

Postoperative methocarbamol, opioid requirements, and pain after extensive spine fusion surgery: a retrospective cohort study

Ryu Komatsu

komatsr@ccf.org

Cleveland Clinic

Dongsheng Yang

Cleveland Clinic

Yufei Li

Cleveland Clinic

Liu Liu

Cleveland Clinic

Nour El Hage Chehade

Cleveland Clinic

Vanessa Bou Sleiman

Cleveland Clinic

Rami Kamel

Cleveland Clinic

Marco Ibrahim

Cleveland Clinic

Jiang Wu

University of Washington

Yian Chen

University of Washington

Research Article

Keywords: Methocarbamol, Spine surgery, Opioid consumption, Target trial emulation, Postoperative pain, Delirium

Posted Date: October 14th, 2026

DOI: <https://doi.org/10.21203/rs.3.rs-10951489/v1>

License: © ⓘ This work is licensed under a Creative Commons Attribution 4.0 International License.
[Read Full License](#)

Additional Declarations: No competing interests reported.

Abstract

Background

Muscle relaxants such as methocarbamol are frequently combined with other analgesics after spine surgery, yet their opioid-sparing and analgesic value is uncertain. We examined how postoperative methocarbamol relates to opioid use, pain, and secondary outcomes after extensive spine fusion, using a target trial emulation.

Methods

This single-center retrospective cohort study used target trial emulation. Adults (N = 1,467) underwent inpatient spine fusion involving at least three vertebral levels between 2018 and August 2024. The primary exposure was methocarbamol initiated within 12 hours postoperatively (N = 845), compared with controls without methocarbamol within 48 hours (N = 622). Primary outcomes were opioid consumption (oral morphine milligram equivalents [MME]) and average pain scores (0–10) over the first 48 postoperative hours; secondary outcomes were hospital length of stay, delirium, and SpO₂/FiO₂ ratio. Inverse probability of treatment weighting and a joint noninferiority framework were used.

Results

Methocarbamol was associated with significantly higher 48-hour opioid consumption (147 [84, 237] vs 98 [36, 209] mg; ratio of geometric means 1.70 [95% CI 1.47–1.96]; noninferiority *P* = .99) and higher pain scores (adjusted mean difference 1.13 [95% CI 0.99–1.27]; noninferiority *P* = .97). However, the methocarbamol group had shorter length of stay (6 vs 7 days), lower delirium (12% vs 34%), and higher SpO₂/FiO₂ ratio.

Conclusions

After extensive spine fusion, postoperative methocarbamol was associated with higher opioid requirements and pain but shorter hospitalization, less delirium, and improved oxygenation.

Background

Each year in the United States roughly 100 million operations are performed, and close to 70% of patients report moderate-to-severe pain afterward [1]. Poorly controlled acute pain is an important precursor of chronic post-surgical pain, a condition experienced by a sizable share of surgical patients [2]. Opioids have long anchored postoperative analgesia, but concern over their adverse effects and potential for persistent use has narrowed their role [3]. Current practice therefore favors multimodal analgesia, combining agents that act on distinct nociceptive pathways [4].

Skeletal muscle relaxants are a common component of such regimens, especially after operations involving substantial muscle handling, including spine surgery [5]. Their use rests on the premise that operative trauma provokes muscle spasm that compounds acute pain [6]. Among centrally acting antispasmodics, methocarbamol is popular because it is perceived as effective while causing comparatively little sedation relative to cyclobenzaprine or baclofen [7]. Its muscle-relaxant action, however, is not well characterized—it does not act directly on striated muscle, the motor end plate, or the nerve fiber, and its benefit is usually ascribed to nonspecific central nervous system depression—so how it might relieve postoperative pain remains uncertain.

Despite widespread use, evidence that these agents lessen pain or spare opioids is mixed and varies by procedure. In total knee arthroplasty, for example, adding a muscle relaxant such as eperisone to a nonsteroidal anti-inflammatory drug (NSAID) appeared to lower pain scores and morphine use [8], yet a randomized spine-surgery trial showed no benefit of single-dose chlorzoxazone over placebo [9]. Retrospective trauma data likewise found no meaningful link between methocarbamol and lower pain scores [10].

Recent work bears more directly on methocarbamol itself. In a retrospective cohort of musculoskeletal surgery patients, postoperative methocarbamol was paradoxically linked to higher acute pain scores and greater opioid use [11], and a spine-surgery target trial emulation found that intravenous methocarbamol did not meaningfully reduce pain or opioid consumption versus usual care [12].

Safety, particularly central nervous system effects, is a further concern. Although methocarbamol is often selected to limit sedation, related drugs carry neurocognitive risk; baclofen and cyclobenzaprine, for instance, have been tied to a higher rate of postoperative delirium after lumbar fusion [13].

Given these inconsistent results and possible harms, the value of methocarbamol in major spine surgery warrants clarification. We therefore examined how postoperative methocarbamol relates to opioid consumption, pain scores, and clinical outcomes after extensive spine fusion, applying a target trial emulation framework to limit the biases inherent in observational data.

Methods

Study population

With institutional review board approval and a consent waiver (Cleveland Clinic IRB 25–452; approved 29 May 2025), we identified adults who underwent inpatient spine fusion spanning at least three vertebral levels under general anesthesia at the Cleveland Clinic Main Campus between 2018 and August 2024 and who stayed at least 48 postoperative hours. When a patient qualified more than once, only the first encounter was retained. We excluded patients given a muscle relaxant other than methocarbamol postoperatively (cyclobenzaprine, carisoprodol, chlorzoxazone, metaxalone, baclofen, dantrolene, or tizanidine), those with methocarbamol allergy, and those not extubated in the operating room. The study is reported in accordance with the STROBE guideline for observational research.

Treatment strategies of the target trial emulation

The target trial we sought to emulate would randomize patients at the end of surgery to standard analgesia alone or standard analgesia plus methocarbamol, the latter given as a 500 mg tablet every 6 hours throughout the postoperative stay.

Using observational data to approximate this trial, we assigned patients to groups according to the care actually delivered. To mirror the protocol, the primary exposure was a first methocarbamol dose within 12 hours of surgery (a pragmatic proxy for the every-6-hour protocol), and the comparator was no methocarbamol during the first 48 postoperative hours. For sensitivity analyses we specified two additional exposures: (1) any methocarbamol within 48 hours; and (2) a cumulative 48-hour dose of at least 2,000 mg (four 500 mg tablets, half the protocol amount over that window).

Follow-up

Time zero was operating-room exit; all patients were followed through 48 postoperative hours for the primary outcomes.

Outcomes

Primary outcomes. The two primary outcomes, both over the first 48 postoperative hours, were opioid use expressed as oral morphine milligram equivalents (MME) and pain intensity. Nurses rated pain on an 11-point numeric rating scale (NRS; 0 = no pain to 10 = worst imaginable), every 15 minutes during the first 2 hours in the post-anesthesia care unit (PACU) and every 4 hours thereafter, per routine inpatient care. We averaged scores within each 4-hour block, producing 12 repeated measures to match the trial's outcome definition.

Secondary outcomes. Secondary outcomes were postoperative hospital length of stay, delirium within the first 96 hours or before discharge (whichever came first), and oxygenation quantified by the $\text{SpO}_2/\text{FiO}_2$ ratio over the first 48 hours. Pulse oximetry provided SpO_2 , and FiO_2 was inferred from the oxygen device and flow rate (Additional file 1: Appendix Table 1). Both were captured electronically about every 15 minutes in the PACU and, on the wards, SpO_2 every 4 hours until discharge. Implausible readings ($\text{SpO}_2 < 10\%$, $\text{FiO}_2 < 21\%$, or $\text{FiO}_2 > 100\%$) were discarded. Delirium was flagged by any positive 3D-CAM screen within 96 hours or before discharge, whichever came first. Ward nurses administered the 3D-CAM—a validated three-minute tool—twice daily, and any positive screen after the first methocarbamol dose counted as postoperative delirium.

Table 1

Baseline characteristics and surgical factors by methocarbamol use (≤ 12 h, postop) vs no use (≤ 48 h, postop), before and after inverse probability of treatment weighting (IPTW).

Factor	Methocarbamol (≤ 12 h) N = 845	No use (≤ 48 h) N = 622	Unadjusted ASD	ASD after IPTW
Age, years	66 $\pm$ 11	59 $\pm$ 20	0.489	0.125
Female	428 (51)	304 (49)	0.036	0.003
White	720 (85)	537 (86)	0.032	0.009
Body mass index, kg/m ²	30 $\pm$ 6.1	29 $\pm$ 6.9	0.157	0.042
Medical history				
Depression	300 (36)	211 (34)	0.033	0.015
Tobacco use	464 (55)	292 (47)	0.160	0.061
Substance abuse	99 (12)	75 (12)	0.011	0.011
Alcohol use	54 (6.4)	32 (5.1)	0.053	0.000
Opioid use disorder	63 (7.5)	47 (7.6)	0.004	0.014
Chronic obstructive pulmonary disease	217 (26)	141 (23)	0.070	0.011
Asthma	138 (16)	89 (14)	0.056	0.011
Obstructive sleep apnea	250 (30)	160 (26)	0.086	0.002
Hypertension	669 (79)	402 (65)	0.328	0.075
Congestive heart failure	90 (11)	81 (13)	0.073	0.003
Coronary artery disease	224 (27)	130 (21)	0.132	0.020
Diabetes mellitus	256 (30)	170 (27)	0.065	0.038
Stroke	80 (9.5)	70 (11)	0.059	0.017
Transient ischemic attack	66 (7.8)	30 (4.8)	0.123	0.013
Chronic kidney disease	170 (20)	125 (20)	0.001	0.001
Cognitive impairment	158 (19)	116 (19)	0.001	0.021
Dementia	17 (2.0)	18 (2.9)	0.057	0.008

Data are presented as % of patients, mean $\pm$ SD, or median [Q1, Q3]. ASA = American Society of Anesthesiologists Physical Status Classification System; ASD = absolute standardized difference; IPTW = inverse probability of treatment weighting. Any covariate with an ASD > 0.10 was considered imbalanced and adjusted for in the analysis. Stabilized weights were truncated at the 1st and 99th percentiles. Body mass index and spine approach had 28 and 11 missing data points, respectively.

Factor	Methocarbamol (≤ 12 h) N = 845	No use (≤ 48 h) N = 622	Unadjusted ASD	ASD after IPTW
Preoperative medications				
Opioids	358 (42)	242 (39)	0.070	0.005
Benzodiazepine	145 (17)	120 (19)	-0.055	0.030
Antidepressants	358 (42)	221 (36)	0.141	0.002
Gabapentinoids	399 (47)	239 (38)	0.178	0.026
Muscle relaxant agent	303 (36)	129 (21)	0.340	0.031
Surgical parameters				
Spine location			0.469	0.096
Cervical	146 (17)	69 (11)		
Thoracic	62 (7.3)	88 (14)		
Lumbar	222 (26)	75 (12)		
Combined	415 (49)	390 (63)		
Spine approach			0.132	0.046
Anterior	52 (6.2)	29 (4.7)		
Posterior	667 (79)	519 (84)		
Both	122 (15)	67 (11)		
Spine levels	4.0 [3.0, 6.0]	5.0 [4.0, 7.0]	0.363	0.071
ASA status			0.013	0.004
1	1 (0.12)	23 (3.7)		
2	89 (11)	80 (13)		
3	649 (77)	398 (64)		
4	105 (12)	120 (19)		
5	1 (0.12)	1 (0.16)		
Elective surgery	755 (89)	525 (84)	0.147	0.001
<i>Data are presented as % of patients, mean $\pm$ SD, or median [Q1, Q3]. ASA = American Society of Anesthesiologists Physical Status Classification System; ASD = absolute standardized difference; IPTW = inverse probability of treatment weighting. Any covariate with an ASD > 0.10 was considered imbalanced and adjusted for in the analysis. Stabilized weights were truncated at the 1st and 99th percentiles. Body mass index and spine approach had 28 and 11 missing data points, respectively.</i>				

Factor	Methocarbamol (≤ 12 h) N = 845	No use (≤ 48 h) N = 622	Unadjusted ASD	ASD after IPTW
Surgical minutes	362 $\pm$ 123	385 $\pm$ 138	0.174	0.026
Epidural analgesia	507 (60)	247 (40)	0.414	0.022
Intraoperative medications				
Acetaminophen	23 (2.7)	99 (16)	0.466	0.096
Nonsteroidal anti-inflammatory drugs	47 (5.6)	90 (14)	0.300	0.091
Ketamine	158 (19)	147 (24)	0.121	0.020
Lidocaine	818 (97)	564 (91)	0.255	0.064
Benzodiazepine	389 (46)	290 (47)	0.012	0.022
Scopolamine	0 (0.0)	0 (0.0)	0	0
Oral morphine equivalent, mg	96 [60, 246]	168 [69, 393]	0.282	0.088
Year of surgery			0.812	0.086
2018	68 (8.0)	147 (24)		
2019	110 (13)	132 (21)		
2020	76 (9.0)	120 (19)		
2021	103 (12)	86 (14)		
2022	155 (18)	66 (11)		
2023	179 (21)	39 (6.3)		
2024	154 (18)	32 (5.1)		
<i>Data are presented as % of patients, mean $\pm$ SD, or median [Q1, Q3]. ASA = American Society of Anesthesiologists Physical Status Classification System; ASD = absolute standardized difference; IPTW = inverse probability of treatment weighting. Any covariate with an ASD > 0.10 was considered imbalanced and adjusted for in the analysis. Stabilized weights were truncated at the 1st and 99th percentiles. Body mass index and spine approach had 28 and 11 missing data points, respectively.</i>				

Causal contrasts

The primary contrast was the per-protocol effect among patients starting methocarbamol within 12 hours; those beginning it between 12 and 48 hours were omitted from the primary analysis. A sensitivity analysis instead included everyone who received methocarbamol within 48 hours.

Confounding adjustment

Because the data were nonrandomized, we prespecified candidate confounders—demographics, preoperative medications, comorbidities, surgical characteristics, and intraoperative medications—shown in Table 1. Comorbidities were ascertained from International Classification of Diseases, Tenth Revision (ICD-10) codes carrying a present-on-admission flag.

Statistical analysis

To emulate randomization, we used inverse probability of treatment weighting (IPTW). For each patient, a propensity score—the probability of receiving the first methocarbamol dose within 12 hours—was modeled by logistic regression on the prespecified demographic, baseline, and intraoperative variables in Table 1. Postoperative medications were left out of this model because their use is itself shaped by whether methocarbamol was given. Stabilized weights were then formed as the marginal probability of the received treatment divided by its estimated propensity, and were truncated at the 1st and 99th percentiles.

Covariate balance was judged by the absolute standardized difference (ASD)—the absolute difference in means or proportions over the pooled standard deviation—with any variable exceeding 0.1 additionally adjusted for in every model.

The primary analysis evaluated methocarbamol versus control on opioid use and pain using a joint hypothesis-testing approach, positing that methocarbamol over the first 48 hours would lower opioid requirements without raising pain scores relative to non-use. Efficacy required first establishing noninferiority for both opioid use and pain; only if both met noninferiority would superiority be examined for either. Each outcome was tested one-sided, with margins of a 20% increase in opioids (a geometric-mean ratio of 1.2) and a 1-point rise in mean pain, at a significance level of 0.025. Because both tests had to be significant before proceeding, no multiplicity adjustment was needed (an intersection-union test) [14].

Given its strong right skew and near-log-normal shape, 48-hour opioid use was log-transformed (with 1 mg added when use was zero); an IPTW-weighted linear regression then estimated the effect as a ratio of geometric means. Pain scores were modeled with an IPTW-weighted linear mixed-effects regression that accommodated within-patient correlation via an AR(1) or unstructured structure. Decisions used two-sided 95% confidence intervals: methocarbamol was deemed noninferior when the upper limit lay below the margin and inferior when the lower limit lay above it. Had both outcomes been noninferior, superiority would have been tested one-sided with Holm-Bonferroni control of the type I error at 0.025 [15].

For secondary outcomes, length of stay was analyzed with an IPTW-weighted Cox proportional hazards model, yielding a hazard ratio (HR) for time to discharge. The SpO₂/FiO₂ ratio was compared with an IPTW-weighted linear mixed-effects model using an autoregressive (AR(1)) structure for repeated

measures. Delirium (yes/no) was analyzed with an IPTW-weighted log-binomial generalized linear model to obtain relative risks (RRs) with 95% confidence intervals. All outcomes were repeated in the two sensitivity analyses. Analyses used SAS 9.4 (SAS Institute, Cary, NC, USA).

Handling of missing data

Because missingness was low, baseline gaps were filled by simple imputation—medians for continuous and modes for categorical variables. For the longitudinal pain outcome, a single primary-exposure patient (methocarbamol within 12 hours, $\geq 2,000$ mg over 48 hours) had acute pain but no recorded 48-hour scores; we conservatively assigned this patient the maximum score of 10.

Sample size consideration

In an earlier musculoskeletal-surgery cohort, patients not given methocarbamol in the first 48 hours had a median [Q1, Q3] opioid dose of 190 [60, 248] MME and a mean $\pm$ standard deviation (SD) pain score of 4.3 ± 2.1 [11]. Treating a 20% relative fall in opioid use as the minimally important effect, we sized the study for 90% power at a one-sided significance level of 0.0125 across opioid coefficients of variation from 0.6 to 1.5, which required between 310 and 1,178 patients. For pain, taking a 1-point difference as minimally important and an expected standard deviation of 2.1, 222 patients would afford 90% power at the same one-sided threshold. Because a preliminary query returned at least 600 patients per group, power exceeded 90% for both primary outcomes.

Results

Patient characteristics in the primary and secondary exposure groups

Between 2018 and 31 August 2024, 2,059 patients met eligibility criteria; 1,437 (70%) received methocarbamol within 48 hours and 622 (30%) did not (Fig. 1). The 845 patients starting methocarbamol within 12 hours formed the primary exposure group, whereas the full set of 1,437 within-48-hour users and the 1,063 receiving $\geq 2,000$ mg over 48 hours served as secondary exposure groups for sensitivity analyses. Median imputation filled missing body mass index for 35 patients, and modal imputation filled missing spine-approach data for 14.

In the primary exposure group, the mean (SD) methocarbamol dose was $3,017 \pm 1,592$ mg; these patients averaged 66 ± 11 years and were 51% female, versus 59 ± 20 years and 49% female among controls. Weighting balanced nearly all baseline and surgical characteristics except age (ASD > 0.10 ; Table 1, Additional file 1: Appendix Fig. 1), which was therefore carried as a covariate in every primary-exposure model. Propensity-score histograms showed good overlap (69%; Additional file 1: Appendix Fig. 2). For both secondary exposure groups, weighting achieved balance across all baseline and surgical variables relative to controls (Additional file 1: Appendix Tables 2 and 3).

Table 2

Joint noninferiority (NI) analysis of methocarbamol at 12 and 48 hours postoperatively vs no use on 48-hour pain scores and opioid consumption, weighted by IPTW.

Outcome	Methocarbamol ($\leq$ 12 h) N = 845	No use ($\leq$ 48 h) N = 622	NI margin	Ratio of geometric means or mean difference (95% CI)	NI P
Primary analysis					
Opioid consumption, mg	147 [84, 237]	98 [36, 209]	1.2	1.70 (1.47, 1.96)	.99
Pain score – methocarbamol $\times$ time					.047
Pain score – overall	5.13 $\pm$ 2.51	4.03 $\pm$ 2.80	1.0	1.13 (0.99, 1.27)	.97
Sensitivity analysis: methocarbamol ($\leq$ 48 h), N = 1,437					
Opioid consumption, mg	147 [75, 243]	98 [36, 209]	1.2	1.22 (1.34, 1.73)	.99
Pain score – methocarbamol $\times$ time					.14
Pain score – overall	5.07 $\pm$ 2.53	4.03 $\pm$ 2.80	1.0	1.01 (0.89, 1.13)	.58
Sensitivity analysis: methocarbamol $\geq$ 2,000 mg ($\leq$ 48 h), N = 1,063					
Opioid consumption, mg	156 [87, 255]	98 [36, 209]	1.2	1.67 (1.46, 1.91)	.99
Pain score – methocarbamol $\times$ time					.024
Pain score – overall	5.23 $\pm$ 2.47	4.03 $\pm$ 2.80	1.0	1.13 (1.01, 1.26)	.98

Data are presented as mean $\pm$ SD or median [Q1, Q3]. CI = confidence interval; IPTW = inverse probability of treatment weighting; NI = noninferiority. Total opioid consumption over 48 hours was converted to oral morphine milligram equivalents (mg). The pain-score outcome was the average pain score within 4-hour intervals over the first 48 hours (12 time points). Ratios of geometric means (methocarbamol vs no use) were estimated from an IPTW-weighted linear regression of opioid consumption, adjusting for imbalanced age in the primary analysis; opioid values were log-transformed with 1 mg added to zero values. Mean differences (methocarbamol – no use) in pain scores were estimated using an IPTW-weighted linear mixed-effects model with an AR(1) covariance structure, adjusting for imbalanced age in the primary analysis. No covariates were included in the sensitivity analyses, as all were balanced. P values were from one-sided t tests in the prespecified direction. Although the interaction term was statistically significant in the primary and $\geq$ 2,000 mg analyses, the direction of the treatment effect over time was consistent across groups; results from the main-effects model without the interaction term are presented.

Table 3

Secondary outcomes comparing postoperative methocarbamol use versus no use within 48 hours after surgery, weighted by IPTW.

Secondary outcome	Methocarbamol (≤ 12 h) N = 845	No use (≤ 48 h) N = 622	Effect size (95% CI)	P
Primary analysis				
Hospital length of stay, days	6 [4, 8]	7 [4, 10]	HR: 1.56 (1.40, 1.74)	< .001
Postoperative delirium (≤ 96 h), no. (%)	98 (12)	181 (34)	RR: 0.43 (0.35, 0.54)	< .001
SpO ₂ /FiO ₂ ratio (≤ 48 h) – methocarbamol $\times$ time				.25
SpO ₂ /FiO ₂ ratio (≤ 48 h) – overall	389 $\pm$ 68	385 $\pm$ 76	MD: 10 (6, 15)	< .001
Sensitivity analysis: methocarbamol (≤ 48 h), N = 1,437				
Hospital length of stay, days	6 [4, 8]	7 [4, 10]	HR: 1.41 (1.28, 1.55)	< .001
Postoperative delirium (≤ 96 h), no. (%)	194 (14)	181 (34)	RR: 0.47 (0.39, 0.56)	< .001
SpO ₂ /FiO ₂ ratio (≤ 48 h) – methocarbamol $\times$ time				.32
SpO ₂ /FiO ₂ ratio (≤ 48 h) – overall	389 $\pm$ 68	385 $\pm$ 76	MD: 8 (4, 12)	< .001
Sensitivity analysis: methocarbamol $\geq 2,000$ mg (≤ 48 h), N = 1,063				
Hospital length of stay, days	5 [4, 8]	7 [4, 10]	HR: 1.46 (1.32, 1.62)	< .001
Postoperative delirium (≤ 96 h), no. (%)	92 (10)	181 (34)	RR: 0.36 (0.29, 0.46)	< .001
SpO ₂ /FiO ₂ ratio (≤ 48 h) – methocarbamol $\times$ time				.40

Data are presented as mean $\pm$ SD, median [Q1, Q3], or N (%). CI = confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment weighting; MD = mean difference; RR = relative risk. The SpO₂/FiO₂ ratio outcome was the average ratio within 4-hour intervals over the first 48 hours (12 time points). HR was estimated from a Cox proportional hazards model; for patients who died in hospital, length of stay was assigned as the observed length of stay plus 1 day, and an HR > 1 indicates a higher probability of discharge (shorter stay) in the methocarbamol group. RR was estimated from a log-binomial generalized linear model; MD from a linear mixed-effects model with an AR(1) covariance structure. Imbalanced age was adjusted for in the primary analysis; no covariates were included in the sensitivity analyses, as all were balanced. Delirium had 2, 84, and 1 missing data points in the respective groups.

Secondary outcome	Methocarbamol (≤ 12 h) N = 845	No use (≤ 48 h) N = 622	Effect size (95% CI)	P
Primary analysis				
SpO ₂ /FiO ₂ ratio (≤ 48 h) – overall	390 $\pm$ 68	385 $\pm$ 76	MD: 10 (5, 14)	< .001
Data are presented as mean $\pm$ SD, median [Q1, Q3], or N (%). CI = confidence interval; HR = hazard ratio; IPTW = inverse probability of treatment weighting; MD = mean difference; RR = relative risk. The SpO₂/FiO₂ ratio outcome was the average ratio within 4-hour intervals over the first 48 hours (12 time points). HR was estimated from a Cox proportional hazards model; for patients who died in hospital, length of stay was assigned as the observed length of stay plus 1 day, and an HR > 1 indicates a higher probability of discharge (shorter stay) in the methocarbamol group. RR was estimated from a log-binomial generalized linear model; MD from a linear mixed-effects model with an AR(1) covariance structure. Imbalanced age was adjusted for in the primary analysis; no covariates were included in the sensitivity analyses, as all were balanced. Delirium had 2, 84, and 1 missing data points in the respective groups.				

Primary outcomes

Table 2 presents the primary and secondary exposures against controls for 48-hour pain and opioid use. Mean (SD) pain was 5.13 $\pm$ 2.51 in treated patients and 4.03 $\pm$ 2.80 in controls. The treatment effect varied across the 48 hours (treatment-by-time interaction $P = .047$), but its direction held at every time point (Additional file 1: Appendix Fig. 3), so this quantitative interaction is summarized by the overall effect. In the age-adjusted main-effect model, pain was higher with methocarbamol (adjusted mean difference 1.13; 95% CI 0.99, 1.27; noninferiority $P = .97$; Table 2, Fig. 2); with the upper confidence limit above the margin of 1, noninferiority was not met.

Median [Q1, Q3] opioid use was 147 [84, 237] mg with methocarbamol versus 98 [36, 209] mg in controls (Table 2, Additional file 1: Appendix Fig. 4). The geometric-mean ratio was 1.70 (95% CI 1.47, 1.96), signifying greater opioid use with treatment (noninferiority $P = .99$; Table 2, Fig. 2); as the lower limit exceeded the 1.2 margin, methocarbamol was not noninferior and was in fact inferior.

Both secondary-exposure sensitivity analyses agreed with the primary result: methocarbamol was tied to higher pain and higher opioid use, noninferiority failed throughout (all one-sided noninferiority $P > .025$), and opioid use was again inferior to control.

Secondary outcomes

By contrast, early methocarbamol was linked to better secondary outcomes (Table 3). Length of stay, modeled as time to discharge alive, was shorter with methocarbamol (median [Q1, Q3] 6 [4, 8] vs 7 [4, 10] days; adjusted HR 1.56; 95% CI 1.40, 1.74; $P < .001$), and delirium within 96 hours was far less frequent (12% vs 34%; adjusted RR 0.43; 95% CI 0.35, 0.54; $P < .001$).

Oxygenation by the SpO₂/FiO₂ ratio was modestly higher with methocarbamol (mean 389 $\pm$ 68 vs 385 $\pm$ 76; adjusted mean difference 10; 95% CI 6, 15; $P < .001$), with no time-varying effect over the 48 hours (P

= .25). The secondary-exposure sensitivity analyses reached identical conclusions. Table 4 summarizes medications administered within 48 hours.

Table 4
Medications administered within 48 hours after surgery.

Medication within 48 h postoperatively	Methocarbamol (≤ 12 h) N = 845	No use (≤ 48 h) N = 622
Acetaminophen	779 (92)	517 (83)
Ketamine	16 (1.9)	15 (2.4)
Lidocaine	199 (24)	82 (13)
Diphenhydramine	78 (9.2)	77 (12)
NSAIDs	321 (38)	219 (35)
Gabapentinoids	435 (51)	295 (47)
Antidepressants	356 (42)	221 (36)
Benzodiazepine	163 (19)	231 (37)
<i>Data are presented as N (%). NSAIDs = nonsteroidal anti-inflammatory drugs.</i>		

Discussion

In this target trial emulation among patients having extensive spine fusion, postoperative methocarbamol was associated with greater 48-hour opioid use than standard care (median 147 vs 98 mg MME) and with pain scores about 1.1 points higher. Sensitivity analyses reinforced these findings, so methocarbamol failed to achieve its intended reduction in pain or opioids.

Our design most resembles that of Potnuru et al. [12], who used target trial emulation to study intravenous (IV) methocarbamol in spine surgery. They found no difference in opioids or pain between groups [12], whereas we saw increases in both. Route, dose, and observation window may account for the divergence: their patients received IV methocarbamol (≥ 500 mg within 2 hours), with outcomes assessed over the next 6 hours [12], while ours received oral (PO) methocarbamol begun within 12 hours—typically 500 mg per dose under our order set—with outcomes followed for 48 hours. No validated IV-to-PO conversion exists, but IV dosing reaches peak plasma levels quickly, whereas the oral form has slower onset and lower bioavailability, as animal pharmacokinetic data suggest [16]. Plasma concentrations were thus probably higher in their study than in ours during outcome assessment.

The comparison with our earlier musculoskeletal-surgery study is also instructive [11]. There, in a University of Washington cohort, methocarbamol was reserved for a small group whose pain clinicians expected to be harder to control, a pattern likely to generate confounding by indication that inflated the drug group's pain and opioid use [11]. Here, methocarbamol was a default element of the spine-surgery

order set and thus used far more broadly. Even with this more routine use—which should have diluted selection bias—pain and opioid requirements remained higher, implying the association reflects limited efficacy rather than patient selection alone. It also raises the possibility that muscle spasm contributes little to acute post-spine-surgery pain despite marked disruption of the paraspinal muscles.

Several limitations temper interpretation. Although we applied a target trial emulation, exposure was ascertained over the first 12 postoperative hours while outcomes were counted from operating-room exit, so the design retains potential immortal time bias that weighting does not fully remove [17]. Receipt of methocarbamol was also nonrandom despite the order set—clinicians could withhold it and patients could decline it—so treated patients may differ systematically, for example in motivation to mobilize, in ways that could independently influence opioid use, length of stay, and oxygenation. Finally, as a single-center study conducted at one tertiary academic centre, the findings warrant external confirmation.

Although analgesia did not improve, methocarbamol was associated with much less delirium (12% vs 34%; RR 0.43). This opposes Perez et al., who reported a doubling of delirium risk (RR 2.00) with baclofen or cyclobenzaprine on postoperative day one in older lumbar-fusion patients [13]. The difference may reflect their older cohort and different multimodal regimens, including greater gabapentinoid use [13], as well as the drugs' distinct profiles—cyclobenzaprine is more sedating than methocarbamol [18], and baclofen more so than cyclobenzaprine [19]. Heavier sedation from those agents plausibly raised delirium risk in the Perez study. A biologically plausible route to methocarbamol's apparent protection is better mobility: by easing muscle spasm and enabling earlier physical therapy, it may harness the established antidelirium effect of early mobilization [20].

Methocarbamol was likewise tied to a shorter stay (median 6 vs 7 days; HR 1.56), echoing our musculoskeletal-surgery study [11] and a trauma series in rib fractures [21]. The shorter stay and the small oxygenation gain ($\text{SpO}_2/\text{FiO}_2$ ratio) may again trace to greater mobility, which helps prevent respiratory problems such as atelectasis.

Conclusions

After extensive spine fusion, postoperative methocarbamol was associated with greater opioid use and pain yet also with shorter hospitalization, less delirium, and better oxygenation. These findings do not support a reflexive expectation of opioid sparing or improved analgesia from methocarbamol in this setting, and they motivate randomized evaluation that aligns exposure and outcome timing to resolve the residual potential for immortal time bias.

Abbreviations

3D-CAM

3-minute Diagnostic Confusion Assessment Method

AR(1)

first-order autoregressive

ASA
American Society of Anesthesiologists
ASD
absolute standardized difference
CI
confidence interval
FiO₂
fraction of inspired oxygen
HR
hazard ratio
ICD-10
International Classification of Diseases, Tenth Revision
IPTW
inverse probability of treatment weighting
IV
intravenous
MME
morphine milligram equivalents
NRS
numeric rating scale
NSAID
nonsteroidal anti-inflammatory drug
PACU
post-anesthesia care unit
PO
oral (per os)
RR
relative risk
SD
standard deviation
SpO₂
peripheral oxygen saturation
STROBE
Strengthening the Reporting of Observational Studies in Epidemiology.

Declarations

Ethics approval and consent to participate

This retrospective observational study was approved by the Institutional Review Board of the Cleveland Clinic (IRB 25–452; approved 29 May 2025) and was conducted in accordance with the Declaration of

Helsinki. The Institutional Review Board waived the requirement for individual informed consent because the study used existing clinical records and involved no research intervention.

Consent for publication

Not applicable.

Clinical trial number

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was internally supported by the Integrated Hospital-Care Institute, Cleveland Clinic. The funding source had no role in the study design; in the collection, analysis, or interpretation of data; in the writing of the report; or in the decision to submit the article for publication.

Author Contribution

RK conceptualized and designed the study, contributed to methodology, investigation, resources, and project administration, and drafted the manuscript. DY and LL performed the formal analysis and contributed to methodology, data curation, and investigation. YL contributed to methodology and investigation. NEHC, VBS, RaK, MI, JW, and YC contributed to supervision. All authors contributed to writing—original draft and writing—review and editing, and read and approved the final version of the manuscript.

Acknowledgements

None.

Data Availability

The datasets used and analysed during the current study are not publicly available because of institutional privacy regulations but are available from the corresponding author on reasonable request.

References

1. Gan TJ. Poorly controlled postoperative pain: prevalence, consequences, and prevention. *J Pain Res.* 2017;10:2287–98.
2. Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. *Lancet.* 2006;367:1618–25.
3. Brat GA, Agniel D, Beam A, Yorkgitis B, Bicket M, Homer M, Fox KP, Knecht DB, McMahonill-Walraven CN, Palmer N, Kohane I. Postsurgical prescriptions for opioid naive patients and association with overdose and misuse: retrospective cohort study. *BMJ.* 2018;360:j5790.
4. Chou R, Gordon DB, de Leon-Casasola OA, Rosenberg JM, Bickler S, Brennan T, Carter T, Cassidy CL, Chittenden EH, Degenhardt E, Griffith S, Manworren R, McCarberg B, Montgomery R, Murphy J, Perkal MF, Suresh S, Sluka K, Strassels S, Thirlby R, Viscusi E, Walco GA, Warner L, Weisman SJ, Wu CL. Management of postoperative pain: a clinical practice guideline from the American Pain Society, the American Society of Regional Anesthesia and Pain Medicine, and the American Society of Anesthesiologists' Committee on Regional Anesthesia, Executive Committee, and Administrative Council. *J Pain.* 2016;17:131–57.
5. Bongiovanni T, Gan S, Finlayson E, Ross JS, Harrison JD, Boscardin J, Steinman MA. Use of muscle relaxants after surgery in traditional Medicare Part D enrollees. *Drugs Aging.* 2024;41:615–22.
6. Blumenkopf B. Combination analgesic-antispasmodic therapy in postoperative pain. *Spine (Phila Pa 1976).* 1987;12:384–7.
7. See S, Ginzburg R. Skeletal muscle relaxants. *Pharmacotherapy.* 2008;28:207–13.
8. Gong L, Dong JY, Li ZR. Effects of combined application of muscle relaxants and celecoxib administration after total knee arthroplasty (TKA) on early recovery: a randomized, double-blind, controlled study. *J Arthroplasty.* 2013;28:1301–5.
9. Nielsen RV, Fomsgaard JS, Siegel H, Martusevicius R, Mathiesen O, Dahl JB. The effect of chlorzoxazone on acute pain after spine surgery. A randomized, blinded trial. *Acta Anaesthesiol Scand.* 2016;60:1152–60.
10. Aljuhani O, Kopp BJ, Patanwala AE. Effect of methocarbamol on acute pain after traumatic injury. *Am J Ther.* 2017;24:e202–6.
11. Komatsu R, Singleton MD, Wu J, Dinges EM, Bollag LA. Association between postoperative methocarbamol and postoperative pain opioid dose requirements: a retrospective cohort study. *Clin J Pain.* 2023;39:452–7.
12. Potnuru P, Baranov A, Khudirat M, Turan A. Intravenous methocarbamol for acute pain after spine surgery: a target trial emulation. *Reg Anesth Pain Med.* 2025. <https://doi.org/10.1136/rapm-2025-107010>.
13. Perez EA, Ray E, Gold CJ, Park BJ, Piscopo A, Carnahan RM, Banks M, Sanders RD, Olinger CR, Mueller RN, Woodroffe RW. Postoperative use of the muscle relaxants baclofen and/or

- cyclobenzaprine associated with an increased risk of delirium following lumbar fusion. *Spine (Phila Pa 1976)*. 2023;48:1733–40.
14. Mascha EJ, Turan A. Joint hypothesis testing and gatekeeping procedures for studies with multiple endpoints. *Anesth Analg*. 2012;114:1304–17.
 15. Holm S. A simple sequentially rejective multiple test procedure. *Scand J Stat*. 1979;6:65–70.
 16. Rumpler M, Colahan P, Sams R. The pharmacokinetics of methocarbamol and guaifenesin after single intravenous and multiple-dose oral administration of methocarbamol in the horse. *J Vet Pharmacol Ther*. 2014;37:25–34.
 17. Hernán MA, Sterne JA, Higgins JP, Shrier I, Hernández-Díaz S. A structural description of biases that generate immortal time. *Epidemiology*. 2025;36:107–14.
 18. Preston EJ. A double-blind, multicenter trial of methocarbamol (Robaxin) and cyclobenzaprine (Flexeril) in acute musculoskeletal conditions. *Today's Ther Trends*. 1984;1:1–11.
 19. van Tulder MW, Touray T, Furlan AD, Solway S, Bouter LM. Muscle relaxants for non-specific low back pain. *Cochrane Database Syst Rev*. 2003;(2):CD004252.
 20. Wang YY, Yue JR, Xie DM, Carter P, Li QL, Gartaganis SL, Chen J, Inouye SK. Effect of the tailored, family-involved hospital elder life program on postoperative delirium and function in older adults: a randomized clinical trial. *JAMA Intern Med*. 2020;180:17–25.
 21. Patanwala AE, Aljuhani O, Kopp BJ, Erstad BL. Methocarbamol use is associated with decreased hospital length of stay in trauma patients with closed rib fractures. *Am J Surg*. 2018;214:738–42.

Figures

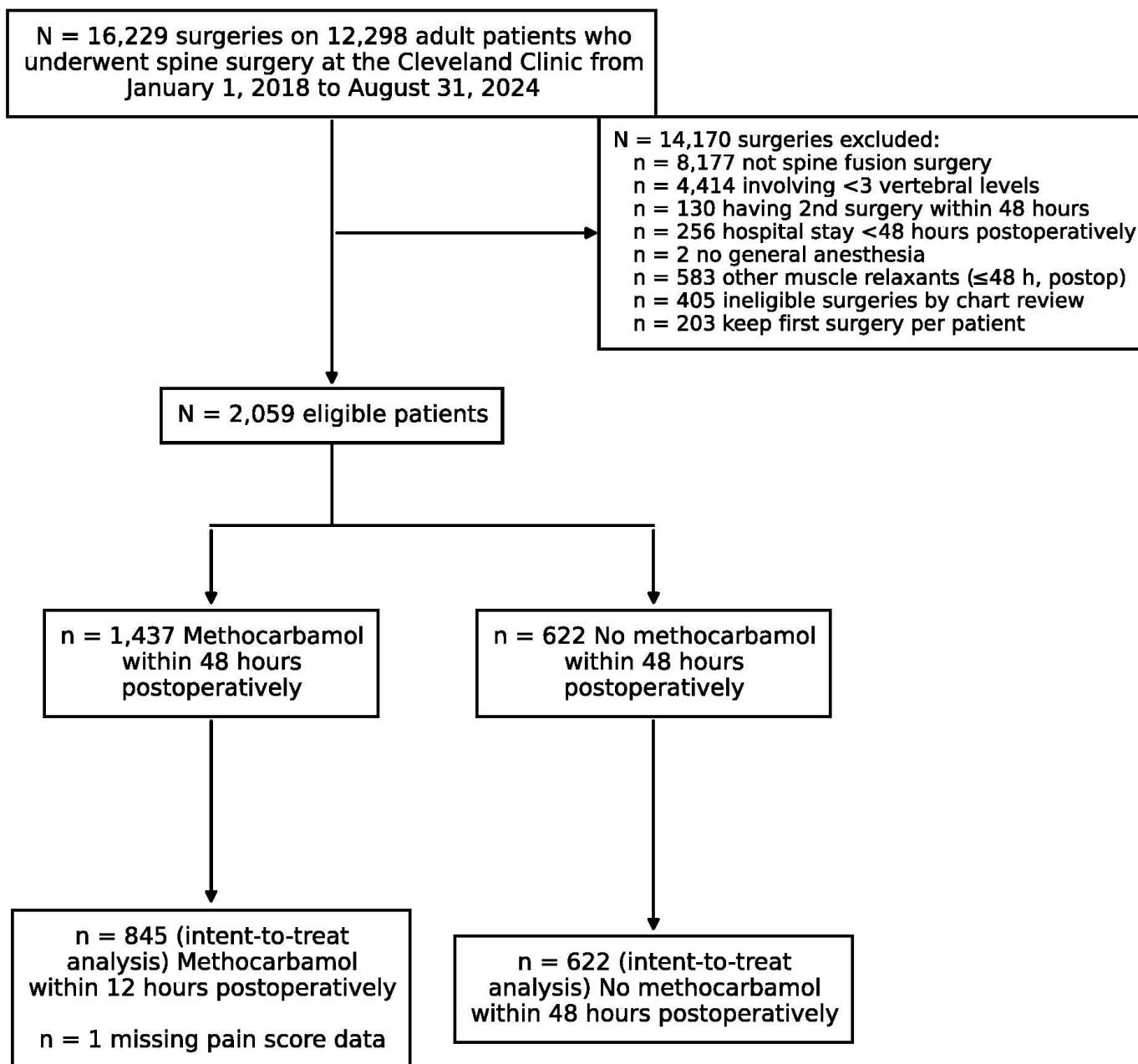


Figure 1

Study flow chart.

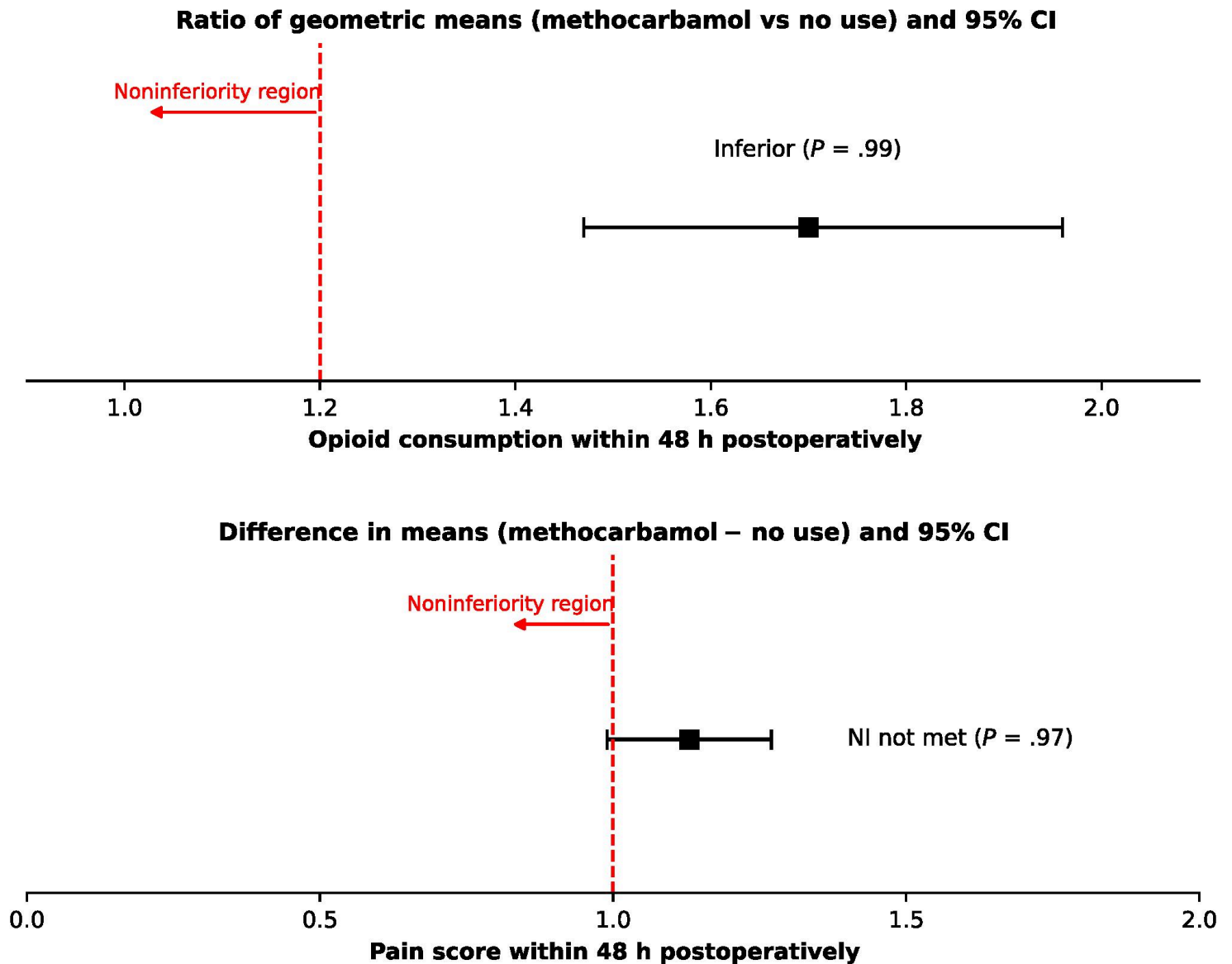


Figure 2

Estimated 95% confidence intervals (CIs) for the treatment effect (methocarbamol – no methocarbamol) on opioid consumption and pain scores. The noninferiority (NI) margin was 1 point for the pain score and a ratio of geometric means of 1.2 for opioid consumption. The 95% CI for opioid consumption was estimated from a multivariable regression model, and the 95% CI for pain scores from a linear mixed-effects model with an AR(1) covariance structure. One-sided P values were obtained from t tests based on the estimated treatment effects and standard errors from the multivariable models. Because the upper bounds of the confidence intervals for both primary outcomes exceeded the prespecified noninferiority margins, methocarbamol did not meet the criteria for noninferiority. Furthermore, methocarbamol was statistically inferior to the control group (no use within 48 hours postoperatively) for cumulative opioid consumption, as the entire confidence interval fell strictly above the noninferiority margin.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [Additionalfile1AppendixFiguresandTablesMethocarbamolBMCAesthesiology.pdf](#)