



Perioperative Glucocorticoids in Patients With Rheumatoid Arthritis Having Total Joint Replacements: Help or Harm?

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Objective. The optimal strategy for perioperative glucocorticoid (GC) management in patients with rheumatoid arthritis (RA) on chronic GCs is unknown. Although there is a concern for hypotension if inadequate doses are used, higher GC exposure may increase perioperative complications. We aimed to investigate the relationships between perioperative GCs with hemodynamic instability and short-term postoperative complications following total hip arthroplasty (THA) and total knee arthroplasty (TKA) in patients with RA.

Methods. This retrospective study included patients with RA who underwent THA and TKA. GC exposure was assessed by the total cumulative dose (in prednisone equivalents) during hospitalization. Perioperative complications and hypotension were assessed.

Results. Of 432 patients, 387 (90%) received supraphysiologic perioperative GC. Thirty percent of patients were using chronic GCs (mean daily dose, 7 ± 4 mg). Half (54%) underwent TKA. The median age was 65 years, and 79% were women. The median cumulative GC dose during hospitalization was 37 mg (interquartile range, 27–53.3). A lower cumulative dose of GC did not increase odds of hypotension during hospitalization (unadjusted odds ratio, 1.00 [95% confidence interval, 0.99–1.01]; $P = 0.66$). However, postoperative complications were higher among patients who received higher cumulative doses after adjustment for age, body mass index, home GC use, smoking, and Charlson Comorbidity Index. Risk of short-term complications increased by 8.4% ($P = 0.017$) for every 10-mg increase in GC dose.

Conclusion. A lower GC dose was not associated with increased hypotension. However, patients with higher GC exposure were more likely to have hyperglycemia and other complications. These findings suggest that harms may be associated with high perioperative GC doses. Further research is needed to determine the optimal perioperative regimen for patients with RA.

INTRODUCTION

Glucocorticoids (GCs) are often used perioperatively to reduce postoperative nausea, vomiting, and pain in patients with or without chronic GC use and to reduce hemodynamic instability for patients chronically treated with GCs (1). The optimal dose is unknown and may differ in those receiving chronic GC therapy. This is a particularly critical issue for patients with rheumatoid arthritis (RA), in whom GCs remain an essential part of treatment despite the widespread use of disease-modifying antirheumatic drugs

(DMARDs). This is also a population that often requires total joint arthroplasty (TJA) because of destructive disease (2,3). Patients with the most active disease who require GCs are also often those who also undergo TJA; in a recent study, 32% of patients with RA presenting for TJA were using chronic GCs (4). These patients may also be at an increased risk for postoperative infection. Some prior reports have found an increased risk of postoperative infection in patients with RA whose chronic daily prednisone dose was greater than 10 mg (5–9). In addition, RA disease activity has been shown to be associated with negative outcomes, including

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increased mortality (10). However, little is known about the overall risk–benefit profile of perioperative GCs in patients with RA.

Hypotension is a well-recognized risk of inadequate GC replacement in patients with primary or secondary adrenal insufficiency. Prior studies have demonstrated that stress-induced adrenal crisis during and after surgery in patients treated chronically with GC is infrequent but has been reported when the GC dose is withheld for 18 to 36 hours prior to surgery (11,12). Whether stress doses are necessary for patients taking chronic low doses of GCs undergoing elective total hip arthroplasty (THA) or total knee arthroplasty (TKA) in the setting of modern anesthetic and surgical techniques is questionable. However, the management of perioperative GCs in patients who do not have adrenal insufficiency is quite variable in clinical practice. In patients with adrenal insufficiency undergoing TJA, intravenous hydrocortisone (25 mg every 8 hours) is recommended until recovery from surgery by some guidelines (13). However, there is limited evidence to guide optimal perioperative GC dosing regimens in patients with RA on

chronic low-dose GC therapy (14). The 2017 American College of Rheumatology guidelines recommend continuing the same chronic GC dose perioperatively in patients receiving a daily dose of prednisone or equivalent that is less than 20mg (2). However, higher doses of GCs are often administered to avoid potential relative adrenal insufficiency and to prevent nausea and vomiting. These high doses may increase the risk of adverse events, including hyperglycemia, which has been associated with postoperative complications, length of stay, and mortality (15–18).

In addition, the impact of perioperative GC dosing regimen on early surgical outcomes is not known in individuals with RA. We performed this retrospective cohort study to investigate the relationships between GC exposure during hospitalization (cumulative prednisone equivalent dose) and short-term outcomes following TJA. We hypothesized that patients with RA undergoing THA or TKA who had greater perioperative GC exposure would have less hypotension but higher rates of postoperative complications.

Table 1. Baseline characteristics of the cohort

Variables	Steroids (N = 387)	No Steroids (N = 45)	P Value
Age, years	65 [57.0-71.0]	65 [69.0-72.0]	0.61
Female, sex, n (%)	305 (79%)	30 (67%)	0.06
Race, n (%)			0.10
White	304 (79)	40 (89)	-
Black	36 (9)	2 (4)	-
Other	41 (11)	3 (7)	-
Declined	6 (2)	-	-
Ethnicity group, n (%)			0.92
Hispanic or Latino	31 (8)	4 (9)	-
Not Hispanic or Latino	350 (90)	40 (89)	-
Declined	6 (2)	1 (2)	-
Body mass index, kg/m ²	28.4 [24.4-32.9]	28.3 [24.6,-33.5]	0.99
Surgery type, n (%)			0.82
Hip replacement	179 (46)	20 (44)	-
Knee replacement	208 (54)	25 (56)	-
Anesthesia type, n (%) ^e			0.17
Regional	345 (89)	43 (96)	-
Peripheral nerve block	2 (1)	-	-
Neuroaxial nerve block	21 (5)	-	-
General	19 (5)	2 (4)	-
Charlson Comorbidity Index	1.0 [1.0-2.0]	1.0 [1.0-2.0]	0.12
Diabetes, n (%)	34 (9)	8 (18)	0.05
Home insulin use, n (%)	6 (2)	1 (2)	0.74
Insulin administered during admission, n (%)	30 (8)	8 (18)	0.03
Systolic blood pressure prior to surgery	132 [121-145]	130 [118,-143]	0.44
Antirheumatic medications, n (%)			
TNF inhibitors	99 (26)	13 (29)	0.63
Non-TNF biologics	47 (12)	8 (18)	0.28
Conventional synthetic DMARDs	269 (70)	26 (58)	0.11
Chronic home GC (prednisone equivalent) use, n (%)	129 (33)	N/A	-
Mean dose, mg ± SD	7 ± 4	N/A	-
Number of GC doses over entire admission	1.0 [1.0-4.0]	N/A	-
Cumulative GC dose (prednisone equivalent) over entire admission, mg	36.7 [26.7-53.3]	N/A	-
Number of patients who received only one GC dose, n (%)	238 (61)	N/A	-

Abbreviation: DMARD, disease-modifying antirheumatic drug; GC, glucocorticoid; N/A, not applicable; TNF, tumor necrosis factor.

PATIENTS AND METHODS

A retrospective review of the electronic medical record was conducted to identify patients with RA who underwent elective THA or TKA at our institution between February 1, 2016, and July 1, 2018. Patients with confirmed RA who were over the age of 18 and were undergoing primary THA or primary TKA were eligible. Revision and bilateral procedures were excluded. We used the International Classification of Disease (ICD) codes for RA to screen records. RA diagnosis was confirmed if one of the following criteria was met: 1) the RA ICD code was entered by a rheumatologist at our institution and/or 2) patients had the diagnosis code for RA and were taking or had ever previously taken one or more DMARDs. This study was approved by the Hospital for Special Surgery Institutional Review Board.

Data pertaining to demographics, medications, comorbidities, and type of anesthesia were collected. The Charlson Comorbidity Index was calculated from ICD-10 codes as previously described (19). All GC doses were converted to prednisone equivalents. GC exposure during hospitalization was assessed by the total cumulative prednisone-equivalent dose during the hospitalization. The chronic home GC dose was recorded. All patients received their chronic home GC dose on the day of surgery either at home or in the hospital the morning of the procedure, as per institutional guidelines. All patients received preoperative antibiotic prophylaxis.

The primary outcomes were postoperative hypotension (systolic blood pressure <90 mm Hg) and short-term in-hospital postoperative complications. Short-term complications were defined as any of the following: myocardial infarction, catheter-associated urinary tract infection (CAUTI), deep vein thrombosis, pulmonary embolism, mechanical complications, prosthetic joint infection (PJI), pneumonia, sepsis, surgical site infections (SSIs), wound complications, bleeding, and hyperglycemia. Mechanical complications included joint dislocation, broken prosthetic joint implant, and periprosthetic fracture around the prosthetic joint. Hyperglycemia was defined as a serum or point-of-care blood glucose (BG) greater than or equal to 180 mg/dl. To determine the severity of hyperglycemia, the percentage of BG levels greater than or equal to 180 was calculated. The correlation between cumulative GCs during hospitalization and percentage of BG greater than or equal to 180 mg/dl was assessed. Other outcomes included length of stay and vasopressor use.

Statistical analysis. Descriptive statistics (including mean, SD, median, interquartile range [IQR], frequency, and percentage) were calculated to examine the baseline characteristics of the study sample where applicable. Univariate predictors of perioperative complications were assessed by the use of χ^2 tests or Fisher's exact test for categorical predictors and t test or Mann-Whitney U tests for continuous predictors.

Multivariable logistic regression analysis was used to evaluate the independent effect of Charlson Comorbidity Index, body mass index (BMI), age at admission, home GC use, and cumulative GC dose on the development of perioperative complications in patients

who received GCs during hospitalization. Predictors of the multivariable logistic regression model were included on the basis of clinical relevance or a significant univariate association between the variable and outcome. A two-sided *P* value of less than 0.05 was considered statistically significant for all tests. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the risk factors of interest were estimated from the multivariable model.

Statistical analyses were performed using R version 3.5.1 (R Foundation for Statistical Computing).

RESULTS

Baseline characteristics of subjects. Of 432 patients, 387 (90%) received supraphysiologic perioperative GCs. Forty-five patients (10%) did not receive any GCs during hospitalization. Approximately 30% of patients were using chronic GCs (mean daily dose, 7 ± 4 mg). Table 1 provides the baseline characteristics of our cohort. The median age was 65 years, and the BMI was in the overweight range (28 kg/m^2). Approximately half the cohort underwent TKA. The median cumulative perioperative GC dose was 37 mg (IQR, 27-53.3). The GCs administered included hydrocortisone, dexamethasone, and methylprednisone. Multiple doses of GCs were administered to 39% of patients. The median Charlson Comorbidity Index was 1.0 (IQR, 1.0-2.0), with 9% to 18% of subjects having diabetes. Only 2% had insulin-dependent diabetes. RA was managed by conventional synthetic DMARDs, tumor necrosis factor (TNF) inhibitors, and non-TNF biologics in 70%, 26%, and 12% of patients who received perioperative GCs, respectively. Baseline characteristics were similar among patients who did and did not receive GCs. However, those who did not receive any GCs tended to have a higher prevalence of diabetes and insulin use.

Perioperative complications. The incidence of perioperative hypotension in patients who received GCs during hospitalization was 14% compared with 11% in patients who did not receive perioperative GCs (*P* = 0.44). Vasopressors were used during hospitalization in 10% of patients who received perioperative GCs

Table 2. Perioperative complications and hyperglycemia in patients who received glucocorticoids during hospitalization

	Steroids	No Steroids	<i>P</i> Value
Hypotension, n (%)	55 (14)	5 (11)	0.57
Vasopressor use, n (%)	40 (10)	3 (7)	0.44
LOS, midnights [IQR]	3.0 [2.0-4.0]	3.0 [2.0-4.0]	
Complications	63	8	0.80
Hyperglycemia, n (%)	49 (78)	7 (88)	-
CAUTI, n (%)	6 (10)	0 (0)	-
Sepsis, n (%)	3 (5)	0 (0)	-
PJI, n (%)	2 (3)	0 (0)	-
SSI, n (%)	2 (3)	1 (12)	-
DVT, n (%)	1 (2)	0 (0)	-

Abbreviation: CAUTI, catheter-associated urinary tract infection; DVT, deep vein thrombosis; IQR, interquartile range; LOS, length of stay; PJI, prosthetic joint infection; SSI, surgical site infection.

Table 3. Multivariable logistic regression models predicting perioperative complications in patients who received glucocorticoid during hospitalization

Predictor	Adjusted Odds Ratio	95% CI	P Value
Charlson Comorbidity Index	1.85	1.39-2.51	<0.001
Age at admission	1.03	0.997-1.06	0.088
BMI	1.07	1.02-1.12	0.006
Cumulative GC dose	1.01	1.00-1.02	0.017
Chronic home steroid	1.22	0.62-2.36	0.564
Smoking	0.80	0.43-1.47	0.476

Abbreviation: BMI, body mass index; CI, confidence interval; GC, glucocorticoid.

(Table 2). In addition, a lower cumulative dose of GCs did not have greater odds of hypotension during hospitalization in patients who received perioperative GCs (unadjusted odds ratio, 1.00 [95% confidence interval, 0.99-1.01]; $P = 0.66$).

Sixty-three complications were observed in patients who received perioperative GCs (Table 2). In a multivariable logistic regression model, factors associated with any complication included: higher BMI (aOR, 1.07 [1.02-1.12]; $P = 0.006$), higher Charlson Comorbidity Index (aOR 1.85 [1.39-2.51]; $P < 0.001$), and higher cumulative GC dose during admission (aOR, 1.01 [1-1.02]; $P = 0.017$). Chronic home GC use was not associated with increased risks of any complication (home GC use: aOR, 1.22 [0.62-2.36]; $P = 0.564$) (Table 3). For every 10-mg increase in cumulative GC dose (prednisone equivalent), there was an 8.4% increase in the odds of a patient experiencing an early postoperative complication.

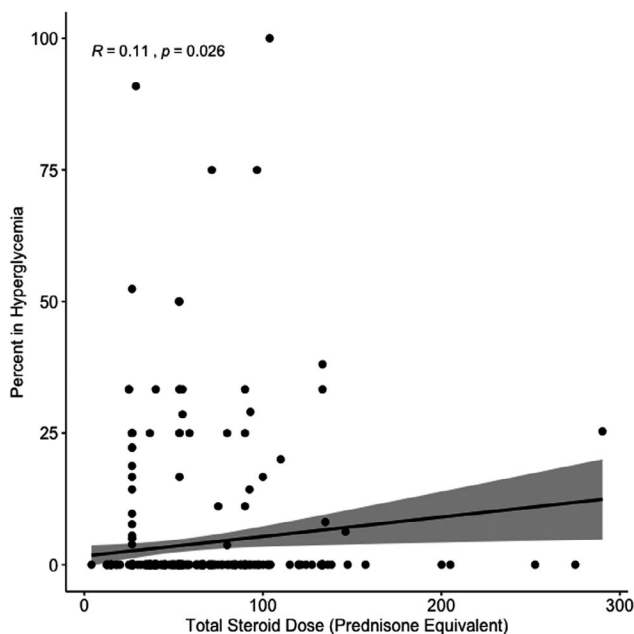


Figure 1. A correlation between total cumulative glucocorticoid dose and hyperglycemia (percent of blood glucose values greater than 180 mg/dl).

In patients who received GCs perioperatively, there was a small but significant dose-response relationship between the cumulative GC dose and the percentage of BG values greater than 180 mg/dl ($r = 0.11$; $P < 0.03$) (Figure 1).

DISCUSSION

In this study, we found that higher perioperative GC exposure in patients with RA was associated with a higher rate of early complications following TJA. In addition, a higher Charlson Comorbidity Index was significantly associated with a higher rate of complications. This relationship persisted even after adjustment for chronic home GC dose. In contrast, we did not find that patients who received fewer doses of GC had more hypotension.

The main infectious complication that we observed in patients receiving GCs perioperatively was CAUTI. It is notable that, although CAUTI was observed in six patients who received steroids, there were no cases among patients who did not, although the numbers were too small to detect a statistically significant difference.

Further investigation into this topic is of importance, as CAUTI is a potentially serious postoperative complication that can contribute to a longer length of stay, urosepsis, and penalization by the Centers for Medicare and Medicaid Services. Although we observed a few infectious complications, such as postoperative PJI, sepsis, and SSI, the number was low because we did not have a long duration of follow-up. We also did not have the sample size necessary to achieve the power needed to assess these variables individually. Surprisingly, we did record two episodes of PJI in our brief follow-up period. In two previous studies in non-RA populations, a single perioperative dose of dexamethasone did not increase the overall rate of prosthetic joint infections in patients undergoing THA or TKA (18;20-22). Our results suggest that risks may be additive and that there may be negative consequences associated with higher cumulative GC doses in patients with RA.

In our cohort, we demonstrated a small but significant positive linear correlation between the cumulative GC dose during hospitalization and the percentage of random BG greater than 180 mg/dl. This indicates that patients who received a higher cumulative GC dose were hyperglycemic for longer periods. The impact of GCs on BG and other complications is likely more significant in patients with more severe diabetes at baseline. Previous studies have demonstrated that perioperative hyperglycemia is strongly associated with increased hospital complications, LOS, and mortality in patients undergoing noncardiac surgery (17). They support adherence to the American Diabetes Association recommendation of a target BG of less than 180 mg/dl in hospitalized patients (23). Although the incidence of hyperglycemia was similar between the two groups, it is possible that providers chose not to administer perioperative GCs to patients with more poorly controlled diabetes. We did observe a greater prevalence of diabetes

as well as insulin administration during the hospital stay among that group. In this study, we did not have the duration of follow-up or the sample size necessary to achieve the power needed to investigate the association between hyperglycemia and these complications.

There has been long-standing concern that withholding supraphysiologic GC doses (“stress-dose steroids”) might increase the risk of hypotension among patients on chronic GC therapy, such as patients with RA. Small studies have suggested that high GC doses administered at the time of TJA are associated with hemodynamic stability (24). We did not find this to be the case. Our findings are consistent with those of other studies in different surgical populations (25–27). Friedman et al showed that continuing chronic doses of GCs without additional perioperative GCs (mean, 10 mg) was not associated with adrenocortical insufficiency after major orthopedic surgery (28). It is important to emphasize that, although most patients who had a higher perioperative GC exposure were on chronic GC therapy, the mean chronic GC dose and the risk of hypotension in our cohort were not high enough to meet the American College of Rheumatology (ACR) recommendations for high perioperative GC doses to prevent hypotension (2). Of note, the ACR uses a consensus method for guidelines when there is little published evidence (2). However, higher doses than those recommended by guidelines were administered because of theoretical concern for prevention of adrenal crisis or for other indications (eg, providing analgesia and prevention of nausea and vomiting). The effects on hypotension should be further explored in future studies investigating patients at increased risks of adrenal insufficiency.

There are several limitations of this study, including its retrospective design. Importantly, GC dose and frequency were determined on the basis of an individual provider preference, which may have introduced bias to the findings. It is possible that the decision to administer more GCs was determined on the basis of other clinical factors not captured in our retrospective design. We could not account for individual provider practices in our analysis because of the high number of providers at our institution (35 arthroplasty surgeons). Moreover, we were unable to perform a detailed analysis to better characterize patients who were on chronic home GC therapy because the vast majority received multiple and higher doses. Furthermore, this study was conducted at a single institution during the inpatient surgical admission, and we were not able to investigate for long-term complications and readmissions, as patients may have presented to other medical centers for these occurrences. Additionally, data on RA activity and severity were not available, as many patients were under the care of rheumatologists outside of our institution. This is an important limitation, as other studies have shown that higher disease is a risk factor for postoperative complications (10).

A higher cumulative GC dose during hospitalization for arthroplasty was associated with an increased risk of perioperative complications in patients with RA. Lower GC exposure was

not associated with the development of hypotension or the need for vasopressors. Our results, although preliminary, suggest that the use of high doses of GCs during hospitalization for arthroplasty may have a negative impact on early postoperative outcomes after TJA. Future studies are necessary to confirm our findings and to define optimal dosing strategies for perioperative GC use. Data investigating the relationship between perioperative GC exposure and long-term complications are also necessary. At present, providers should consider using the lowest possible cumulative dose to minimize the risk of perioperative complications and hyperglycemia in patients with RA undergoing arthroplasty.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Chukir takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Stein, Goodman, Russell, Figgie, Sculco, Mehta, Chukir, Sigmund.

Acquisition of data. Tornberg, Chukir, Do.

Analysis and interpretation of data. Do, Thomas, Chukir, Stein, Goodman, Sculco, Mehta, Russell, Figgie.

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