ANESTHESIOLOGY

Postoperative Pain and Analgesic Requirements in the First Year after Intraoperative Methadone for Complex Spine and Cardiac Surgery

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ABSTRACT

Background: Methadone is a long-acting opioid that has been reported to reduce postoperative pain scores and analgesic requirements and may attenuate development of chronic postsurgical pain. The aim of this secondary analysis of two previous trials was to follow up with patients who had received a single intraoperative dose of either methadone or traditional opioids for complex spine or cardiac surgical procedures.

Methods: Preplanned analyses of long-term outcomes were conducted for spinal surgery patients randomized to receive 0.2 mg/kg methadone at the start of surgery or 2 mg hydromorphone at surgical closure, and for cardiac surgery patients randomized to receive 0.3 mg/kg methadone or 12 μg/kg fentanyl intraoperatively. A pain questionnaire assessing the weekly frequency (the primary outcome) and intensity of pain was mailed to subjects 1, 3, 6, and 12 months after surgery. Ordinal data were compared with the Mann–Whitney U test, and nominal data were compared using the chi-square test or Fisher exact probability test. The criterion for rejection of the null hypothesis was $P < 0.01$.

Results: Three months after surgery, patients randomized to receive methadone for spine procedures reported the weekly frequency of chronic pain was less (median score 0 on a 0 to 4 scale [less than once a week] *vs.* 3 [daily] in the hydromorphone group, $P = 0.004$). Patients randomized to receive methadone for cardiac surgery reported the frequency of postsurgical pain was less at 1 month (median score 0) than it was in patients randomized to receive fentanyl (median score 2 [twice per week], $P = 0.004$).

Conclusions: Analgesic benefits of a single dose of intraoperative methadone were observed during the first 3 months after spinal surgery (but not at 6 and 12 months), and during the first month after cardiac surgery, when the intensity and frequency of pain were the greatest.

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- The intraoperative administration of methadone is effective in reducing postoperative pain
- Preventative analgesic interventions may provide protection against the development of persistent postoperative pain

What This Article Tells Us That Is New

- Using data from two previously completed trials, it was observed that a single intraoperative dose of methadone was associated with fewer episodes of pain during the first month after cardiac surgery and the first 3 months after spinal surgery
- Fewer spine surgery patients who received methadone intraoperatively were receiving opioids 3 months after surgery, suggesting a possible reduction in chronic opioid use

A primary focus of research in pain medicine has been development of strategies that can be used perioperatively to reduce acute postoperative pain, minimize opioid consumption, and prevent the transition from acute to chronic postsurgical pain. The traditional practice of treating pain only after it has been well established has been replaced by a "preventive analgesic" approach in which the objective of therapy is to inhibit the tissue injury-induced afferent barrage of nociceptive signals into the central nervous system, attenuate the resultant activation of inflammatory and neurochemical cascades, and prevent amplification of acute pain and development of chronic postsurgical pain.[1] Preventive analgesia is defined as any antinociceptive intervention used to block development of sustained pain throughout the perioperative period and inhibit central neuronal sensitization.[2] Medications that produce preventive analgesia are those for which analgesic benefits persist beyond their clinical duration of action (defined as more than 5.5 half lives of the agent).[1]

A number of medications have been studied as potential preventive analgesic interventions that may reduce the risk of chronic postsurgical pain, including gabapentin,[3] pregabalin,[3] ketamine,[4] steroids,[5] lidocaine,[6] clonidine,[7] and dexmedetomidine.[8] An additional potential preventive

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analgesic agent is methadone. Methadone is a potent μ-opioid receptor agonist with the longest elimination half life of the clinically used opioids. When administered in larger doses (at least 20 mg), the clinical duration of effect approximates its half life (24 to 36 h).[9] Patients administered intravenous methadone at induction of anesthesia had lower pain scores and analgesic requirements during the first 72 postoperative hours, compared to subjects given conventional opioids.[10–13] The intensity of acute postoperative pain during the first 1 to 3 postoperative days has been reported to be one of the strongest predictors of the development of chronic postsurgical pain across a variety of surgical procedures.[14–17] In addition, methadone is a potent *N*-methyl-D-aspartate (NMDA) receptor antagonist.[18,19] Activation of the NMDA receptor has been implicated in the development of opioid tolerance, hyperalgesia, and chronic postsurgical pain.[1,20,21] Finally, methadone inhibits reuptake of the neurotransmitters serotonin and norepinephrine in the brain;[22,23] medications like duloxetine that elevate these neurotransmitters may provide a mood elevation and analgesic effect in the postoperative period.[24,25] Based on these data, there is a potential role of methadone as a preventive analgesic and an agent that attenuates development of chronic postsurgical pain.

The purpose of this study was to follow up with patients who had participated in two clinical trials comparing pain scores and analgesic requirements in subjects administered either a single intravenous dose of methadone at induction of anesthesia or standard intraoperative opioids (hydromorphone in spine surgery patients and fentanyl in cardiac surgical patients).[12,13] In these studies, pain intensity was lessened, opioid requirements were reduced, and overall satisfaction with pain management was enhanced during the first 72 h after surgery in subjects given methadone. The aim of the current investigation was to determine whether these analgesic benefits persisted beyond the hospital discharge date (1, 3, 6, and 12 months postoperatively). We hypothesized that patients administered methadone would have fewer episodes of pain per week during the first postoperative year.

Materials and Methods

Study Population and Perioperative Management

The current study was a follow-up to two randomized, double-blinded investigations comparing the effect of intraoperative methadone to traditional opioids on postoperative pain scores and analgesic requirements (a secondary analysis of two previous trials).[12,13] The NorthShore University HealthSystem Institutional Review Board (Evanston, Illinois) reviewed and approved the initial and follow-up clinical investigations, which were registered at ClinicalTrials.gov (NCT02107339, NCT01542645). All patients gave their written consent to participate in the follow-up studies.

In the first clinical trial, patients undergoing posterior spinal fusion were given either methadone 0.2 mg/kg at anesthetic induction (62 patients) or 2 mg of hydromorphone at surgical closure (53 patients).[12] Anesthesia was maintained with 1% sevoflurane, remifentanil 0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$, and a propofol infusion titrated to between 50 and 150 $\mu g \cdot kg^{-1} \cdot min^{-1}$. Postoperative pain was managed using hydromorphone *via* a patient-controlled analgesia device and oral 10 mg hydrocodone, 325 mg acetaminophen tablets. Patients were assessed for pain (using an 11-point verbal analog scale from 0 = no pain to 10 = worst pain imaginable at rest, with coughing, and with movement) and analgesic requirements at postanesthesia care unit admission, 1 and 2 h after postanesthesia care unit admission, and on the mornings and late afternoons of postoperative days 1, 2, and 3. In the methadone group, the need for opioid analgesics was decreased by 60% and pain scores were reduced by approximately 30 to 40% during the first 72 postoperative hours, compared to patients administered intraoperative hydromorphone.

In the second clinical trial, patients undergoing fast-track cardiac surgery with an anticipated short period of postoperative ventilation (less than 6 h) were randomized to receive either 0.3 mg/kg of methadone (77 patients) or 12 μg/kg of fentanyl (79 patients) before cardiopulmonary bypass.[13] Intraoperative anesthetic (propofol and rocuronium for induction, sevoflurane for maintenance) and surgical management was carefully standardized, as was postoperative analgesic therapy (intravenous morphine and oral 10 mg hydrocodone, 325 mg acetaminophen tablets). Patients were assessed for pain and analgesic requirements as in the previous trial at 2, 4, 8, 12, 24, 48, and 72 h postextubation. For the first 3 postoperative days, total intravenous morphine requirements were reduced by 43% and pain scores were decreased by 30 to 40% in patients administered methadone, compared to those given fentanyl intraoperatively.

Follow-up Surveys

Patients participating in the two clinical trials were informed that they would be sent questionnaires after their surgery and requested to complete and return the questionnaire within 1 week. A self-addressed, stamped envelope containing the survey questions was mailed 1, 3, 6, and 12 months after the surgery date, and patients were contacted by telephone at these times and reminded to fully answer all of the questions.

Patients were questioned about the frequency of any pain related to surgery (0 = less than once per week, 1 = once per week, 2 = twice per week, 3 = daily, 4 = constantly), which was the primary outcome defined *a priori*. Patients were also asked to record levels of pain that were present at the time the surveys were completed using an 11-point scale (0 = no pain, 10 = worst pain imaginable). For patients completing the spine surgery study, back pain (incisional) and leg pain (neuropathic) scores were documented at rest, with movement, and with coughing. For those completing

the cardiac study, chest pain (sternal, nonanginal), leg pain (incisional), and back pain scores at rest, with coughing, and with movement were recorded. The presence of any chronic postsurgical pain was determined when the respondents recorded any number greater than 0 on the questions related to pain listed above.

The requirements for any oral opioid analgesic medications (yes/no), as well as the frequency of use (0 = none, 1 = less than twice per week, 2 = twice per week or more, 3 = daily) was determined. Patients recorded whether they had sought the care of a physician to treat pain directly related to the surgery. Functional impairment due to persistent surgical pain was assessed with two questions using an 11-point scale: pain interference with sleep (0 = none, 10 = complete) and pain interference with daily activities (0 = none, 10 = complete).

Statistics

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 and analyzed as such. Data are reported as mean ± SD, median (interquartile range), or number (percentage) of patients. Data reported as mean ± SD were compared with the unnpaired *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 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, those primary and secondary outcome data reported as the median (interquartile range) were compared between groups at each time using the Mann–Whitney U test, while those data reported as number of patients (%) were compared using the chi-square test or Fisher exact probability test. Because of the large number of comparisons, mean differences, median differences, and differences in proportions are reported with their 99% CI. The criterion for rejection of the null hypothesis was $P < 0.01$ throughout for the same reason. All statistical analyses were conducted with StatsDirect (Cambridge, United Kingdom)

The sample size for this study was not estimated because it is a follow-up to (secondary analysis of) two published randomized, double-blinded clinical trials comparing the effect of intraoperative methadone to traditional opioids on postoperative pain scores and analgesic requirements.

Results

Complex Spinal Surgical Patients

For patients enrolled in the spinal surgery clinical trial, questionnaires were returned from 75 (65%), 66 (57%), 74 (64%), and 66 (57%) subjects at 1, 3, 6, and 12 months, respectively (fig. 1). Among the respondents, there were no differences between the methadone and hydromorphone (control) groups in sex, weight, height, American Society of Anesthesiologists physical status classification, or preoperative level of pain at rest (data are presented in table 1 for patients responding 3 months after their operation).

The two groups differed in the frequency of postsurgical pain at 3 months (primary outcome), with the patients in the methadone group reporting a median frequency score of less than once a week (interquartile range less than once a week to daily) and those in the hydromorphone group reporting a median frequency score of daily (interquartile range once a week to daily, $P = 0.004$; fig. 2 and table 2).

Pain scores (median [interquartile range] on an 11-point scale, with 0 = no pain and 10 = worst pain imaginable) at rest, with coughing, and with movement 1, 3, 6, and 12 months after surgery are presented in table 3. Patients in the methadone group reported that back pain with movement was less at 1 month (2 [1 to 4] *vs.* 4.5 [3 to 6] in the hydromorphone group, median difference [99% CI] 2 [0 to 4], $P = 0.002$) and at 3 months (0 [0 to 2] *vs.* 3 [1 to 4] in the hydromorphone group, median difference [99% CI] 1 [0 to 3], $P = 0.006$). Similarly, back pain scores with coughing were lower in the methadone group at 3 months (0 [0 to 1]) compared to the hydromorphone group (2 [0 to 4], median difference [99% CI] 1 [0 to 3], $P = 0.001$). Although reported back pain scores at rest were lower in the methadone patients at 1 through 6 months, these differences were not statistically significant ($P = 0.03$ to 0.086). Leg pain scores at rest, with coughing, and with movement did not significantly differ between the study groups at any assessment time, with the exception of leg pain with coughing at 6 months (median difference [99% CI] 0 [0 to 0], $P = 0.008$), a difference that is likely to be clinically insignificant and possibly due to outliers in the hydromorphone group at that time.

Further data on analgesic requirements and postoperative pain are presented in table 2. The percentage of spinal surgical patients requiring any opioid analgesic medications was lower in the methadone group at the 3-month assessment (10% of the methadone patients *vs.* 41% of the hydromorphone patients, percent difference [99% CI] 30% [3 to 57%], $P = 0.009$). The two study cohorts did not differ in pain interference with sleep or daily activities on an 11-point scale (0 = none, 10 = complete), with the exception of sleep at 3 months (0 [0 to 1] methadone group, 2 [0 to 3] hydromorphone group, median difference [99% CI] 1 [0 to 3], $P = 0.007$).

Cardiac Surgical Patients

The number of patients responding to the cardiac surgical study were 104 (67%), 100 (64%), 83 (53%), and 65 (42%) at 1, 3, 6, and 12 months, respectively (fig. 3). No significant differences were observed between the respondents in the methadone and fentanyl (control) groups in sex, age, height, weight, or type of cardiac surgical procedure (data

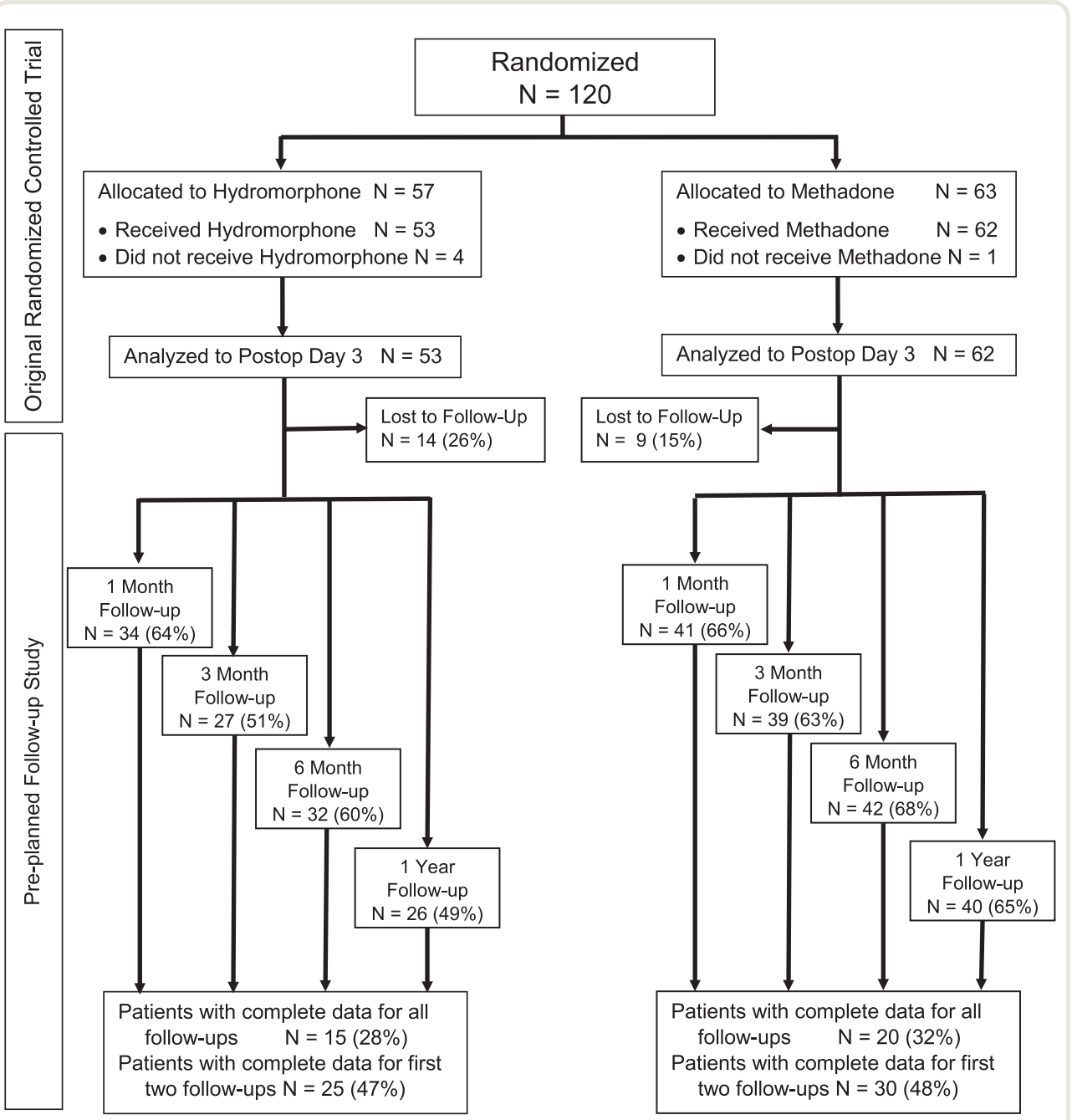

Fig. 1. Patient flow diagram for the randomized controlled trial of methadone and hydromorphone in patients undergoing complex spine surgery. The diagram represents both the original randomized controlled trial and the preplanned long-term follow-up study. The diagram identifies the number of patients completely lost to long-term follow-up, the number of patients who reported the weekly frequency of pain (the primary outcome) at each of the four long-term follow-up times (*i.e.*, at 1 month, 3 months, 6 months, and 1 yr after the operation), and the number of patients from whom responses were obtained at both 1 month and 3 months as well as at all four follow-up times.

are presented in table 4 for patients responding 1 month after their operation).

Overall pain scores in the cardiac surgical patients were lower than those reported in the complex spinal surgical cohort. The two cardiac groups differed in the frequency of postsurgical pain at 1 month (primary outcome), with the patients in the methadone group reporting a median frequency score of less than once a week (interquartile range less than once a week to twice per week) and those in the fentanyl group reporting a median frequency score of twice per week (interquartile range less than once a week to daily, median difference [99% CI] 1 [0 to 1], $P = 0.004$; fig. 4 and

Table 1. Characteristics of Patients Receiving Hydromorphone or Methadone Intraoperatively during Spine Surgery Responding 3 Months after Their Operation

	Hydromorphone	Methadone	Difference (99% CI)	*P* Value
N	27	39	—	—
Sex, female/male	15 (56%)/12 (44%)	20 (53%)/18 (47%)	8% (–23 to 37%)	0.272*
Age, yr	58 ± 13	65 ± 10	– 7 (–15 to 0)	0.013
Weight, kg	77 ± 20	82 ± 19	–6 (–18 to 8)	0.329
Height, cm	168 ± 10	170 ± 10	–2 (–9 to 5)	0.401
American Society of Anesthesiologists Physical Status classification	II (II to II)	II (II to III)	0 (0 to 0)	0.260
Preoperative level of pain at rest	3 (2 to 6)	3 (1 to 6)	0 (–2 to 2)	0.692

Data are mean ± SD, median (interquartile range), or number (percentage) of patients. A difference (99% CI) is the difference between percentages (risk), the difference between medians, or the difference between means and the 99% CI for that difference. Level of pain was scored on a 0 to 10 scale: 0 = no pain to 10 = worst pain imaginable.

*These data were tested by the chi-square test.

table 5). However, the frequency of postoperative pain was low thereafter (less than once per week) in both cohorts and not significantly different.

Chest pain scores at rest, with coughing, and with movement were low at all assessments in both groups; although the reported pain intensities were statistically lower at 1 month in the methadone cohort compared to the fentanyl cohort (all scores $P < 0.0001$; table 6), these differences are likely to be clinically insignificant and possibly due to outliers in the fentanyl group at that time. Similarly, leg pain scores were minimal in both groups at rest, with coughing, and with movement during the first postoperative year, and were statistically significantly but likely to be not clinically significantly less at 3 months at rest in the methadone group ($P = 0.004$). No differences in back pain scores were reported by respondents.

Although fewer patients in the methadone group required postoperative opioid medications, the overall number of cardiac surgical patients needing analgesics by 3 months was small, and no differences between respondent groups were observed at any time (table 5). Similarly, by 3 months, few patients reported pain interference with sleep or daily activity in either cohort, and no differences between groups were observed during the first postoperative year.

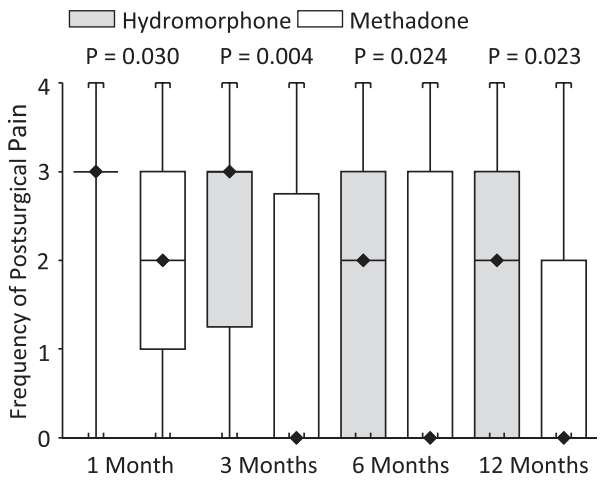

Fig. 2. Box plots of the frequency of postsurgical pain in patients randomly assigned to receive perioperative hydromorphone (*gray boxes*) or methadone (*plain boxes*) perioperatively 1 month, 3 months, 6 months, and 12 months after complex spine surgery. The frequency of any pain related to surgery was measured using an ordinal scale, with 0 = less than once per week, 1 = once per week, 2 = twice per week, 3 = daily, and 4 = constantly. *Horizontal lines* with *black diamonds* in their center across the boxes represent medians; *lower and upper edges* of the boxes represent the first and third quartiles; *whiskers* indicate the data range. The frequencies of postsurgical pain were compared between groups at the various times using the Mann–Whitney U test. The resulting *P* values are indicated above the data used in the analyses. The criterion for rejection of the null hypothesis was $P < 0.01$. Sample sizes range from 34 and 41 in the hydromorphone and methadone groups, respectively, at 1 month, to 26 and 40, respectively, at 12 months.

Discussion

In the current study, the potential preventive analgesic effects of a single intraoperative dose of methadone in patients undergoing complex spine surgery and cardiac surgical procedures were examined in a 1-yr postal follow-up. Respondents who underwent spine surgery and received intraoperative methadone reported fewer episodes of pain per week 3 months after surgery than those given hydromorphone. In addition, patients given methadone noted a lower intensity of back pain 1 and 3 months after the surgical procedure, as well as a decreased need for opioid analgesic medications at 3 months. In subjects undergoing cardiac surgery, the frequency of episodes of pain per week at 1 month was less in patients given intraoperative methadone than in those administered fentanyl. These data suggest the use of methadone as a preventive analgesic medication may attenuate development of chronic postsurgical pain.

Table 2. Occurrence and Frequency of Postsurgical Pain, Analgesic Medication Requirement and Frequency, and Pain Interference with Sleep and Daily Activities in Patients Receiving Hydromorphone or Methadone Intraoperatively during Spinal Surgery

	Hydromorphone	Methadone	Difference (99% CI)	*P* Value
Any chronic postsurgical pain (yes/no)				
1 Month	31/34 (91%)	32/41 (78%)	13% (–10 to 35%)	0.220|||
3 Months	22/26 (85%)	19/38 (50%)	35% (3 to 59%)	0.010|||
6 Months	20/32 (63%)	16/42 (38%)	24% (– 6 to 51%)	0.065|||
12 Months	16/26 (62%)	16/40 (40%)	22% (–11 to 50%)	0.145|||
Postsurgical pain (0 < once a week, 1 = once per week, 2 = twice per week, 3 = daily, 4 = constant)				
1 Month	3 (3 to 3)*	2 (1 to 3)†	0 (0 to 1)	0.030
3 Months	3 (1 to 3)‡	0 (0 to 3)§	1 (0 to 2)	0.004
6 Months	2 (0 to 3)||	0 (0 to 3)#	0 (0 to 2)	0.024
12 Months	2 (0 to 3)**	0 (0 to 2)††	1 (0 to 2)	0.023
Analgesic medication requirement (yes/no)				
1 Month	23/34 (68%)	21/41 (51%)	16% (–13 to 43%)	0.229|||
3 Months	11/27 (41%)	4/39 (10%)	30% (3 to 57%)	0.009|||
6 Months	10/32 (31%)	6/42 (14%)	17% (–8 to 43%)	0.141|||
12 Months	3/26 (12%)	3/40 (8%)	4% (–16 to 30%)	0.673##
Analgesic medication frequency (0 = none 1 < twice per week, 2 ≥ twice per week, 3 = daily)				
1 Month	3 (0 to 3)*	1 (0 to 3)†	0 (0 to 3)	0.035
3 Months	0 (0 to 3)‡	0 (0 to 0)‡‡	0 (0 to 3)	0.011
6 Months	0 (0 to 2.5)||	0 (0 to 0)†	0 (0 to 0)	0.157
12 Months	0 (0 to 0)§§	0 (0 to 0)††	0 (0 to 0)	0.804
Pain interference with sleep (0 = none to 10 = complete)				
1 Month	3.5 (2 to 5)*	2 (0 to 4)†	1 (0 to 3)	0.058
3 Months	2 (0 to 3)‡	0 (0 to 1)§	1 (0 to 3)	0.007
6 Months	0 (0 to 2)||	0 (0 to 1)#	0 (0 to 1)	0.304
12 Months	0 (0 to 1)**	0 (0 to 1)††	0 (0 to 0)	0.857
Pain interference with daily activities (0 = none to 10 = complete)				
1 Month	4 (2 to 6)*	3 (1 to 5)†	1 (–1 to 2)	0.205
3 Months	2 (1 to 5)‡	0 (0 to 3)§	1 (0 to 2)	0.010
6 Months	1.5 (0 to 4)||	0 (0 to 3)#	0 (0 to 2)	0.279
12 Months	1 (0 to 4)**	0 (0 to 2.5)††	0 (0 to 2)	0.408
Saw doctor for pain (yes/no)				
1 Month	8/34 (24%)	5/41 (12%)	11% (–12 to 35%)	0.325|||
3 Months	5/27 (19%)	4/39 (10%)	8% (–15 to 35%)	0.469##
6 Months	6/32 (19%)	6/42 (14%)	4% (–18 to 30%)	0.843|||
12 Months	4/26 (15%)	10/40 (25%)	–10% (–34 to 19%)	0.532|||

Data are median (interquartile range) or number (percentage) of patients. Data reported as median (interquartile range) were compared using the Mann–Whitney U test, while data reported as number of patients (%) were compared using the chi-square test (with Yates correction) unless at least one expected frequency was less than 5, in which case the Fisher exact probability test was used. A difference (99% CI) is either the difference between percentages (risk) or between medians and the 99% CI for that difference.

*N = 34. †N = 41. ‡N = 27. §N = 39. ||N = 32. #N = 42. **N = 26. ††N = 40. ‡‡N = 38. §§N = 24. |||These data were tested by the chi-square test. ##These data were tested by the Fisher exact test.

Despite application of analgesic strategies designed to enhance postoperative recovery, more than half of patients experience moderate to severe pain, even after relatively "minor" surgical procedures.[26,27] Ten to sixty percent of patients with high pain scores during the first 1 to 3 days after surgery will go on to develop chronic postsurgical pain.[28] Chronic postsurgical pain is "pain persisting at least 3 months after surgery, that was not present before surgery, or that had different characteristics or increased intensity from preoperative pain, localized to the surgical site or referred area, and other possible causes of the pain were excluded."[29] High postoperative pain intensity is one of the strongest predictors for the development of chronic postsurgical pain,[14–16,26,30] and a 10% increase in the percentage of time in severe pain on the first postoperative day was associated with a 30% increase in the incidence of chronic postsurgical pain at 12 months.[17]

Methadone is a unique opioid with a long half life that provides prolonged stable blood concentrations after a single intraoperative dose, without the fluctuations associated with repeated injections of higher clearance opioids like morphine or hydromorphone. Randomized clinical trials in patients undergoing complex spinal,[10,13] cardiac,[12,31] gynecologic,[32] pediatric,[11] and general surgical procedures[33,34] have documented that patients administered methadone had lower pain scores and analgesic requirements during the first 1 to 3 postoperative days compared to subjects administered traditional, shorter-acting opioids. However, only one investigation examined the potential preventive analgesic effects of perioperative methadone. Komen *et al.* randomized 60 ambulatory surgery patients to methadone or control groups (fentanyl, hydromorphone).[35] During the month after discharge, patients given methadone 0.15 mg/kg

Table 3. Back Pain and Leg Pain at Rest, with Coughing, and with Movement at 1 Month, 3 Months, 6 Months, and 12 Months in Patients Receiving Hydromorphone or Methadone Intraoperatively during Spine Surgery

	Hydromorphone	Methadone	Median Difference (99% CI)	*P* Value
Back pain at rest				
1 Month	3 (1 to 4)*	1 (0 to 3)†	1 (0 to 3)	0.030
3 Months	1 (0 to 3)‡	0 (0 to 2)§	0 (0 to 1)	0.086
6 Months	0.5 (0 to 3.5)‖	0 (0 to 1)†	0 (0 to 2)	0.065
12 Months	0 (0 to 1)#	0 (0 to 1)**	0 (0 to 0)	0.801
Back pain with coughing				
1 Month	3.5 (1 to 5)*	1 (0 to 3)†	2 (0 to 3)	0.015
3 Months	2 (0 to 4)‡	0 (0 to 1)§	1 (0 to 3)	0.001
6 Months	1 (0 to 3.5)‖	0 (0 to 1)†	0 (0 to 2)	0.035
12 Months	0 (0 to 1)#	0 (0 to 1)**	0 (0 to 0)	0.726
Back pain with movement				
1 Month	4.5 (3 to 6)*	2 (1 to 4)†	2 (0 to 4)	0.002
3 Months	3 (1 to 4)‡	0 (0 to 2)§	1 (0 to 3)	0.006
6 Months	2.5 (0 to 4.5)‖	0 (0 to 3)**	1 (0 to 3)	0.030
12 Months	2 (0 to 5)#	0 (0 to 2.5)**	1 (0 to 3)	0.033
Leg pain at rest				
1 Month	0 (0 to 3)*	0 (0 to 2)†	0 (0 to 1)	0.292
3 Months	0 (0 to 0)‡	0 (0 to 0)§	0 (0 to 0)	0.552
6 Months	0 (0 to 0)‖	0 (0 to 0)††	0 (0 to 0)	0.606
12 Months	0 (0 to 0)#	0 (0 to 1)**	0 (0 to 0)	0.277
Leg pain with coughing				
1 Month	0 (0 to 2)*	0 (0 to 0)†	0 (0 to 1)	0.031
3 Months	0 (0 to 0)‡	0 (0 to 0)§	0 (0 to 0)	0.550
6 Months	0 (0 to 0.5)‖	0 (0 to 0)††	0 (0 to 0)	0.008
12 Months	0 (0 to 0)#	0 (0 to 0)**	0 (0 to 0)	0.881
Leg pain with movement				
1 Month	2 (0 to 4)*	0 (0 to 2)†	0 (0 to 2)	0.065
3 Months	1 (0 to 3)‡	0 (0 to 1)§	0 (0 to 2)	0.028
6 Months	0 (0 to 2.5)‖	0 (0 to 0)††	0 (0 to 1)	0.016
12 Months	0.5 (0 to 6)#	0 (0 to 1.5)**	0 (0 to 3)	0.058

Data are reported as median (interquartile range) and were compared using the Mann–Whitney U test. A median difference (99% CI) is the difference between medians and the 99% CI for that difference.

*N = 34. †N = 41. ‡N = 27. §N = 39. ‖N = 32. #N = 26. **N = 40. ††N = 42

reported less pain at rest and used 50% fewer opioid pills than the control group. However, patients were not followed beyond 1 month to determine if a more prolonged analgesic effect was observed.

The highest incidence of chronic postsurgical pain has been reported in patients undergoing complex spine surgery, with 55 to 60% of patients reporting pain at 1 yr[17] (which is comparable to the 62% observed in the hydromorphone group in our study). A number of factors may contribute to development of chronic postsurgical pain in this patient population, including high levels of preoperative and postoperative pain and opioid use, as well as the complexity of the operative procedure.[14] In the current study, a preventive analgesic effect was observed in subjects given methadone, particularly during the first 3 postoperative months when higher pain scores were reported. At 3 months, spinal patients administered methadone reported a lower frequency of weekly pain, reduced back pain scores with coughing and movement, and less pain interference with sleep, and opioid pain medications were needed less often. However, by 6 and 12 months after surgery, pain intensity had decreased in both study cohorts, and respondents reported no statistically significant differences in the frequency of weekly pain, pain scores, need for analgesic medications, or pain interference with sleep or daily activities. These findings suggest the analgesic benefits of intraoperative methadone are observed during the first 3 postoperative months when the intensity and frequency of pain are greatest.

Previous investigations have reported that chronic postsurgical pain is common in patients undergoing cardiac surgical procedures (35 to 40% at 3 months, 10 to 27% at 1 yr),[17,36,37] although the intensity and incidence is lower than in those undergoing complex spine surgery.[17] Potential mechanisms involved in the genesis of chronic postsurgical pain in this patient population include musculoskeletal trauma during sternal retraction, entrapment neuropathy, nerve damage during internal mammary artery dissection, or pain secondary to sternal wires or cautery use.[37,38] In our follow-up study of patients randomized to receive either methadone or fentanyl for cardiac surgery, the primary analgesic benefits of methadone were observed at the first postoperative month (the time period when the weekly frequency of pain was

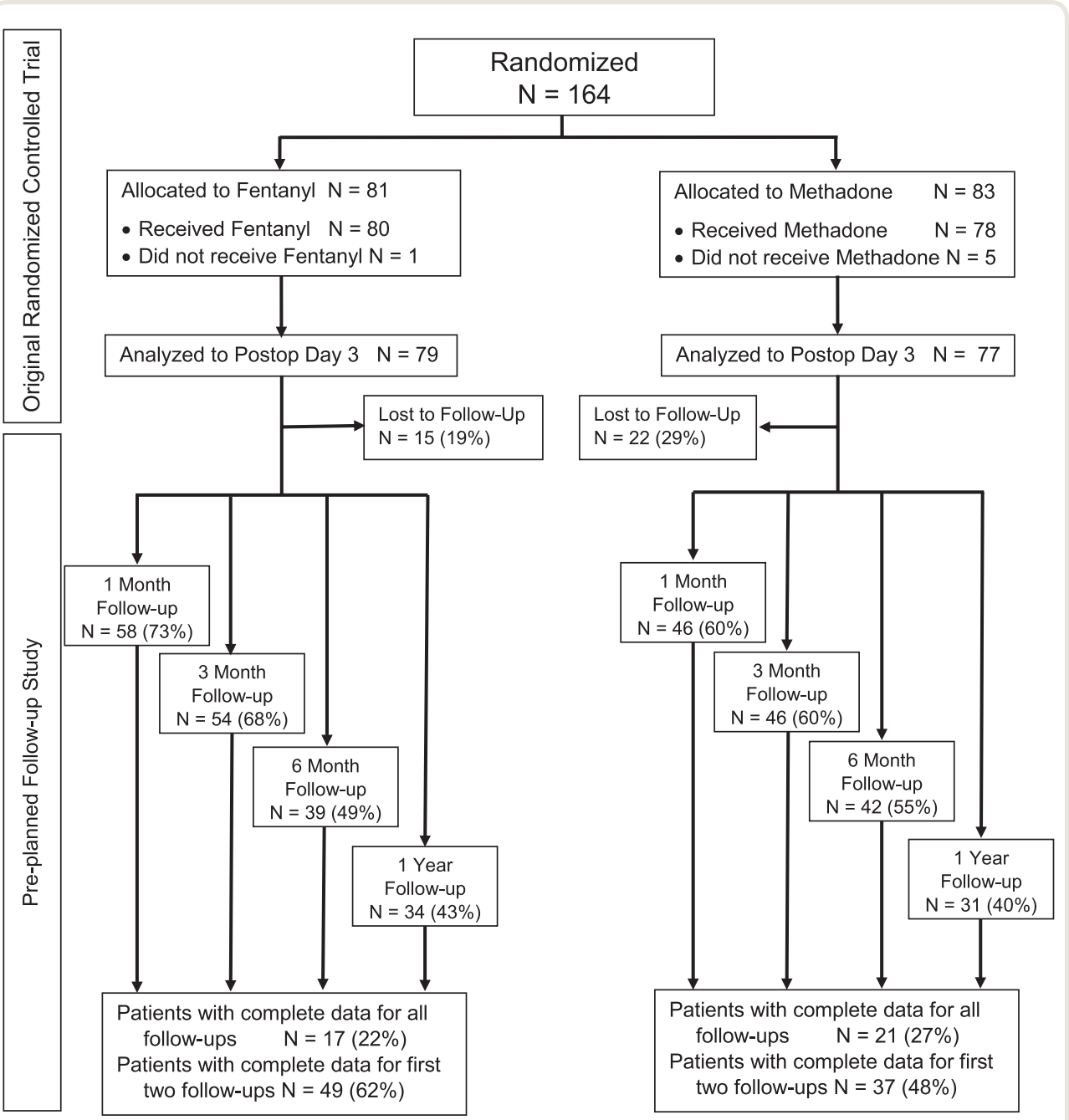

Fig. 3. Patient flow diagram for the randomized controlled trial of methadone and fentanyl in patients undergoing complex spine surgery. The diagram represents both the original randomized controlled trial and the preplanned long-term follow-up study. The diagram identifies the number of patients completely lost to long-term follow-up, the number of patients who reported the weekly frequency of pain (the primary outcome) at each of the four long-term follow-up times (*i.e.*, at 1 month, 3 months, 6 months, and 1 yr after the operation), and the number of patients from whom responses were obtained at both 1 month and 3 months as well as at all four follow-up times.

significantly lower in the methadone cohort compared to the fentanyl cohort). However, respondents noted no differences in pain 3, 6, or 12 months after surgery. Given the low median pain scores reported by respondents over the first postoperative year, it is not unexpected that significant differences were not observed between groups beyond month 1. Although a preventive analgesic effect of methadone was observed in this patient population at the first postoperative month, a significant effect of methadone on chronic postsurgical pain ("pain persisting at least 3 months after surgery") was not documented by respondents. These findings suggest the long-term analgesic benefits of methadone may be more

Table 4. Characteristics of Patients Receiving Fentanyl or Methadone Intraoperatively during Cardiac Surgery Responding 1 Month after Their Operation

	Fentanyl	Methadone	Difference (99% CI)	*P* Value
N	58	46	—	—
Sex, female/male	14 (24%)/44 (76%)	14(30%)/32 (70%)	–8% (–35 to 19%)	0.620*
Age, yr	67 ± 12	67 ± 11	0 (–6 to 6)	0.950
Weight, kg	85 ± 23	88 ± 18	–3 (–13 to 8)	0.520
Height, cm	173 (165 to 180)	173 (165 to 178)	0 (–5 to 5)	0.901
Operation			—	0.447†
Coronary artery bypass graft	25 (43%)	17 (37%)		
Valve	25 (43%)	26 (56%)		
Coronary artery bypass graft and valve	6 (11%)	3 (7%)		
Atrial septal defect	2 (3%)	0 (0%)		

Data are mean ± S.D., median (interquartile range) or a number (percentage) of patients. A Difference (99% CI) is the difference between percentages (risk), the difference between medians, or the difference between means and the 99% CI for that difference.

*These data were tested by the chi-square test. †These data were tested by the Fisher–Freeman–Halton exact test.

pronounced in patient populations with an expected higher risk of chronic postsurgical pain.

In the control groups, the choice of opioid, dose of opioid, and timing of administration could affect the findings of the current investigation. In the initial studies, the type and doses of opioid selected for use in the control groups (hydromorphone in the spine study and fentanyl in the cardiac study) reflected the standard clinical practices at NorthShore University HealthSystem. Previous publications have also suggested that doses of methadone and hydromorphone[39,40] and methadone and fentanyl[41,42] used in the studies were approximately equipotent, although the pharmacokinetics of the three opioids differ significantly. Additionally, in the initial study in patients undergoing spine surgery, methadone was administered at anesthetic induction, whereas hydromorphone was given at surgical closure. Although dosing both opioids at the start or conclusion of surgery would have removed the confounding variable of the time of opioid administration, use of hydromorphone at induction could result in inadequate postoperative pain relief (due to the short [2 h] half life of the drug),[43] whereas administration of methadone at the end of surgery could induce postoperative respiratory depression.[9]

There are several limitations to the study. First, a number of patients were lost to follow-up. It is possible that selection bias occurred (*i.e.*, patients with more severe pain did not return questionnaires), but we had no information about the patients who did not respond. Second, the study may have been underpowered to detect differences in some outcome measures, as the initial investigations were powered to examine differences in analgesic requirements between methadone and control groups, not longer-term pain scores or opioid use. Third, the mechanism(s) by which methadone induced a preventive analgesic effect (*via* a reduction in acute postoperative pain, a decrease in opioid use and resultant tolerance and hyperalgesia, NMDA receptor antagonism, or some combination of these processes) were not determined in this investigation. Several studies (although not all) have documented that the intravenous use of ketamine, another potent NMDA antagonist, can

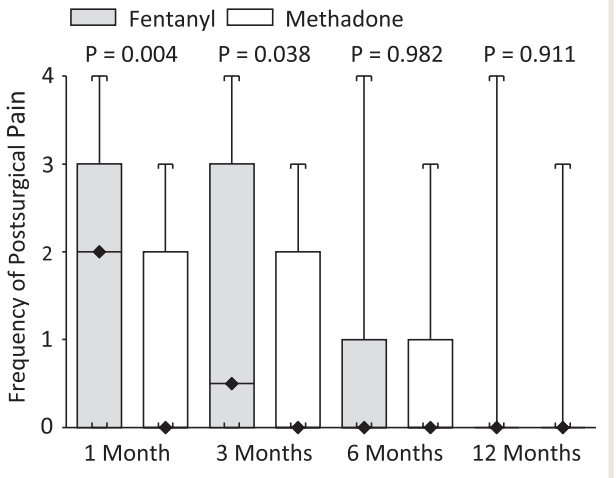

Fig. 4. Box plots of the frequency of postsurgical pain in patients randomly assigned to receive perioperative fentanyl (*gray boxes*) or methadone (*plain boxes*) perioperatively 1 month, 3 months, 6 months, and 12 months after cardiac surgery. The frequency of any pain related to surgery was measured using an ordinal scale, with 0 = less than once per week, 1 = once per week, 2 = twice per week, 3 = daily, and 4 = constantly. *Horizontal lines* with *black diamonds* at their center across the boxes represent medians; *lower and upper edges* of the boxes represent the first and third quartiles; *whiskers* indicate the data range. The frequencies of postsurgical pain were compared between groups at the various times using the Mann–Whitney U test. The resulting *P* values are indicated above the data used in the analyses. The criterion for rejection of the null hypothesis was $P < 0.01$. Sample sizes range from 58 and 46 in the fentanyl and methadone groups, respectively, at 1 month, to 34 and 31, respectively, at 12 months.

Table 5. Occurrence and Frequency of Postsurgical Pain, Analgesic Medication Requirement and Frequency, and Pain Interference with Sleep and Daily Activities in Patients Receiving Fentanyl or Methadone Intraoperatively during Cardiac Surgery

	Fentanyl	Methadone	Difference (99% CI)	*P* Value
Any chronic postsurgical pain (yes/no)				
1 Month	39/58 (67%)	20/46 (43%)	24% (–2 to 46%)	0.026|||
3 Months	27/54 (50%)	15/46 (33%)	17% (–8 to 41%)	0.120|||
6 Months	11/41 (27%)	12/42 (29%)	– 2% (–27 to 24%)	> 0.999|||
12 Months	2/33 (6%)	3/32 (9%)	– 3% (–26 to 18%)	0.672##
Postsurgical pain (0 < once a week, 1 = once per week, 2 = twice per week, 3 = daily, 4 = constant)				
1 Month	2 (0 to 3)*	0 (0 to 2)†	1 (0 to 1)	0.004
3 Months	0.5 (0 to 3)‡	0 (0 to 2)†	0 (0 to 1)	0.038
6 Months	0 (0 to 1)§	0 (0 to 1)‖	0 (0 to 0)	0.982
12 Months	0 (0 to 0)#	0 (0 to 0)**	0 (0 to 0)	0.911
Analgesic medication requirement (yes/no)				
1 Month	22/58 (38%)	11/46 (24%)	14% (–10 to 36%)	0.189|||
3 Months	6/55 (11%)	4/46 (9%)	2% (–16 to 19%)	0.752##
6 Months	2/39 (5%)	0/42 (0%)	5% (–9 to 22%)	0.229##
12 Months	0/34 (0%)	0/31 (0%)	0% (–18 to 16%)	> 0.999##
Analgesic medication frequency (0 = None, 1 < twice per week, 2 ≥ twice per week, 3 = daily)				
1 Month	0 (0 to 3)*	0 (0 to 0)†	0 (0 to 0)	0.074
3 Months	0 (0 to 0)††	0 (0 to 0)†	0 (0 to 0)	0.319
6 Months	0 (0 to 0)§	0 (0 to 0)‡‡	0 (0 to 0)	0.469
12 Months	0 (0 to 0)#	0 (0 to 0)§§	0 (0 to 0)	> 0.999
Pain interference with sleep (0 = none to 10 = complete)				
1 Month	2 (0 to 3)*	1 (0 to 2)†	1 (0 to 2)	0.024
3 Months	0 (0 to 2)‡	0 (0 to 1)†	0 (0 to 1)	0.089
6 Months	0 (0 to 0)§	0 (0 to 0)‖	0 (0 to 0)	0.341
12 Months	0 (0 to 0)#	0 (0 to 0)**	0 (0 to 0)	0.410
Pain interference with daily activities (0 = none to 10 = complete)				
1 Month	2 (0 to 4)*	0 (0 to 2)†	1 (0 to 2)	0.018
3 Months	0 (0 to 2)‡	0 (0 to 1)†	0 (0 to 0)	0.178
6 Months	0 (0 to 0)§	0 (0 to 0)‖	0 (0 to 0)	0.684
12 Months	0 (0 to 0)#	0 (0 to 0)**	0 (0 to 0)	0.976
Saw doctor for pain (Yes/No)				
1 Month	3/58 (5%)	2/46 (4%)	1% (–15 to 15%)	> 0.999##
3 Months	9/54 (17%)	3/46 (7%)	10% (–8 to 28%)	0.213|||
6 Months	3/39 (8%)	1/42 (2%)	5% (–11 to 24%)	0.347##
12 Months	2/34 (6%)	0/31 (0%)	6% (–13 to 25%)	0.493##

Data are median (interquartile range) or number (percentage) of patients. Data reported as median (interquartile range) were compared using the Mann–Whitney U test while data reported as number of patients (%) were compared using the chi-square test (with Yates correction) unless at least one expected frequency was less than 5, in which case the Fisher exact probability test was used. A difference (99% CI) is either the difference between percentages (risk) or between medians and the 99% CI for that difference.

*N = 58. †N = 46. ‡N = 54. §N = 39. ‖N = 42. #N = 34. **N = 31. ††N = 53. ‡‡N = 41. §§N = 32. |||These data were tested by the chi-square test. ##These data were tested by the Fisher exact test.

reduce development of chronic postsurgical pain 3 and 6 months after surgery.[44] Fourth, it has been recommended that health-related quality of life outcomes should be measured in chronic postsurgical pain trials using validated tools to examine physical (Multidimensional Pain Inventory Interference Scale, Brief Pain Inventory Interference Scale) and emotional (Beck Depression Inventory, Profile of Mood States) functioning.[45] In our study, patients were questioned about only two functional outcomes (pain interference with sleep and daily activities on a 0 to 10 scale, 0 = none, 10 = complete). The findings of this study may have been strengthened if validated tools to measure functional impairment from chronic postsurgical pain had been utilized. Similarly, the use of a 5-point ordinal scale to assess the primary outcome measure may not have been ideal, given the relatively small cohorts. Finally, the effect of methadone on chronic pain was only examined in patients undergoing major surgical procedures. The role of this long-acting agent in patients undergoing less painful procedures, particularly in conjunction with other opioid-sparing drugs, requires further investigation.

Initiation of opioid therapy for acute postoperative pain often leads to continued use for months to years after hospital discharge. Therefore, clinicians are faced with the challenge of optimizing pain management during hospitalization while simultaneously reducing pain and opioid use during the first months after surgery. We observed that patients undergoing spine surgery randomized to receive methadone had less pain during the first 3 postoperative months, and fewer subjects in this group required opioid analgesics at 3 months. In addition, cardiac surgical patients given a single intraoperative

Table 6. Chest Pain, Leg Pain, and Back Pain at Rest, with Coughing, and with Movement at 1 Month, 3 Months, 6 Months, and 12 Months in Patients Receiving Fentanyl or Methadone Intraoperatively during Cardiac Surgery

	Fentanyl	Methadone	Median Difference (99% CI)	*P* Value
Chest pain at rest				
1 Month	0 (0 to 2)*	0 (0 to 0)†	0 (0 to 1)	< 0.0001
3 Months	0 (0 to 1)‡	0 (0 to 1)†	0 (0 to 0)	0.678
6 Months	0 (0 to 0)§	0 (0 to 0)‖	0 (0 to 0)	0.465
12 Months	0 (0 to 0)#	0 (0 to 0)**	0 (0 to 0)	0.389
Chest pain with coughing				
1 Month	0 (0 to 3)††	0 (0 to 0)†	0 (0 to 2)	< 0.0001
3 Months	1 (0 to 4)‡	1 (0 to 2)†	0 (–1 to 1)	0.623
6 Months	0 (0 to 1)‡‡	0 (0 to 1)‖	0 (–1 to 1)	0.181
12 Months	0 (0 to 1)#	0 (0 to 0)§§	0 (0 to 0)	0.413
Chest pain with movement				
1 Month	0 (0 to 3)*	0 (0 to 0)†	0 (0 to 2)	< 0.0001
3 Months	0 (0 to 2)‡	0 (0 to 2)†	0 (0 to 0)	0.645
6 Months	0 (0 to 1)‡‡	0 (0 to 1)‖	0 (0 to 0)	0.521
12 Months	0 (0 to 0)#	0 (0 to 0)§§	0 (0 to 0)	0.422
Leg pain at rest				
1 Month	0 (0 to 1)*	0 (0 to 0)†	0 (0 to 0)	0.041
3 Months	0 (0 to 2)‡	0 (0 to 0)†	0 (0 to 1)	0.004
6 Months	0 (0 to 0)§	0 (0 to 0)‖	0 (0 to 0)	0.559
12 Months	0 (0 to 0)‖‖	0 (0 to 0)§§	0 (0 to 0)	0.939
Leg pain with coughing				
1 Month	0 (0 to 1)*	0 (0 to 0)†	0 (0 to 0)	0.037
3 Months	0 (0 to 0)‡	0 (0 to 0)†	0 (0 to 0)	0.081
6 Months	0 (0 to 0)§	0 (0 to 0)‖	0 (0 to 0)	0.971
12 Months	0 (0 to 0)‖‖	0 (0 to 0)§§	0 (0 to 0)	0.826
Leg pain with movement				
1 Month	0 (0 to 1)*	0 (0 to 0)†	0 (0 to 0)	0.032
3 Months	0 (0 to 1)‡	0 (0 to 0)†	0 (0 to 0)	0.036
6 Months	0 (0 to 0)§	0 (0 to 0)‖	0 (0 to 0)	0.491
12 Months	0 (0 to 0)‖‖	0 (0 to 0)§§	0 (0 to 0)	0.820
Back pain at rest				
1 Month	0 (0 to 2)*	0 (0 to 0)†	0 (0 to 0)	0.062
3 Months	0 (0 to 0)‡	0 (0 to 0)†	0 (0 to 0)	0.402
6 Months	0 (0 to 0)‡‡	0 (0 to 0)‖	0 (0 to 0)	0.479
12 Months	0 (0 to 0)‖‖	0 (0 to 0)§§	0 (0 to 0)	0.766
Back pain with coughing				
1 Month	0 (0 to 2)*	0 (0 to 1)†	0 (0 to 0)	0.540
3 Months	0 (0 to 0)‡	0 (0 to 0)†	0 (0 to 0)	0.597
6 Months	0 (0 to 0)‡‡	0 (0 to 0)‖	0 (0 to 0)	0.135
12 Months	0 (0 to 0)‖‖	0 (0 to 0)§§	0 (0 to 0)	0.905
Back pain with movement				
1 Month	0 (0 to 2)*	0 (0 to 1)†	0 (0 to 0)	0.268
3 Months	0 (0 to 1)‡	0 (0 to 0)†	0 (0 to 0)	0.395
6 Months	0 (0 to 0)‡‡	0 (0 to 0)‖	0 (0 to 0)	0.646
12 Months	0 (0 to 0)‖‖	0 (0 to 0)§§	0 (0 to 0)	0.282

Data are reported as median (interquartile range) and were compared using the Mann–Whitney U test. A median difference (99% CI) is the difference between medians and the 99% CI for that difference.

*N = 58. †N = 46. ‡N = 55. §N = 38. ‖N = 42. #N = 35. **N = 31. ††N = 57. ‡‡N = 39. §§N =30. ‖‖N = 34.

dose of methadone reported a lower frequency of weekly pain 1 month after the procedure. These findings suggest that a single intraoperative dose of methadone may provide analgesic benefits that persist when the intensity and frequency of pain are the greatest after hospital discharge.

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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. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: dgmurphy2@yahoo.com. Raw data available at: dgmurphy2@yahoo.com.

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