ANESTHESIOLOGY

Multimodal Analgesic Regimen for Spine Surgery

A Randomized Placebo-controlled Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Multimodal analgesia is a strongly advocated approach for perioperative pain management
- Multimodal analgesia has not been carefully evaluated for spine surgery

What This Article Tells Us That Is New

- Adult spine surgery patients were randomized to placebo or to the combination of acetaminophen, gabapentin, ketamine, and lidocaine
- The Quality of Recovery was similar in each group, as were pain scores and opioid consumption

ABSTRACT

Background: Various multimodal analgesic approaches have been proposed for spine surgery. The authors evaluated the effect of using a combination of four nonopioid analgesics *versus* placebo on Quality of Recovery, postoperative opioid consumption, and pain scores.

Methods: Adults having multilevel spine surgery who were at high risk for postoperative pain were double-blind randomized to placebos or the combination of single preoperative oral doses of acetaminophen 1,000 mg and gabapentin 600 mg, an infusion of ketamine 5 μg/kg/min throughout surgery, and an infusion of lidocaine 1.5 mg/kg/h intraoperatively and during the initial hour of recovery. Postoperative analgesia included acetaminophen, gabapentin, and opioids. The primary outcome was the Quality of Recovery 15-questionnaire (0 to 150 points, with 15% considered to be a clinically important difference) assessed on the third postoperative day. Secondary outcomes were opioid use in morphine equivalents (with 20% considered to be a clinically important change) and verbal-response pain scores (0 to 10, with a 1-point change considered important) over the initial postoperative 48 h.

Results: The trial was stopped early for futility per *a priori* guidelines. The average duration ± SD of surgery was 5.4 ± 2.1 h. The mean ± SD Quality of Recovery score was 109 ± 25 in the pathway patients (n = 150) *versus* 109 ± 23 in the placebo group (n = 149); estimated difference in means was 0 (95% CI, –6 to 6, $P = 0.920$). Pain management within the initial 48 postoperative hours was not superior in analgesic pathway group: 48-h opioid consumption median (Q1, Q3) was 72 (48, 113) mg in the analgesic pathway group and 75 (50, 152) mg in the placebo group, with the difference in medians being –9 (97.5% CI, –23 to 5, $P = 0.175$) mg. Mean 48-h pain scores were 4.8 ± 1.8 in the analgesic pathway group *versus* 5.2 ± 1.9 in the placebo group, with the difference in means being –0.4 (97.5% CI; –0.8, 0.1, $P = 0.094$).

Conclusions: An analgesic pathway based on preoperative acetaminophen and gabapentin, combined with intraoperative infusions of lidocaine and ketamine, did not improve recovery in patients who had multilevel spine surgery.

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Standardized care pathways like Enhanced Recovery After Surgery programs promise to improve perioperative outcomes.[1,2] Multimodal analgesic regimens are an essential component of Enhanced Recovery After Surgery programs, potentially reducing postoperative complications[3] and improving recovery.[4–6] While multimodal analgesia is recommended by the American Society of Regional Anesthesia and Pain Medicine (Pittsburgh, Pennsylvania),[7] perioperative opioid administration remains the dominant component of most pain management plans.[8]

Postoperative pain control is especially challenging in spine surgery patients. Acetaminophen,[9] gabapentin,[10–12] lidocaine,[13,14] and ketamine[15–17] can potentially improve acute pain but are not consistently used. To improve pain control of spine surgery patients, our anesthesia and surgery teams devised a multimodal analgesic pathway that included acetaminophen, gabapentin, lidocaine, and ketamine.

The drugs, doses, and routes we considered were selected based on best available evidence and team consensus. Acetaminophen and gabapentin decrease perioperative opioid use, and perhaps reduce persistent incisional pain.[18,19] Even a single preoperative dose of acetaminophen reportedly improves postoperative pain control.[20] Similarly, single-dose gabapentin 600 mg is reported to

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reduce postoperative pain.[21] Ketamine blocks *N*-methyl-D-aspartate excitatory glutamate receptors, and intraoperative infusions are widely reported to reduce postoperative opioid use.[22–24] Similarly, lidocaine infusion has analgesic, antihyperalgesic, and antiinflammatory properties, which help control postoperative pain.[14,25]

Our goal was to improve Quality of Recovery and pain control while minimizing opioid use.[26] We therefore tested the primary hypothesis that patients given multimodal analgesia consisting of oral gabapentin and acetaminophen combined with infusions of lidocaine and ketamine have superior Quality of Recovery scores 3 days after multilevel spine surgery. Secondarily, we tested the hypotheses that multimodal analgesia reduces opioid consumption and pain scores during the initial 48 postoperative hours; we also compared the opioid related side effects at first and second postoperative days.

Our exploratory outcomes were (1) postanesthesia care unit (PACU) length of stay; (2) postoperative nausea and vomiting 24 h after surgery; (3) need for acute pain consultation, as determined by clinicians; (4) patient satisfaction with pain management at discharge (numeric rating scale 1–100); (5) hospital length of stay; (6) Quality of Recovery at 1 month; (7) EuroQol (EQ-5D) at 3 months; (8) chronic postsurgical pain at 3 months; and (9) pain disability questionnaire at 3 months.

Materials and Methods

After Institutional Review Board (IRB No. 16-012) approval in July 2016, we conducted a double-blinded, placebo-controlled, parallel-group, randomized controlled trial at the Cleveland Clinic Main Campus (Cleveland, Ohio) from August 2016 to December 2018 (fig. 1). The trial was registered at ClinicalTrials.gov before the first patient was enrolled (NCT00517127, Principal Investigator: Kamal Maheshwari). We enrolled patients scheduled for multilevel posterior spine elective surgery who were at high risk for postoperative pain. We considered two or more of the following factors to constitute high risk[27,28]: age less than 60 yr; female sex; history of chronic pain exceeding 3 months; preoperative visual analog pain scale 7/10 or greater; high anxiety level based on the Amsterdam Preoperative Anxiety and Information Scale[29] when any of the questions were marked as 4 and 5 corresponding to very large and extreme level of worry; and complex spine surgery with instrumentation. We excluded patients who had allergies or hypersensitivities to lidocaine, ketamine, acetaminophen, or gabapentin; who had abused drugs within 6 months; who had heart failure with ejection fraction less than 30%; or who had liver dysfunction manifested by twice normal liver enzymes and International Normalized Ratio equal to or greater than 2.

Protocol

The study statistician generated an allocation sequence table corresponding to 1:1 randomization with random-sized blocking and without stratification. An investigator screened patients in the preanesthesia evaluation clinic for potential eligibility and obtained informed consent during the visit. A total of 299 adults scheduled for multilevel posterior spine surgery were assigned to study groups with a Web-based system that concealed allocation until shortly before surgery.

All patients received general inhalational anesthesia with endotracheal intubation and standard American Society of Anesthesiologists (Schaumburg, Illinois) monitors. Clinicians provided anesthesia care per clinical routine including hemodynamic monitoring, intraoperative administration of opioid medications, and muscle relaxants. Enrolled patients were instructed not to take any acetaminophen or gabapentin at home on the day of surgery. Patients assigned to the analgesic pathway were given single preoperative oral doses of 1 g acetaminophen[20] and 600 mg gabapentin[21]; they were also given an intraoperative infusion of 1.5 mg/kg/h lidocaine[14] (maximum individual dose, 200 mg/h) and 5 μg/kg/min ketamine.[30] Ketamine was stopped at wound closure. Lidocaine was reduced to 1 mg/kg/h at wound closure and was continued for the initial hour in the PACU so long as the total duration did not exceed 8 h. Epidural analgesia or local wound infiltration were performed by the surgeons on a preference basis. Oral acetaminophen was continued in most patients after surgery. Gabapentin was continued at the discretion of the surgery team.

Patients assigned to the placebo group received placebo acetaminophen and gabapentin, along with placebo ketamine and lidocaine. No other aspect of intraoperative and postoperative care was controlled by the study protocol. All study medications were prepared by the Cleveland Clinic research pharmacy; clinicians, patients, and investigators were thus fully blinded.

Measurements

Baseline characteristics as well as primary and exploratory outcomes were recorded by investigators. Pain scores and opioid consumption were obtained from patients' electronic medical records.

Our primary outcomes were Quality of Recovery score (range, 0 to 150) on the third postoperative day. This survey is a valid, reliable, responsive, and multidimensional measure of Quality of Recovery after anesthesia and surgery. It includes physiologic values, functional recovery, and patient-reported outcomes.[31]

Postoperative pain was evaluated with numeric rating scores (0 to 10) at 15-min intervals for the initial two postoperative hours, and thereafter every 4 h by ward nurses. Time-weighted average pain scores were calculated over the initial 48 postoperative hours or until discharge, whichever came first. A time-weighted average pain score is equal to the sum of the portion of each time interval (as a decimal, such as 0.25 h) multiplied by the levels of the pain (0 to

10 numeric rating scores) during the time period divided by 48 h. Opioid consumption within the initial 48 h was converted to IV morphine equivalents using the conversions specified in Supplemental Digital Content 1 (http://links.lww.com/ALN/C178). Opioid-related symptom distress was evaluated on the first two postoperative mornings.[32] Chronic postsurgical pain was assessed by a phone call using numeric rating scale (0 to 10) where a score of 0 is "no pain" and a score of 10 is "pain as bad as it could be." Postoperative nausea and vomiting was obtained from electronic health record nursing progress notes; severity was 0 = none, 1 = mild, 2 = moderate, and 3 = severe.

Statistical Analysis

The analysis was intent-to-treat, and thus included all randomized patients. We assessed the balance of the two randomized groups on baseline and procedural characteristics using absolute standardized difference, defined as the absolute difference in means, mean ranks, or proportions divided by the pooled SD. Baseline variables with absolute standardized difference greater than 0.2 were considered to be imbalanced and would be adjusted for in primary, secondary, and exploratory analyses as well as sensitivity and *post hoc* analyses. SAS statistical software version 9.4 (SAS Institute, USA) for 64-bit Microsoft Windows (USA) was used for statistical analysis.

Primary Outcome. We estimated the effect of analgesic pathway care approach on Quality of Recovery scores with an independent samples *t* test, which was justified because the scores were normally distributed. We report differences in means Quality of Recovery scores, along with 95% CIs.

Among 299 randomized patients, 41 (14%) were discharged before the third postoperative day. Missing Quality of Recovery scores were imputed by multivariable single imputation with five imputations: the imputation model included all the baseline variables listed in table 1 together with exposure and all the primary, secondary, and exploratory outcomes. We ran two sensitivity analyses: (1) in the "complete cases" analysis, patients without 3-day postoperative Quality of Recovery score were excluded from the analysis; and (2) we assumed that patients who were discharged before completing the Quality of Recovery survey had the average score in their randomized group. We also conducted two separate *post hoc* subgroup analyses to assess whether the relationship between analgesic approaches and Quality of Recovery score differed in patients with histories of chronic pain or opioid use. The interaction terms between analgesic approaches and history of chronic pain and opioid use were added to a multivariable linear regression model, and significant interaction was claimed if the corresponding *P* value was more than 0.10.

Secondary Outcomes. We assessed the effectiveness of analgesic pathway compared to placebo on cumulative opioid consumption and pain intensity scores within the first 48 h after surgery, using a joint hypothesis testing framework.[33] We considered the analgesic pathway to be superior to placebo on postoperative pain management if both opioid consumption (Supplemental Digital Content 1, http://links.lww.com/ALN/C178) and pain scores were noninferior (*i.e.*, not worse) and at least one of the outcomes was superior for analgesic pathway patients. We defined the *a priori* noninferiority pain score delta as 1 point (on a scale of 0 to 10) and the opioid delta as 20% change from IV morphine equivalent doses.

We first estimated CIs for the treatment effect for both pain score and opioid consumption. Opioid consumption had highly skewed distribution, with many patients having consumption of zero. We therefore evaluated the difference in median IV morphine equivalent dose between the two groups using Hodges–Lehmann estimation of location shift.[34] To evaluate the difference in mean pain scores, we used a linear regression model to assess the exposure effect on the time-weighted average pain score outcome.

Joint hypothesis testing of pain score and opioid consumption was conducted at the overall 0.025 significance level (Bonferroni-corrected for two secondary hypotheses), and all tests were one-tailed in the direction favoring the novel pain management approach. Noninferiority of analgesic pathway *versus* placebo was assessed for each outcome at the 0.025 level (no Bonferroni correction) since noninferiority is required on both outcomes. Therefore, noninferiority (being "not worse") was concluded for both outcomes at the significance level of 0.025 if the upper limit of 95% CI was below the corresponding noninferiority delta. If noninferiority on both outcomes was found, superiority was assessed on each. We adjusted for two outcomes for the superiority testing only, using a significance criterion of 0.0125 for each outcome (*i.e.*, 0.025/2, Bonferroni correction), since superiority on either outcome would suffice. Superiority thus was claimed for a particular outcome if the 97.5% interval limits were below zero for both pain score and opioid consumption. No multiple testing adjustment was required for assessing both noninferiority and superiority since significance for both was required to reject the null hypothesis, and also because superiority falls in the noninferiority rejection region.

For *post hoc* analysis, we assessed whether the effect of the analgesic on 48-h pain management is different for opioid-naïve patients than patients who had a history of opioid use. Specifically, we added an interactions term between the exposure and history of opioid use in the pain and opioid models (with a criterion for significant interaction of $P < 0.10$). Additionally, we evaluated the effect of two study groups on pain management at 24 h postoperatively.

Opioid-related side effects scores were log-transformed to normalize the distributions and compared with a log-normal linear regression model; the percent difference in geometric means scores are reported, along with 95% CI and corresponding *P* values. *Post hoc*, we considered interactions between randomized assignment and several baseline risk factors for poor postoperative pain control, with the significance criterion for interactions being $P < 0.10$.

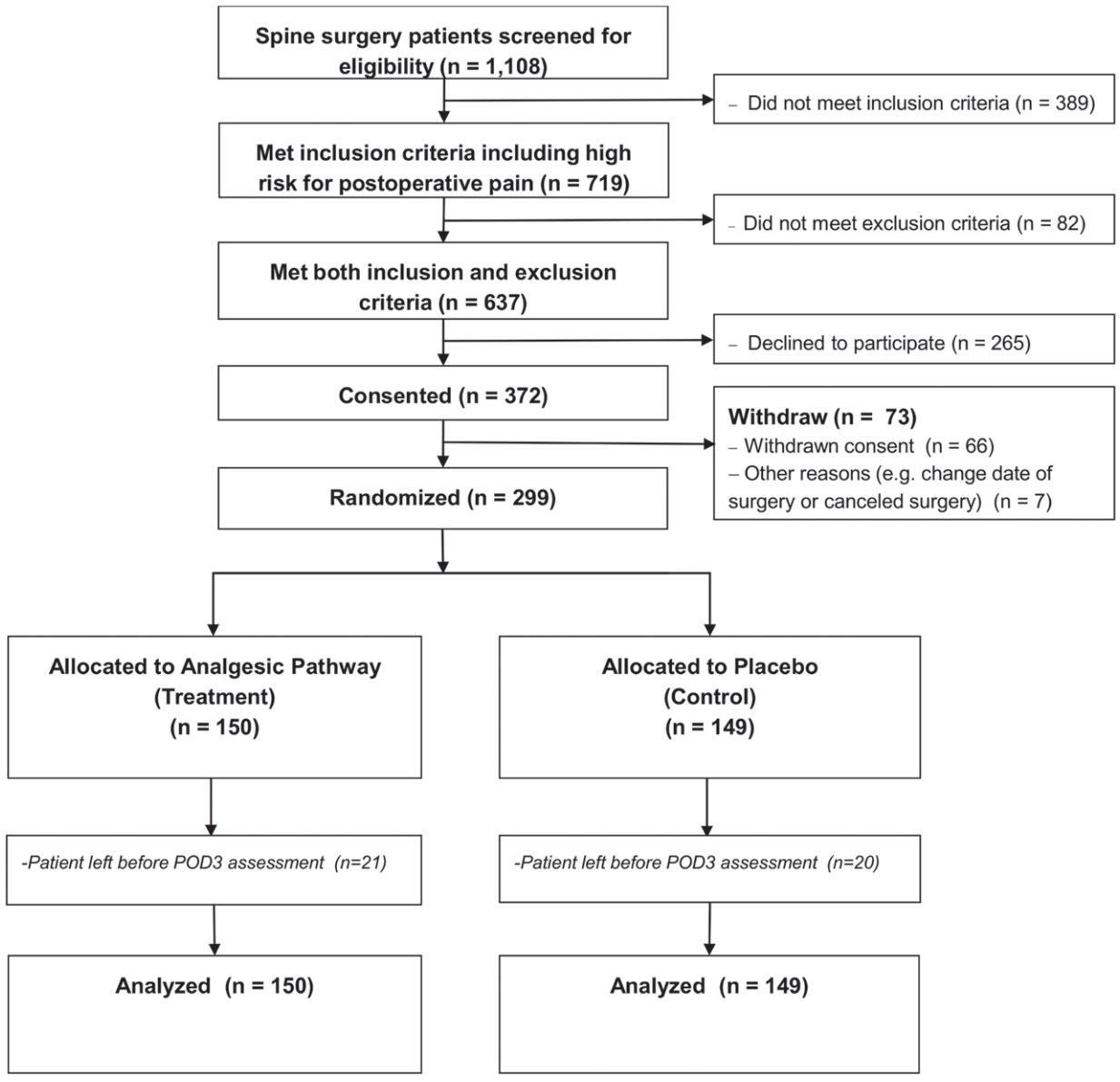

Fig. 1. Trial diagram. POD3, third postoperative day.

Sample Size and Power Consideration. This study was designed to have 90% power at the 0.05 significance level to detect a ratio in geometric means of 1.15 or higher of Quality of Recovery score comparing the analgesic pathway to placebo, assuming that the Quality of Recovery coefficient of variation (SD/mean before log-transformation) was 0.43 for both groups. After accounting for an anticipated dropout rate of 10% (due to surgery cancelation, withdrawals and other unexpected events) and for two interim and one final analyses, we concluded that we would need to enroll a maximum of N = 440 patients for this study (N = 220 patients per group).

We used a group sequential design[35] to test for efficacy and futility to maintain the significance level for the primary outcome at 5% and the power at 90% across the interim analyses. Efficacy and futility are specific interim analysis terms used for overwhelmingly positive and convincing negative results.[35,36] Specifically, we employed a gamma spending function (gamma = –4 for efficacy and –1 for futility)[37]; the originally planned efficacy and futility boundaries are displayed in figure 2.The final boundary for the primary outcome was $P < 0.047$ for efficacy.

After enrolling 299 patients, we recalculated the power of the independent samples *t* test using the actual study

Table 1. Demographic, Baseline, and Morphometric Characteristics of Participants

Factor	Analgesic Pathway (N = 150)	Placebo (N = 149)	ASD
Demographic and baseline			
Age, y	62 ± 12	63 ± 11	0.11
Female, No. (%)	69 (46)	78 (52)	0.13
BMI, kg/m^2	31 ± 7	32 ± 7	0.10
Race, No. (%)			0.15
White	144 (97)	140 (95)	
Black or African American	5 (3)	6 (4)	
Other	0 (0)	2 (1)	
Smoking, No. (%)	71 (47)	73 (49)	0.03
History of diabetes, No. (%)	33 (22)	25 (17)	0.13
History of chronic pain, No. (%)	120 (80)	108 (73)	0.18
Previous opioid use, No. (%)	80 (53)	81 (54)	0.02
High anxiety before surgery,* No. (%)	54 (36)	54 (36)	0.01
Preoperative pain score (0–10 verbal response pain scores)	5.3 ± 2.8	5.3 ± 2.7	< 0.01
ASA status, No. (%)			0.16
I	1 (1)	2 (1)	
II	32 (21)	21 (14)	
III	117 (78)	126 (85)	
Charlson comorbidity index, No. (%)			0.12
0	80 (53)	83 (56)	
1	36 (24)	34 (23)	
2	21 (14)	20 (13)	
3	4 (3)	7 (5)	
4 and above	9 (6)	5 (3)	
No. of risk factors for uncontrolled postoperative pain,† No. (%)			< 0.01
1	3 (2)	0 (0)	
2	40 (27)	40 (27)	
3	44 (29)	42 (28)	
4	32 (21)	47 (32)	
5	26 (17)	18 (12)	
6	5 (3)	2 (1)	
Surgical characteristics			
Surgical duration (h)	5.4 ± 2.1	5.4 ± 2.1	0.02
Surgery type, No. (%)			0.05
1–2 Level with no instrumentation	8 (5)	6 (10)	
Multilevel with instrumentation	141 (94)	142 (95)	
Multilevel with no instrumentation	1 (1)	1 (1)	
Epidural analgesia, No. (%)	2 (1.3)	0 (0)	0.16
Local wound infiltration, No. (%)	39 (26)	32 (22)	0.11
Intraoperative sevoflurane use, No. (%)	45 (30)	46 (31)	0.02
Intraoperative isoflurane use, No. (%)	107 (71)	107 (72)	0.01
Intraoperative muscle relaxant use, No. (%)	150 (100)	147 (99)	0.17
Intraoperative vasopressors, mg	15 [6, 26]	9 [3, 18]	0.32
Fluids volume (crystalloids, colloids), cc	2,825 [2,000, 4,000]	2,800 [1,800, 3,800]	0.16
Intraoperative RBC transfusion, No. (%)	15 (10)	10 (7)	0.12
Intraoperative opioid infusion, No. (%)	149 (99)	149 (100)	0.12
Sufentanil	44 (30)	36 (24)	0.12
Remifentanil	3 (2)	1 (0.7)	0.12
Fentanyl	147 (99)	146 (98)	0.05
Alfentanil	0 (0)	0 (0)	NA
Total intraoperative dose, in mg IV morphine equivalent	25 [18, 55]	30 [20, 61]	0.19
Amount of intraoperative hypotension (AUC MAP below 65 mmHg)	45 [4, 102]	29 [3, 99]	0.16

Summary statistics are reported as No. (%), means ± SDs, or medians [Q1, Q3] as appropriate.

*Patient has high anxiety if in Amsterdam Preoperative Anxiety and Information Scale questionnaire any of the questions were marked as 4 and 5, corresponding to very large and extreme level of worry. †The risk factors for uncontrolled postoperative pain were defined in the protocol and included young age (60 yr old and younger), female sex, chronic pain for more than 3 months, high preoperative pain score (VAS scale ≥7), preoperative high anxiety level, and multilevel surgery.

ASA, American Society of Anesthesiologists; ASD, absolute standardized difference; AUC, area under the curve; BMI, body mass index; IV, intravenous; MAP, mean arterial pressure; NA, not applicable; RBC, red blood cells; VAS, visual analogue scale.

estimates of coefficient of variation (0.22). We did not use the observed treatment effect, but rather assessed power to detect the planned 15% relative increase in geometric mean Quality of Recovery score at the overall 0.05 significance level. With 299 patients, we had 99% power to detect a 15% relative increase in Quality of Recovery score.

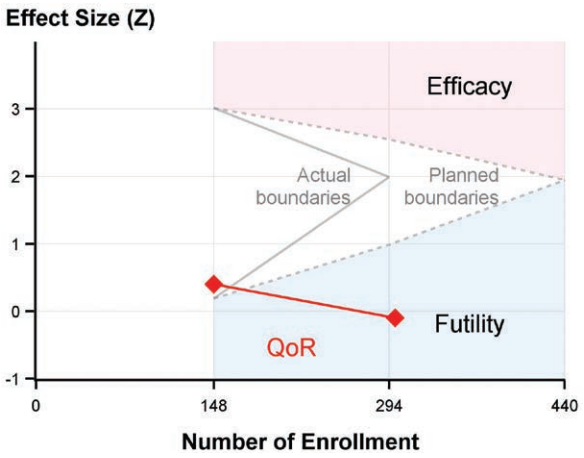

Fig. 2. Interim analysis sequential stopping boundaries: the originally planned efficacy and futility boundaries along with actual boundaries after the trial was stopped, along with the treatment effect estimates. QoR, Quality of Recovery.

Results

The trial was stopped per protocol after the second interim analysis when results crossed our predefined futility boundary. At that point, there were 150 (50%) patients randomized to the analgesic pathway group and 149 (50%) patients randomized to the standard of care group (fig. 1). Demographic, baseline, and surgical characteristics are presented in table 1; all potential confounders were balanced at the baseline. About half of the patients were women, half were smokers, and 80% were American Society of Anesthesiologists Physical Status III.

Quality of recovery at 3 days, our primary outcome, is reported by study groups in table 2, figure 3, and Supplemental Digital Content 2 (http://links.lww.com/ALN/C179; individual questions of Quality of Recovery survey). The treatment effect on Quality of Recovery outcome was not significant ($P = 0.920$), with the estimated difference in means of 0 (95% CI, −6 to 6). Results of both sensitivity analyses were consistent with primary analysis. Per *post hoc* analysis, there were no significant interactions between analgesic approaches and history of chronic pain or history of opioid use ($P = 0.733$ and $P = 0.696$), meaning the relationship between postoperative analgesic approaches and Quality of Recovery outcome was not modified by these two factors.

Pain management within the initial 48 postoperative hours was not superior with the analgesic pathway per our predefined joint hypothesis rules (table 3): both 48-h pain and opioid were noninferior in the analgesic pathway group (both noninferiority $P < 0.001$); however, neither of two outcomes was significantly lower in the analgesic pathway group (superiority $P = 0.175$ in opioids and $P = 0.094$ in pain). Per *post hoc* analysis, there were no significant interactions between history of opioid use and the exposure on 48-h pain scores outcome ($P = 0.775$) and on opioids consumption outcome ($P = 0.202$).

Both 24-h pain scores and opioid use were noninferior in patients randomized to the analgesic pathway (both noninferiority $P < 0.001$). Pain scores were significantly lower in the analgesic pathway group (superiority $P = 0.025$), but not by a clinically important amount. Opioid-related side effects (table 4) were similar in each group on both the first ($P = 0.819$) and second ($P = 0.530$) postoperative days.

None of the exploratory outcomes including PACU length of stay, postoperative nausea and vomiting, patient satisfaction with pain management at discharge from the hospital, Quality of Recovery score at 1 month, and health-related quality of life EQ-5D at 3 months differed by clinically important amounts (table 5).

Discussion

In spine surgery patients at high risk of postoperative pain, a multimodal analgesic pathway that included acetaminophen, gabapentin, lidocaine, and ketamine did not improve

Table 2. Primary Outcome: The Effect of an Analgesic Pathway on Quality of Recovery on the Third Postoperative Morning (N = 299)

	Analgesic Pathway (N = 150)		Placebo (N = 149)		Difference in Means (95.3% CI)†	*P* Value‡
	Missing	Estimate*	Missing	Estimate*		
Primary outcome						
QoR score on the third postoperative morning (ranging 0–150): multiple imputation	21	109 ± 25	20	109 ± 23	0 (–6 to 6)	0.920
Sensitivity analysis						
"Complete" cases	0	109 ± 25	0	109 ± 23	0 (–6 to 6)	0.971
Assigned "average" group score for missing outcome	0	109 ± 25	0	109 ± 23	0 (–5 to 5)	0.966

*Quality of Recovery (QoR) scores are presented as means ± SDs for nonmissing patients. †Confidence limits reflect the correction for interim analyses in order to maintain overall Type I error rate at 5%. ‡*P* value corresponded to two-sample *t* test.

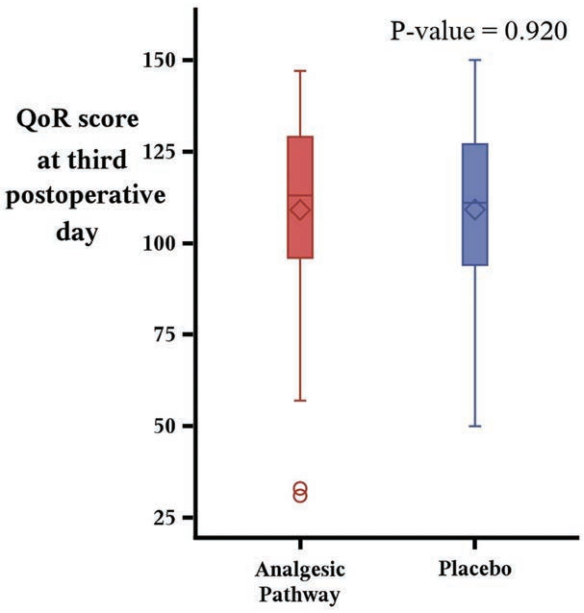

Fig. 3. Primary results: effect of anesthesia care approach (analgesic pathway *vs.* placebo) on Quality of Recovery (QoR) scores on the third postoperative morning in spinal surgical patients (N = 299). *Boxes* represent the first quartile, median, and third quartile, while *whiskers* represent the most extreme observations within 1.5 times the interquartile range of the first and third quartiles. *Diamonds* represent mean. Values exceeding 1.5 times the interquartile range are displayed with *circles*.

Quality of Recovery. Presumably, Quality of Recovery was similar in the treatment and placebo groups because there were no clinically important differences in the most obvious mediators, postoperative opioid consumption and pain scores. It was surprising that the combination of four established analgesics proved ineffective in our patients. There are at least four potential explanations, including the surgical setting; the analgesic combination, doses, and routes; trial design; and the chosen primary outcome.

Surgical Setting

We enrolled patients at high risk for postoperative pain, and studied an operation that is especially painful. Spine surgery differs from most other surgical procedures in provoking both neuropathic and muscle pain. Neuropathic pain is notoriously difficult to treat, and spasmodic muscle pain also responds poorly to many conventional analgesics. It is thus possible that the combination we tested would have been more effective for other procedures. In contrast, local anesthetic infiltration or epidural analgesia might have been more effective in our patients.

Analgesic Combination, Doses, and Routes

Each of the four drugs we tested is reported to improve postoperative analgesia.[9,14,17,21] Two of the drugs, acetaminophen and gabapentin, were given orally as a single preoperative dose. While there are reports supporting this approach,[9,10,21] both are relatively short-acting, and it seems somewhat

Table 3. Secondary Outcome: The Effect of an Analgesic Pathway on Opioid Consumption and Pain Intensity Scores within the Initial 48 Postoperative h (N = 299)

Outcome	Analgesic Pathway (N = 150)	Placebo (N = 149)	Test	Delta	CL*	Difference in Medians† (CI)*	*P* Value
Secondary outcome							
48-h opioid consumption (mg morphine equivalents)	72 [48, 113]	75 [50, 152]	NI	15	95%	–9 (–21 to 3)	< 0.001
			SUP	0	97.5%	–9 (–23 to 5)	0.175§
						Difference in means‡ (CI)*	
48-h time-weighted average pain score	4.8 ± 1.8	5.2 ± 1.9	NI	1	95%	–0.4 (–0.8 to 0.1)	< 0.001
			SUP	0	97.5%	–0.4 (–0.8 to 0.1)	0.094
Post hoc analysis for 24-h postoperative pain management						Difference in medians† (CI)*	
24-h opioid consumption (mg morphine equivalents)	47 [26, 68]	45 [33, 81]	NI	9	95%	–0.1 (–0.3 to 0.1)	< 0.001
			SUP	1	97.5%	–0.1 (–0.3 to 0.1)	0.171§
						Difference in means‡ (CI)*	
24-h time-weighted average pain score	4.8 ± 1.9	5.3 ± 2.0	NI	1	95%	–0.5 (–1.0 to –0.1)	< 0.001
			SUP	0	97.5%	–0.5 (–1.0 to 0.0)	0.025

Results at 24 h are based on a *post hoc* analysis. Summary statistics are reported as means ± SDs or medians [Q1, Q3].

*Joint hypothesis testing of pain score and opioid consumption was conducted at the overall 0.025 significance level (Bonferroni-corrected for two secondary hypotheses), and all tests were one-tailed in the direction favoring a novel pain management approach. Noninferiority of analgesic pathway group to placebo group was assessed for each outcome at the 0.025 level (no Bonferroni correction) since noninferiority was required on both outcomes. Therefore, noninferiority (being "not worse") was concluded for both outcomes at the significance level of 0.025 if the upper limit of 95% CI was below the corresponding noninferiority delta. Since the noninferiority on both outcomes was found, superiority were assessed on each outcome. We adjusted for two outcomes for the superiority testing only, using a significance criterion of 0.0125 for each outcome (*i.e.,* 0.025/2, Bonferroni correction), since superiority on either outcome would suffice. Superiority would be claimed for a particular outcome if the 97.5% interval limits were below zero for pain score and opioid consumption. †Difference in medians of analgesic pathway *versus* placebo was estimated with Hodges–Lehmann estimator of location shift between two study groups. ‡Difference in time-weighted average pain score means based on a linear regression model. §Wilcoxon rank-sum test to compare skewed postoperative opioid consumption outcome.

CL, confidence level; NI, noninferiority; SUP, superiority.

Table 4. The Effect of an Analgesic Pathway on Opioid-related Side Effects (N = 299)

Outcome	Analgesic Pathway (N = 150)	Placebo (N = 149)	Ratio of Means* (CI)	*P* Value
Secondary outcome				
Opioid related side effects (ORSDS) score POD 1	2 [1, 3]	2 [1, 3]	1.0 (0.6–1.6)	0.819
Opioid related side effects (ORSDS) score POD 2	2 [1, 3]	2 [1, 2]	1.2 (0.6–2.4)	0.530

Summary statistics are reported as median [Q1, Q3].

*Ratio of geometric means estimated as exponentiated treatment effect parameter from a multivariable linear regression on log opioid consumption.

ORSDS, opioid-related symptom distress.

Table 5. Exploratory Outcomes (N = 299)

	Analgesic Pathway (N = 150)		Placebo (N = 149)	
Outcome	Missing	Estimate	Missing	Estimate
QoR score at 1 months (ranging 0–150)	13	125 ± 22	13	122 ± 20
Patient satisfaction with pain management at discharge from the hospital (NRS 1-100)	5	78 ± 22	7	81 ± 20
Health-related quality of life EQ-5D questionnaire				
Baseline	7	8.6 ± 2.0	10	9.1 ± 2.4
At 3 months	24	7.0 ± 2.0	34	7.3 ± 2.1
Chronic postsurgical pain at 3 months (0-10 NRS scale)	23	2.6 ± 2.5	32	2.9 ± 2.9
PACU length of stay (h)	1	3.6 [2.6, 5.0]	3	3.3 [2.6, 4.4]
Postoperative nausea and vomiting in PACU, No. (%)	4		2	
None		91 (62)		95 (65)
Mild		27 (19)		30 (20)
Moderate		15 (10)		12 (8)
Severe		13 (9)		10 (7)
Postoperative length of hospital stay (days)	0	3 [1, 5]	0	4 [1,6]
Need for acute pain consultation, as determined by clinical need, No. (%)	31	16 (13)	28	13 (11)
Additional outcomes added *post hoc*				
Postoperative acetaminophen within 48 h, No. (%)	0	141 (94)	0	136 (91)
Postoperative gabapentin within 48 h, No. (%)	0	59 (39)	0	59 (40)
Postoperative tramadol within 48 h, No. (%)	0	1 (0.7)	0	7 (4.7)
Postoperative ketorolac within 48 h, No. (%)	0	38 (25)	0	38 (26)
Postoperative suboxone within 48 h, No. (%)	0	0 (0)	0	0 (0)
Postoperative PCA use within 48 h, No. (%)	0	90 (60)	0	81 (54)

Summary statistics are reported as No. (%), means ± SDs, or medians [Q1, Q3] as appropriate.

EQ-5D, standardized measure of health status developed by EuroQol group; NRS, numeric rating scale; PACU, postanesthesia care unit; PCA, patient-controlled analgesia; QoR, Quality of Recovery.

unlikely that either would provide clinically important analgesia for several postoperative days. Each presumably provided a degree of preemptive analgesia, but most trials do not identify long-term benefit from preemptive analgesia.[38] Acetaminophen could have been given intravenously, but there is no evidence that efficacy is improved.[39]

From a practical perspective, ketamine and lidocaine were our most important interventions. Both were given by infusion throughout surgery, providing a reasonable exposure. The dose of lidocaine, 1.5 mg/kg/h, is similar to that used in many previous trials that reported benefit, and is probably near the safety threshold. The dose of ketamine, 5 μg/kg/min (about 0.3 mg/kg/h in a 70-kg patient), was on the low end of the typical range for use as a perioperative analgesic adjuvant. However, it is well within recent consensus guidelines suggesting that 0.1 to 0.5 mg/kg/h provides a good balance between analgesia and adverse effects.[40] Our trial was predicated on the assumption that each of the four tested drugs is individually effective. In fact, the evidence for effectiveness is relatively weak. It is also possible that benefit would have been observed at a higher dose, with some risk of toxicity.

Trial Design

The specific combination of drugs we evaluated has not previously been rigorously tested, although many trials evaluated each individually. Why the combination would prove ineffective, given the apparent benefit from the individual components, remains unclear. A remote possibility is that the drugs interacted antagonistically. However, it seems unlikely

that antagonistic interactions explain our negative results. We evaluated the combination of all four drugs simultaneously, but an alternative would have been to use a factorial design that would evaluate individual effects. With enough patients, about four times the number we studied, it would have been possible to formally evaluate interactions among the drugs. In contrast to our rigorous blinded randomized design, many previous studies reporting benefit used scientifically weak before–after designs[41] that suffer from the Hawthorne effect, regression to the mean, and time-dependent confounding (*e.g.*, practice improvements over time).

We enrolled 299 patients, making our trial considerably larger than nearly all previous perioperative trials of the drugs we tested. The trial was stopped because results were well into the futility range. Our results showing lack of benefit from multimodal analgesic pathway are robust (a difference in quality of recovery of 0 units), rather than representing an underpowered study or uncertain results.

Primary Outcome

Spine surgery is often performed to limit disability and improve quality of life, and we believe it should be the goal. Therefore, we chose Quality of Recovery as the primary outcome, which is a valid, reliable, and responsive measure of functional recovery after surgery.[26,42] The Quality of Recovery instrument evaluates the following domains: pain, physical comfort, physical independence, psychologic support, and emotional state. Our trial evaluated four analgesics, so the most obvious benefit would be in the pain domain. Consequent opioid sparing might improve ambulation and thus the physical independence domain. Opioid sparing might also improve emotional state. The effects of ketamine are less obvious and might either improve or worsen emotional state. In fact, pain scores were not improved and opioid use was comparable in both trial groups. It is therefore unsurprising that Quality of Recovery was also similar in each group.

Multimodal analgesia is a component of many care pathways or Enhanced Recovery After Surgery protocols. The assumption is that combining various nonopioid analgesics will reduce the need for opioids and consequently opioid-related complications. For example, the American Society of Anesthesiologists Taskforce on Acute Pain Management recommends multimodal analgesia, a recommendation largely based on class C evidence defined as "informal opinion."[7] In most cases, the assumption that multimodal analgesia is beneficial has not been rigorously tested—which was the basis for our trial. Unfortunately, widespread implementation of Enhanced Recovery After Surgery programs is often based on weak evidence.[43] Our negative findings suggest that care pathways should be formally tested in each clinical context. For example, Bragato and Jacobs noted success with care pathways in orthopedic units, but not in trauma units, and cautioned against universal implementation of care pathways in all clinical areas.[44]

We did not control postoperative use of acetaminophen and gabapentin. However, use was similar in each group. For example, about 90% of the patients in each group were given acetaminophen, and about 40% of each group was given gabapentin. Pain scores at rest were evaluated by nurses in their clinical routine. Possibly pain scores would have differed with activity if analgesia was disproportionately effective at higher pain intensities. We included patients at moderate-high risk of pain, who are most likely to benefit from multimodal analgesia. Although it seems unlikely, patients at lower or much higher risk might possibly benefit.

To summarize, use of multimodal analgesic pathway based on preoperative single-dose acetaminophen and gabapentin, and intraoperative infusions of lidocaine and ketamine, did not improve day 3 Quality of Recovery or reduce pain scores or 48-h opioid consumption. This combination of four analgesics was not beneficial for patients having multilevel spine surgery. The lack of benefit in spine surgery patients suggests that multimodal analgesia should be formally tested in each clinical context.

Research Support

Support was provided solely from institutional and/or departmental resources.

Competing Interests

Dr. Krishnaney reports a relationship as a consultant with Stryker Corp. (Kalamazoo, Michigan). Dr. Machado reports a relationship as a consultant with Abbott (Abbott Park, Illinois), Medtronic (Minneapolis, Minnesota), Enspire (Austin, Texas), and Cardionomic Inc. (New Brighton, Minnesota) intellectual property distribution rights. Dr. Rosenquist is a member of the Clinical Events Review Committee, Mainstay Medical (Dublin, Ireland); member of the Board of Directors for KURE Pain Holdings, LLC (Wilmington, Delaware); receives royalties from and is an educational content developer for UpToDate (Waltham, Massachusetts); receives royalties from Oxford University Press (Oxford, United Kingdom) and Springer (Berlin, Germany); and received honoraria for content development and presentation of risk evaluation and mitigation strategy material from the American Society of Anesthesiologists (Schaumburg, Illinois). The other authors declare no competing interests.

Reproducible Science

Full protocol available at: maheshk@ccf.org. Raw data available at: maheshk@ccf.org.

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