

## ANESTHESIOLOGY

## Enhanced Recovery after Lumbar Spine Fusion

## A Randomized Controlled Trial to Assess the Quality of Patient Recovery

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## EDITOR'S PERSPECTIVE

## What We Already Know about This Topic

- Recovery from surgery may be improved by optimizing pre-, intra-, and postoperative management.
- Enhanced recovery pathways involving spine surgery have scarcely been evaluated.

## What This Article Tells Us That Is New

- Use of an enhanced recovery pathway for patients undergoing one- or two-level lumbar spinal fusion was associated with higher (better) Quality of Recovery-40 scores 3 days after surgery. This difference was not deemed clinically significant, however.
- Several secondary endpoints including time to oral intake, duration of patient-controlled analgesia use, and day 1 opioid consumption were improved by use of the enhanced recovery pathway.
- Further refinement of enhanced recovery strategies for spinal surgery is required.

Enhanced recovery pathways reduce length of stay and costs while improving outcomes and patient satisfaction after surgery.<sup>1</sup> Enhanced recovery also functions as a framework through which evidence-based, standardized care can be organized and delivered at the individual and health-system levels.<sup>2</sup> A proposed physiologic mechanism

## ABSTRACT

**Background:** Prospective trials of enhanced recovery after spine surgery are lacking. We tested the hypothesis that an enhanced recovery pathway improves quality of recovery after one- to two-level lumbar fusion.

**Methods:** A patient- and assessor-blinded trial of 56 patients randomized to enhanced recovery (17 evidence-based pre-, intra-, and postoperative care elements) or usual care was performed. The primary outcome was Quality of Recovery-40 score (40 to 200 points) at postoperative day 3. Twelve points defined the clinically important difference. Secondary outcomes included Quality of Recovery-40 at days 0 to 2, 14, and 56; time to oral intake and discharge from physical therapy; length of stay; numeric pain scores (0 to 10); opioid consumption (morphine equivalents); duration of intravenous patient-controlled analgesia use; complications; and markers of surgical stress (interleukin 6, cortisol, and C-reactive protein).

**Results:** The analysis included 25 enhanced recovery patients and 26 usual care patients. Significantly higher Quality of Recovery-40 scores were found in the enhanced recovery group at postoperative day 3 ( $179 \pm 14$  vs.  $170 \pm 16$ ;  $P = 0.041$ ) without reaching the clinically important difference. There were no significant differences in recovery scores at days 0 ( $175 \pm 16$  vs.  $162 \pm 22$ ;  $P = 0.059$ ), 1 ( $174 \pm 18$  vs.  $164 \pm 15$ ;  $P = 0.050$ ), 2 ( $174 \pm 18$  vs.  $167 \pm 17$ ;  $P = 0.289$ ), 14 ( $184 \pm 13$  vs.  $180 \pm 12$ ;  $P = 0.500$ ), and 56 ( $187 \pm 14$  vs.  $190 \pm 8$ ;  $P = 0.801$ ). In the enhanced recovery group, subscores on the Quality of Recovery-40 comfort dimension were higher (longitudinal mean score difference, 4; 95% CI, 1, 7;  $P = 0.008$ ); time to oral intake ( $-3$  h; 95% CI,  $-6$ ,  $-0.5$ ;  $P = 0.010$ ); and duration of intravenous patient-controlled analgesia ( $-11$  h; 95% CI,  $-19$ ,  $-6$ ;  $P < 0.001$ ) were shorter; opioid consumption was lower at day 1 ( $-57$  mg; 95% CI,  $-130$ ,  $-5$ ;  $P = 0.030$ ) without adversely affecting pain scores ( $-2$ ; 95% CI,  $-3$ ,  $0$ ;  $P = 0.005$ ); and C-reactive protein was lower at day 3 (6.1; 95% CI, 3.8, 15.7 vs. 15.9; 95% CI, 6.6, 19.7;  $P = 0.037$ ).

**Conclusions:** Statistically significant gains in early recovery were achieved by an enhanced recovery pathway. However, significant clinical impact was not demonstrated.

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by which enhanced recovery achieves positive results is modulation of the surgical stress response.<sup>3</sup>

Despite decades of research into pathway-based care, there is sparse evidence to support application to spine surgery. Indeed, a special edition of *Neurosurgical Focus* devoted to enhanced recovery for spine surgery highlights this point: there are no randomized controlled trials investigating the merits of enhanced recovery pathways for spine surgery, and more evidence with higher quality data is urgently needed.<sup>4</sup> Further, published data focus on length

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of stay and readmission after spine surgery as surrogates for pathway safety and effectiveness.<sup>5–10</sup> Unlike other surgical subspecialties, there are no studies in spine surgery cohorts that assess the effects of an enhanced recovery pathway on patient quality of recovery, intermediate-to-long term outcomes, or associated biochemical markers of surgical stress.

These issues are not unique to spine surgery. A recent editorial called for reevaluation of the global direction of enhanced recovery research, less emphasis on the routine extrapolation of methods and results from one surgical domain to another, and a return to core enhanced recovery principles.<sup>11</sup> Chief among these were a return to conducting high-quality, prospective studies focusing on patient-relevant outcomes and studies that incorporate evidence of biologic plausibility to inform patient care.

Trends in care and future projections in an ageing population predict rising demand for spinal fusion.<sup>12</sup> Although outcomes are overall favorable, postoperative complications and morbidity can be significant, including cardiac, renal, or pulmonary injury, infection, thromboembolism, and ongoing pain.<sup>13</sup> Thus, strategies to facilitate recovery and minimize resource consumption after lumbar fusion are required.

Given these knowledge gaps, we designed an evidence-based enhanced recovery pathway for one- and two-level open lumbar fusion based on enhanced recovery after surgery principles of care.<sup>1</sup> Our primary aim was to investigate the effect of the pathway on patient quality of recovery compared with usual care in a randomized controlled trial at an orthopedic specialty hospital. Our secondary aim was to assess effects of the pathway on opioid consumption, length of stay, time to meeting physical therapy discharge criteria, and indices of surgical stress. Our hypothesis was that patients randomized to pathway care would have higher scores on the Quality of Recovery 40 (QoR40) index after lumbar fusion compared with patients who received usual care. We additionally hypothesized that the pathway would impact pain scores, lower opioid consumption, reduce time to meeting physical therapy discharge criteria, and length of stay and modify the profile of serum markers of the surgical stress response.

## Materials and Methods

This randomized controlled trial was approved by the Hospital for Special Surgery Institutional Review Board (approval number 2016-617) and registered at clinicaltrials.gov (NCT02949518, Principal Investigator Ellen M. Soffin, November 28, 2016). Written informed consent was obtained from all participating patients. The study was conducted at the Hospital for Special Surgery, New York, New York, between December 2016 and October 2018. This article adheres to the applicable Consolidated Standards of Reporting Trials guidelines. The full trial protocol is available on request from the corresponding author.

## Participants and Recruitment

All patients aged 21 or older presenting for primary one- or two-level lumbar fusion were eligible for participation. Exclusion criteria included baseline cognitive impairment, kidney, liver or bowel disease, allergy or contraindication to any pathway care element, patients with other chronic pain conditions (unrelated to the surgical indication) on chronic opioid or gabapentinoid therapy, and patients whose primary or preferred language was not English.

## Randomization and Blinding

This is a randomized patient- and assessor-blinded controlled trial. After informed consent, the patients were randomized to enhanced recovery pathway or usual care based on a 1:1 schedule with blocks of 4 created using SAS software, version 9.3 (SAS Institute, USA). Randomization was stratified by planned surgery (one- or two-level fusion). The schedule was generated by a statistician not otherwise involved in the study, and treatment assignments were performed by opaque, sealed envelopes prepared by a member of the research division not otherwise involved in the study.

Because of the nature of the intervention, full blinding of all study personnel was not feasible. However, to minimize bias, we attempted to blind patients, practitioners (where possible), research assistants, and data analysts. We additionally performed an analysis of blinding success of patients and research assistants using Bang's Blinding Index.<sup>14</sup> To achieve patient blinding, during the informed consent process, we described both treatment arms as comprising multimodal, multidisciplinary care. However, we explained patients may receive different components of care, different quanta of care, or care at different intervals, depending on group allocation. As patients moved through the perioperative phases of care, members of the care team (including nurses, physician assistants, and nutritionists) were informed verbally, and *via* an electronic message when the patient chart was opened, that the patient was in the study. Group allocation was not shared. The surgical team was blinded until after the procedure was complete. All outcome assessments and data collection and management were performed by a blinded research assistant. Data analysts were blinded until analysis was complete. It was not feasible to blind the intraoperative anesthesiologist or physical therapist performing therapy on postoperative day 0 for patients randomized to the enhanced recovery arm. The physical therapist(s) caring for the patient after postoperative 0 were unaware of group allocation.

## Enhanced Recovery Pathway

An evidence review and rationale for inclusion of individual care elements in an enhanced recovery pathway for lumbar surgery has been previously reported by our group.<sup>5</sup> We tailored the pathway with procedure-specific elements supported by the evidence and applied it to lumbar fusion. The anesthesiologist in charge of patients randomized to

the usual care arm had sole discretion over intraoperative treatment. Differences between the usual care and enhanced recovery arms are provided in table 1, and further description of the enhanced recovery pathway is detailed below.

### Preoperative Enhanced Recovery Care

Patients randomized to enhanced recovery received a specifically created patient-education module focused on expectations for recovery, pain, physical therapy and nutrition goals, use of multimodal analgesia, how opioids are used, and the role of the patient in recovery. On the day of surgery, patients received oral acetaminophen (1,000 mg) and gabapentin (300 mg) in the holding area. A risk assessment for postoperative nausea and vomiting was performed, and scopolamine patches were placed for patients deemed at high risk. A 125-ml clear carbohydrate-rich beverage was provided 4 h before surgery.

### Intraoperative Enhanced Recovery Care

All patients received general anesthesia with endotracheal intubation and mechanical ventilation. Per our institutional practice, a radial arterial catheter and a second peripheral iv catheter were placed. The arterial catheter was also placed to facilitate postoperative collection of study-related blood samples. In the enhanced recovery group, induction of anesthesia was performed with propofol (1 to 2 mg · kg<sup>-1</sup>) and vecuronium (0.1 mg · kg<sup>-1</sup>). Fentanyl was permitted (up to 2 µg · kg<sup>-1</sup>). Anesthesia was maintained with propofol (25 to 100 µg · kg · min<sup>-1</sup>), ketamine (0.1 to 0.5 mg · min<sup>-1</sup>), and dexmedetomidine (0.3 to 0.5 µg · kg · h<sup>-1</sup>) infusions supplemented with isoflurane in oxygen-enriched air (up to 0.3 minimum alveolar concentration) as needed to achieve hemodynamic and depth of anesthesia goals. Additional opioids were permitted at the discretion of the anesthesiologist (suggested limit of 2 mg of hydromorphone). Ketorolac

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**Table 1.** Summary of Enhanced Recovery Pathway *versus* Usual Care with Supporting Evidence

Item	Enhanced Recovery Pathway	Usual Care
Patient education, goal and expectation setting	Content tailored to spine surgery patients: goals for postoperative pain management, use of opioids, oral intake, mobilization, role of patient in recovery <sup>15</sup>	Patients invited to optional education class with general content (what to bring to the hospital; visiting hours; anticipated length of stay)
Preoperative fasting and complex carbohydrate loading	Preoperative fasting: 4 h for liquids and 6 h for solids; Preoperative carbohydrate drink: 12.5% maltodextrin-based drink 4 h before surgery. <sup>16</sup>	Preoperative fasting per institutional guidelines (4 h for liquids and 6 h for solids); note that institutional change in practice implemented after study start made carbohydrate beverage part of usual care
Preemptive analgesia	Single doses of oral gabapentin (300 mg) and acetaminophen (1,000 mg) to be given within 60 min of surgery <sup>17-19</sup>	None specified
Preventing and treating postoperative nausea and vomiting	All patients: preoperative risk assessment for postoperative nausea and vomiting <sup>20</sup> High risk (3-4 risk factors): preoperative scopolamine patch <sup>21</sup> All patients: intraoperative prophylaxis: 4-8 mg of dexamethasone on induction; 4-8 mg of ondansetron 30 min before emergence from anesthesia <sup>20</sup>	None specified Risk factors for postoperative nausea and vomiting: female, nonsmoker, history of motion sickness or postoperative nausea and vomiting, anticipated need for postoperative narcotics; patients with 1-2 risk factors benefit from dexamethasone <i>or</i> ondansetron at induction or emergence; patients with 3-4 risk factors benefit from both <sup>20</sup> ; scopolamine patch is effective for early and late postoperative nausea and vomiting <sup>21</sup>
Standard anesthetic protocol	Multimodal, total intravenous-based anesthetic technique, with propofol, <sup>22</sup> dexmedetomidine, <sup>23</sup> ketamine, <sup>24</sup> and up to 0.3% minimum alveolar concentration inhaled anesthetic, no nitrous oxide. <sup>25</sup>	None specified
Antimicrobial prophylaxis	Single-dose antibiotic with Gram-positive coverage, within 1 h of incision <sup>26</sup>	Institutional guidelines: single-dose antibiotic with Gram-positive coverage, within 1 h of incision <sup>12</sup>
Maintenance of normothermia	Convective, ambient, and warmed intravenous fluids, to a targeted core temperature of 36-38°C <sup>27</sup>	Not specified
Maintenance of normovolemia	Intravenous fluid regimen targeted to hemodynamics and urine output, but no formal goal-directed fluid management technique required <sup>28</sup>	Not specified
Multimodal analgesia	Intraoperative intravenous ketorolac, <sup>29</sup> lidocaine, <sup>30</sup> and ketamine <sup>24</sup>	Not specified
Early mobilization	Encourage mobilization and independence; physical therapy/out of bed within 2 h of postanesthesia care unit admission <sup>31</sup>	Not specified
Early nutrition	Commence oral diet "at will" after recovery from anesthesia <sup>32</sup>	Not specified
Preventing postoperative constipation and ileus	Intraoperative lidocaine infusion, <sup>33</sup> ongoing opioid sparing multimodal analgesia, <sup>19</sup> early mobilization, <sup>31</sup> postoperative bowel regimen, and oral nutrition <sup>32</sup>	Not specified
Effective postoperative multimodal analgesia	An opioid-sparing, multimodal analgesic regimen <sup>19,34</sup> : acetaminophen, <sup>18</sup> ketorolac, <sup>30</sup> gabapentin, <sup>17</sup> tramadol, <sup>35</sup> and dextromethorphan <sup>36</sup> ; hydromorphone iv patient-controlled analgesia until postoperative day 1 at 7:00 PM	Not specified

(15 or 30 mg, depending on age and weight) was administered during closure of the surgical incision. Lidocaine bolus ( $1 \text{ mg} \cdot \text{kg}^{-1}$ ) and infusion ( $2 \text{ mg} \cdot \text{kg} \cdot \text{h}^{-1}$ ) were started after patient positioning. Dual antiemetic agents were provided (dexamethasone [4 to 8 mg] before surgical incision and ondansetron [4 mg] during closure). Normothermia was targeted *via* a forced-air warming blanket and warmed iv fluid administration; where insufficient, the ambient temperature in the operating room was raised. We did not include goal-directed fluid administration or formally assess volume status, given the low anticipated blood loss, minimal fluid pathology associated with the surgical procedure, and otherwise comprehensive pathway. All patients were extubated before transfer to the postanesthesia care unit (PACU) for observation.

### Postoperative Enhanced Recovery Care

All patients were provided hydromorphone iv patient-controlled analgesia (PCA;  $0.2 \text{ mg} \cdot \text{ml}^{-1}$ ; no basal infusion; 0.2-mg demand dose every 10 min) and acetaminophen (1,000 mg every 6 h, iv followed by oral). All patients received iv and oral antiemetic medications on an as-needed basis. All patients received deep vein thromboembolism prophylaxis with pneumatic compression devices.

The electronic order for the iv PCA was preset to expire at 7:00 AM on postoperative day 1 but could be renewed as needed depending on patient condition. Ketorolac (15 or 30 mg every 8 h), gabapentin (300 mg every 8 h), and dextromethorphan (45 mg every 8 h) were provided on a scheduled basis. Oral opioids were ordered on a sliding numeric rating scale of reported pain, with tramadol (50 or 100 mg) or oxycodone (5 or 10 mg) available for pain scores of 3 to 4, 5 to 6, 7 to 8, or 9 to 10, respectively. Oral intake (fluid and solid) was permitted immediately after recovery from anesthesia in the PACU. All iv fluid administration was stopped when oral intake commenced. Patients received at least one physical therapy session on the day of surgery and twice daily until deemed independently mobile and able to safely navigate stairs. The physical therapy discharge criteria included satisfactory completion of graduated tasks, starting with bed-based activity (ankle, knee, and hip flexion and extension), transfer from bed-to-chair, ambulation, and navigation of stairs.

### Primary and Secondary Outcome Measures

The primary outcome was quality of recovery, as assessed by the QoR40 score at postoperative day 3. The QoR40 is a 40-item questionnaire that assesses five dimensions of recovery after surgery and anesthesia: comfort, emotions, physical independence, patient support, and pain and has a mean time to completion of 5 min.<sup>37</sup> The QoR40 has been validated for both clinical and research use,<sup>38</sup> including in patients recovering from spine surgery.<sup>23, 39, 40</sup> We measured QoR40 at six time points: in the PACU (after recovery from anesthesia) and at postoperative days 1, 2, 3, 14, and 56.

Secondary outcome measures included the trend of QoR40 scores over time, time to discharge from physical therapy, highest pain score with physical therapy, iv PCA duration, total opioid consumption in oral morphine equivalents (mg), time to first oral intake, length of stay, and complications (incidence of nausea/vomiting, ileus, confusion/delirium, infection, or respiratory and thromboembolic events, including pulmonary embolus and deep vein thrombosis). Complications were assessed continuously between admission to the PACU and hospital discharge. Length of stay was defined as the time between PACU arrival and discharge from the hospital. We also measured serum markers of inflammation and metabolic status (interleukin 6, C-reactive protein, and cortisol) in the PACU and at postoperative days 1 and 3. Compliance with process measures was tracked by review of the electronic medical record. Percentage compliance with an individual care element was determined by (number of patients in the group receiving the element/number of patients in the group  $\times$  100). Overall percentage of pathway compliance was determined by calculating the mean of the percentage of all elements provided.

### Statistical Analyses

The sample size calculation was based on a study of QoR40 score change after surgery, in which a 12-point difference in scores was found between patients with and without severe postoperative nausea and vomiting.<sup>41</sup> The mean  $\pm$  SD QoR40 score in a population of patients undergoing spine surgery was reported to be  $160 \pm 15$ .<sup>39</sup> Assuming  $\alpha = 0.05$  and 80% power to detect a 12-point difference between the groups, a sample size of 25 patients/group was required. To account for attrition, enrollment was increased by 10%, resulting in 28 patients per group, or 56 patients total.

Balance on demographics was compared by calculating standardized differences where the difference in means or proportions was divided by the pooled SD. An imbalance was defined as a standardized difference with an absolute value greater than  $1.96 \times (2/26)^{1/2} = 0.543$ .<sup>42</sup>

Continuous variables are summarized as means with SD or medians with interquartile range. Categorical variables are summarized as counts and percentages.

All analyses were performed on an intention-to-treat basis. All tests of hypotheses were two-sided, and  $P < 0.05$  was considered significant. The primary outcome was analyzed by two-sample *t* test comparing QoR40 scores at postoperative day 3 between the enhanced recovery and usual care groups without applying any stratification variable. To evaluate the impact of missing data for the primary outcome (4 of 51 patients), a sensitivity analysis was performed. The geometric mean difference of QoR40 scores at postoperative day 3 was calculated using multiple imputation methods. In this analysis, we assumed that data were missing at random. For the imputation procedure, earlier (PACU to postoperative day 2) and follow-up QoR40 (postoperative

days 14 and 56) scores (allowing for the dependence of later time points on earlier time points), treatment group, and a stratification variable (number of levels fused) were used to impute nine data sets. The imputed data sets were then analyzed using generalized linear modeling, and the results were combined to obtain a pooled geometric mean difference estimate.<sup>43</sup>

For secondary outcomes measured at a single time point per patient, continuous variables were compared between treatment groups using two-sample *t* tests or Wilcoxon rank sum tests based on data distribution. Categorical variables were compared between groups using chi-square or Fisher's exact tests, as appropriate. Secondary outcomes measured at multiple time points per patient were compared between groups using the generalized estimating equation approach to account for the correlation between repeated measurements for the same patient. Statistical analyses were performed with SAS, version 9.4 (SAS Institute).

**Results**

The trial was conducted in accordance with the original protocol and stopped when the target sample size was reached. Fifty-one patients were included in the analysis

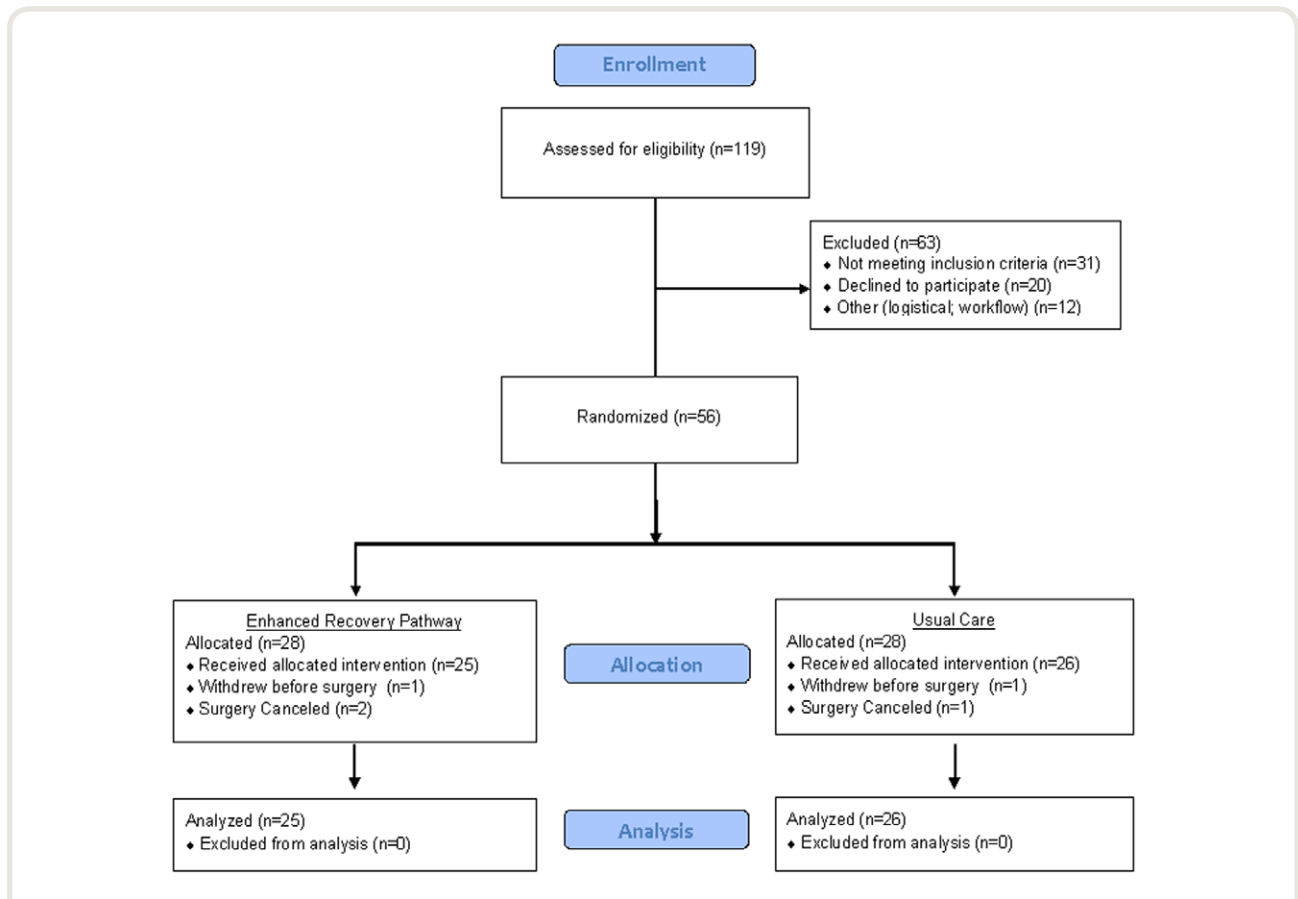
(fig. 1). Patient and surgical characteristics are shown in table 2. There were no baseline differences between the groups.

**Primary Outcome**

The mean QoR40 score difference at postoperative day 3 was 9 points (95% CI, 0.4, 18; *P* = 0.041) with higher scores reported by patients in the enhanced recovery group (179 ± 14) compared with patients given usual care (170 ± 16; fig. 2; Supplemental Digital Content, table 1, <http://links.lww.com/ALN/C381>). This difference remained significant after multiple imputation for missing QoR40 scores at postoperative day 3 (mean difference in scores, 9 points; 95% CI, 0.2, 17; *P* = 0.038).

**Secondary Outcomes**

QoR40 scores rose over time in both groups, but a greater change in scores was found in the usual care group (fig. 2). Patients in the enhanced recovery group had significantly higher scores on the comfort dimension of the QoR40 up to postoperative day 3 (longitudinal mean score difference, 4; 95% CI, 1, 7; *P* = 0.008; Supplemental Digital Content, table 1, <http://links.lww.com/ALN/C381>). There were no



**Fig. 1.** Consolidated Standards of Reporting Trials flow diagram.

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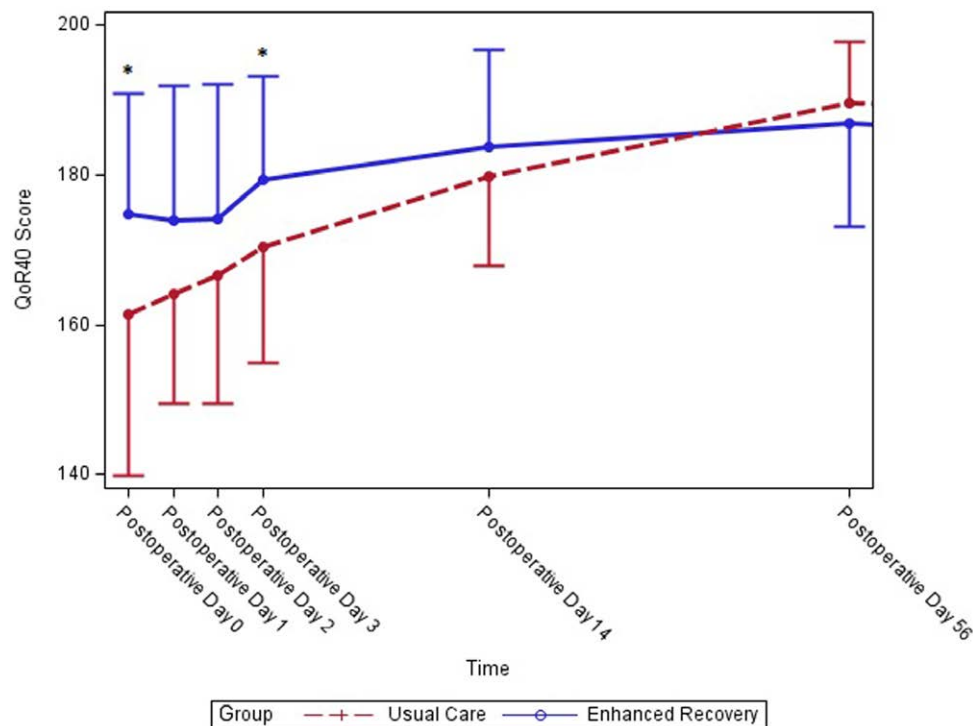
**Table 2.** Patient and Intraoperative Characteristics

Patient Characteristics	Enhanced Recovery (n = 25)	Usual Care (n = 26)	Standardized Difference
Age (yr), mean $\pm$ SD	55 $\pm$ 18	54 $\pm$ 13	0.04
Sex (male/female), n	14/11	8/18	-0.53
Body mass index, mean $\pm$ SD	27 $\pm$ 4	29 $\pm$ 5	-0.41
ASA status (I/II/III), n	6/18/1	6/19/1	0.02
Hypertension, n (%)	9 (36)	8 (31)	0.11
Asthma/pulmonary disease, n (%)	1 (4)	0 (0)	0.29
Coronary artery disease, n (%)	1 (4)	1 (4)	0.01
Obstructive sleep apnea, n (%)	3 (12)	4 (15)	0.30
Smoker/nonsmoker, n (%)	3 (12)	1 (4)	0.31
Levels fused (I/II), n	21/4	21/5*	-0.18
Race (white/nonwhite), n	24/1	22/4	0.39
<b>Intraoperative characteristics</b>			
Intraoperative monitoring	25	26	
Total anesthesia time, min (median, interquartile range)	269 (57)	269 (64)	0.08
Total surgery time, min (median, interquartile range)	183 (54)	192 (62)	-0.09

Intraoperative monitoring comprised somatosensory evoked potentials and electromyography.

\*One patient was scheduled for one-level fusion but received two-level fusion.

ASA, American Society of Anesthesiologists physical class I, II, or III.

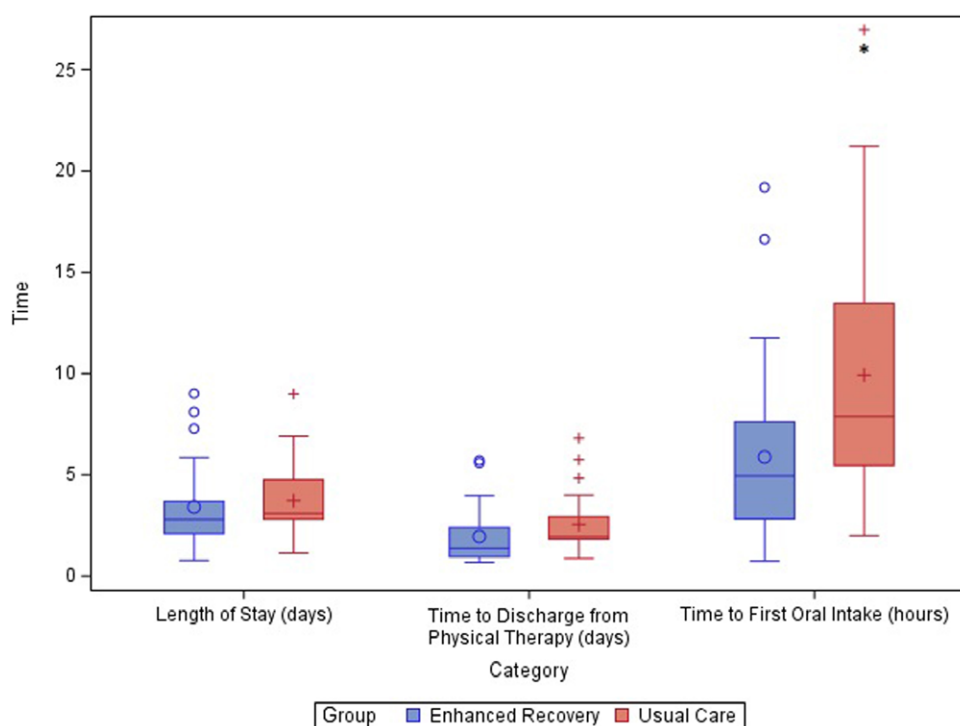


**Fig. 2.** Changes in global Quality of Recovery 40 (QoR40) scores between postoperative days 0 (postanesthesia care unit) and 56. The scores are presented as means (plots) and SD (error bars). \*Significant differences ( $\alpha = 0.05$ ) in mean QoR40 scores between the groups.

other differences in the subdimensional scores between the groups at other times.

Median time to oral intake was significantly shorter in the enhanced recovery group compared with patients

given usual care ( $-3$  h; 95% CI,  $-6, -0.5$ ;  $P = 0.010$ ; fig. 3). Median length of stay was 2.8 days (interquartile range, 2.1 to 3.7) in the enhanced recovery group and 3.1 days (interquartile range, 2.8 to 4.8) in usual care (Hodges-Lehmann



**Fig. 3.** Time to meeting recovery milestones. Box and whisker plots show median (*horizontal line*), 25th and 75th percentiles (*boxes*), range (*bars*), and outliers (*open plots*; greater or less than 1.5× interquartile range) for time to discharge from hospital (length of stay), oral intake, and discharge from physical therapy. \*Significance at  $\alpha = 0.05$ .

estimate of location shift [enhanced recovery – usual care],  $-0.67$  [ $-1.19, 0.20$ ];  $P = 0.112$ ; fig. 3). Median time to meeting physical therapy discharge criteria was 1.4 days (interquartile range, 1.0 to 2.4) in the enhanced recovery group and 1.9 days (interquartile range, 1.8 to 2.9) in the usual care group ( $P = 0.116$ ; fig. 3). More patients completed a physical therapy session on postoperative day 0 in the enhanced recovery group (17 of 25) compared with patients in usual care (3 of 26).

Median duration of iv PCA use was shorter in the enhanced recovery group ( $P < 0.001$ ; table 3) and patients consumed less opioid in the first 24h after surgery compared with patients in the usual care group ( $P = 0.030$ ; table 3). Pain scores were lower at the postoperative day 1 physical therapy session in the enhanced recovery group ( $P = 0.005$ ) but not at other times (table 3).

The overall compliance with process elements in the enhanced recovery group was 92% (fig. 4). The same care elements were assessed retrospectively in the usual care patients to determine the extent of crossover between the two groups. In the usual care group, 16 of 17 process elements were provided to at least 1 patient, and the overall provision of elements was 43%. Elements with the highest rates of concordant administration (given to more than 75% of usual care patients) were antibiotic administration

before incision, preoperative carbohydrate beverage, and a balanced anesthetic including propofol and ketamine infusions. Elements of care with the lowest rates of concordant administration (given to less than 20% of usual care patients) were preemptive gabapentin, preoperative education, and early mobilization (found in 0, 4, and 12% of usual care patients, respectively).

Complications were rare in both groups, with no significant differences found for nausea ( $P = 0.258$ ), vomiting ( $P = 0.668$ ), ileus ( $P = 0.727$ ), mental status changes ( $P = 0.999$ ), infection (one in one enhanced recovery patient), or thromboembolic events (one deep vein thrombosis was found in one enhanced recovery patient) between the groups. Two patients in the enhanced recovery group and one in usual care required supplemental oxygen after discharge from the PACU ( $P = 0.999$ ; table 4).

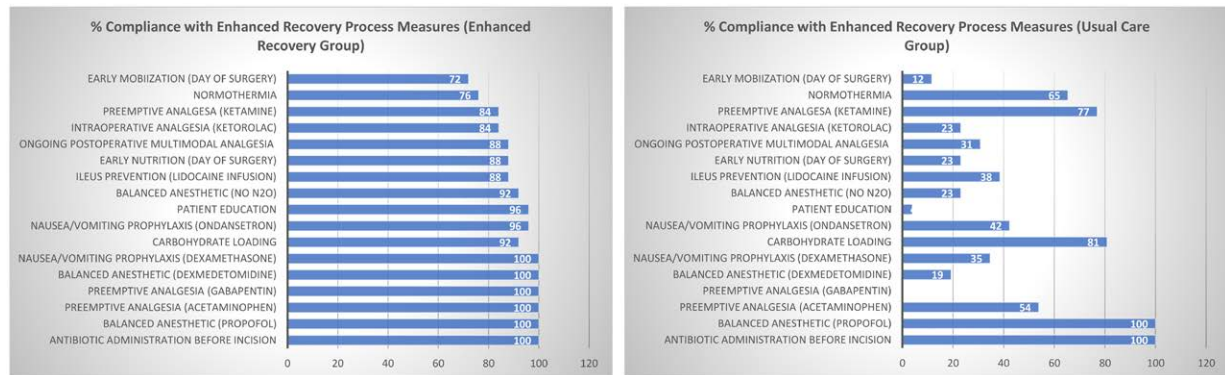
C-reactive protein was significantly higher in the usual care group at postoperative day 3 (measured in 14 enhanced recovery and 22 usual care patients;  $P = 0.037$ ) but not at other times (table 5). There were no significant differences in levels of interleukin 6 or cortisol between the two groups at any time points measured.

Finally, Bang's Blinding Index indicated 24% more patients in enhanced recovery (0.24 CI, 0.03, 0.45;  $P = 0.032$ ) and 7.7% more patients in usual care (0.77 CI,

**Table 3.** Early Postoperative Pain Scores and Opioid Consumption

Parameter	Enhanced Recovery		Usual Care		Hodges–Lehmann Estimate of Location Shift	P Value
	N	Median (Interquartile Range)	N	Median (Interquartile Range)		
Highest pain score after physical therapy session						
Postoperative day 1	24	3 (3)	23	4 (2)	−2 (−3, −1)	0.005
Postoperative day 2	9	2 (2)	19	4 (5)	−2 (−4, 0)	0.078
Opioid consumption						
0–24 h	24	62 (78)	26	133 (179)	−57 (−130, −5)	0.030
24–48 h	18	30 (78)	25	75 (92)	−25 (−68, 0)	0.053
iv PCA duration, h	24	16 (7)	25	26 (21)	−11 (−18, −6)	< 0.0001

Opioid consumption is expressed in total oral morphine equivalents (mg). Pain scores are expressed as a numeric rating scale between 0 (pain-free) and 10 (worst pain imaginable). PCA, patient-controlled analgesia.



**Fig. 4.** Enhanced recovery pathway compliance. Horizontal bars (terminal figures, in %) indicate the proportion of patients who received each process element in the pathway. Ongoing postoperative multimodal analgesia included ketorolac, acetaminophen, gabapentin, and dextromethorphan.

−0.14, 0.30;  $P = 0.281$ ) guessed that they were assigned to the enhanced recovery group than would be expected by chance. The blinded research assistants correctly guessed the group assignment for enhanced recovery patients 0% more of the time than would be expected by chance (0 CI, −0.19, 0.19;  $P = 0.500$ ) and guessed the group assignment for the usual care patients 19% less of the time than would be expected by chance (−0.19 CI, −0.37, −0.01;  $P = 0.962$ ).

### Discussion

Patients randomized to an enhanced recovery pathway for lumbar spine fusion achieved higher early quality of recovery compared with patients given usual care. Although statistically significant, the mean difference in QoR40 scores at postoperative day 3 failed to reach the prespecified minimum clinically important difference. Modest reductions in time to oral intake, duration of iv PCA use, opioid

consumption, pain scores, and C-reactive protein were also found in the pathway-care arm. There were no significant differences in other outcomes, including length of stay, time to physical therapy discharge, the incidence of complications, or other markers of inflammation and metabolic status.

Despite early calls to apply enhanced recovery to spine surgery,<sup>44</sup> few reports have been described. Most are retrospective and associate pathway-based care with short length of stay, low opioid use, and low rates of morbidity and readmission after spine surgery.<sup>5–10</sup> In contrast, two recent studies failed to find significant benefits of an enhanced recovery pathway<sup>45</sup> or a package of standardized multimodal analgesia<sup>46</sup> on quality of recovery, pain scores, or opioid consumption after lumbar fusion. We likewise found surprisingly modest effects of the pathway on length of stay, pain scores, and opioid use, suggesting that pain may not be the primary factor limiting recovery after spine surgery. Given the resource-intensive nature of pathway-based care,



**Table 4.** Comparison of Postoperative Complications between Groups

Complication*	Enhanced Recovery	Usual Care	Odds Ratio Enhanced Recovery vs. Usual Care (95% CI)	P Value
Any nausea, count (%)	8 (32)	13 (50)	0.48 (0.13, 1.67)	0.258
Any vomiting, count (%)	3 (12)	2 (8)	1.62 (0.17, 21.11)	0.668
Any ileus, count (%)	4 (16)	6 (23)	0.64 (0.12, 3.18)	0.727
Any delirium/confusion, count (%)	1 (4)	2 (8)	0.51 (0.01, 10.34)	> 0.999
Any deep vein thrombosis/pulmonary embolus, count (%)	1 (4)	0 (0)	Not available	0.490
Any infection, count (%)	1 (4)	0 (0)	Not available	0.490
Any respiratory, count (%)	2 (8)	1 (4)	0.51 (0.01, 10.34)	> 0.999

\*Given that complication events were rare, a complication was treated as a binary variable.

**Table 5.** Comparison of Plasma Biomarkers between Groups in the Early Postoperative Period

Biomarker	Enhanced Recovery		Usual Care		Ratio of Geometric Means (95% CI)	P Value
	n		n			
Interleukin 6, pg · ml <sup>-1</sup>						
Postoperative day 0	25	2.5 (2.5, 5)	25	2.5 (2.5, 5)	1.02 (0.73, 1.43)	0.917
Postoperative day 1	25	5 (2.5, 7)	25	5 (2.5, 8)	0.83 (0.53, 1.28)	0.396
Postoperative day 3	14	8 (6, 19)	22	8 (6, 21)	1.01 (0.58, 1.76)	0.974
Cortisol, µg · dl <sup>-1</sup>						
Postoperative day 0	25	6.3 (2.4, 7.9)	26	5.4 (2.2, 14)	0.82 (0.47, 1.46)	0.507
Postoperative day 1	25	0.5 (0.5, 0.5)	26	0.5 (0.5, 1.5)	0.74 (0.44, 1.24)	0.256
Postoperative day 3	14	8.3 (3.1, 10.6)	22	8.9 (6.9, 13.9)	0.86 (0.45, 1.62)	0.633
C-reactive protein, mg · dl <sup>-1</sup>						
Postoperative day 0	25	0.4 (0.4, 0.7)	26	0.4 (0.4, 0.7)	1.02 (0.74, 1.42)	0.887
Postoperative day 1	25	1.6 (0.9, 2.5)	26	1.6 (1.1, 2.2)	0.92 (0.66, 1.28)	0.617
Postoperative day 3	14	6.1 (3.8, 15.7)	22	15.9 (6.6, 19.7)	0.55 (0.32, 0.96)	0.037

these data highlight the importance of determining which care elements (or combinations thereof) are necessary and sufficient for changing outcomes after spine surgery.

These data also suggest relevant outcomes need to be further defined in enhanced recovery research. Most studies assess length of stay as a surrogate for recovery and effectiveness. However, length of stay is more likely to reflect a collection of biologic discharge criteria rather than true recovery.<sup>47,48</sup> Recent calls have been made to improve the evaluation of pathway effectiveness by incorporating global measures of recovery that are important to patients.<sup>11,48,49</sup>

Accordingly, we chose quality of recovery as the primary outcome. Two studies report increased patient satisfaction after implementing enhanced recovery for complex spine surgery,<sup>9,10</sup> but none evaluate quality of life or recovery. The QoR40 has been validated in spine surgery<sup>23,39,40</sup> and in pathway-effectiveness research in colorectal surgery.<sup>48,50</sup> When we designed our study, there was no accepted benchmark of QoR40 score change to define “recovery.” A subsequent analysis suggested that a score change of 6 points at the first postoperative visit supports a perioperative intervention as clinically important.<sup>51</sup> Although we

found a statistically significant difference in QoR40 scores of 9 points at postoperative day 3, this failed to reach our predefined primary outcome of a 12-point difference. This may be due at least in part to the crossover of care components between the enhanced recovery and usual care groups, such that a substantial proportion of recovery was driven by a few care elements found in common. Although it is unclear which elements (or combinations thereof) led to the positive findings, the pathway facilitated early mobilization and early enteral nutrition. These two milestones have been identified as among the most important determinants of positive outcomes after colorectal surgery within an enhanced recovery framework.<sup>52</sup> We also found significantly higher scores on the comfort dimension of the QoR40 in the enhanced recovery group. This dimension comprises questions related to short-to-intermediate effects of anesthesia and surgery. Consistent with our results, previous studies have associated enhanced recovery pathways,<sup>48</sup> total intravenous anesthesia,<sup>53</sup> and intraoperative dexmedetomidine use<sup>23</sup> with higher scores on this dimension.

Kehlet’s early hypotheses<sup>3</sup> on mechanisms underlying enhanced recovery after surgery effectiveness centered on

minimizing the surgical stress response. C-reactive protein, interleukin 6, and cortisol have been implicated in the stress response after spine surgery and can be modulated by individual anesthetic agents, including dexmedetomidine.<sup>23</sup> Except for C-reactive protein at postoperative day 3, we did not find any significant influence of the pathway on these candidate biomarkers. It is possible the magnitude of the surgical stress response to one- to two-level lumbar fusion was overall insufficient to reveal effects of the pathway on the markers studied here.

Enhanced recovery after surgery effectiveness has also been attributed to improved organization and delivery of health care.<sup>1,2,5</sup> Within this domain, electronic order sets may be independent drivers of successful pathway implementation and sustainability.<sup>54</sup> Our findings that the enhanced recovery group achieved earlier oral intake and shorter duration of iv PCA were likely facilitated by electronic orders that targeted times to achieve both of these milestones. These data support health information technology within enhanced recovery pathways as an additional mechanism to impact outcomes after spine surgery.<sup>55</sup>

## Limitations

- (1) Incomplete blinding may have contributed to performance bias. Blinding is a common difficulty in trials randomizing patients to pathway *versus* usual care<sup>56</sup> and has chiefly been addressed by concealing group allocation from the study personnel who perform outcome assessments and data collection.<sup>57–59</sup> Our assessment of blinding confirmed research assistants and analysts were successfully blinded, and patients in both groups were more likely to guess they were allocated to enhanced recovery care. This helps to mitigate, but cannot fully eliminate, the possibility that the gains reported here were due to ineffective blinding.
- (2) It was neither ethical nor practical to include placebo or active placebo elements in the usual care arm. Both are likely to affect recovery, pain, and opioid consumption after surgery. This has recently been demonstrated in a study comparing gabapentin to active and placebo controls, in which no differences in postoperative pain were found, but time to opioid cessation was shorter in patients receiving gabapentin.<sup>60</sup>
- (3) We found a high rate of crossover of care elements between the pathway and usual care, which will tend to confirm the null hypothesis. Conversely, the high rate of crossover of care elements in the usual care arm suggests that the pathway may provide greater gains in practice settings with fewer elements already in place as part of routine spine care.
- (4) This was a single-center study conducted at an orthopedic specialty hospital limiting the generalizability of our results. Our cohort was relatively young, without significant comorbidities, at low baseline anesthetic/surgical risk, and we excluded patients with chronic pain conditions on opioids. These factors threaten the external validity of our results and may create a ceiling effect of the pathway, whereby potentially greater gains may have been found if we had included a more diverse patient sample.
- (5) We did not establish preoperative QoR40 scores. Although we cannot fully exclude baseline differences in QoR40 scores as contributory to our findings, we propose that it is more likely that the higher QoR40 scores found in the enhanced recovery group were due to the effect of the intervention. First, we found no differences in baseline demographics or surgical characteristics between groups to suggest an effect of randomization on the results. Second, in the general population undergoing spine surgery, mean QoR40 scores rise from 160 to 170 over postoperative days 1 to 3.<sup>39</sup> We found similar QoR40 scores and score change in the usual care group, suggesting that our sample was representative of the spine surgery population. Finally, preoperative QoR40 scores may not be the optimal anchor for comparing recovery after surgery because of baseline differences in patient state (pain, anxiety, and medical complexity).<sup>37</sup> Rather, comparison of early recovery scores with scores after complete recovery may be more instructive.
- (6) The study was not designed or powered to detect differences in complications between the groups, and the absence of complications cannot be attributed to the pathway. We excluded patients with significant renal, hepatic, and cognitive disease. Patients with advanced age and multiple comorbidities are at higher risk for complications associated with polypharmacy. Importantly, the risk for respiratory depression associated with gabapentin (alone and in combination with opioids) has recently been established and may require dose adjustments and/or prolonged monitoring in individual patients.<sup>61–63</sup>

## Future Studies

Having defined an enhanced recovery pathway for lumbar fusion, future research should focus on comparing elements of care within the pathway in a systematic fashion to determine which are essential to positive outcomes and which can be removed. Well designed studies would include placebo and active placebo controls. Defining and studying outcomes in addition to length of stay and complications and those that are patient-focused should be incorporated into spine care research. Whether and how to adapt pathways to individual patients remains to be determined, particularly the appropriateness of applying a single pathway to all subtypes of spine surgery, to opioid-tolerant and -naïve patients, and to patients at high risk for polypharmacy-induced side effects. Finally, based on the proposed mechanism of action of enhanced recovery pathways, trials should incorporate indices of the surgical stress response. This is particularly relevant given the heterogeneity of “spine surgery” and likely differences in the magnitude of the response.

## Conclusions

Significantly higher early quality of recovery was found in patients randomized to an enhanced recovery pathway for lumbar spine fusion. It is unclear which pathway elements or combinations of elements underlie the benefits reported here. Despite several caveats, the results support the potential for enhanced recovery pathways to optimize recovery after lumbar spinal fusion.

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## Competing Interests

Dr. Memtsoudis declares a financial relationships with Teikoku (San Jose, California), Sandoz (Princeton, New Jersey), and HATH (Bedford Hills, New York). Dr. Schwab declares financial relationships with Medtronic (New York, New York), International Spine Study Group (Denver, Colorado), and Medtronic (Minneapolis, Minnesota); receives research support from DePuy (Raynham, Massachusetts), K2M (Leesburg, Virginia), NuVasive (San Diego, California), Globus (Audubon, Pennsylvania), Allosource (Centennial, Colorado), Orthofix (Lewisville, Texas), and SIBone (Santa Clara, California); and is a consultant for Globus Medical, Zimmer Biomet (Warsaw, Indiana), and K2M. Dr. Cammisa receives research support from Spinal Kinetics (Union, New Jersey), DePuy, Bacterin (Belgrade, Montana), Integra (Planesboro Center, New Jersey), Nutech (Houston, Texas), Vertical Spine (Township, New Jersey), and NuVasive and is a consultant for NuVasive. Dr. Kim receives research support from Alphatec, International Spine Study Group, the National Institutes of Health, Cervical Spine Research Society (Milwaukee, Wisconsin), and North American Spine Society (Burr Ridge, Illinois); receives royalties for intellectual property from Zimmer Biomet and K2M; and is a member of the AO Development Incubator Board (Davos, Switzerland). The other authors declare no competing interests

## Reproducible Science

Full protocol available at: [soffine@hss.edu](mailto:soffine@hss.edu). Raw data available at: [soffine@hss.edu](mailto:soffine@hss.edu).

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## ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

# Beacon, Not Buccaneer: Ramón Betances, Puerto Rican Patriot and Chloroform Pioneer



Nicknamed “*El Padre de la Patria*” (upper left), Ramón Emeterio Betances y Alacán (1827 to 1898)—physician, writer, abolitionist, and Freemason—was the first political leader to espouse Puerto Rican nationalism. This gold-plated medallion celebrates the 185th anniversary of his birth in Cabo Rojo, or “*El Pueblo de Cofresí*”—hometown of infamous pirate Cofresí and historic lighthouse *Faro de Morrillos* (lower right). A bust of Betances appears next to the Masonic Lodge (*Logia Cuna de Betances*, upper left) that was built upon his birthplace. Betances completed most of his education, including medical school, in France, where he embraced the principles of liberty and equality. Upon his return to Puerto Rico, he promoted public health by burning slave barracks during a cholera epidemic. Later, while in exile for his revolutionary ideals, Betances used the pseudonym “*El Antillano*” (upper left) to champion Antillean freedom from European and North American imperialism. In 1862, during a rare stint in Puerto Rico, Betances enlisted the help of Pedro Arroyo, Venezuelan anesthesiologist, to perform the first surgery under chloroform on the island. (Copyright © the American Society of Anesthesiologists’ Wood Library-Museum of Anesthesiology.)

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