Perioperative Statin Use May Reduce Postoperative Arrhythmia Rates After Total Joint Arthroplasty

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Abstract

Background: Postoperative arrhythmias are associated with increased morbidity and mortality in total joint arthroplasty (TJA) patients. HMG-CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitors (statins) decrease atrial fibrillation rates after cardiac surgery, but it is unknown if this cardioprotective effect is maintained after joint reconstruction surgery. We aim to determine if perioperative statin use decreases the incidence of 90-day postoperative arrhythmias in patients undergoing primary TJA.

Methods: We performed a single-center retrospective cohort study in which 231 primary TJA patients (109 hips, 122 knees) received simvastatin 80 mg daily during their hospitalization as part of a single surgeon's standard postoperative protocol. This cohort was matched to 966 primary TJA patients (387 hips and 579 knees) that did not receive simvastatin. New-onset arrhythmias (bradycardia, atrial fibrillation/tachycardia/flutter, paroxysmal supraventricular tachycardia, and ventricular tachycardia) and complications (readmissions, thromboembolism, infection, and dislocation) within 90 days of the procedure were documented. Categorical variables were analyzed using Fisher's exact tests. Our study was powered to detect a 3% difference in arrhythmia rates.

Results: Within 90 days postoperatively, arrhythmias occurred in 1 patient (0.4%) who received a perioperative statin, 39 patients (4.0%) who did not receive statins ($P = .003$), and 24 patients (4.2%) who were on outpatient statins ($P = .005$). This is 10-fold reduction in the relative risk of developing a postoperative arrhythmia within 90 days of arthroplasty and an absolute risk reduction of 3.6%.

Conclusion: Treating as few as 28 patients with perioperative simvastatin prevents one new cardiac arrhythmia within 90 days in statin-naïve patients undergoing TJA.

Keywords

total joint arthroplasty; total knee arthroplasty (TKA); total hip arthroplasty (THA); arrhythmia; statin; atrial fibrillation

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In 2014, an estimated 680,000 total knee arthroplasties (TKAs) and 370,000 total hip arthroplasties (THAs) were performed in the United States [1]. By 2030, these numbers are expected to grow 85% and 71% [1], respectively, so perioperative medical optimization is critical to improving outcomes and minimizing costs. Postoperative arrhythmias are associated with increased morbidity, mortality, length of stay, and readmissions in total joint arthroplasty (TJA) patients [2–4]. Arrhythmias occur in as high as 6% of patients after TJA [5], and risk factors include older age, male gender, hyperthyroidism, hypertension, diabetes, coronary artery disease, heart failure, chronic kidney disease, and chronic obstructive pulmonary disease [6].

The inflammation and stress response from surgery cause increased hormonal and sympathetic activity that may predispose some patients to arrhythmias [7]. Both corticosteroids and nonsteroidal anti-inflammatory medications decrease the incidence of postoperative arrhythmias after cardiac surgery [8,9]. However, given the effects of these medications on wound healing [10] and bleeding [11], 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors (eg, statins) have been investigated due to their anti-inflammatory and antiarrhythmic properties [12–16].

Statins are widely used to treat hypercholesterolemia due to their inhibition of HMG-CoA reductase in the liver [17]. However, statins are "pleiotropic" and have a number of other beneficial effects [17]. Statins have been found to reduce serum C-reactive protein (CRP) concentrations in both healthy people and those with chronic diseases [15], as well as decrease pulmonary arterial smooth muscle cells' response to CRP in vitro [12]. Potential mechanisms include suppression of toll-like receptor 4 expression on immune cells [13], as well as the nuclear factor-kB pathway, which is involved in the production of proinflammatory cytokines [14,18]. In addition, statins have been shown to decrease the beta-adrenergic response of cardiac myocytes via reduced isoprenylation of G-protein γ-subunits [19].

Several clinical trials have demonstrated that preoperative statin use decreases postoperative atrial fibrillation in the setting of both cardiac [20–30] and noncardiac surgery [25,31]. There are limited data regarding the use of statins in the TJA population. In a recent, large retrospective review of Medicare patients, Chen et al [5] found that statin use is associated with less postoperative cardiac arrhythmia after THA. In this study, all patients were on a statin for at least 1 year prior to their procedure and also had significantly more preoperative medical comorbidities. Our study aims to determine if perioperative statin use in statin-naïve patients decreases the incidence of 90-day postoperative arrhythmias after primary TJA.

Materials and Methods

Samples

We performed a single-center retrospective cohort study from 2014 to 2018 in which 231 primary TJAs (109 hips and 122 knees) received simvastatin 80 mg daily beginning the day of their procedure and continuing each day of hospitalization as part of a single surgeon's standard perioperative protocol. This cohort was matched to 966 primary TJAs (387 hips and

579 knees) that did not receive simvastatin perioperatively. We also identified 572 primary TJA patients (164 hips and 408 knees) who were already on an outpatient statin medication, which was continued during their hospitalization. Exclusion criteria included revision TJA, uni-compartmental TKA, and oncologic procedures. All surgeries were performed by 4 fellowship-trained, board-certified adult reconstruction surgeons. For THA, 3 surgeons used a posterior approach, while 1 used an anterolateral approach. Specific implants varied based on surgeon preference and patient anatomy with the goal of restoring leg length and offset. For TKA, a medial parapatellar approach was used in all cases. One surgeon used computer navigation, while the others used a measured resection technique based on patient anatomy. Although implants also varied based on surgeon preference, a cemented, posterior-stabilized design with patellar resurfacing was used for the majority of cases.

Measures

Patients were identified by medical record numbers, and all measures were drawn from the electronic health records. Demographic variables included gender and age. Health variables included body mass index (BMI), American Society of Anesthesiologist (ASA) classification, history of atrial fibrillation, history of beta-blocker, prior statin medication, and diagnosis (Table 1). New-onset arrhythmias (eg, bradycardia, atrial fibrillation, atrial tachycardia, atrial flutter, paroxysmal supraventricular tachycardia, and ventricular tachycardia) within 90 days of the index procedure were documented in physician progress notes (Table 2). Complications included 90-day readmissions, venous thromboembolism, infection, and dislocation (Table 3). A systematic chart review was performed for each patient for any documentation of the aforementioned arrythmias and complications, including the use of the global search function, as well as individual review of inpatient progress notes and clinic follow-up notes within 90 days.

Statistical Analysis

The primary analysis examined differences between the perioperative statin group and the no-statin group. Descriptive statistics were reported for gender, history of atrial fibrillation, and diagnosis. Differences between the groups were compared using the chi-squared (χ^2) and Fisher's exact tests. Means and standard deviations (SD) were reported for age, BMI, and ASA classification and differences by statin use were compared using independent samples t-tests. Postoperative total arrhythmia and atrial fibrillation rates were examined for all patients, patients without a history of atrial fibrillation, and patients without a history of a beta-blocker. Differences by statin use were examined using Fisher's exact tests. Number needed to treat was calculated by taking the inverse of the absolute risk reduction. Complications, including venous thromboembolism and infection as well as 90-day read-mission, were calculated and differences by statin use were examined using Fisher's exact tests.

Two sets of exploratory analyses were conducted following the same analysis plan described for the primary analyses. First, patients who were started on perioperative statins were compared to patients who were already on a statin medication as an outpatient (prior statin use). Second, patients who had no history of statin use (prior or perioperatively) were compared to all patients who were taking statin medications during their hospitalization

(prior and perioperatively). All analyses were conducted in R and RStudio using the psych R package, with statistical significance set at $P < .05$ [32–34].

Results

In total, 231 primary TJAs (109 hips and 122 knees) received simvastatin 80 mg daily beginning the day of their procedure and continuing each day of hospitalization as part of a single surgeon's standard perioperative protocol. On average, these patients received 3.39 doses (SD 1.11) of the statin prior to discharge. Thirty-nine of 966 arthroplasty patients (4.0%) who did not receive a perioperative statin developed a postoperative arrhythmia, and only 1 of 231 arthroplasty patients (0.4%) who received a perioperative statin developed a postoperative arrhythmia ($P = .003$; Table 2). When eliminating patients on beta-blockers or with a history of atrial fibrillation, patients who were started on statins perioperatively similarly had lower postoperative arrhythmia rates than patients not on any statins, although not statistically significant ($P = .069$ and $P = .225$, respectively; Table 2).

Patients who were taking statins prior to their surgery also developed significantly more postoperative arrhythmias (n = 24, 4.2%) than statin-naïve patients who were started on statins perioperatively (n = 1, 0.4%, $P = .005$). There was no significant difference in arrhythmia rates when comparing patients who did not receive any statins to all patients who were taking statin medications during their hospitalization (prior and perioperatively) ($P = .309$). There was no difference in age ($P = .917$), BMI ($P .219$), or history of atrial fibrillation ($P = .621$) between patients who received perioperative statin dosing and those with no statins (Table 1). The average length of stay for patients in the perioperative statin group (2.39 days, SD 1.11) was shorter than patients not taking a statin (2.77 days, SD 0.92, $P < .001$) and patients who were taking statins prior to surgery (2.83 days, SD 0.83, $P < .001$; Table 1). Statin use was not associated with any differences in 90-day readmissions ($P = .107$), venous thromboembolism ($P = 1.00$), infection ($P = .819$), or dislocation ($P = .322$; Table 3). There were no reported side effects of perioperative statin dosing, including unexplained myalgias, new-onset diabetes, and cognitive decline.

Discussion

Although statins are commonly used to treat hypercholesterolemia, several clinical trials [20–30] demonstrate that statins decrease rates of postoperative atrial fibrillation. Data regarding statin use in the TJA population are limited; therefore, we aimed to determine the effect of perioperative statin use on postoperative arrhythmias in patients undergoing primary TJA. In our study, statin-naïve patients who were started on statins perioperatively were found to have a 10-fold reduction in the relative risk of developing a postoperative arrhythmia within 90 days of arthroplasty. This is an absolute risk reduction of 3.6% and indicates that treating as few as 28 patients with perioperative simvastatin has the potential to prevent one new cardiac arrhythmia postoperatively.

Our data further support the growing evidence that statins have pleiotropic anti-inflammatory properties and are not just a cholesterol-inhibiting drug. Sicouri et al [35] showed that simvastatin exhibits a direct antiarrhythmic effect on pulmonary vein tissue

in canines. Milajerdi et al [15] found that statin use was associated with a reduction in serum CRP concentrations, and Li et al [12] found that pulmonary arterial smooth muscle cells incubated with atorvastatin secreted significantly less interleukin 6 and monocyte chemoattractant protein 1 when stimulated by CRP. They concluded that atorvastatin has an inhibitory effect on the CRP-induced nuclear factor-kB pathway. In addition, Mühlhäuser et al [16] found that atorvastatin reduces the B-adrenergic responsiveness of cardiac myocytes. This effect is similar to beta-blockers and may contribute to the mortality reduction that has also been associated with statin use [36,37].

Clinically, the effect of statins on arrhythmias following cardiac surgery has been extensively studied in the literature. Six randomized controlled trials involving 1180 patients found a statistically significant beneficial effect of prophylactic statins on the incidence of postoperative atrial fibrillation [20–25]. Atorvastatin 40 mg/d for 7 days had the largest effect in preventing arrhythmias, with an absolute risk reduction of 22% ($P = .017$) compared to placebo [25]. These studies concluded that the anti-inflammatory effect of statins makes them protective against postoperative atrial fibrillation following cardiac surgery.

The positive outcomes in the cardiac literature lead to the investigation of the potential effect of statins on arrhythmia development after various noncardiac surgeries. In a retrospective review of 370,447 patients, Bhave et al [31] found statin use in non-cardiac surgeries to be associated with a significantly lower postoperative atrial fibrillation rate (2.6%) compared to those patients who were not taking statins (3.0%). Oesterle et al [38] recently performed a meta-analysis reviewing different prophylactic agents against postoperative atrial fibrillation in noncardiac surgeries. Statins were found to reduce the incidence of postoperative atrial fibrillation vs a placebo, with an absolute risk reduction of 10% and number needed to treat of 10.

To our knowledge, only one other study has evaluated the effect of statins on postoperative arrhythmias specifically in the TJA population. Chen et al [5] found that statin use is associated with less postoperative cardiac arrhythmia after THA. In this study, statin users were identified by searching prescription bills within 1 year prior to their procedure and included the following generic names: atorvastatin, fluvastatin, lovastatin, pravastatin, pitavastatin, and simvastatin. New-onset cardiac arrhythmias within 90 days were identified using International Classification of Diseases, Ninth Revision codes, and the incidence after THA was 5.4% in statin users vs 6.3% in patients not on statins ($P = .001$). These results are comparable to our study in which we found a postoperative arrhythmia rate of 4.0% in patients who did not receive a statin and 4.2% in patients who were on a long-term statin. More notably, we found that the postoperative arrhythmia for statin-naïve patients who were started on a statin perioperatively was only 0.4%. Not only was this reduction in the number of arrhythmias significant when compared to patients who were not on statins at the time of surgery, but it also remained significant when compared to patients who were already on a statin as an outpatient medication.

The findings of this study suggest that patients who are on outpatient statins and those who are started on statins perioperatively may represent two distinct populations. Statin

use is associated with diabetes, hypertension, angina, and congestive heart failure [39], and patients on statins tend to have more preoperative medical comorbidities than nonstatin users [5]. In our cohort, patients already on a statin as an outpatient tended to have higher ASA grades than patients who were started on a statin perioperatively (58% vs 48% ASA 3; Table 1), which could make them more susceptible to postoperative arrhythmias. However, we also found that patients who were not on any statins (preoperatively or perioperatively) had lower ASA grades (38% ASA 3) but similar rates of postoperative arrhythmias to the prior statin group. This suggests that the protective benefit of statin use may be limited to statin-naïve patients in the acute setting. A number of studies have shown that the acute administration of statins has cardioprotective effects, including reduction of infarct size in animal models [40] and decreased mortality when administered within the first 24 hours after acute myocardial infarction [41,42]. One proposed mechanism involves activating the phosphatidylinositol-3 kinase pathway [43], which reduces ischemia and reperfusion injury by activating endothelial nitric oxide synthase 3, mitochondrial adenosine triphosphate-dependent potassium channel activation, and mitochondrial permeability transition pore inhibition [44]. Mensah et al [45] demonstrated that atorvastatin reduced infarct size when given for less than 3 days before an ischemic event, but lost its cardioprotective effect when administered for 1 or 2 weeks before ischemia. In this study, longer term statin treatment was associated with upregulation of phosphatase and tensin homolog deleted on chromosome ten (PTEN), a protein phosphatase that inhibits phosphatidylinositol-3 kinase pathway [46]. This is similar to a study by Zelvyte et al [47] that showed chronic statin treatment resulted in increased activity of peroxisome proliferator-activated receptor gamma in monocytes, which similarly increases PTEN expression. The authors concluded that although acute statin treatment may increase phosphatidylinositol-3 kinase activity, chronic statin treatment may counteract phosphatidylinositol-3 kinase activation, and its cardioprotective effects, by increasing PTEN expression. At our institution, patients are now routinely started on simvastatin 80 mg beginning the day of their surgery and are continued on it while in the hospital. Thus, the effect of statins in this cohort can be attributed to their acute administration in the perioperative setting.

There are several limitations to this study. Surgeon selection bias is present given that the perioperative statin protocol was employed by a single surgeon (D.F.A.) at our institution. We were unable to control for this in a multivariate regression model, since the outcomes in question were so rare. Nonetheless, we did not find any significant differences between the perioperative and no-statin groups with regard to age, BMI, or history of atrial fibrillation. There was a difference between groups with regard to ASA grade, particularly with regard to ASA class 3 (47.2% of perioperative statin patients vs 38.1% of patients not on statins; Table 1). However, this supports the positive benefit of statins given that the perioperative statin group had less postoperative arrhythmias despite having more medical comorbidities. In addition, the arrhythmia and complication rates may be underestimated as our chart review will only reflect complications seen at our institution or those documented in the patient chart. Because patients in the perioperative statin group were discharged earlier, it is possible that there were subclinical or unrecognized arrhythmias that occurred when they were being monitored less closely at home. The timing and duration of each postoperative arrhythmia episode was also unavailable for review, which would have provided further insight into the

clinical significance of the event. There also may be multiple factors that may confound our results, including use of antiarrhythmic medications or other medical comorbidities. Our sub-group analyses when controlling for beta-blockers and history of atrial fibrillation, did not show a protective benefit of perioperative statin use, but they had a strong trend toward significance. This suggests that the loss of an effect in these sub-group analyses is a result of the reduction in cohort size. We also recognize that not all arrhythmias are of similar clinical significance and that we relied on accurate documentation of these episodes in physician progress notes. Finally, given the retrospective nature, there is an inherent selection bias that would best be addressed with a multicenter, blinded, randomized controlled trial.

Conclusion

Perioperative statin use may reduce postoperative arrhythmia rates in statin-naïve patients undergoing primary TJA. Treating as few as 28 patients with perioperative simvastatin has the potential to prevent one new cardiac arrhythmia within 90 days. This is a low risk addition to the current oral perioperative regimen and warrants accelerated investigation in a multicenter, blinded, randomized clinical trial.

Source of Funding:

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Table 1

Total Joint Arthroplasty Demographic Characteristics.

Variable	No Statin (n = 966)	Prior Statin (n = 572)	Perioperative Statin (n = 231)	Perioperative Statin vs No Statin P-Value	No Statin vs Perioperative + Prior Statin P-Value	Perioperative Statin vs Prior Statin P-Value
Gender				.013	.002	.581
Female (%)	621 (64.2%)	330 (57.7%)	128 (55.4%)			
Male (%)	344 (35.6%)	241 (42.1%)	103 (44.6%)			
Age	63.09 (12.74)	71.01 (9.26)	63.18 (11.47)	.917	<.001	<.001
BMI	29.65 (6.28)	30.18 (5.67)	30.18 (5.88)	.219	.060	1.00
ASA				.012	<.001	<.001
1	59 (6.1%)	0 (0.0%)	12 (5.2%)			
2	538 (55.7%)	242 (42.3%)	108 (46.8%)			
3	368 (38.1%)	326 (57%)	109 (47.2%)			
4	1 (0.1%)	4 (0.7%)	2 (0.87%)			
History of AF (%)	51 (5.3%)	64 (11.2%)	10 (4.3%)	.621	.001	.003
Length of stay (d), mean (SD)	2.77 (0.92)	2.83 (0.83)	2.39 (1.11)	<.001	.151	<.001

AF, atrial fibrillation; ASA, American Society of Anesthesiologists; BMI, body mass index; SD, standard deviation.

Table 2

Total Joint Arthroplasty 90 d Postoperative Arrhythmia Rates.

Variable	No Statins	Prior Statins	Perioperative Statin Use	Perioperative Statin vs No Statin *P*-Value	No Statin vs Perioperative + Prior Statin *P*-Value	Perioperative Statin vs Prior Statin *P*-Value
All patients	(n = 966)	(n = 572)	(n = 231)			
Total arrhythmia (%)	39 (4.0%)	24 (4.2%)	1 (0.4%)	.003	.309	.005
AF (%)	20 (2.1%)	12 (2.1%)	1 (0.4%)	.100	.597	.184
Patients without a history of AF	(n = 915)	(n = 508)	(n = 221)			
Total arrhythmia (%)	25 (2.7%)	19 (3.7%)	1 (0.5%)	.225	.245	.035
AF (%)	10 (1.1%)	3 (0.6%)	1 (0.5%)	.702	.287	1.00
Patients without a history of a beta-blocker	(n = 828)	(n = 404)	(n = 175)			
Total arrhythmia (%)	29 (3.5%)	16 (4.0%)	1 (0.6%)	.069	.649	.069
AF (%)	14 (1.7%)	7 (1.7%)	1 (0.6%)	.047	.648	.070

AF, atrial fibrillation.

Table 3

Total Joint Arthroplasty Complications and Readmission Rates.

Variable	No Statins (n = 966)	Prior Statins (n = 572)	Perioperative Statin (n = 231)	Perioperative Statin vs No Statin *P*-Value	No Statin vs Perioperative + Prior Statin *P*-Value	Perioperative Statin vs Prior Statin *P*-Value
90-d readmission (%)	38 (3.9%)	31 (5.4%)	15 (6.5%)	.107	.092	.615
MUA (%)	7 (0.7%)	2 (0.3%)	3 (1.3%)	.417	1.00	.498
VTE (%)	15 (1.6%)	10 (1.7%)	3 (1.3%)	1.00	1.00	1.00
Infection (%)[a]	26 (2.7%)	19 (3.3%)	5 (2.2%)	.819	.774	.798
Dislocation (%)[b]	5 (0.5%)	1 (0.6%)	2 (1.9%)	.322	1.00	.483

MUA, manipulation under anesthesia; VTE, venousthromoembolic event.

[a] Infections included both superficial and deep wound infections, urinary tract infections, respiratory and gastrointestinal infections.

[b] Total hip arthroplasty patients only.