Methylprednisolone Does Not Reduce Persistent Pain after Cardiac Surgery

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ABSTRACT

Background: Persistent incisional pain is common after cardiac surgery and is believed to be in part related to inflammation and poorly controlled acute pain. Methylprednisolone is a corticosteroid with substantial antiinflammatory and analgesic properties and is thus likely to ameliorate persistent surgical pain. Therefore, the authors tested the primary hypothesis that patients randomized to methylprednisolone have less persistent incisional pain than those given placebo.

Methods: One thousand forty-three patients having cardiopulmonary bypass for cardiac surgery *via* a median sternotomy were included in this substudy of Steroids in Cardiac Surgery (SIRS) trial. Patients were randomized to 500 mg intraoperative methylprednisolone or placebo. Incisional pain was assessed at 30 days and 6 months after surgery, and the potential risk factors were also evaluated.

Results: Methylprednisolone administration did not reduce pain at 30 days or persistent incisional pain at 6 months, which occurred in 78 of 520 patients (15.7%) in the methylprednisolone group and in 88 of 523 patients (17.8%) in the placebo group. The odds ratio for methylprednisolone was 0.93 (95% CI, 0.79 to 1.09, $P = 0.37$). Furthermore, there was no difference in worst pain and average pain in the last 24 h, pain interference with daily life, or use of pain medicine at 6 months. Younger age, female sex, and surgical infections were associated with the development of persistent incisional pain.

Conclusions: Intraoperative methylprednisolone administration does not reduce persistent incisional pain at 6 months in patients recovering from cardiac surgery. **(ANESTHESIOLOGY 2015; 123:1404-10)**

PERSISTENT incisional pain is defined by pain at a surgical incisional site lasting at least 3 months for which other causes (*i.e.*, malignancy, ischemia, or chronic infection) have been excluded.[1] Persistent incisional pain is especially common after hernia repair, breast surgery, thoracotomies, and sternal incisions.[2] The incidence of persistent incisional pain after cardiac surgery with median sternotomy is reported to range from 11 to 56% and significantly impairs quality of life.[3–6] The number of patients affected is substantial because cardiac surgery is among the most common surgical procedures performed worldwide, with more than 400,000 patients having open coronary artery bypass procedures annually in the United States.

What We Already Know about This Topic

- Persistent pain after surgery might reflect peripheral or central inflammatory processes and might be made less likely with perioperative steroid treatment

What This Article Tells Us That Is New

- In 1,043 patients having cardiopulmonary bypass for cardiac surgery, administration of 500 mg dexamethasone during surgery did not alter the incidence of pain at 1 or 6 months after surgery compared with placebo

The causes of persistent incisional pain remain poorly understood, but locally released inflammatory mediators in response to tissue injury at surgical sites may be causative.

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These mediators reduce the activation threshold of nociceptors, thus enhancing pain sensitivity at the site of tissue injury, a phenomenon known as peripheral sensitization.[7,8] Normally, inflammation decreases during healing, and acute postoperative pain subsides. In certain patients, though, inflammation apparently persists. Ongoing inflammation increases excitability of the spinal neurons, which is known as central sensitization.[7,8] Reducing intensity of the inflammatory response to surgical tissue injury thus seems likely to decrease peripheral and central sensitization, both of which contribute to the development of persistent incisional pain.

Steroids are potent antiinflammatory drugs; they peripherally inhibit phospholipase, thereby decreasing pain-aggravating products of the cyclooxygenase and lipoxygenase pathways.[9] Furthermore, it is well established that steroids decrease acute postoperative pain after various surgical procedures.[9–12] Uncontrolled acute postoperative pain is strongly associated with persistent pain and possibly also provokes central sensitization by increasing the excitability of spinal neurons.[2,3] Steroids might reduce the risk or intensity of persistent incisional pain by moderating acute pain and/or reducing ongoing inflammation. Therefore, we tested the primary hypothesis that patients randomized to the steroid methylprednisolone have less persistent incisional pain than patients given placebo.

Smokers generally have reported more postoperative pain than nonsmokers.[13] There are also studies demonstrating significant association between smoking and various chronic pain syndromes.[13,14] We also tested the secondary hypothesis that smokers have more persistent incisional pain than nonsmokers. Simultaneously, we evaluated other potential risk factors for persistent incisional pain after cardiac surgery.

Materials and Methods

With approval of the institutional ethics review boards of all contributing centers and after obtaining informed consent, patients undergoing elective, urgent, or emergent cardiac surgery were enrolled in the Steroids in Cardiac Surgery (SIRS) trial (ClinicalTrials.gov, NCT00427388, https://clinicaltrials.gov/ct2/show/NCT00427388, Richard Whitlock, M.D., January 26, 2007).[15] The methodology of the SIRS trial has previously been detailed.[16] The current analysis was restricted to eight centers in four countries that chose to participate in this substudy of persistent incisional pain.

Briefly, adults having cardiopulmonary bypass for cardiac surgery *via* a median sternotomy with a European System for Cardiac Operative Risk Evaluation (EuroSCORE) of at least 6 were included. Patients were excluded from the study if they were taking systemic steroids, had a history of bacterial or fungal infection in the last 30 days, had an allergy or intolerance to corticosteroids, were receiving aprotinin, or had previously participated in SIRS.

By using a computerized randomization phone service or interactive web randomization system, patients were allocated to (1) 500 mg of methylprednisolone divided into two intravenous doses of 250 mg each, one during anesthetic induction and the other on cardiopulmonary bypass initiation; and (2) placebo solution, given comparably. Based on randomization, the unblinded pharmacist prepared the methylprednisolone or matching placebo and provided the study drug to the blinded surgical staff. All clinicians and investigators were thus fully blinded to allocation. Intraoperative and postoperative clinical care was per institutions' guidelines and practices, including postoperative analgesic management.

Demographic data, cardiac history, comorbidities, and surgical procedure were recorded. Blinded investigators evaluated patients for persistent surgical pain at 30 days with questionnaires: the modified brief pain inventory[17] and the neuropathic pain questionnaire sort form.[18] After 6 months, patients were contacted and asked to rate incisional chest pain on an 11-point verbal response scale. Patients who reported any incisional chest pain at 6 months were asked to complete the Modified Brief Pain Inventory and the neuropathic pain questionnaire short form. Both questionnaires are well validated.[19,20]

Statistical Analysis

Our primary outcomes were incisional pain assessed at 30 days and 6 months after surgery using an 11-point verbal response scale. A score of 0 indicated no incisional pain, and a score of 10 indicated the most severe incisional pain. Secondarily, we evaluated the potential risk factors for incisional pain at 6 months: smoking, age, gender, preoperative history of pain, body mass index (BMI), and deep sternal wound infection.

Baseline characteristics were compared using the Pearson chi-square test, *t* test, or nonparametric test as appropriate. All analyses were conducted using the intention-to-treat approach except for an on-treatment sensitivity analysis of the primary outcome. The proportions of patients developing the primary outcome were compared using the Pearson chi-square test. The relative risks associated with methylprednisolone and their 95% CIs were calculated. Another sensitivity analysis was performed using a worst-case scenario approach where all patients with missing data for the primary outcome in the methylprednisolone group were hypothesized to have developed persistent incisional pain, whereas no patients in the placebo group were hypothesized to have incisional pain.

All secondary outcomes were compared using the Pearson chi-square test and nonparametric test, as the data were not normally distributed. No imputation was performed for missing data for the secondary outcomes.

We performed subgroup analyses using logistic regression for gender, age (both as categorical and continuous variables), BMI (both as categorical and continuous variables), history of chronic pain, and smoking status. *A priori*, we stated the expected direction of effect in the subgroups. The test of interaction between each

subgroup factor and the treatment group was done by including a product term in the model already containing treatment and the subgroup factor, designated as significant at $P < 0.05$.

We evaluated the association between smoking status and persistent incisional pain using logistic regression analysis. Other potential risk factors for persistent incisional pain were forced simultaneously in the regression model (age, gender, preoperative history of pain, BMI, deep postoperative surgical wound infection, and methylprednisolone). We assessed for colinearity using the variance inflation factor and tolerance statistics. A type 1 error of 0.05 was used for all analyses. Analyses were performed using IBM SPSS Statistics version 22 (IBM Corporation, USA).

Results

A total of 1,110 patients were recruited into this substudy of SIRS, for whom pain data were collected in 1,043; 523 patients were randomized to steroids and 520 to placebo. Twenty patients died before 6 months and therefore could not contribute to the primary outcome. For 34 patients, the primary outcome was missing. Surgery was cancelled in three enrolled patients who were all in the placebo group (fig. 1).

Demographic characteristics, coexisting medical conditions, and preoperative medications are presented in table 1. Patients randomized to steroid and placebo groups were well balanced on all of the baseline characteristics. The effect of steroid administration was similar across prespecified subgroups including age, sex, BMI, preoperative history of pain, and smoking status.

The primary outcome, incisional pain at 6 months, was reported by 166 of 1043 (15.9%) patients. Average pain intensity was 1.4 ± 1.6 (mean ± SD), worst pain intensity was 2.6 ± 2.3 (mean ± SD), and 64 (39%) of the patients who reported any pain were still using analgesic medication for pain at 6 months.

The use of methylprednisolone did not significantly affect persistent incisional pain at 6 months, which occurred in 78 of 520 patients (15.7%) in the methylprednisolone group and in 88 of 523 patients (17.8%) in the placebo group. The odds ratio for the methylprednisolone group was 0.93 (95% CI, 0.79 to 1.09, $P = 0.37$, table 2 and fig. 1). Furthermore, there was no difference in worst pain and average pain in the last 24 h, pain interference with daily life, or use of pain medicine at 6 months (table 3).

Administration of methylprednisolone also did not significantly impact the secondary outcomes. Pain at 30 days

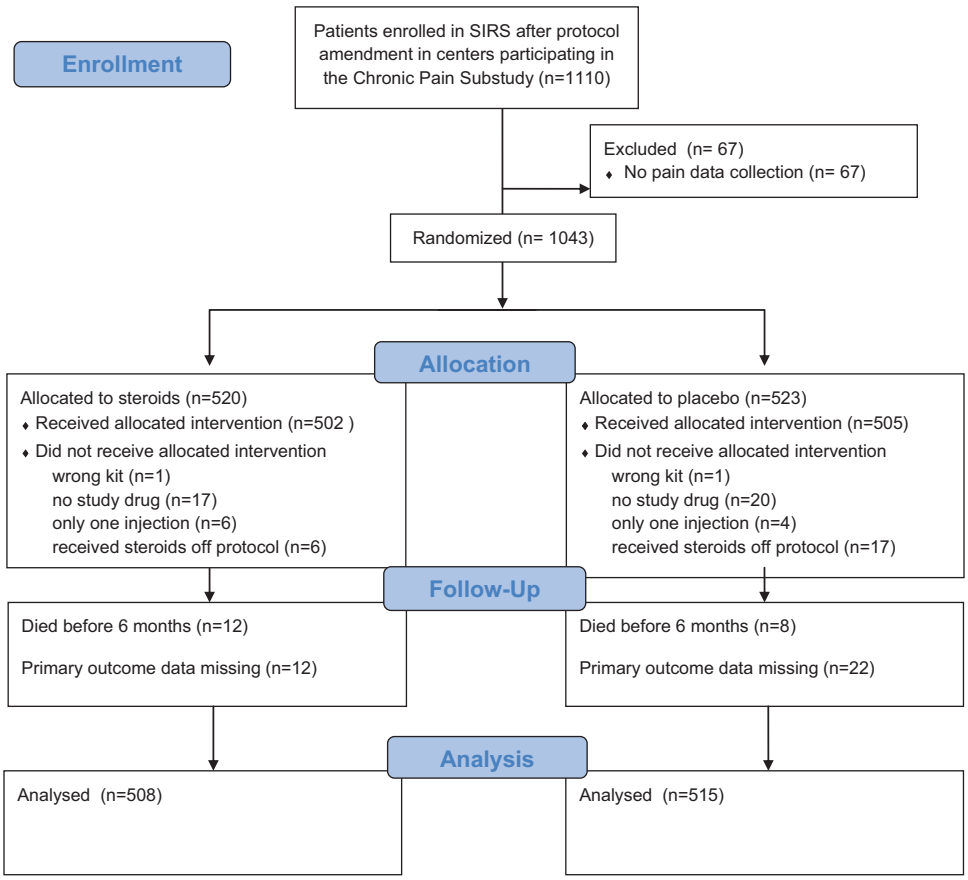

Fig. 1. Study flow diagram. SIRS = steroids in cardiac surgery.

Table 1. Baseline Characteristics of Patients

Characteristic	Methylprednisolone (N = 520)	Placebo (N = 523)	*P* Value
Demographics			
Age (SD)	71.1 (11.5)	71.4 (11.6)	0.70
Male (%)	308 (59.2)	301 (57.6)	0.58
Height (cm)	167.8 (10.4)	167.8 (10.5)	0.92
Weight (kg)	79.9 (19.8)	79.1 (19.2)	0.50
Coexisting medical conditions (%)			
Previous MI	127 (24.4)	126 (24.1)	0.90
Dialysis	33 (6.3)	37 (7.1)	0.87
Diabetes	148 (28.5)	129 (24.7)	0.17
Smoking status (%)			
Recent	58 (11.2)	63 (12.1)	0.84
Former	237 (45.8)	242 (46.4)	
Never	223 (43.1)	216 (41.5)	
EuroSCORE (mean)	7.33 (1.8)	7.30 (1.88)	0.78
Chronic pain	92 (17.7)	94 (18.0)	0.89
Operative			
Repeat cardiac surgery	107 (20.6)	97 (18.5)	0.41
Procedure (%)			
Isolated CABG	93 (17.9)	97 (18.7)	0.75
Isolated valve	196 (37.7)	207 (39.8)	0.48
Any valve procedure	393 (75.6)	390 (75.0)	0.83
Isolated aorta (without CABG or valve)	22 (4.2)	17 (3.3)	0.51
Other (not a valve, not a CABG, not an aorta)	4 (0.8)	3 (0.6)	1.0
Received treatment as assigned (%)			
Wrong kit	1 (0.2)	1 (0.2)	0.98
Only one injection	6 (1.2)	4 (0.8)	0.55
No study drug	17 (3.3)	20 (3.8)	0.63

CABG = coronary artery bypass graft; EuroSCORE = European System for Cardiac Operative Risk Evaluation; MI = myocardial infarction.

occurred in 247 of 503 patients (49.1%) in the methylprednisolone group and in 249 of 504 patients (49.4%) in the placebo group. The odds ratio for the methylprednisolone group was thus 0.99 (95% CI, 0.77 to 1.27, $P = 0.92$, table 2 and fig. 1). There was also no significant effect of methylprednisolone on worst or average pain in the last 24 h, pain interference with daily life, and use of pain medicine at 30 days (table 3). Sensitivity analyses did not show any change in results.

Only 26% of the pain reported at 30 days and 5% of the pain reported at 6 months had neuropathic characteristics. Methylprednisolone administration did not significantly affect the fraction of pain with neuropathic characteristics at 30 days (4.6 *vs.* 5.2%) or 6 months (0.3 *vs.* 0.7%).

Smoking status (recent, 12%; former, 46%; and never, 42%) did not significantly affect the incisional pain at 6 months. However, pain at 6 months was significantly related to younger age, female sex, and deep surgical site infections (tables 3 and 4).

Discussion

Almost half of the patients in this substudy reported incisional pain 1 month after surgery; but by 6 months, the overall prevalence of persistent incisional pain was 17%. Both the prevalence at 6 months and the reduction over time is consistent with previous work demonstrating a prevalence of 40% at 3 months and 22% at 6 months.[21] However, it is likely that

Table 2. Primary Outcomes at 6 Months

Primary Outcomes	Methylprednisolone	Placebo	RR (95% CI)	*P* Value
Primary: Persistent incisional pain at 6 mo (%)	78 (15.7)	88 (17.8)	0.88 (0.66–1.18)	0.37
Worst-case scenario: All patients lost to follow-up in the steroids group developed chronic pain	91 (17.9)	88 (17.8)	1.00 (0.76–1.32)	0.99
On treatment analysis: Patients in the steroids group who did not receive study drug changed to placebo, and patients in the placebo group who received at least one dose of steroids changed to the steroids group	81 (16.3)	85 (17.3)	0.94 (0.70–1.25)	0.66
Secondary: Persistent postsurgical pain at 30 d (%)	247 (49.1)	249 (49.4)	0.99 (0.77–1.27)	0.92

RR = relative risk.

Table 3. Secondary Outcomes in Patients Reporting Any Pain at 30 Days and at 6 Months

Secondary Outcomes	Methylprednisolone	Placebo	*P* Value
At 30 d			
Patients reporting any pain	247	249	
Overall MBPI			
Median	15 (6–28)	14 (7–27)	0.89
Mean	20.3 (18.4)	19.5 (16.8)	0.61
Worst pain in the last 24 h			
Median	4 (2–6)	4 (2–6)	0.71
Mean	4.1 (2.2)	4.3 (2.4)	0.28
Average pain in the last 24 h			
Median	2 (1–3)	2 (1–3)	0.94
Mean	2.4 (1.8)	2.3 (1.7)	0.57
Pain interference			
Median	6 (0–14)	6 (0–15)	0.76
Mean	10.7 (13.5)	9.9 (12.3)	0.48
Neuropathic pain (%)	24 (4.6)	27 (5.2)	0.68
Current usage of pain medicine (%)	203 (39.6)	191 (37.3)	0.46
Worst pain ≥ 4	140 (56.2)	145 (58.2)	0.73
Worst pain ≥ 6	66 (46.8)	75 (30.1)	0.40
At 6 mo			
In patients reporting any pain	78	88	
Overall MBPI			
Median	5.5 (2–14)	5 (2–13)	0.93
Mean	12.4 (18.0)	10.9 (14.9)	0.54
Worst pain in the last 24 h			
Median	2 (1–4)	2 (1–4)	0.57
Mean	2.6 (2.4)	2.5 (2.2)	0.68
Average pain in the last 24 h			
Median	1 (0–2)	1 (0–2)	0.78
Mean	1.4 (1.7)	1.4 (1.6)	0.83
Pain interference			
Median	1 (0–7)	1 (0–7)	0.88
Mean	6.7 (13.3)	5.6 (10.7)	0.54
Neuropathic pain (%)	3 (0.3)	7 (0.7)	0.34*
Current usage of pain medicine (%)	37 (47.4)	27 (30.7)	0.06
Worst pain ≥ 4	20 (25.6)	27 (30.7)	0.47
Worst pain ≥ 6	12 (15.4)	8 (9.1)	0.21

* Fisher exact test.

MBPI = modified brief pain inventory.

various factors other than elapsed time influence persistent pain including surgical and anesthetic techniques, postoperative analgesic management, and enhanced recovery pathways.

The intensity of persistent incisional pain was mild to moderate at 30 days, which gradually decreased and was mostly rated as low at 6 months, although 39% of the patients with pain continued to use pain medications. Even with current management approaches, one sixth of the patients in our study reported incisional pain 6 months after surgery. Although pain intensity among those reporting pain was not very high, analgesic use remained common. Therefore, our results suggest that persistent pain is a substantial and clinically meaningful risk of cardiac surgery with median sternotomy and should therefore be included among the risks disclosed to patients.

In contrast to our primary hypothesis, moderate-dose methylprednisolone (500 mg) did not reduce the prevalence of incisional pain at either 1 or 6 months after surgery. Furthermore, there was also no effect of methylprednisolone on worst pain and average pain scores, pain interference with daily life, or analgesic use at 1 or 6 postoperative months.

Our results are consistent with the single relevant previous study, a trial of methylprednisolone (125 mg) after augmentation mammoplasty, which also failed to demonstrate any benefit on persistent pain at 1 yr but decreased hyperesthesia.[22] Mammoplasty produces far less inflammation than median sternotomy and cardiopulmonary bypass. However, in that study, the overall reported prevalence of persistent pain was 13%. Furthermore, Romundstad *et al.*[22] only randomized 145 patients, which restricted their power for identifying potentially clinically important benefits. Although we included more than 1,000 patients, we are also limited in our power because of the observed low incidence of persistent pain (we have 90% power to detect a relative risk of less

Table 4. Logistic Regression Predicting Likelihood of CPSP at 6 Months

	B	SE	Wald	df	*P* Value	Odds Ratio	95% CI
Steroids	−0.172	0.177	0.946	1	0.331	0.842	0.596–1.190
Gender	0.589	0.187	9.908	1	0.002	1.80	1.249–2.601
BMI	0.002	0.015	0.017	1	0.897	1.002	0.972–1.033
Age	−0.029	0.007	16.108	1	< 0.001	0.971	0.958–0.985
Recent smoking	0.037	0.275	0.018	1	0.892	1.038	0.606–1.778
Former smoking	−0.374	0.210	3.165	1	0.075	0.688	0.455–1.039
Preoperative chronic pain	0.124	0.232	0.284	1	0.594	1.132	0.718–1.784
Deep surgical site infection	2.124	0.789	7.247	1	0.007	8.362	1.782–39.250
Constant	−0.290	0.790	0.135	1	0.713	0.748	

Reference for gender = male; reference for smoking = never.

B = slope; BMI = body mass index; CPSP = chronic postsurgical pain; df = degrees of freedom.

than or equal to 0.60 [40% reduction] using the observed incidence of 18% in the placebo group at the significance of 0.05).

Although methylprednisolone did not reduce the prevalence or intensity of incisional pain 1 or 6 months after cardiac surgery, it remains possible that steroids reduce persistent pain under other circumstances. Dose may matter; 500 mg is a moderate dose of steroids but may be insufficient to counter the enormous inflammatory response to median sternotomy and cardiopulmonary bypass. Duration may matter as well; we split the dose of methylprednisolone, with the second dose being given at initiation of bypass. Methylprednisolone is among the most effective antiinflammatory steroids, and its action probably lasted at least 3 days,[11,23] but the inflammatory response to surgery surely persisted much longer. It thus remains possible that steroid administration in higher doses or over a longer period might prove effective.

Another potential explanation for our negative results is simply that inflammation is not, in fact, a major cause of persistent incisional pain. However, immunosuppressive therapy in patients recovering from lung transplantation seems to reduce persistent pain,[24] suggesting that inflammation does contribute. It may be that some more specific (or intense) type of immunomodulation than that offered by steroids is necessary to reduce persistent pain.

Persistent surgical pain after sternotomy has been described as having predominantly neuropathic features. However, we found that among patients who reported persistent pain, only 10.3% at 1 month and 6% at 6 months seemed to be neuropathic. This fraction is considerably less than the previously reported 30 to 40% after sternotomy. We note, though, that we evaluated pain characteristics with the neuropathic pain questionnaire short form. This questionnaire is well validated,[18,19] but presumably more neuropathic pain will be identified with quantitative sensory testing in a clinic than with a phone questionnaire. Just as there was no overall benefit of methylprednisolone administration on persistent pain, there was no apparent effect on patients with neuropathic pain. However, our power to distinguish an effect of steroids was limited in this small subgroup.

We found that younger age, female sex, and deep surgical site infections were associated with development of persistent incisional pain, which is consistent with previous reports.[5,6,8] Others have reported that acute postoperative pain, psychologic factors, and anesthetic technique are also predictors, but we did not evaluate these factors in our patients.[5,6,8] Surprisingly, we did not find an association between smoking and persistent incisional pain, although several previous studies identified an association between smoking and various chronic pain conditions.[13,14] Furthermore, several small prospective studies report increases in analgesic consumption and pain after surgery in smokers.[25,26] The reported magnitudes were small, and the association between smoking and pain may be well confounded by psychologic factors, such as depression, that are hard to assess.

In summary, methylprednisolone is a corticosteroid with substantial antiinflammatory and analgesic properties that was hypothesized to ameliorate chronic persistent surgical pain. However, 500 mg of methylprednisolone given during cardiac surgery did not significantly reduce the incidence and intensity of persistent incisional pain at 30 days and 6 months. Steroids are unlikely to be used just to prevent *acute* pain because less-toxic drugs are available. But persistent pain is common after sternotomy and can markedly degrade quality of life for years. Steroids might thus well be considered if they markedly reduced the risk of persistent pain. There were compelling reasons to believe that they might because inflammation was believed to be an important cause of persistent pain. The fact that our best antiinflammatory drugs did not reduce the incidence of persistent pain suggests that other mechanisms dominate and that future research should be directed at strategies other than moderating inflammation. Smoking was not associated with likelihood of persistent incisional pain. However, younger age, female gender, and deep surgical site infections were associated with increased likelihood of persistent incisional pain at 6 months.

The results of the full SIRS trial show that methylprednisolone in patients undergoing cardiac surgery does not reduce mortality, a composite of serious complications, or the incidence of new-onset atrial fibrillation.[15] The results

of this substudy show that methylprednisolone also does not reduce the risk of persistent incisional pain.

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Competing Interests

The authors declare no competing interests.

Reproducible Science

Full protocol available at: richard.whitlock@phri.ca. Raw data available at: emilie.belley-cote@phri.ca.

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