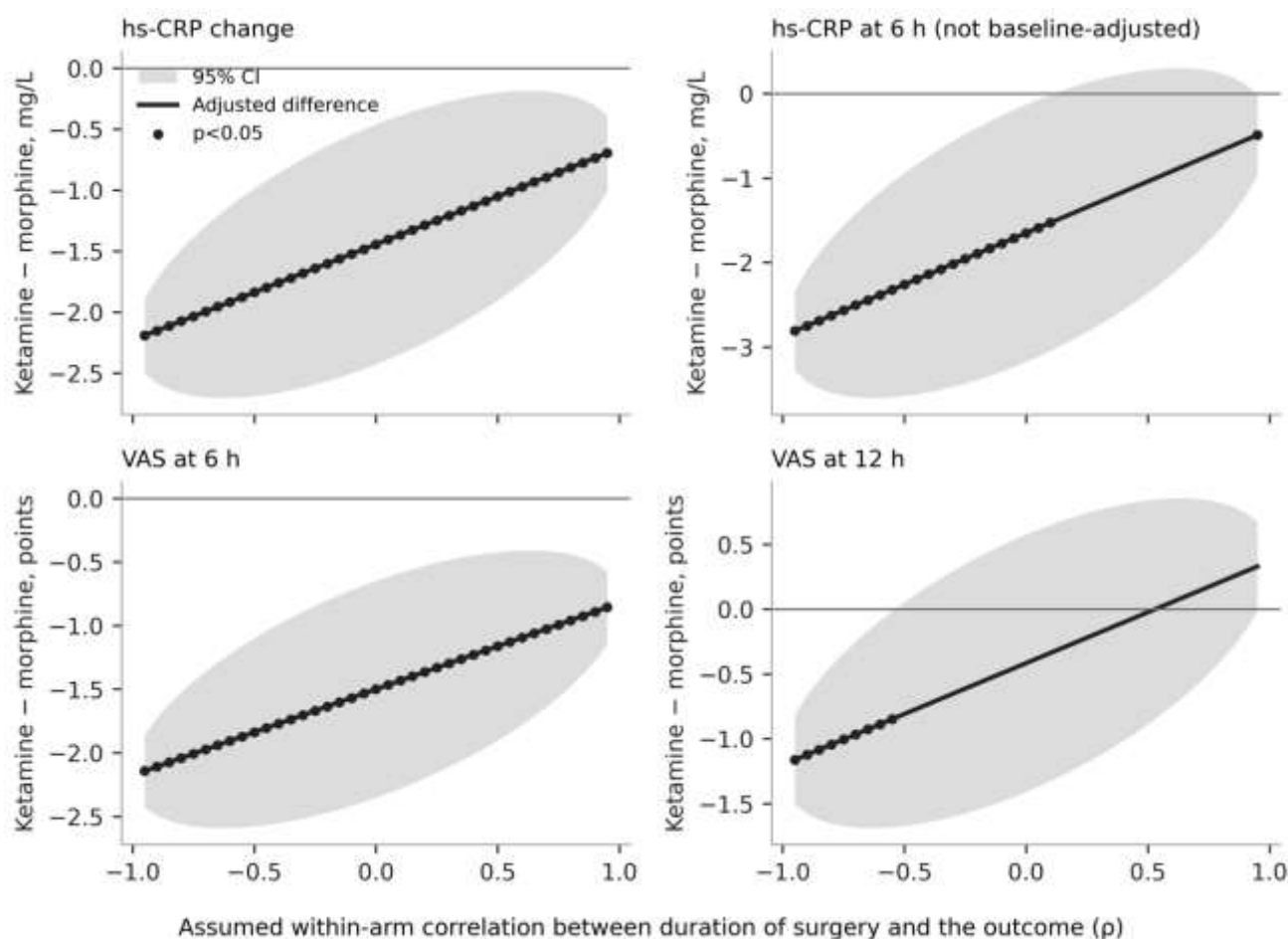


Figure 5. Tipping-point analysis for confounding by duration of surgery. Each panel shows the duration-adjusted ketamine-minus-morphine difference (line) and its 95% confidence interval (gray band) as a function of the assumed within-arm correlation (ρ) between duration and the outcome; dots mark values of ρ at which the adjusted difference remains statistically significant ($p < 0.05$).

We then allowed the within-arm correlations to differ between arms (Table 6, Figure 6). The exact attainable range was -2.19 to -0.70 mg/L for the duration-adjusted hs-CRP rise and -2.14 to -0.86 points for 6-hour pain. Duration alone could not reverse or remove either effect. Each model used 40,000 sampled structures. The baseline-adjusted 6-hour hs-CRP adjusted for duration was significant in 98.0% of them. With age, BMI and duration together, the adjusted effect kept the same direction in 99.9% (hs-CRP rise) and 99.8% (baseline-adjusted 6-hour

hs-CRP) of structures, and it was significant in 94.4% and 94.1%, respectively. For 6-hour pain, the corresponding proportions significant were 100% with duration alone and 98.4% with all three covariates. The 12-hour difference was significant in only 14.3% of structures. Its sign was unstable. Hill-climbing found the most extreme values, and these crossed zero only in the three-covariate models of the hs-CRP rise (up to 0.40 mg/L) and 6-hour pain (up to 0.08 points), at the edge of the admissible space.

Table 6. Multivariable bounds across admissible within-arm correlation structures.

Outcome Covariates	Unadjusted K-M	Median (central 95%) of admissible adjusted K-M	% of admissible structures with $p < 0.05$	% with the same sign as unadjusted	Most extreme values found*
hs-CRP change duration	-1.44	-1.44 (-2.05 to -0.83)	100.0	100.0	-2.19 to -0.70
hs-CRP change age, BMI, duration	-1.44	-1.45 (-2.16 to -0.74)	94.4	99.9	-3.25 to 0.40
hs-CRP 6 h baseline, duration	-1.65	-1.28 (-1.82 to -0.75)	98.0	99.9	-2.74 to -0.51
hs-CRP 6 h baseline, age, BMI, duration	-1.65	-1.28 (-1.98 to -0.58)	94.1	99.8	-2.57 to -0.11
VAS 6 h duration	-1.50	-1.50 (-2.03 to -0.97)	100.0	100.0	-2.14 to -0.86
VAS 6 h age, BMI, duration	-1.50	-1.50 (-2.13 to -0.88)	98.4	100.0	-3.03 to 0.08
VAS 12 h age, BMI, duration	-0.42	-0.42 (-1.15 to 0.31)	14.3	86.7	-2.07 to 1.43

Notes: For each model, 40,000 within-arm correlation matrices were drawn independently for each arm through a partial-correlation (C-vine) parameterization that spans every positive-definite matrix; the baseline-6-h hs-CRP correlation was fixed at its derived value. *Hill-climbing from 40 random starts in each direction over non-degenerate matrices (smallest eigenvalue ≥ 0.05); for duration-only models the search converged (38–39 of 40 restarts within 0.01 of the extreme) and the range is exact; for the other models only 1–3 restarts reached the reported value, so these are the most extreme values found and bound the attainable range from inside. The percentages depend on the sampling measure and are descriptive.

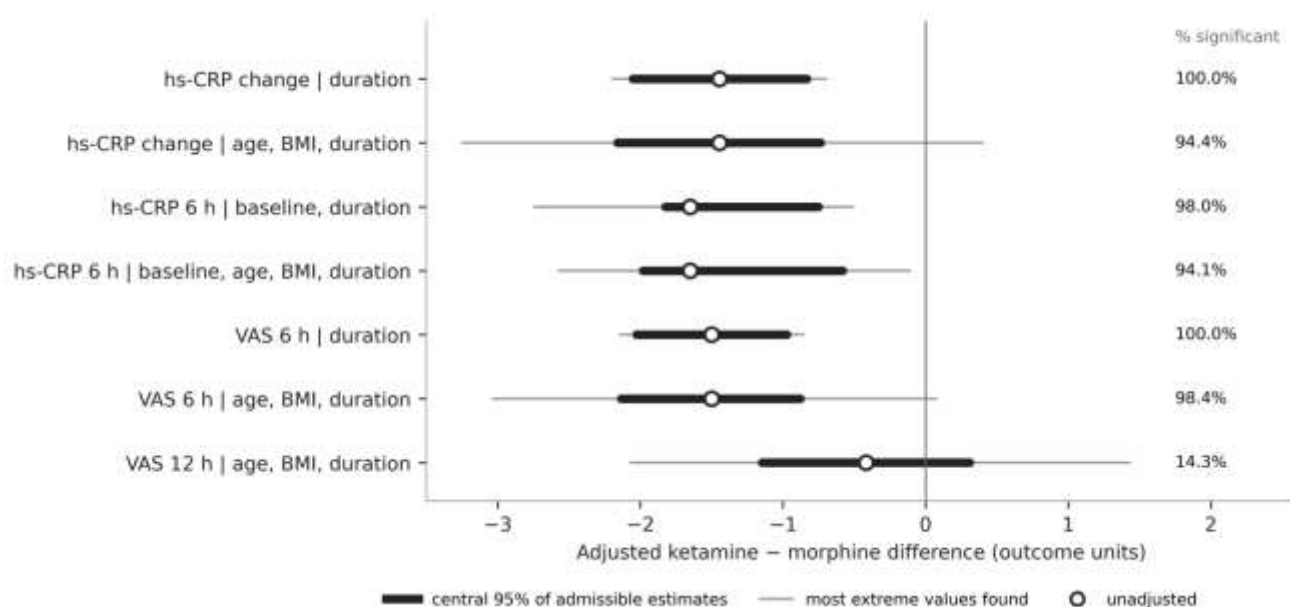


Figure 6. Multivariable bounds for the treatment effect. For each outcome and covariate set, the thick bar shows the central 95% of adjusted ketamine-minus-morphine differences across 40,000 admissible within-arm correlation structures, the thin line the most extreme values found by hill-climbing, and the open circle the unadjusted difference; the column on the right gives the percentage of admissible structures in which the adjusted difference was significant.

3.7. Association between pain and inflammation

The patient-level association between pain and inflammation could not be identified (Figure 8). The between-arm difference alone implies a pooled correlation of 0.38 between 6-hour VAS and the hs-CRP rise. The

within-arm correlations were not recorded, and depending on them the pooled correlation could lie anywhere from -0.23 to 0.99 . Of the admissible configurations, 46.4% yield a significant positive correlation and 53.6% a non-significant one. None yields a significant negative one. For 12-hour pain, the attainable range was -0.67 to 0.90 .

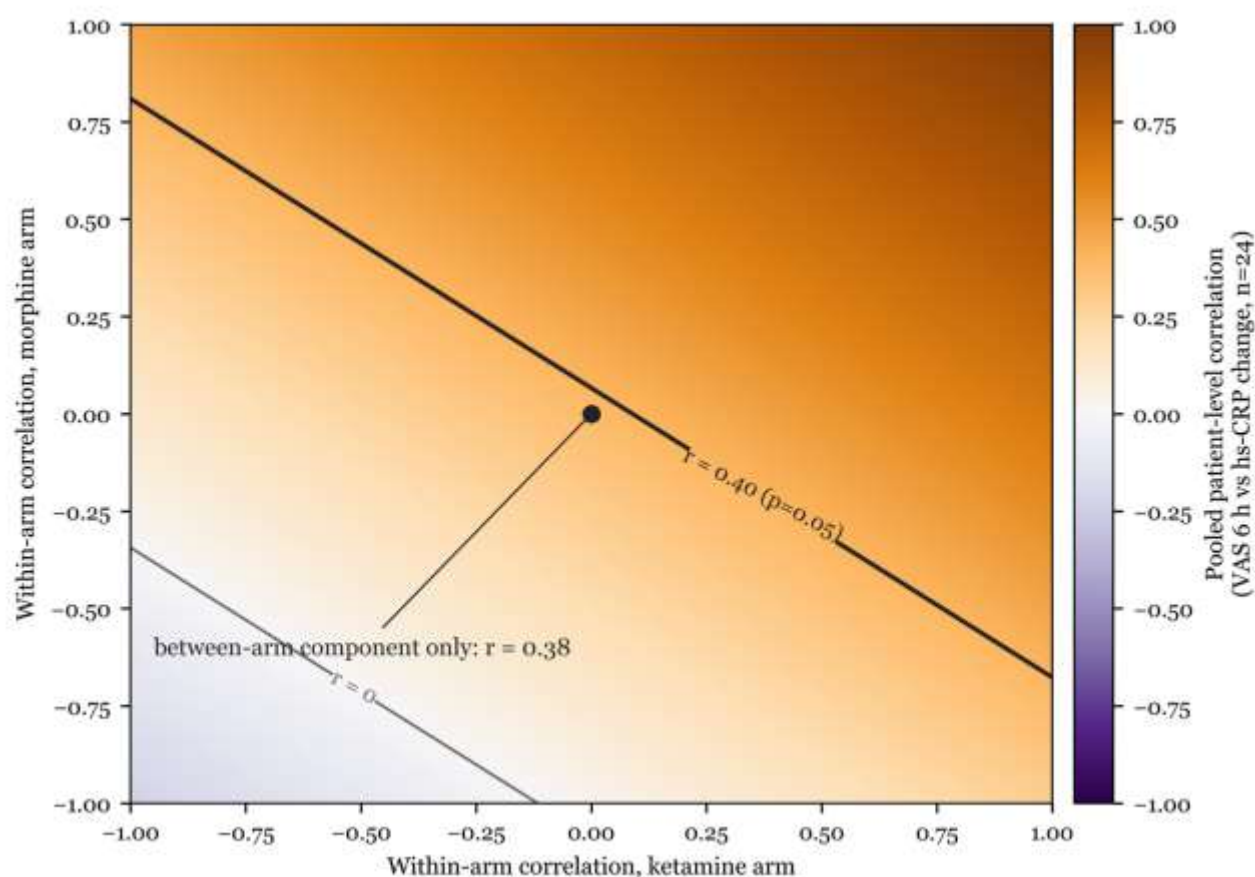


Figure 7. Attainable patient-level correlation between 6-h pain (VAS) and the hs-CRP rise across all 24 patients, as a function of the unreported within-arm correlations. Contours mark $r = 0$ and the significance threshold $r = 0.40$ ($p = 0.05$, $n = 24$); the point marks the value implied by the between-arm difference alone.

3.8. Comparison with published cohorts

Table 7 and Figure 8 place the present data beside published cohort proportions, which are described without formal testing because the cohorts used different scales, time windows and settings. The proportion of patients with VAS >4 at 12 hours (83.3%) was higher than

the 56.9% with a mean pain score above 4 in the first 24 hours after 1,294 spine operations.¹ The proportion with VAS ≥4 at 12 hours (100%) was higher than the 48.7% with moderate-to-severe pain on the first day after surgery in a population-based cohort.² At 6 hours, 8.3% of ketamine patients had VAS ≥4, which is lower than that benchmark. The morphine arm (50.0%) was close to it.

Table 7. Pain-threshold proportions compared with published cohort proportions.

Proportion in this trial	n/N (%) [95% CI]	Benchmark	Benchmark source	Difference, pp
VAS >4 at 12 h (all patients)	20/24 (83.3) [64.1–93.3]	56.9%	Mean NRS >4 in the first 24 h, 1,294 spine operations ¹	+26.4
VAS ≥4 at 12 h (all patients)	24/24 (100.0) [86.2–100.0]	48.7%	Moderate-to-severe pain on day 1, 26,193 surgical patients ²	+51.3
VAS ≥4 at 6 h, morphine arm	6/12 (50.0) [25.4–74.6]	48.7%	As above ²	+1.3
VAS ≥4 at 6 h, ketamine arm	1/12 (8.3) [1.5–35.4]	48.7%	As above ²	-40.4

Notes: Wilson 95% CI for the trial proportions. The benchmarks use different scales, time windows, populations and regimens and are contextual, not causal, comparisons; no formal test is applied. Difference, trial proportion minus benchmark, in percentage points (pp).

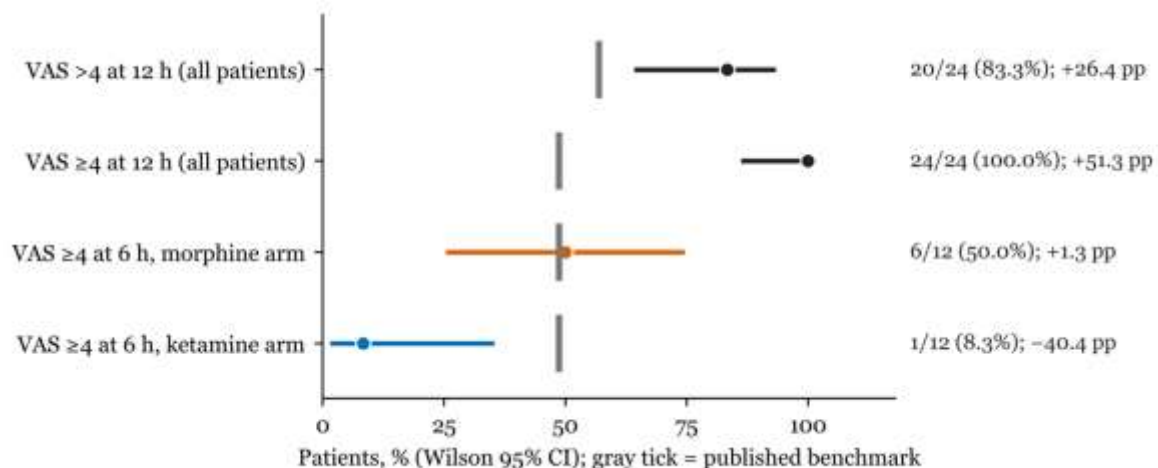


Figure 8. Pain-threshold proportions in this trial (Wilson 95% confidence intervals) compared with published spine-surgery and surgical cohort proportions (gray ticks); counts and differences are shown on the right.

3.9. Precision

Figure 10 shows the precision the trial achieved. With 12 patients per arm, power to detect the planned 1-point difference (standardized difference 1.0) was 65%.

Reaching 80% power would have needed 17 patients per arm, and detecting the observed 12-hour difference (standardized difference 0.39) would need about 104 patients per arm.

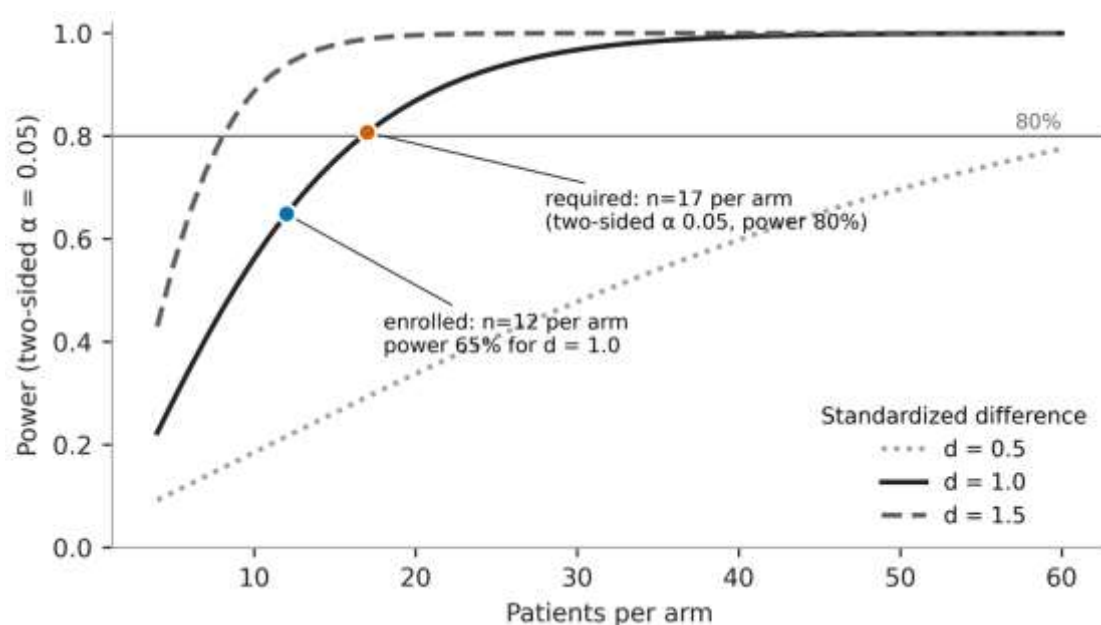


Figure 10. Power of a two-sided two-sample t test ($\alpha = 0.05$) as a function of the number of patients per arm for standardized differences of 0.5, 1.0 and 1.5. The enrolled sample (12 per arm) had 65% power for the planned 1-point difference (SD 1, $d = 1.0$); 17 per arm would have been required for 80% power.

4. Discussion

4.1. Principal findings

This double-blind randomized trial was run at Dr. Moewardi Regional General Hospital, where patients received either a ketamine infusion of 10 µg/kg/min or a micro-dose morphine infusion during thoracolumbar laminectomy. Ketamine lowered pain 6 hours after surgery by 1.5 VAS points relative to morphine. The advantage was gone by 12 hours. At that point 20 of 24 patients scored above the rescue threshold. Ketamine also blunted the early hs-CRP rise. After adjustment for baseline, the 6-hour value was 1.28 mg/L lower, and the mean increase was half of that seen in the morphine arm. This inflammatory difference was the more consistent of the two findings in the sensitivity analyses. It held after multiplicity adjustment and under every admissible degree of confounding by duration of surgery, and its direction was unchanged in more than 99.8% of admissible multivariable structures. Pain was a different matter. The data could not show whether patients with more inflammation had more pain. The shared mechanism proposed in the earlier report remains a hypothesis.

The comparator needs a close look first. The morphine arm ran at 10 µg/kg/h for a mean of 157 minutes. That amounts to about 26 µg/kg in total, or roughly 1.8 mg for a 70-kg adult across the whole operation, given after a single 2-µg/kg dose of fentanyl at induction. Maintenance in both arms was therefore close to opioid-free. The trial asks whether adding ketamine to an opioid-minimal anesthetic improves early recovery, and it does not test whether ketamine is superior to adequately dosed morphine. This framing places the trial among recent spine-surgery studies of opioid-free or opioid-sparing anesthesia. In multilevel fusion, an opioid-free regimen of dexmedetomidine and lidocaine cut first-day morphine consumption from 27.96 to 17.28 mg and reduced nausea, though it required more antihypertensive treatment and a longer PACU stay.³² In thoracolumbar surgery, ketamine-based opioid-free anesthesia extended the pain-free period from 6.93 to 9.86 hours.³³ In lumbar spine surgery, preemptive epidural analgesia lowered 24-hour fentanyl use from 62.6 to 32.2 µg compared with control,³⁴ and an opioid-sparing multimodal pathway lowered opioid use and pain for 24–48 hours after posterior lumbar fusion.³⁵ Against this background, the ketamine infusion in the present trial is best seen as one component of an opioid-minimal strategy. Its benefit lies in the first hours after surgery.

4.2. Comparison with the published literature

The 6-hour difference matches the randomized evidence in spine surgery in direction, but it is larger than most pooled estimates. One meta-analysis of 30 trials found that low-dose ketamine lowered pain at 12, 24 and 48 hours and reduced postoperative nausea and vomiting, without excess central nervous system effects. Benefit beyond 24 hours was limited to regimens continued after surgery.¹⁶ A second meta-analysis, with trial sequential analysis, confirmed a 24-hour opioid reduction of about 18 mg but graded the evidence as low.¹⁵ Individual trials agree. Sub-anesthetic esketamine lowered pain at rest at 1, 3 and 6 hours, and on movement up to 24 hours, after lumbar interbody fusion.³⁶ Intraoperative ketamine 0.1 mg/kg/h reduced VAS scores and opioid use from the recovery room to 24 hours after posterior spinal fusion,³⁷ while

esketamine 0.5 mg/kg/h lowered PACU pain but prolonged emergence.³⁸ Ketamine 0.3 mg/kg/h added to methadone more than halved first-day hydromorphone use and lowered pain at 23 of 24 assessments.³⁹ S-ketamine added to oxycodone patient-controlled analgesia cut 24-hour oxycodone use by 25%, with only a small effect on pain.⁴⁰ The standardized difference observed here (Hedges g –1.59) exceeds what these trials suggest. The lower end of its confidence interval is the more cautious estimate of the true effect. Small trials that reach significance systematically overestimate effects, and the fragility of anesthesiology trials is well documented.^{41,42} In clinical terms, the point estimate of 1.5 points equals the distribution-based minimal clinically important difference reported for postoperative pain⁴³ and sits at the lower end of the 15–18-mm thresholds (1.5–1.8 points on the 0–10 scale) most often used in analgesic trials.⁴⁴ The lower confidence limit of the effect (0.72 points) falls short of them.

The inflammatory finding enters a literature with mixed results. Several trials favor esketamine. It reduced TNF- α , IL-1 β and IL-6 on postoperative days 1, 3 and 7 in elderly patients after laminectomy and fusion for lumbar stenosis.¹⁷ It lowered IL-6 and CRP 24 hours after proximal femoral nailing, compared with remifentanyl,¹⁸ and reduced IL-6 at 12 hours and CRP at 72 hours after off-pump coronary surgery.⁴⁵ After hip arthroplasty in older patients, IL-6 and CRP were lower at 24 and 72 hours.⁴⁶ Ketamine and dexmedetomidine both reversed the rising trajectory of pentraxin 3, serum amyloid A and hepcidin after liver resection, where inflammation also correlated with pain.⁴⁷ Other trials found nothing. Neither ketamine nor lidocaine altered IL-6, IL-8 or CRP after open colorectal resection,¹⁹ and ketamine did not change IL-6, TNF- α or CRP in colorectal cancer surgery.²⁰ Meta-analyses mirror this uncertainty. Across 14 trials, eight of them in cardiopulmonary bypass surgery, ketamine reduced the early rise in IL-6 (pooled mean difference –71 pg/mL, 95% CI –101 to –41; six studies),²¹ whereas a meta-analysis of perioperative esketamine rated the certainty of the IL-6 reduction as very low.⁴⁸ Most positive trials used esketamine, measured cytokines rather than CRP, and used placebo or remifentanyl as the comparator. The present trial differs on all three counts. It used racemic ketamine without a loading dose, measured hs-CRP, and compared ketamine with an opioid-minimal regimen. Its estimate, a rise 50% smaller with a confidence interval from 23% to 73%, is consistent in direction with that literature, although, like the pain estimate, it is probably inflated by the small sample. In absolute terms the difference was 1.28 mg/L, at concentrations below 7 mg/L in every patient. That is about nine times lower than the day-7 CRP threshold of 64.1 mg/L that signaled early surgical-site infection after instrumented spinal surgery.⁴⁹ Here hs-CRP serves as a mechanistic marker of the early response. It is not a surrogate for complications or recovery, and the trial measured neither.

These findings matter for Indonesia and neighboring countries. Evidence there remains thin and largely single-center, and it consists of an Indonesian pilot trial of thoracolumbar interfascial plane block,²⁵ and an Indonesian study in which low-dose ketamine gave sedation and analgesia comparable to fentanyl–midazolam in postoperative intensive care.²⁶ Thai trials examined nefopam after laminectomy with fusion²⁸ and erector spinae plane block after open lumbar surgery.²⁷ A Malaysian trial found that adding ketamine to morphine

patient-controlled analgesia roughly halved morphine consumption after colorectal surgery.²⁹ Ketamine is already familiar in Indonesian perioperative practice, including postoperative intensive care sedation.²⁶ The regimen tested here needs nothing beyond a standard syringe pump, which makes it a realistic option for public referral hospitals. Anesthesiology trials worldwide are smaller and less often externally funded than trials in other specialties (median phase 3–4 sample of 84, industry funding in 4.5%),⁵⁰ and Indonesian trials face the same constraints. Multicenter collaboration is needed.

4.3. Interpretation and possible mechanisms

Losing the effect by 12 hours is what pharmacology predicts. The infusion ended at skin closure. The analgesic action of a short ketamine infusion fades within hours, so pain in the ketamine arm rose more steeply between 6 and 12 hours. This reflected the loss of an early advantage, because pain at 12 hours, conditional on the 6-hour score, was not higher than with morphine. Trials that carried ketamine or esketamine into the postoperative period report more durable benefit. In one, esketamine 0.12 mg/kg/h for 48 hours after resection of spinal tumors, combined with pregabalin, reduced moderate-to-severe pain over 48 hours from 60.5% to 27.3% (odds ratio 0.25).⁵¹ In another, a minidose esketamine–dexmedetomidine supplement to patient-controlled analgesia cut moderate-to-severe pain within 72 hours after scoliosis correction from 86.0% to 65.7%.⁵² A bariatric trial continued ketamine for up to 24 hours. Opioid consumption fell, but pain scores did not change.⁵³ The pooled evidence points the same way: analgesia reaches 48 hours only with postoperative or combined administration.¹⁶ Ketamine given during surgery alone should therefore not be expected to protect patients beyond the first hours after surgery.

The timing of the hs-CRP sample shapes how this effect should be read. After posterior lumbar interbody fusion, CRP peaks on the third postoperative day,²² and the same day-3 peak occurred after laminotomy without instrumentation in the same patients.²³ A later peak on the fifth day was reported in a larger trial cohort, in which uncomplicated patients declined after day 3. After major thoracic surgery, IL-6 peaks at about 6 hours while CRP is still rising at 24 hours.²⁴ A 6-hour hs-CRP therefore captures the speed of the early rise, not the size of the response, and it cannot show whether ketamine lowered the peak or merely delayed it. What drives the response also matters. Operating time, number of fused levels and blood loss together explained almost half of the variation

in peak CRP after fusion (R^2 0.47).²² Less invasive discectomy techniques produced lower CRP and IL-6,⁵⁴ and lower creatine kinase,⁵⁵ and minimally invasive interbody approaches altered the acute-phase and angiogenic profile compared with open transforaminal fusion.⁵⁶ Surgery in the ketamine arm was 23.6 minutes shorter. The tipping-point analysis shows that this imbalance cannot account for the hs-CRP difference. Even if duration correlated perfectly with the hs-CRP rise within each arm, the adjusted difference would stay at least 0.66 mg/L in favor of ketamine and remain statistically significant (Table 5, Figure 6). The number of operated levels and blood loss were not recorded, however. They could carry information about surgical trauma that duration does not capture, and that gap remains.

Figure 11 separates what was measured from what was inferred about how a ketamine infusion might slow the acute-phase response. Rodent and cell models offer several candidate routes. Esketamine suppresses spinal astrocytic activation after nerve injury,¹² and it inhibits the microglial JNK/c-Jun pathway in bone cancer pain.¹³ In traumatic brain injury in mice, esketamine shifts macrophages from pro-inflammatory to anti-inflammatory phenotypes through STAT3-dependent glycolysis,¹⁴ partially corrects the glycolytic reprogramming that stress induces in microglia after incision,⁵⁷ and reduces microglial phagocytosis of perineuronal nets in neuropathic pain.⁵⁸ At sub-anesthetic but not anesthetic doses, it inhibits NF- κ B/NLRP3-mediated neuroinflammation after surgery.⁵⁹ The earlier report put the higher hs-CRP in the morphine arm down to TLR4 activation by morphine. Morphine does activate TLR4 and the cGAS–STING pathway in microglia and macrophages *in vitro*.⁹ In mice, microglial HMGB1–TLR4 signaling sustains opioid-induced hyperalgesia,¹⁰ repeated morphine aggravates allodynia and spinal microgliosis after burn injury,¹¹ and TLR4 signaling regulated by TCF7L2 contributes to morphine tolerance.⁶⁰ Human data are mixed. High-dose remifentanyl produced measurable hyperalgesia,⁶¹ yet remifentanyl dose was not associated with postoperative opioid use within a multimodal scoliosis protocol,⁶² and patients on long-term morphine show altered plasma and cerebrospinal-fluid cytokine profiles.⁶³ No study used an exposure comparable to 26 μ g/kg infused over 2–3 hours, so a pro-inflammatory effect of morphine at that exposure is speculative. We therefore withdraw the TLR4 explanation. The more parsimonious reading is that the difference reflects an effect of ketamine, measured against a comparator that was close to no analgesic infusion at all.

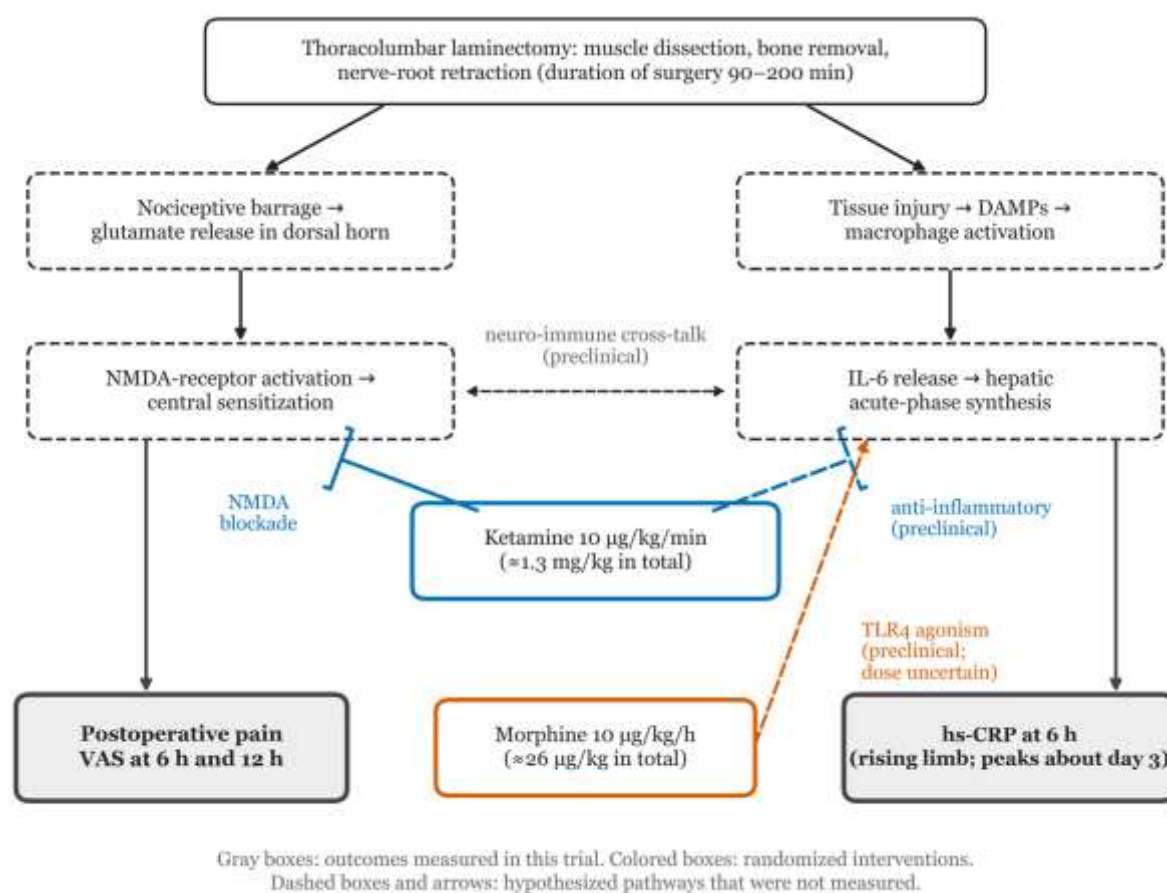


Figure 11. Hypothesized pathways linking laminectomy, ketamine and morphine to the measured outcomes. Gray boxes are the outcomes measured in this trial; colored boxes are the randomized infusions; dashed boxes and arrows are pathways supported by preclinical or indirect evidence that were not measured here; the morphine–TLR4 arrow rests on in-vitro and animal data only.

The trial cannot establish a mechanistic link between pain and inflammation in these patients. The arm with less pain had less inflammation. That compares two group means. At the patient level, the correlation between 6-hour pain and the hs-CRP rise could lie anywhere between -0.23 and 0.99 , depending on within-arm correlations that were not recorded. Fewer than half of the admissible configurations yield a significant positive correlation (Figure 8), so the data leave the question open. The literature is no clearer. Intraoperative disc IL-6 expression tracked postoperative back pain after lateral lumbar fusion,⁶⁴ and CRP-based inflammatory indices correlated weakly with pain after disc surgery (r 0.21 – 0.39).⁶⁵ CRP, however, did not correlate with pain after hip or knee arthroplasty⁶⁶ or radical prostatectomy,⁶⁷ and lower cerebrospinal-fluid IL-6 was associated with persistent neuropathic pain after surgery for lumbar stenosis.⁶⁸ An Indonesian pilot trial measured IL-6 and pain at the same time points as the present trial, but it was too small to test the association.²⁵ Whether reducing early inflammation contributes to analgesia needs patient-level data, ideally with IL-6 rather than CRP as the early marker.

4.4. Implications for practice

For practice, the absolute level of pain at 12 hours matters more than the difference between arms. Every patient scored at least 4. A total of 83.3% scored above 4, a proportion higher than in a cohort of 1,294 spine operations, where 56.9% had a mean score above 4 in the first 24 hours,¹ and in a population-based cohort in which 48.7% reported moderate-to-severe pain on the first day after surgery² (Table 7, Figure 9). Scales, time windows and

populations differ, so these comparisons are only contextual. Their direction is clear. After a single dose of paracetamol and an intraoperative-only infusion, the analgesic plan left most patients in moderate pain 12 hours after surgery. In the larger cohort, poor pain control predicted failure to reach a clinically important improvement in long-term patient-reported outcomes.¹ Acute pain intensity also predicts failure to reach clinically important improvement after lumbar fusion⁸ and high opioid-use trajectories.⁷ The rescue window closed at the 12-hour assessment. Rescue use within it was low in both arms, and in the morphine arm it matched exactly the three patients who exceeded the threshold at 6 hours. How the pain present at 12 hours was managed afterwards lies outside the trial. The practical lesson is that a ketamine-based intraoperative regimen needs a scheduled postoperative plan. Options include continued low-dose ketamine, regular non-opioid analgesics, or a regional block such as the erector spinae plane block, which reduced 24-hour morphine use by 42.9% after open lumbar surgery in Thailand.²⁷

In practice, the findings support intraoperative ketamine as one component of opioid-minimal anesthesia for laminectomy, with two qualifications. First, the analgesic benefit is brief. It lasts only a few hours unless the drug is continued or followed by scheduled analgesia. The 12-hour pain burden seen in both arms is the more urgent target. Second, adverse events were not systematically recorded. The trial therefore says nothing about safety. Other trials report ketamine-related risks that vary widely in kind and frequency. Mild dissociative symptoms occurred in 18.2% of patients given 48-hour esketamine after spinal tumor

surgery.⁵¹ In a Thai surgical intensive care unit, a ketamine infusion that reduced fentanyl use by 15% was associated years later with more frightening or delusional memories of the stay (65% vs 41%).⁶⁹ A spine-surgery meta-analysis found no evidence of more serious adverse events, although with very low certainty.¹⁵ Esketamine combined with dexmedetomidine lowered early postoperative cognitive dysfunction in older adults after lumbar spine surgery, although awakening was longer than with esketamine alone,⁷⁰ while an enhanced-recovery protocol did not shorten stay after single-level lumbar arthrodesis.⁷¹ Drug choice alone will not transform recovery.

4.5. Strengths

The trial has clear strengths. Allocation was randomized and concealed. Outcomes were assessed blind. An independent resident prepared the infusions, which patients and clinicians could not tell apart. The trial paired a patient-reported outcome with an objective biomarker, follow-up was complete, and every published statistic was reproduced exactly from the trial's output. The re-analysis recovered the full pain distributions instead of relying on means. It estimated the inflammatory effect with the most efficient unbiased method. It also quantified, rather than merely asserted, how well each conclusion withstands covariates that were not recorded jointly with the outcomes.

The re-analysis shows that a small trial can report far more than its *p* values. The pain scores were whole numbers, so their complete distributions could be recovered exactly from the trial's summary output. That allowed medians, threshold proportions and exact tests without access to individual records. The SDs of the baseline, 6-hour and change values of hs-CRP were all reported, so the within-arm covariance, and with it an exact ANCOVA, could be derived. ANCOVA is the preferred analysis for a continuous outcome with a baseline measurement, and change scores diverge from it when arms are imbalanced at baseline.³¹ Several conclusions of the earlier report did not survive this scrutiny. The sample-size calculation was one-sided, the analgesic effect was transient rather than sustained, and rescue use cannot distinguish the regimens. No mechanistic link between pain and inflammation can be identified from these data. Selective emphasis of favorable findings is common in anesthesiology trials,⁷² and reporting the full set of effect sizes, intervals and robustness checks is the most effective safeguard against it.

4.6. Limitations

The limitations are considerable. With 12 patients per arm, the trial had 65% power for its planned effect (Figure 10). Its estimates are imprecise. The significant effects are likely to be overestimates. The comparator was a micro-dose morphine infusion, not placebo or an equianalgesic opioid, so the results speak to ketamine within an opioid-minimal anesthetic and not to the relative potency of ketamine and morphine. Pain was assessed at only two time points. It was not assessed in the PACU. The rescue window closed at the 12-hour assessment, and no outcome extended beyond 12 hours. hs-CRP was sampled once after surgery, during its rising phase, and IL-6 was not measured. Adverse events were not systematically recorded, and blinding success was not assessed. Perceptible effects of ketamine during emergence could have unblinded some patients or nurses, which would tend to exaggerate the subjective pain difference. The covariate

adjustments assumed linear, additive effects, so nonlinear or arm-specific effects of duration fall outside the bounds. Screening numbers were not recorded. Participants were relatively healthy adults with ASA status I or II at a single public hospital, which limits generalizability. Finally, patient-level records were not available for the re-analysis. Covariate adjustment and the pain–inflammation association could therefore be addressed only by bounds, which show what the data can and cannot support but cannot replace the analyses that individual records would allow.

4.7. Recommendations for future research

The next trial should be built around these gaps. We propose a multicenter Indonesian trial in adults undergoing one- or two-level thoracolumbar decompression. Patients would be randomized to three arms on a common background of scheduled paracetamol and a non-steroidal anti-inflammatory drug: intraoperative ketamine followed by a 24-hour low-dose infusion, intraoperative ketamine alone, and saline placebo. The primary outcome should be the proportion of patients with moderate-to-severe pain (VAS ≥ 4) at any assessment during the first 24 hours, assessed at 1, 6, 12 and 24 hours. A responder-over-time analysis should serve as a secondary end point, because rescue-related imputation complicates the interpretation of summed pain-intensity end points.⁷² Detecting a reduction in moderate-to-severe pain from 67% to 45% with 80% power at a two-sided α of 0.05 requires 79 patients per arm. Inflammation should be measured as IL-6 at 6 hours and CRP at 24, 48 and 72 hours. This captures the peak. A baseline correlating at about 0.85 with the follow-up value, as observed here, allows ANCOVA adjustment. A difference of 0.5 SD can then be detected with 18 patients per arm instead of the 63 needed for an unadjusted comparison, so the inflammatory question can be answered within the same trial. Duration of surgery, number of levels, blood loss and instrumentation should be recorded as prespecified covariates. Psychotomimetic effects should be assessed with a structured instrument, and chronic postsurgical pain at 3 months. Detecting a reduction in chronic pain from 35% to 25%, within the range observed after spinal surgery,³ would require 328 patients per arm. Only a multicenter network could reach it.

5. Conclusion

In adults undergoing thoracolumbar decompressive laminectomy at Dr. Moewardi Regional General Hospital, an intraoperative ketamine infusion of 10 $\mu\text{g/kg}$ lowered pain 6 hours after surgery compared with a micro-dose morphine infusion (difference -1.50 VAS points, 95% CI -2.28 to -0.72). The effect was absent at 12 hours, when 83.3% of all patients had pain above the rescue threshold. Ketamine also attenuated the early hs-CRP rise (baseline-adjusted difference -1.28 mg/L, 95% CI -2.03 to -0.53). The effect held despite the imbalance in duration of surgery. Whether lower inflammation contributed to lower pain remains undetermined. Intraoperative ketamine may be considered as a component of opioid-minimal anesthesia for spinal decompression, provided that scheduled postoperative analgesia follows, because neither regimen controlled pain beyond the first hours after surgery; safety was not assessed. Before the anti-inflammatory effect of ketamine can be translated into clinical benefit, adequately powered multicenter trials are needed, and they should extend ketamine into the

postoperative period, measure IL-6 and serial CRP, record surgical extent and adverse effects, and follow patients for chronic pain.

6. Declarations

Ethics approval and consent to participate. The protocol was approved by the CMHC Ethics Committee, Indonesia (Approval No. 2024/8333) in 2024, before enrollment began. Written informed consent was obtained from every participant before randomization. The trial was conducted in accordance with the Declaration of Helsinki.

Consent for publication. Not applicable; the article contains no identifiable individual data.

Availability of data and materials. The research data is available from the corresponding author on reasonable academic request.

Artificial intelligence (AI) use statement. The authors declared no artificial intelligence was used in the preparation, design and analysis of manuscript

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