ANESTHESIOLOGY

Perioperative Methadone and Ketamine for Postoperative Pain Control in Spinal Surgical Patients

A Randomized, Double-blind, Placebo-controlled Trial

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ABSTRACT

Background: Despite application of multimodal pain management strategies, patients undergoing spinal fusion surgery frequently report severe postoperative pain. Methadone and ketamine, which are *N*-methyl-D-aspartate receptor antagonists, have been documented to facilitate postoperative pain control. This study therefore tested the primary hypothesis that patients recovering from spinal fusion surgery who are given ketamine and methadone use less hydromorphone on the first postoperative day than those give methadone alone.

Methods: In this randomized, double-blind, placebo-controlled trial, 130 spinal surgery patients were randomized to receive either methadone at 0.2 mg/kg (ideal body weight) intraoperatively and a 5% dextrose in water infusion for 48 h postoperatively (methadone group) or 0.2 mg/kg methadone intraoperatively and a ketamine infusion (0.3 mg · kg^{-1} · h^{-1} infusion [no bolus] intraoperatively and then 0.1 mg · kg^{-1} · h^{-1} for next 48 h [both medications dosed at ideal body weight]; methadone/ketamine group). Anesthetic care was standardized in all patients. Intravenous hydromorphone use on postoperative day 1 was the primary outcome. Pain scores, intravenous and oral opioid requirements, and patient satisfaction with pain management were assessed for the first 3 postoperative days.

Results: Median (interquartile range) intravenous hydromorphone requirements were lower in the methadone/ketamine group on postoperative day 1 (2.0 [1.0 to 3.0] *vs.* 4.6 [3.2 to 6.6] mg in the methadone group, median difference [95% CI] 2.5 [1.8 to 3.3] mg; $P < 0.0001$) and postoperative day 2. In addition, fewer oral opioid tablets were needed in the methadone/ketamine group on postoperative day 1 (2 [0 to 3] *vs.* 4 [0 to 8] in the methadone group; $P = 0.001$) and postoperative day 3. Pain scores at rest, with coughing, and with movement were lower in the methadone/ketamine group at 23 of the 24 assessment times. Patient-reported satisfaction scores were high in both study groups.

Conclusions: Postoperative analgesia was enhanced by the combination of methadone and ketamine, which act on both *N*-methyl-D-aspartate and μ-opioid receptors. The combination could be considered in patients having spine surgery.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Ketamine is an *N*-methyl-D-aspartate antagonist that provides analgesia in various contexts
- Whether adding low-dose ketamine to methadone, also an *N*-methyl-D-aspartate antagonist, improves analgesia remains unknown

What This Article Tells Us That Is New

- In a randomized trial of 130 spinal surgery patients, adding ketamine to methadone reduced pain scores from 4 to 2 points on an 11-point Likert scale and roughly halved postoperative opioid use
- Adding low-dose ketamine to methadone improves analgesia and reduces opioid requirement and could be considered in patients recovering from spine surgery

In the United States, 80% of surgical patients reported postoperative pain, with 88% of these patients describing pain intensity as moderate to severe.[1] Poorly controlled postoperative pain can contribute to adverse events, including morbidity, increased hospitalization costs, impaired quality of life, prolonged opioid use, and chronic postsurgical pain.[1] Patients undergoing spinal fusion surgery are at high risk for moderate-to-severe postoperative pain and associated complications. In a study comparing pain scores in 179 surgical procedures, 3 of the 6 surgeries with a median pain score of 7 on postoperative day 1 (rating scale of 0 to 10) were major spinal procedures.[2] Risk factors for severe postoperative pain in this patient population include significant surgical trauma, preexisting neuropathic pain, preoperative opioid use (and associated tolerance, hyperalgesia, and allodynia),[3] and perioperative anxiety/mood disorders.[4] Therefore, techniques to reduce postoperative pain are essential in optimizing outcomes in these patients.

Multimodal pain management regimens, which involve use of additive or synergistic combinations of analgesics, are

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effective in reducing postoperative pain, decreasing opioid use, and attenuating complications. Therapeutic strategies utilizing acetaminophen, nonsteroidal anti-inflammatory agents, steroids, lidocaine, and long-acting local anesthetics have been shown to improve postoperative pain outcomes and enhance recovery.[1,5] Antagonists of the *N*-methyl-D-aspartate (NMDA) receptor, such as ketamine and methadone, have also been used as components of multimodal anesthetic protocols. Postoperative pain scores and opioid use are significantly reduced in spinal surgical patients given ketamine[6–8] or methadone[9] compared to control groups. Furthermore, enhanced-recovery-after-surgery protocols for spine surgery have recommended use of methadone and ketamine as part of a multimodal therapeutic approach for postoperative pain.[5,10] In an experimental neuropathy model, a supra-additive synergy between methadone and ketamine to produce antinociception has been documented.[11,12] Currently, however, there is limited evidence of the efficacy of a combination of the two agents on outcomes in this patient population.

Recent literature has supported the safety of intraoperative methadone; studies have documented that the incidences of adverse outcomes did not differ between patients given this long-acting agent and those given traditional shorter-acting opioids.[9] In a previous investigation, we observed that patients undergoing spinal fusion surgery given intraoperative methadone required less opioid medication and had lower postoperative pain scores than those given conventional opioids, with no differences in adverse outcomes observed between groups.[13] However, postoperative hydromorphone use remained relatively high in the methadone group (4.6 mg in the first 24 h), and moderate pain was reported in these subjects (median scores of 4 to 6 on a 0 [no pain] to 10 [worst pain imaginable] numeric rating scale).[13] The aim of this randomized, double-blind, placebo-controlled trial in spinal surgical patients was to determine whether addition of a ketamine infusion to a methadone-based opioid regimen would further reduce opioid requirements and pain scores (to mild levels, scores of 3 or lower) after spine surgery. We therefore tested the primary superiority hypothesis that adding ketamine to methadone reduces hydromorphone requirement on the first postoperative day after spine surgery compared to methadone alone. Secondary outcome measures included hydromorphone requirements on postoperative days 2 and 3, pain scores, patient satisfaction with pain management, and any potential complications associated with methadone or ketamine administration.

Materials and Methods

Study Population and Perioperative Management

The Institutional Review Board of NorthShore University HealthSystem (Evanston, Illinois) approved this randomized, double-blind, placebo-controlled clinical trial (registry, ClinicalTrials.gov; registration number, NCT02827526; date of registration, July 1, 2016; principal investigator, Glenn Murphy). The investigation was conducted at a single tertiary medical center (NorthShore Evanston Hospital), and written informed consent was obtained from all subjects. Patients were approached by research assistants and enrolled on the day of surgery. Study staff evaluated eligibility, obtained informed consent, managed the conduct of the trial, and collected and managed the data.

A total of 130 patients, ages 18 to 80 yr, undergoing elective spinal fusion surgery of one or more sacral, lumbar, and/or thoracic levels were enrolled. Exclusion criteria included American Society of Anesthesiologists (Schaumburg, Illinois) Physical Status IV or V, preoperative renal insufficiency or failure (serum creatinine ≥ 2 mg/dl), pulmonary disease necessitating home oxygen therapy, significant liver disease (cirrhosis or hepatic failure), recent history of alcohol or opioid abuse, allergy to methadone, hydromorphone, or ketamine, poor comprehension of the English language, or inability to use a patient-controlled analgesia (PCA) pump (due to intellectual impairment, disorientation, or confusion).

Patients were assigned to one of two groups using a computer-generated randomization table (simple randomization without restrictions): a methadone group (intraoperative methadone and a dextrose 5% in water infusion) or a methadone/ketamine group (intraoperative methadone and a ketamine infusion). The allocation sequence was generated by one of the study investigators, who provided the randomization assignments to the operating room pharmacy that assigned patients to the study groups and prepared all of the study medications. Care providers, researchers, and patients were blinded to group assignment. Clinicians delivering intraoperative care were provided with a 3-ml syringe labeled "methadone" that contained 0.2 mg/kg of methadone (based on ideal body weight, up to a maximal dose of 20 mg). This dose was selected based on data establishing effectiveness and safety of methadone 0.2 mg/kg in patients undergoing spine surgery[13–15] and other procedures.[16] The contents of the syringe labeled "methadone" were given to all study subjects over 5 min at induction of anesthesia. In addition, the pharmacy prepared sequentially numbered, identical-appearing 500-ml bags of dextrose 5% in water. For patients assigned to the methadone/ketamine group, 250 mg of ketamine was added to the dextrose 5% in water bag (total volume 500 ml), whereas patients assigned to the methadone group received only an infusion of dextrose 5% in water (no drug added to the 500 ml volume). The 500 ml bags were connected to a pump that was programed to deliver an infusion of ketamine dosed at ideal body weight (or an equal volume of dextrose 5% in water) at a rate of 0.3 mg · kg^{-1} · h^{-1} from induction of anesthesia until surgical closure, at which time the infusion was decreased to 0.1 mg · kg^{-1} · h^{-1}. The infusion was maintained at a rate of 0.1 mg · kg^{-1} · h^{-1} in the postanesthesia care unit (PACU) and for the next 48 postoperative hours.

Dosing of ketamine was based on recommendations in the literature[17,18] and from clinical experience at our institution.

Patients were given 2 mg of midazolam before entering the operating room. Standard intraoperative monitoring was applied, which included an automatic blood pressure cuff, electrocardiography, capnography, pulse oximetry, and bispectral index monitoring (BIS system, Aspect Medical Systems, USA). Anesthesia was induced with propofol 1 to 2 mg/kg, lidocaine 50 mg, fentanyl 100 μg, rocuronium 0.6 mg/kg, dexamethasone 8 mg, and methadone 0.2 mg/kg. The ketamine or dextrose 5% in water infusion was initiated after induction and dosed as described above. Anesthesia was maintained with sevoflurane 1%, remifentanil 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and a propofol infusion titrated to 50 and 150 $\mu g \cdot kg^{-1} \cdot min^{-1}$ in order to achieve bispectral index values between 40 and 60 and mean arterial pressures within 20% of baseline measures (a combination of lower concentrations of propofol and sevoflurane are used at our institution during spinal surgery in order to allow for acceptable sensory evoked potential monitoring). Redosing of rocuronium was determined based on requirements for motor evoked potential monitoring. The administration of additional fentanyl (up to a total dose of 200 μg) or hydromorphone (1 mg), was at the discretion of the anesthesia care team. Hypotension was treated with phenylephrine 80 μg, ephedrine 5 mg, or a fluid bolus, as indicated. Episodes of hypertension were managed by increasing the propofol infusion rate. Blood glucose concentrations were monitored every hour in insulin-dependent diabetic patients and every 2 to 4 h in non–insulin-dependent diabetic patients, and patients with blood glucose concentrations greater than 180 to 200 mg/dl were treated with insulin. At the conclusion of the procedure, patients were given odansetron 4 mg, and neuromuscular blockade was reversed with neostigmine 50 to 70 μg/kg (with an appropriate dose of glycopyrrolate) or sugammadex 2 to 4 mg/kg. Patients were extubated in the operating room unless concerns about airway edema were raised by the care team.

Patients were assessed for pain by nurses at PACU admission and every 15 min thereafter. Moderate pain was treated with hydromorphone 0.25 mg, and severe pain with hydromorphone 0.5 mg, with the goal of reducing pain scores to less than or equal to 3 on a 0 to 10 numeric rating scale (0, no pain; 10, worst pain imaginable). Patients were transitioned to a hydromorphone PCA device when adequate pain control was achieved (initial programming: a demand dose of 0.2 mg with a 10 min lockout interval, a 1 h limit of 1.2 mg). Discharge to the surgical wards with continuous pulse oximetry monitoring occurred when Aldrete scores of greater than or equal to 8 out of 10 were achieved.

Pain was managed on the first 3 postoperative days using the hydromorphone PCA device, which was discontinued at the discretion of the managing surgical service. Patients were transitioned to hydrocodone 5 mg and acetaminophen 325 mg tablets when able to resume oral intake. Pain was assessed and treated by surgical ward nurses per standard protocols, with the goal of maintaining pain scores less than or equal to 4 on the 0 to 10 numerical rating scale.

Data Collection

In the preoperative holding area, a research team member recorded preoperative levels of pain at rest, with coughing, and with movement using a 0 to 10 numeric rating scale. Preoperative sedation was measured on a 0 to 3 scale (0, fully awake; 1, mildly sedated, seldom drowsy, and easy to awaken; 2, moderately sedated, often drowsy, and easy to awaken; and 3, severely sedated, somnolent, and difficult to awaken). The presence or absence of dizziness, nausea, vomiting, or itching was noted. The use of preoperative opioids was documented.

Anesthesia team members recorded heart rate and mean arterial blood pressures preinduction and then 5, 15, 30, 45, and 60 min postinduction. In addition, the times between the end of surgery and tracheal extubation were noted, as was the use of any additional hydromorphone in the operating room. PACU nurses documented the times from PACU admission until first request for pain medication and the total dose of hydromorphone (nurse-administered and *via* the PCA device). Nurses also recorded the times to meet discharge criteria and to achieve actual discharge. At the time of discharge from the PACU, overall satisfaction with pain management was measured using an 11-point numeric rating scale (0, worst possible; 10, best possible).

On PACU arrival, a research team member assessed patients for pain at rest, with coughing, and with movement using a 0 to 10 numeric rating scale. Level of sedation was determined using the 0 to 3 scale described above. The presence or absence of nausea and vomiting was noted, the severity graded on a 3-point scale (1, mild; 2, moderate; 3, severe), and drugs used to treat these events were recorded. The presence or absence of episodes of itching, hypoxemia (peripheral oxygen saturation less than 90%), hypoventilation (respiratory rate less than 8), dizziness, or hallucinations was documented. The heart rate, respiratory rate, mean arterial pressure, and peripheral oxygen saturation at the time of assessment were noted. All of the outcome variables assessed at PACU arrival, with the addition of patient satisfaction with pain management scores, were again measured 1 h after PACU admission, as well as on the morning (between 8 AM and 10 AM) and late afternoon (between 3 PM and 4 PM) of postoperative days 1, 2, and 3. Total doses of intravenous hydromorphone and oral hydrocodone and acetaminophen tablets used during each of the first 3 postoperative days were recorded.

Data collected from the electronic anesthesia record included anesthesia duration, total volume of crystalloid solutions, blood loss, urine output, and total dose of fentanyl. The electronic medical record was reviewed for any cardiac, respiratory, gastrointestinal, renal, neurologic, or infection complications during the hospitalization. The

duration of hospitalization was obtained from the electronic medical record.

Statistical Analysis

The primary endpoint of this investigation was hydromorphone use on postoperative day 1. In a study of patients undergoing spinal fusion surgery using a standard anesthetic, the average ± SD intravenous hydromorphone dose in the first 24 postoperative hours was 27 ± 10 mg in patients given standard postoperative pain management and 18.5 ± 14 mg in patients given ketamine as an adjunct to that management.[19] We anticipated hydromorphone consumption in the methadone group in the current study would be 19 mg and hypothesized it would be reduced by 40% in the methadone/ketamine group. Because expected group SDs of 14 mg were large relative to the means, sample size was estimated for two-sided Mann–Whitney test using the standard *t* test formulations with a simple adjustment to the sample sizes based on the assumption that data distribution is logistic. Using this approach, group sample sizes of 51 and 51 achieve 81% power to detect a difference of 7.6 mg between the null hypothesis that both group means are 19.0 mg and the alternative hypothesis that the mean of group 2 is 11.4 mg with a significance level (alpha) of 0.05 (PASS 2008 Number Cruncher Statistical System, USA). One hundred thirty patients were enrolled to ensure complete collection of data.

Data for the primary outcome variable, milligrams of intravenous hydromorphone in the first 24 h after the operation, are reported as the median (interquartile range) for both the methadone group and the methadone/ketamine group. These data were compared between groups using the Mann–Whiney U test (StatsDirect, United Kingdom). The median difference and its 95% CI were estimated using the Hodges–Lehmann estimator. The criterion for rejection of the null hypothesis was a two-tailed $P < 0.05$.

All other data, including secondary outcome data, are reported as mean ± SD, median (interquartile range), or number (percentage) of patients. Continuous data were checked for equality of variances; those data that did not meet the assumption of equal variances were reduced to ordinal data and are reported as median (interquartile range). Absolute standardized differences of the baseline characteristics of the patients in the two groups were determined to identify any possible imbalance between the groups. Other data reported as mean ± SD were compared with the unpaired, two-sample *t* test, data reported as the median (interquartile range) were compared with the Mann–Whitney U test, and data reported as the number of patients (%) were compared using the chi-square test (with Yates correction) unless at least one expected frequency was often less than 5, in which case the Fisher exact probability test was used. Because there was no interest in the change in the variables across time, primary and secondary outcome data were only compared between groups at each time. Given the large number of secondary comparisons, mean differences, median differences, and differences in proportions are reported with their 99% CIs. Median differences and their 99% CIs were estimated using the Hodges–Lehmann estimator. The robust approximation of Miettinen and Nurminen was used to construct the CIs for risk differences. The criterion for rejection of the null hypothesis was a two-tailed $P < 0.01$ throughout. All statistical analyses except calculation of absolute standardized differences were conducted with StatsDirect (United Kingdom).

Results

The trial was conducted in accordance with the original protocol, and enrollment ceased when the target sample size was obtained. One hundred thirty patients were enrolled in the study and randomized to receive the study medications. Three patients in the methadone group were excluded before study participation because the pharmacy was unable to provide study drugs before the start of the procedure. Therefore, data were collected and analyzed on a total of 127 subjects (61 patients in the methadone group and 66 patients in the methadone/ketamine group). The flow of patients through the study is presented in figure 1.

The two study groups were similar in preoperative characteristics including age, sex, height, weight, American Society of Anesthesiologists Physical Status, and preexisting medical conditions (table 1). Preoperative sedation scores were similar between groups, as were the incidences of nausea, vomiting, dizziness, and itching. The use of preoperative opioid medications did not differ between groups.

Perioperative data are presented in table 2. The two study groups did not differ in the types of surgical procedures or number of vertebrae fused. Similar amounts of fentanyl and hydromorphone were given to each study group. No differences in the times between the end of surgery and tracheal extubation, the durations of the procedures, or the times to meet PACU discharge criteria or achieve actual discharge were observed between groups.

The time until first hydromorphone rescue in the PACU was longer in the methadone/ketamine group compared to the methadone group (table 2). The use of hydromorphone during the first 24 postoperative hours (total dose from PACU nursing staff and PCA device) was significantly reduced in patients in the methadone/ketamine group compared to those in the methadone group (primary outcome, median [interquartile range], 2.0 [1.0 to 3.0] mg *vs.* 4.6 [3.2 to 6.6] mg; median difference [95% CI], 2.5 [1.8 to 3.3] mg; $P < 0.0001$; table 3). Similarly, the need for PCA hydromorphone was less in this group on postoperative day 2, as was total use over 3 days (2.7 [1.0 to 4.8] mg *vs.* 5.8 [3.9 to 9.2] mg in the methadone group; $P < 0.0001$; fig. 2). Patients in the methadone/ketamine group also requested fewer oral opioid tablets on postoperative days 1 and 3, and the total use over the 3 days was less in this group (11 [4.25 to 16] *vs.* 20 [12 to 30] in the methadone group; $P < 0.0001$; fig. 2).

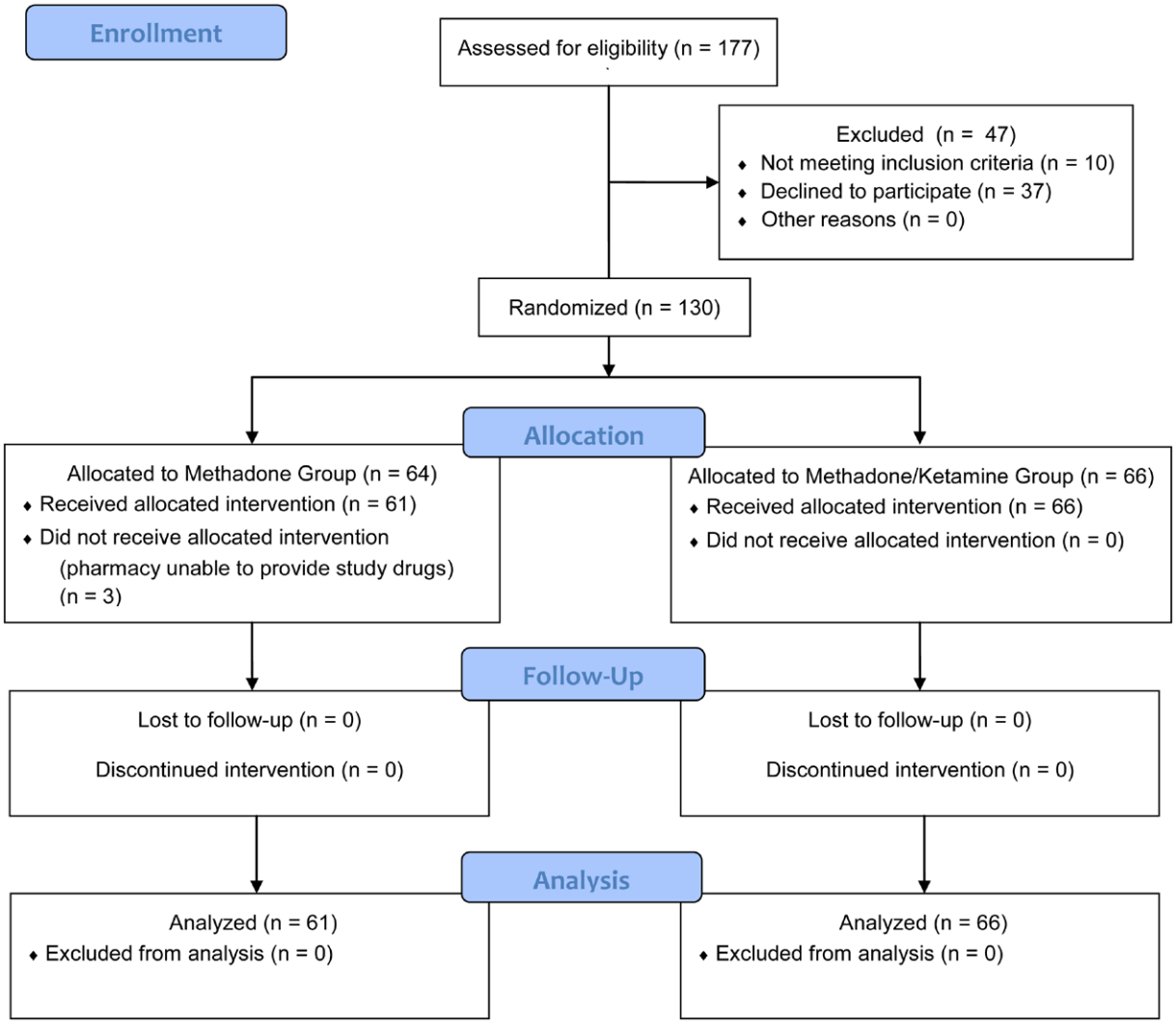


Fig. 1. Consolidate Standards of Reporting Trials (CONSORT) flow diagram for the randomized, placebo-controlled, double-blind trial of methadone (control group) and methadone/ketamine in patients undergoing spinal fusion surgery.

Preoperative pain scores did not differ between the study groups (table 4). Median pain scores at rest, with coughing, and with movement were all significantly less in the methadone/ketamine group, compared to the methadone group, from the time of PACU admission until the afternoon of postoperative day 3 (all $P = 0.006$ to $P < 0.0001$), with the exception of pain at rest on the morning of postoperative day 2 ($P = 0.039$; table 4). Patient satisfaction with pain management, reported on a 0 to 10 numeric rating scale, was improved in patients in the methadone/ketamine group on the morning of the first postoperative day (10 [9 to 10] *vs.* 8 [8 to 10] in the methadone group; $P = 0.008$; table 4). Thereafter, satisfaction scores in both groups were high (all median scores 9 to 10) and did not differ between groups.

Adverse events possibly related to methadone and ketamine administration are reported in Supplemental Digital Content tables 1 (http://links.lww.com/ALN/C570) and 2 (http://links.lww.com/ALN/C571). Median sedation scores were 0 (fully awake) in both study groups on postoperative days 1 through 3 and did not differ between groups. The incidences of nausea, vomiting, need for treatment of emetic episodes, and itching did not differ between groups. The percentage of patients reporting hallucinations during the first 3 postoperative days was low (0 to 6%) and similar in the study groups. No differences between groups in episodes of dizziness were noted during those days. In addition, a similar percentage of patients in both groups had hypoxemic events (0 to 6.6% of patients) and hypoventilation episodes (0 to 11.5% of patients). Hemodynamic variables in the operating room (Supplemental Digital Content table 3, http://links.lww.com/ALN/C572) and during postoperative days 1 through 3 (Supplemental Digital Content

Table 1. Patient Characteristics

Characteristics	Methadone Group	Methadone/Ketamine Group	Absolute Standardized Difference
Patients, No.	61	66	
Sex, female	34 (56%)	34 (52%)	0.08
Age, yr	66 (58 to 72)	61.5 (47.3 to 69)	0.47
Actual body weight, kg	90 ± 21	84 ± 20	0.29
Ideal body weight, kg	62 ± 11	64 ± 11	0.18
Height, cm	169 ± 10	171 ± 10	0.20
American Society of Anesthesiologists Physical Status	2 (2 to 3)	2 (2 to 2)	0.36
Preoperative opioids	38 (62%)	33 (50%)	0.25
No. of opioid tablets per day	2 (0 to 3)*	0 (0 to 2.5)†	0.21
History			
Smoking	9 (15%)	8 (12%)	0.08
Drinking	4 (7%)	7 (11%)	0.14
Steroids	6 (10%)	6 (9%)	0.02
Myocardial infarction	2 (3%)	2 (3%)	0.02
Congestive heart failure	1 (2%)	0 (0%)	0.18
Atrial fibrillation	3 (5%)	2 (3%)	0.10
Hypertension	33 (54%)	36 (55%)	0.01
Chronic obstructive pulmonary disease/emphysema	3 (5%)	2 (3%)	0.10
Obstructive sleep apnea	12 (20%)	8 (12%)	0.21
Liver disease	1 (2%)	0 (0%)	0.18
Renal disease	6 (10%)	3 (5%)	0.21
Thyroid disease	9 (15%)	6 (9%)	0.18
Non–insulin-dependent diabetes mellitus	10 (16%)	6 (9%)	0.22
Insulin-dependent diabetes mellitus	1 (2%)	1 (2%)	0.01
Cerebrovascular accident	3 (5%)	1 (2%)	0.19
Transient ischemic attack	2 (3%)	1 (2%)	0.12
Peripheral vascular disease	0 (0%)	0 (0%)	
Preoperative assessment			
Sedation	0 (0%)	1 (2%)	0.17
Nausea	6 (10%)	10 (15%)	0.16
Vomiting	4 (7%)	3 (5%)	0.09
Itching	13 (21%)	10 (15%)	0.16
Dizziness	9 (15%)	9 (14%)	0.03
Heart rate, beats/min	76 ± 13‡	77 ± 12	0.08
Mean blood pressure, mmHg	95 ± 10‡	95 ± 11	0

The data are mean ± SD, median (interquartile range), or number of patients (%). Drinking history indicates alcohol consumption of more than two drinks per day.
*n = 57. †n = 63. ‡n = 60.

table 2, http://links.lww.com/ALN/C571) did not differ between groups.

Cardiac, respiratory, gastrointestinal, renal, neurologic, or infection complications during the hospitalization were infrequent in both the methadone group (0 to 3.3%) and the methadone/ketamine groups (0%; table 2). The duration of hospitalization was similar in both study cohorts (table 2).

Discussion

Despite advances in surgical techniques and anesthetic management, patients undergoing spinal fusion surgery continue to experience moderate-to-severe postoperative pain. In recent years, clinicians have employed multimodal analgesic regimens in order to reduce postoperative pain, enhance functional recovery, and decrease hospital length of stay. Agents that are antagonists of the NMDA receptor may provide particular analgesic benefit in this patient population *via* an inhibition of sensitization of nociceptive pathways, prevention of opioid-related activation of pronociceptive systems, and attenuation of opioid tolerance and hyperalgesia.[17,18] In this clinical investigation, the antinociceptive effect resulting from the combination of agents acting as both NMDA antagonists and μ-opioid receptor agonists (methadone and ketamine) was assessed. We observed that patients in the methadone/ketamine group required 57% less hydromorphone on the first postoperative day than did those in the methadone group; hydromorphone use was also significantly decreased on postoperative day 2, and total hydromorphone requirements over 3 days was reduced by more than 50%. In addition, pain scores at rest, with coughing, and with movement were lower in patients in the methadone/ketamine group (at 23 of the 24 assessments). The incidences of adverse events were low in both study groups and did

Table 2. Perioperative and Postoperative Data

	Methadone Group	Methadone/Ketamine Group	Difference (99% CI)	*P* Value
Operative sites				
Thoracic	1 (2%)	5 (8%)	–6% (–19 to 6%)	0.210*
Lumbar	61 (100%)	66 (100%)		
Sacral	21 (34%)	33 (50%)	–16% (–37 to 7%)	0.111
Number of levels	1 (1 to 2)	1.5 (1 to 2)	0 (0 to 0)	0.392
Anesthesia time, min	321 ± 117	319 ± 111	2 (–50 to 55)	0.903
Methadone dose, mg	12.5 ± 2.1	12.9 ± 2.2	–0.4 (–1.4 to 0.6)	0.324
Fentanyl dose, μg†	152 ± 96	143 ± 89	9 (–34 to 51)	0.606
IV acetaminophen (1,000 mg)	11 (18%)	15 (23%)	–5% (–23 to 14%)	0.664
Extra hydromorphone in operating room	6 (10%)	5 (8%)	2% (–12 to 18%)	0.891
Extra hydromorphone in operating room dose, mg	0.6 ± 0.3‡	0.6 ± 0.2§	0 (–0.5 to 0.6)	0.853
Fluid volume, ml	2,468 ± 1,040	2,529 ± 975	–61 (–528 to 407)	0.735
Urine output, ml	250 (170 to 500)	350 (213 to 563)	–50 (–150 to 70)	0.311
Estimated blood loss, ml	466 ± 402‖	418 ± 328	48 (–122 to 219)	0.458
Time of tracheal extubation, min	12 (9 to 17)	11 (8 to 17)#	1 (–2 to 4)	0.386
Time (min) from PACU admission to:				
First hydromorphone request	20 (12 to 29)**	30 (17 to 43)††	–10 (–19 to –2)	0.003
Meeting discharge criteria	95 ± 26	94 ± 27	1 (–12 to 12)	0.994
Actual discharge	114 ± 36	113 ± 33	1 (–15 to 17)	0.889
Duration of hospitalization, days	3.5 (3.0 to 4.75)	3.0 (3.0 to 4.0)	0.25 (0 to 1)	0.043
Postoperative complications during hospitalization				
Respiratory	2 (3%)	0 (0%)	3% (–6 to 15%)	0.457*
Gastrointestinal	1 (2%)	0 (0%)	2% (–8 to 13%)	0.961*
Cardiac	2 (3%)	0 (0%)	3% (–6 to 15%)	0.457*
Renal	1 (2%)	0 (0%)	2% (–8 to 13%)	0.961*
Neurologic	1 (2%)	0 (0%)	2% (–8 to 13%)	0.961*
Infection	0 (0%)	0 (0%)		

The data are means ± SD, median (interquartile range), or number of patients (%). The data reported as mean ± SD were compared with the unpaired *t* test, the data reported as median (interquartile range) were compared using the Mann–Whitney U test, and the data reported as the number of patients (%) were compared using the Pearson chi-square test or, when at least one of the cells of the contingency table had an expected n < 5, the Fisher exact probability test. n = 61 in the methadone group, and n = 66 in the methadone/ketamine group, except where indicated.

*Fisher exact probability test. †The fentanyl dose includes the 100 μg allowed by the protocol. ‡n = 6. §n = 5. ‖n = 60. #n = 65. **n = 50. ††n = 45.

IV, intravenous; PACU, postanesthesia care unit.

not differ. These findings demonstrate that the perioperative combination of methadone and ketamine is highly effective in reducing postoperative analgesic consumption and pain intensity in a patient population typically reporting severe postoperative pain.

Methadone is a unique long-acting μ-opioid receptor agonist that produces prolonged analgesia when given in larger doses (24 to 36 h at doses greater than or equal to 20 mg).[20] In addition, methadone may reduce pain by antagonizing NMDA receptors[21,22] and inhibiting reuptake of serotonin and norepinephrine in the central nervous system.[23,24] Two studies have examined the analgesic effects of a single dose of intraoperative methadone in adult patients undergoing spine surgery. Gottschalk *et al.* reported that opioid requirements were 50% lower at 48 h in subjects given 0.2 mg/kg of methadone, compared to those given a continuous sufentanil infusion.[14] Similar findings were observed in a trial randomizing 120 patients to receive 0.2 mg/kg of methadone at induction or 2 mg of hydromorphone at the end of spinal surgery.[13] Although both studies reported that pain scores were lower in patients given methadone, pain intensity was still described as moderate during the first 3 postoperative days in these subjects.[13,14] While methadone provides analgesic benefits in

Table 3. Primary Outcome: Intravenous Hydromorphone Requirements in the First 24 h Postoperatively

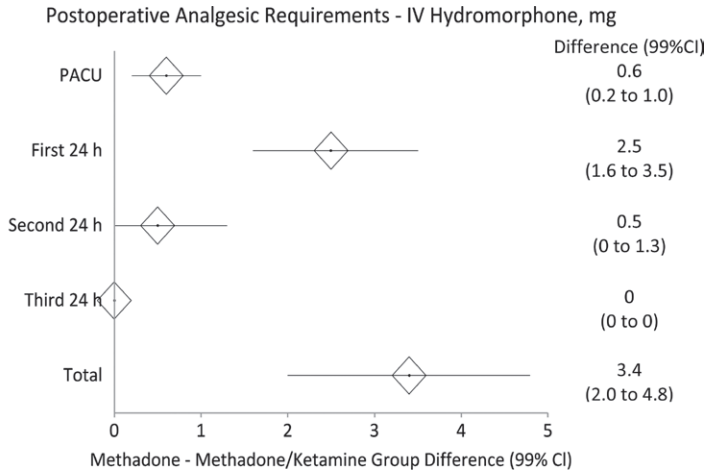
	Methadone Group	Methadone/Ketamine Group	Difference (95% CI)	*P* Value
Intravenous hydromorphone, mg first 24 h	4.6 (3.2 to 6.6)	2.0 (1.0 to 3.0)	2.5 (1.8 to 3.3)	< 0.0001

The data are reported as median (interquartile range) and were compared between groups using the Mann–Whitney U test. These data are also reported in fig. 2A with the difference (99% CI) for the sake of completeness and consistency. n = 61 in the methadone group, and n = 66 in the methadone/ketamine group.

A

Group	Methadone	Methadone/Ketamine
PACU	1.2 (0.5 to 2.2)	0.7 (0 to 1.2)
First 24 h	4.6 (3.2 to 6.6)	2.0 (1.0 to 3.0)
Second 24 h	1.2 (0 to 3.0)	0 (0 to 1.2)
Third 24 h	0 (0 to 0)	0 (0 to 0)
Total	5.8 (3.9 to 9.2)	2.7 (1.0 to 4.8)

Data are reported as median (interquartile range). n = 61 in the methadone group and n = 66 in the methadone/ketamine group.



B

Group	Methadone	Methadone/Ketamine
First 24 h	4 (0 to 8)	2 (0 to 3)
Second 24 h	8 (2 to 12)	6 (2 to 8)
Third 24 h	8 (2 to 12)	3 (0 to 6)
Total	20 (12 to 30)	11 (4.25 to 16)

Data are reported as median (interquartile range). n = 61 in the methadone group and n = 66 in the methadone/ketamine group.

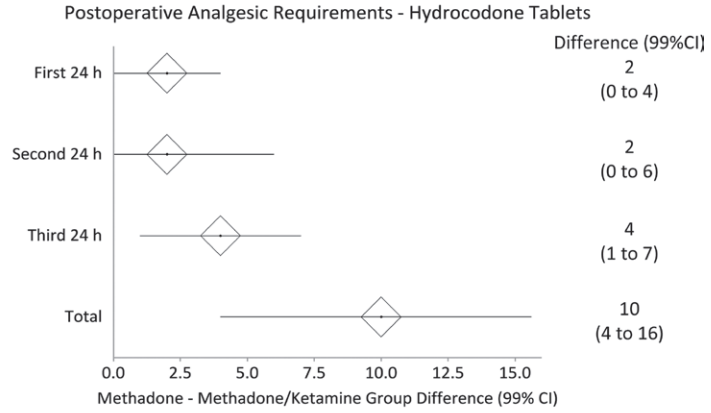


Fig. 2. Analgesic requirements in the postanesthesia care unit (PACU), in the first, second, and third 24 h postoperatively and the total requirements from the PACU to the end of the third 24 h postoperatively. (*A*) Median (interquartile range) intravenous hydromorphone requirements for the patients in the methadone group and those in the methadone/ketamine group with a *forest plot* of the difference (99% CI) between the groups. (*B*) Median (interquartile range) number of hydrocodone 5 mg/acetaminophen 325 mg tablets required by the patients in the methadone group and those in the methadone/ketamine group with a *forest plot* of the difference (99% CI) between the groups.

this patient population, doses of 0.2 mg/kg alone are insufficient to reduce pain to mild levels (less than or equal to 3 on a 0 to 10 scale)[25] in most subjects.

Like methadone, ketamine inhibits the NMDA receptor,[26] binds to the μ-opioid receptor,[27] and increases concentrations of serotonin and norepinephrine in the brain.[28] The use of ketamine in the setting of spinal fusion surgery has been extensively studied. In the largest randomized study enrolling 150 opioid-dependent patients, subjects given an S-ketamine infusion used 35% less morphine at 24 h than did the placebo group.[29] Patients given a ketamine infusion in a similar large trial required 30 to 37% less morphine 24 to 48 h after surgery than patients given saline.[30] However, pain scores at rest were 4 to 6 on a 0 to 10 scale in the ketamine groups in both studies, and did not differ from groups receiving placebo.[29,30] A meta-analysis of 14 randomized trials reported that patients given adjunctive ketamine for spine surgery consumed less opioid in the first 24 h, but had only slightly lower pain scores compared to control groups.[7] These investigations indicate that the use of supplemental ketamine in spinal surgical patients results in lower opioid consumption in the first 24 h, but may have only a small effect on postoperative pain scores.

A supra-additive synergy between methadone and ketamine has been demonstrated in an experimental neuropathy model.[11,12] Only one previous clinical investigation examined the analgesic benefits of combining these two medications. Pacreu *et al.* reported that patients given intraoperative methadone, an intraoperative ketamine infusion, and a methadone/ketamine PCA required 70 to 80% less opioid on the first 2 postoperative days, compared to a group given intraoperative methadone, a saline infusion, and a methadone PCA.[31] Similarly, we observed that hydromorphone requirements during the first 48 postoperative

Table 4. Levels of Pain at Rest, with Coughing, and with Movement, and Overall Satisfaction with Pain Management

	Methadone Group	Methadone/Ketamine Group	Difference (99% CI)	*P* Value
Level of pain at rest				
Preoperative	5 (2 to 7)	4 (2 to 6)*	1 (–1 to 2)	0.329
At PACU admission	6 (3 to 8)†	3.5 (0 to 5)‡	2 (0 to 4)	0.002
1 h after admission	5 (3 to 6)§	3 (2 to 4)‖	2 (1 to 3)	< 0.0001
Postoperative day 1 – AM	4 (3 to 6)#	3 (2 to 3)	2 (1 to 2)	< 0.0001
Postoperative day 1 – PM	4 (3 to 5)	3 (2 to 3)	1 (1 to 2)	< 0.0001
Postoperative day 2 – AM	3 (2 to 4.5)§	3 (2 to 3)‖	1 (0 to 1)	0.039
Postoperative day 2 – PM	4 (2 to 5)#	3 (2 to 3)**	1 (0 to 2)	< 0.001
Postoperative day 3 – AM	4 (3 to 5)††	3 (2 to 3)†	1 (1 to 2)	< 0.0001
Postoperative day 3 – PM	3 (2 to 4)‡‡	2 (2 to 3)§§	1 (0 to 2)	< 0.0001
Level of pain with coughing				
Preoperative	6 (4 to 9)	4 (2 to 7)*	2 (0 to 3)	0.016
At PACU admission	6 (4 to 8)†	4 (0 to 5.75)‡	2 (0 to 4)	0.005
1 h after admission	5 (4 to 7)§	4 (2 to 4)‖	2 (1 to 3)	< 0.0001
Postoperative day 1 – AM	5 (3.75 to 6)#	3 (2 to 4)	2 (1 to 3)	< 0.0001
Postoperative day 1 – PM	4 (3 to 6)#	3 (2 to 4)	1 (1 to 2)	< 0.0001
Postoperative day 2 – AM	4 (3 to 5)§	3 (2 to 4)‖	1 (1 to 2)	< 0.0001
Postoperative day 2 – PM	5 (3 to 6)#	3 (2 to 4)**	2 (1 to 3)	< 0.0001
Postoperative day 3 – AM	4 (3 to 6)††	3 (3 to 4)‖‖	1 (0 to 2)	< 0.0001
Postoperative day 3 – PM	4 (3 to 5)##	3 (2 to 3)***	1 (1 to 2)	< 0.0001
Level of pain with movement				
Preoperative	9 (7 to 9)	8 (6 to 10)*	0 (0 to 1)	0.212
At PACU admission	6 (4 to 8.25)†	4 (0.5 to 6)‡	2 (0 to 4)	0.006
1 h after admission	6 (4 to 7)§	4 (2 to 5)‖	2 (1 to 3)	< 0.001
Postoperative day 1 – AM	5.5 (4 to 7)†††	4 (3 to 5)§	2 (1 to 3)	< 0.0001
Postoperative day 1 – PM	5 (4 to 7)§	4 (3 to 5)‡‡‡	1 (0 to 2)	< 0.0001
Postoperative day 2 – AM	5 (4 to 6)§	4 (3 to 5)**	2 (1 to 2)	< 0.0001
Postoperative day 2 – PM	5.5 (4 to 6)#	4 (3 to 5)**	2 (1 to 2)	< 0.0001
Postoperative day 3 – AM	5 (4 to 6)††	4 (3 to 5)†	1 (0 to 2)	< 0.001
Postoperative day 3 – PM	4 (3 to 5)‡‡	3 (3 to 4)§§	1 (0 to 2)	< 0.001
Overall satisfaction with pain management				
At PACU discharge	6 (5 to 8)‡‡‡	7 (5 to 8)§§§	–1 (–2 to 0)	0.099
Postoperative day 1 – AM	8 (8 to 10)	10 (9 to 10)	0 (–1 to 0)	0.008
Postoperative day 1 – PM	9 (8 to 10)	10 (9 to 10)	0 (–1 to 0)	0.011
Postoperative day 2 – AM	9 (8 to 10)§	9 (9 to 10)‖	0 (–1 to 0)	0.037
Postoperative day 2 – PM	9 (8 to 10)#	9 (8 to 10)**	0 (–1 to 0)	0.087
Postoperative day 3 – AM	9 (8 to 10)‖‖	9.5 (9 to 10)†	0 (–1 to 0)	0.076
Postoperative day 3 – PM	9 (8 to 10)‖‖‖	9 (8 to 10)###	0 (–1 to 0)	0.216

The data are reported as median (interquartile range) and were compared between groups at the various times using the Mann–Whitney U test. No within-group (*i.e.*, across time) comparisons have been made. Level of pain scores on a 0 to 10 scale: 0 = no pain to 10 = worst pain imaginable. Overall satisfaction with pain management on a 0 to 10 scale: 0 = worst possible to 10 = best possible. N = 61 in the methadone group, and n = 66 in the methadone/ketamine group, except where indicated.

*n = 65. †n = 56. ‡n = 62. §n = 59. ‖n = 64. #n = 60. **n = 63. ††n = 58. ‡‡n = 49. §§n = 33. ‖‖n = 55. ##n = 48. ***n = 32. †††n = 54. ‡‡‡n =57. §§§n = 61. ‖‖‖n = 44. ###n = 29.

PACU, postanesthesia care unit.

hours were reduced by more than 50% in patients given methadone and ketamine when compared to patients given methadone alone. Furthermore, the number of oral opioid medications needed was significantly lower in the methadone/ketamine group on postoperative days 1 and 3, and total use was 45% less in this group.

In contrast to the findings of Pacreu *et al.*, we observed that patients given both methadone and ketamine had lower pain scores after surgery compared to those given methadone alone. Median pain scores at rest, with coughing, and with movement were significantly lower in the methadone/ketamine group from the time of PACU arrival until the late afternoon of postoperative day 3, with the exception of the assessment on the morning of postoperative day 2. In addition, median pain at rest and with coughing was reduced to mild levels (less than or equal to 3 on a 0 to 10 scale) in the methadone/ketamine group from the morning of the first postoperative day through the late afternoon of postoperative day 3. These findings are in contrast to other studies using either methadone or ketamine alone for spinal surgery, in which postoperative pain scores were moderate (mean/median scores of 4 to 6 on a 0 to 10 scale) in patients given these agents.[13,29,30]

Primary goals of enhanced recovery after surgery protocols are to reduce hospital length of stay and to enhance patient recovery. Although we observed a greater analgesic

benefit in the methadone/ketamine group for up to 72 h after surgery, these benefits did not translate into a shorter PACU or hospital length of stay. When implementing enhanced recovery after surgery protocols, it is also necessary to document that interventions result in improvements in subjective outcomes that are important to patients, such as overall satisfaction.[32] Previous studies have shown that surgical patients given adjunctive methadone[13] or ketamine[33] reported higher satisfaction scores in the early recovery period. In the current investigation, we observed that patient satisfaction with pain management was better in the methadone/ketamine patients on the morning of the first postoperative day. Thereafter, median satisfaction scores were 9 on scale of 0 to 10 in the methadone group, which did not significantly differ from the scores of the methadone/ketamine group. These results, and findings from previous trials,[34] suggest that patient satisfaction with pain management is high when methadone is used, and that there is little incremental benefit of adding ketamine on this outcome measure.

There are a number of adverse events that may be associated with the use of either methadone or ketamine in the perioperative setting, which include nausea/vomiting, respiratory depression, sedation, itching, tachycardia/hypertension, and hallucinations/vivid dreams.[6–9] Reviews and meta-analyses have reported that the incidences of these adverse outcomes are no higher in patients given either methadone[9,34] or ketamine[6–8] than in control group patients managed with standard care. The risks of using methadone and ketamine together in the perioperative period, however, have not been defined. In this trial, the percentage of patients developing adverse events involving the respiratory system (hypoxemia, hypoventilation), central nervous system (sedation, hallucinations, dizziness), and gastrointestinal system (nausea, vomiting) was low, and no differences between groups were observed. Similarly, the overall incidences of complications during the entire hospitalization (cardiac, respiratory, gastrointestinal, neurologic, infection, and renal) did not differ between the two groups. Although we observed an additive analgesic effect of combining methadone and ketamine, the use of both agents together did not appear to increase the risk of postoperative complications.

There are several limitations to this investigation. First, ideal dosing regimens for methadone and ketamine (when used alone or in combination) are unknown[9,17]; further studies are needed to identify the optimal dose of methadone and ketamine when combined. Second, intraoperative fentanyl and hydromorphone could be given, in addition to the baseline remifentanil infusion, at the discretion of the anesthesia care team (a standard practice at our institution). Quantification of intraoperative opioid requirements would have been simplified if a single opioid had been given. Furthermore, dosing of opioids was at the discretion of the anesthesia care team and was not based on standard criteria such as hemodynamic responses or on data provided from nociception monitors. Third, an intraoperative remifentanil infusion was used in all patients, as is standard practice in major spine surgery at our institution. Remifentanil may produce opioid-induced hyperalgesia, and after methadone administration at anesthetic induction, the additional analgesia provided by the infusion was likely not required. Furthermore, total remifentanil doses were not recorded. However, the doses calculated from actual patient body weights, the durations of anesthesia, and remifentanil infusion rates were similar between groups (3.0 ± 1.5 mg in the methadone group and 2.7 ± 1.2 mg in the methadone/ketamine group).

Postoperative pain is often difficult to manage in patients undergoing spinal fusion surgery. In this clinical trial, spinal surgical patients randomized to receive intraoperative methadone with a perioperative ketamine infusion required significantly less opioid pain medication and reported lower pain scores during the first 3 postoperative days, compared to those given methadone alone. Postoperative analgesia can be significantly enhanced in this patient population by using a combination of agents that act on both the NMDA and μ-opioid receptors.

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Competing Interests

Dr. Murphy has served as a speaker for Merck, Kenilworth, New Jersey. Dr. Avram is the assistant editor-in-chief of Anesthesiology. Dr. Greenberg is editor of the Anesthesia Patient Safety Foundation Newsletter, Rochester, Minnesota, and a speaker for the American Association of Nurse Anesthetists, Park Ridge, Illinois. The other authors declare no competing interests.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Down Periscope: Teaching Laryngoscopy in the Trenches

Direct laryngoscopy, a signature skill of the modern anesthesiologist, can be daunting to learn and difficult to teach. Before the advent of video laryngoscopy, the Dual-Vu Scope (*left*) cleverly applied the physics of a periscope. First designed in 1854 by French inventor Edme Hippolyte Marié-Davy, the periscope consisted of a vertical tube with a mirror at each end. Parallel to each other but at 45 degrees to the tube's axis, the mirrors reflected rays of light, revealing what friend or foe might lie on the other side. During World War I, the battlefield periscope shielded soldiers in the trenches by providing indirect visualization of enemy lines (*right*). Similarly, past anesthesiology residents could peer down barrels of Dual-Vus while instructors safely directed their views to laryngeal targets. Whether in the trenches of the battlefield or residency training, periscope mechanics enhanced tactical vision. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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