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Original Research

Dexamethasone Is Associated With a Statistically Significant Increase in Postoperative Blood Glucose Levels Following Primary Total Knee Arthroplasty

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ABSTRACT

Background: Dexamethasone has the potential to cause a transient increase in blood glucose levels. Recent evidence has suggested the potential for a linearly increased risk of periprosthetic joint infection beginning at blood glucose levels of ≥115 mg/dL and an optimal cutoff of 137 mg/dL. We designed the following study to determine (1) what percentage of our patients had postoperative day 1 (POD1) glucose levels above 137 mg/dL and (2) if the administration of dexamethasone further increased this risk.

Methods: All primary total knee arthroplasties performed from 1998 to 2021 at our institution were identified and retrospectively reviewed. Patient demographics, dexamethasone administration, and perioperative glucose levels were recorded. Outcomes included POD1 glucose levels, infection rate, and all-cause reoperations and revisions.

Results: The average POD1 glucose level for the entire cohort (n = 5353) was 138.7 mg/dL. The percentage of patients with a glucose level of 137 mg/dL or higher was significantly greater in patients that received dexamethasone (55.2% vs 37.7%; $P < .0001$). Significantly higher glucose levels were seen with dexamethasone administration in both diabetic (187.7 vs 173.4 mg/dL; $P < .0001$) and nondiabetic patients (137.7 vs 128.0 mg/dL; $P < .0001$). Dexamethasone use was associated with a nonstatistically significant increase in infection rates (1.7% vs 1.0%; $P = .177$).

Conclusions: Administration of dexamethasone is associated with a statistically significant increase in POD1 glucose levels, regardless of diabetic status. Dexamethasone use should continue to be closely monitored given the potential risks of elevated postoperative glucose levels and the potential for periprosthetic infection.

Introduction

Since the removal of total knee arthroplasty (TKA) from the Medicare inpatient-only procedure list in January 2018, outpatient TKA has become increasingly common [1]. This shift from the hospital to the surgery center setting has been made possible through a variety of techniques including periarticular injections performed during the surgery, perioperative tranexamic acid, early mobilization of patients in the recovery room, and multimodal analgesia strategies [2,3].

Dexamethasone is a commonly utilized glucocorticoid for perioperative pain management following primary TKA [4–6]. The anti-inflammatory effects of dexamethasone attenuate the acute phase response associated with the tissue insult that occurs, leading to a reduction in the hyperinflammatory state which can be monitored directly with the measurement of acute-phase reactants measured on laboratory tests [7]. The use of dexamethasone in the perioperative period has been shown to reduce the consumption of narcotic pain medication and antiemetic medication and ultimately has led to a shorter hospital length of stay [8,9].

However, a single dose of intravenous perioperative dexamethasone has been shown to cause a transient increase in blood

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glucose levels regardless of diabetes status [10,11]. Elevated postoperative blood glucose levels have been shown to be an independent risk factor for wound complications and infection [12,13]. Recent evidence has suggested the potential for a linearly increased risk of periprosthetic joint infection (PJI), beginning at blood glucose levels of ≥115 mg/dL and an optimal cutoff of 137 mg/dL [14]. Large database studies have demonstrated the relative safety of dexamethasone used in the perioperative setting, but, to date, studies assessing the perioperative risk of increased blood glucose levels have been limited to large database studies where individual assessment of patient outcomes is limited [15–18].

Therefore, we designed the following study to determine what percentage of our patients had postoperative day 1 (POD1) glucose levels above 137 mg/dL and if the administration of dexamethasone further increased the risk of PJI. We hypothesized that we would see an increase in POD1 glucose levels in patients that received dexamethasone.

Material and methods

After obtaining institutional review board approval (IRB# 211506), all primary TKAs performed from 1998 to 2021 were identified by the Current Procedural Terminology (CPT) code 27447 and retrospectively reviewed utilizing our institutional database. Patient demographics (including diabetic status), dexamethasone administration, and perioperative glucose levels were recorded. All primary TKA patients with POD1 glucose levels available were included. POD1 glucose levels were not available for patients who had TKA performed in the outpatient setting or those who stayed overnight for observation and discharged without labs. We reviewed a total of 4724 patients who underwent 5353 TKAs. This list was cross-checked with CPT codes for revision surgery, manipulation under anesthesia, and debridement (CPT codes 11043, 27310, 27570, 27486, 27487), and this identified a list of 372 patients who required reoperation or manipulation under anesthesia on their primary TKA. These charts were manually reviewed to determine the cause of reoperation, including infection.

Anesthesia protocol varied throughout the course of the study period. Of all study patients, 79.8% received our standard infection prophylaxis, which utilized a single dose of intravenous cefazolin and vancomycin administered within 1 hour prior to incision, as well as 2 postoperative doses of cefazolin and 1 postoperative dose of vancomycin. This protocol was formed in collaboration with our infectious disease department due to an extremely high prevalence of methicillin resistance in our area among *Staphylococcus* species on our bacterial nomogram. Of all study patients, 11.6% received clindamycin in place of cefazolin due to a documented allergy to penicillin or cefazolin specifically, and 2.8% of patients received only cefazolin and did not receive vancomycin due to documented adverse reactions to vancomycin in the past. Other antibiotic combinations made up 5.7% of our study population. Dexamethasone use became gradually incorporated into our total joint arthroplasty order sets starting in 2015. Currently, the standard protocol of our institution is that all nondiabetic patients receive dexamethasone as a part of their multimodal pain regimen. Patients who were given dexamethasone received a 10-mg dose of intravenous dexamethasone upon induction by anesthesia, as well as a second 10-mg dose on POD1. Blood glucose levels were measured in patients through routine morning labs drawn between 4:00 AM and 6:00 AM that included a basic metabolic panel and complete blood count. All surgeons at our institution utilized a standard medial parapatellar approach with a layered closure for primary TKA throughout the study period. The majority of TKAs performed utilized commercially available antibiotic cement (96.9%). Of the surgeons at our institution, 3.1% used a cementless technique. Aspirin was the most common agent used for thromboembolic chemoprophylaxis (48.2%). Other prophylactic regimens included warfarin (36.1%), warfarin with an enoxaparin bridge (6.0%), warfarin and aspirin (3.9%), and other (5.9%). Postoperatively, patients were discharged to home or a skilled nursing facility, with follow-up appointments commonly at 2 weeks, 6 weeks, 3 months, and 1 year. The primary outcome of the study was POD1 glucose levels. Secondary outcomes included preoperative blood glucose levels, the relationship of dexamethasone and POD1 glucose levels, PJI, and all-cause reoperations and revisions. For this study, PJI was defined as infection that required irrigation and debridement or a revision surgery.

Due to failed normality testing, nonparametric statistical testing was performed throughout. The Mann-Whitney test was used to analyze differences among continuous variables such as glucose values. The Fisher's Exact test was used to analyze the difference between categorical variables such as presence or absence of reoperations. A P value $< .05$ was considered significant. All statistical calculations and figures were generated with GraphPad Prism version 8.0.0 (GraphPad Software, San Diego, CA).

Results

A total of 5353 TKAs were identified, performed by 18 surgeons over the study period. Four of the surgeons accounted for 93.7% of the TKAs. Demographic data and comorbidities are displayed in Table 1. Patients who developed infection had statistically significant higher rates of congestive heart failure ($P = .0271$), lung disease ($P = .0126$), autoimmune disorders ($P = .0003$), neurologic disorders ($P = .0002$), and valvular heart disease ($P = .0011$) than those who did not. Age, sex, race, and the other comorbidities listed were statistically similar. The average POD1 glucose level for the entire cohort (n = 5353) was 138.7 mg/dL. The percentage of patients with a glucose level of 137 mg/dL or higher was significantly greater in patients that received dexamethasone (55.2% vs 37.7%; $P < .0001$). Overall, 39.5% of patients (2112/5353) surpassed the 137-mg/dL threshold. Patients who received dexamethasone (n = 547) had a significant increase in POD1 glucose levels that was not seen in patients who did not receive dexamethasone (n = 4806) ($P < .0001$), and this is shown in Figure 1. Diabetic patients (n = 1135) had significantly higher POD1 glucose levels than nondiabetic patients (n = 4218) (175.5 mg/dL vs 128.8 mg/dL; $P < .0001$). As seen in Figure 2, diabetic patients that received dexamethasone (n = 168) had a significantly higher increase in their POD1 glucose levels than diabetic patients that did not (n = 967) (187.7 mg/dL vs 173.4 mg/dL; $P < .0001$). Nondiabetic patients that received dexamethasone (n = 379) had significantly higher glucose levels than nondiabetic patients that did not (n = 3839) (137.7 mg/dL vs 128.0 mg/dL; $P < .0001$). Changes in glucose levels from POD0 to POD1 are displayed in Figure 3. Dexamethasone use was associated with a nonstatistically significant increase in PJI that required irrigation and debridement or a revision surgery (1.7% vs 1.0%; $P = .177$). On average, the revision surgery occurred 292 days after the initial surgery. Of the infection cases, 59.6% identified a causative organism on cultures, and the bacterial profile of PJI cases is displayed in Table 2. A total of 250 patients (4.7%) underwent manipulation under anesthesia. Reasons for reoperation were classified as PJI (n = 57; 1.1%), aseptic loosening or instability (n = 47; 0.9%), or trauma to the knee joint (n = 18; 0.3%).

Discussion

The present study demonstrated that patients who received dexamethasone as a part of their multimodal pain regimen had statistically significant higher POD1 glucose levels than those who

Table 1
Demographic information and comorbidities.

Variable	Total	Noninfected	Infected	*P* value
Age (±SD, y)	64.9 (±9.6)	64.9 (±10.0)	64.3 (±9.6)	.7620
Sex (number, %)				
Male	2091 (39.1%)	2068 (39.0%)	23 (40.4%)	
Female	3262 (60.9%)	3228 (61.0%)	34 (59.6%)	.8917
Race (number, %)				
Caucasian	4427 (82.7%)	4378 (82.7%)	49 (86.0%)	
Black	504 (9.4%)	499 (9.4%)	5 (8.8%)	
Other/unspecified	422 (7.9%)	419 (7.9%)	3 (5.3%)	.7408
BMI (±SD, kg/m^2)	33.4 (±6.4)	33.4 (±9.1)	34.9 (±6.9)	.4033
Comorbidity (number, %)				
Arrhythmia	917 (17.1%)	908 (17.1%)	9 (15.8%)	1.0000
Malignancy	896 (16.7%)	891 (16.8%)	5 (8.8%)	.1506
Congestive heart failure	677 (12.7%)	664 (12.5%)	13 (22.8%)	**.0271**
Lung disease	659 (12.3%)	645 (12.2%)	14 (24.6%)	**.0126**
Liver disease	615 (11.5%)	605 (11.4%)	10 (17.5%)	.1453
Endocrine disorder	576 (10.8%)	570 (10.8%)	6 (10.5%)	1.0000
Chronic kidney disease	565 (10.6%)	560 (10.6%)	5 (8.8%)	.8293
Hematologic disorder	497 (9.3%)	491 (9.3%)	6 (10.5%)	.6489
Autoimmune disorder	416 (7.8%)	403 (7.6%)	13 (22.8%)	**.0003**
Neurologic disorder	349 (6.5%)	337 (6.4%)	12 (21.1%)	**.0002**
Vascular disease	279 (5.2%)	276 (5.2%)	3 (5.3%)	1.0000
Pulmonary embolism	149 (2.8%)	149 (2.8%)	0 (0%)	.4094
Valvular heart disease	20 (0.4%)	17 (0.3%)	3 (5.3%)	**.0011**

The bold *P* values represent statistical significance ($P < 0.05$).
BMI, body mass index; SD, standard deviation.

did not. While it remains unknown what the magnitude of effect is of a transient increase in blood glucose levels following a primary TKA, in the present study, there was not a statistically significant increase in infection, reoperation, or revision surgery. The benefits of perioperative dexamethasone use including a decrease in postoperative pain scores, opioid consumption, antiemetic consumption, and emesis have been well described in blinded randomized-controlled trials [8,19,20]; however, the nonstatistically significant increase in infection rate in the present study (1.7% with dexamethasone vs 1.0% without; $P = .177$) suggests that dexamethasone administration should be thoughtfully considered.

A recent study by Kheir et al. demonstrated an alarming trend of a linear risk for PJI, starting at a postoperative glucose level of 115 mg/dL, with an optimal cutoff of 137 mg/dL [14]. In our patient

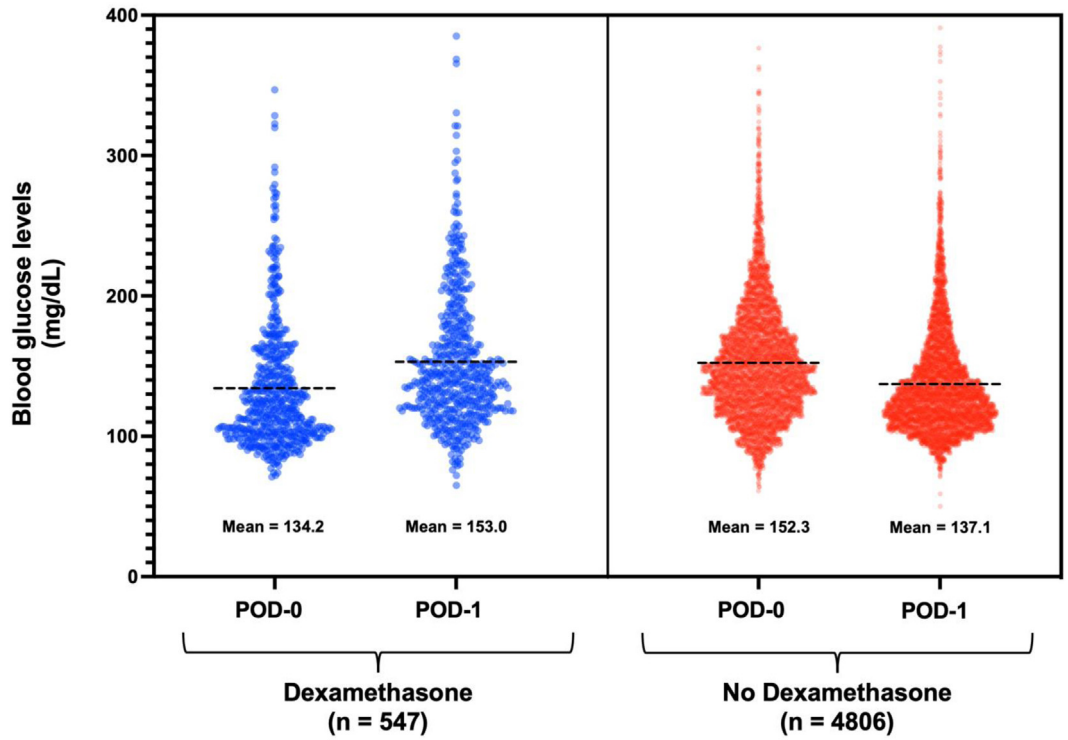

Figure 1. Blood glucose and dexamethasone. Blood glucose levels on postoperative days 0 and 1 for patients that received dexamethasone (left) vs those who did not (right). Patients who received dexamethasone had an average increase in their blood glucose level of 18.8 mg/dL, while patients who did not receive dexamethasone had an average decrease of 15.2 mg/dL from postoperative day 0 to postoperative day 1. These values were statistically significant ($P < .001$).

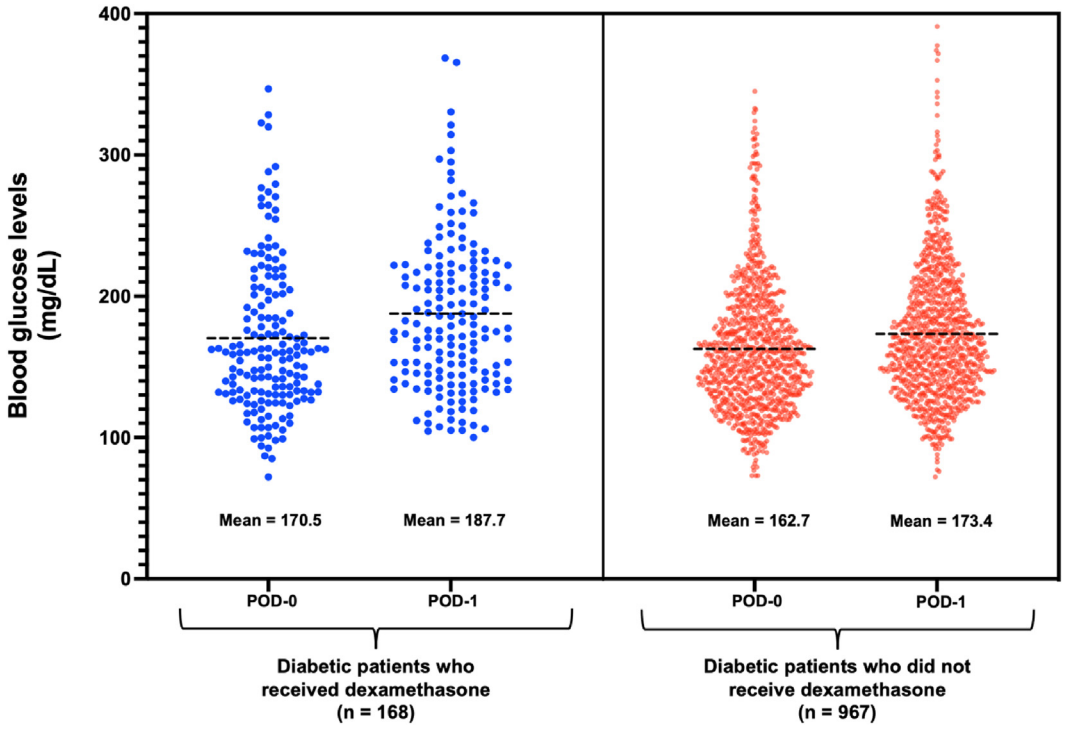

Figure 2. Glucose levels in diabetic patients with and without dexamethasone administration. Blood glucose levels on postoperative days 0 and 1 for diabetic patients who received dexamethasone (left) vs those who did not (right). Diabetic patients who received dexamethasone had an average increase in their blood glucose level of 17.2 mg/dL, compared to diabetic patients who did not receive dexamethasone and had an average increase of 10.7 mg/dL. These values were statistically significant ($P < .001$).

cohort, 39.5% of patients surpassed the 137-mg/dL threshold. Dexamethasone administration was a predictor of exceeding the 137-mg/dL cutoff and was associated with statistically significant increases in blood glucose levels in both the diabetic and nondiabetic patient populations. The model proposed by Kheir et al. demonstrates a PJI risk increase by 1.004 per 1-mg/dL increment. In our patient population, this corresponds to an odds ratio increase of 1.06 for diabetic patients and 1.04 for nondiabetic

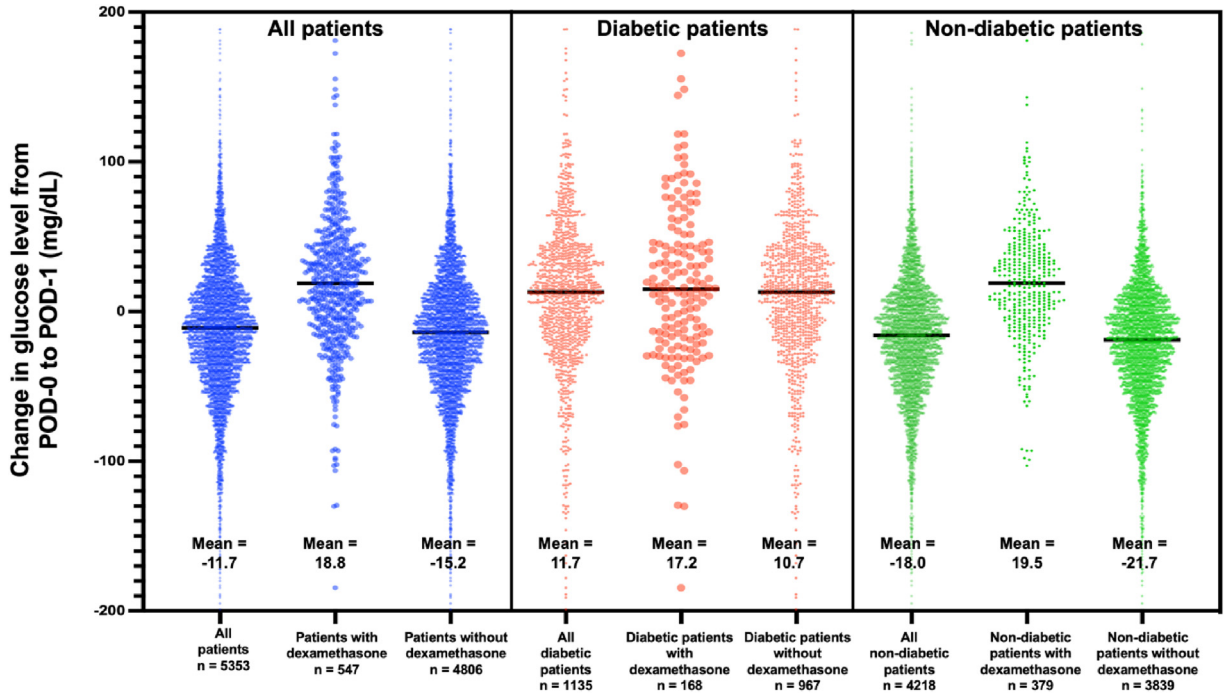

Figure 3. Changes in glucose levels. The changes in blood glucose level (mg/dL) from postoperative day 0 to postoperative day 1 are shown in all patients (left), diabetic patients (middle), and nondiabetic patients (right).

Table 2
Bacterial profile of periprosthetic joint infections.

Organism	Number (%)
No isolate	23 (40.4)
Methicillin-resistant *Staphylococcus aureus*	13 (22.8)
Methicillin-sensitive *Staphylococcus aureus*	3 (5.3)
Staphylococcus epidermidis	4 (7.0)
Other coagulase-negative staph species	6 (10.5)
Streptococcus species	3 (5.3)
Escherichia coli	1 (1.8)
Enterococcus faecium	1 (1.8)
Pasteurella multocida	1 (1.8)
Pseudomonas aeruginosa	2 (3.5)

patients with dexamethasone administration. Their study did not utilize intravenous or oral corticosteroids as part of their multimodal pain protocol.

Diabetes is a known risk factor for PJI after TKA [21–23]. Independent of the diabetic status, postoperative hyperglycemia and variations in glucose levels have been demonstrated to be risk factors for the development of PJI, and the importance of strict glycemic control in the early postoperative period is becoming more evident [14,24,25]. As expected, the highest glucose levels in our study were seen in the cohort of diabetic patients that received dexamethasone, with a mean of 187.7 mg/dL. Although nondiabetic patients who received dexamethasone did not see as dramatic of an increase in postoperative glucose levels as diabetic patients (14 mg/dL), they did have an increase of nearly 10 mg/dL, which was statistically significant.

High-quality prospective studies demonstrate the efficacy of dexamethasone in terms of analgesia but do not have the follow-up length necessary to adequately detect PJI [19,20]. Metanalyses that comment on the safety of perioperative glucocorticoid use have significant heterogeneity in terms of administration route (periarticular injection vs intravenous administration), dosing, and glucocorticoid used (methylprednisolone, dexamethasone, etc.) [4,26,27]. In a retrospective review of 238 patients, O'Connell et al. demonstrated an increase in postoperative hyperglycemia in diabetic patients who received dexamethasone as part of their preoperative multimodal pain regimen [11]. This correlates with our findings where diabetic patients who received dexamethasone were found to have an average blood glucose level 14.3 mg/dL higher than those who did not. Due to the rarity of PJI and, thus, the difficulty to study in prospective randomized trials, the most reliable data on the long-term safety of dexamethasone use have been limited to large retrospective database reviews. Richardson et al. performed a retrospective review of 6294 patients who underwent a primary total hip or knee arthroplasty, 557 of whom received a single dose of dexamethasone [15]. The rate of PJI in this group was 1.3%, and this was not statistically different from the 1.2% rate of the group that did not receive dexamethasone. These findings correlate with those of Vuorinen et al., who performed the largest retrospective review of perioperative dexamethasone administration to date [16]. They analyzed 18,872 total hip or knee arthroplasties, including revisions, and found statistically similar PJI rates of 1.1% in the group that received dexamethasone and 1.0% in the group that did not. They did not comment on results after removing revision operations. Both studies differ from our study in that patients only received a single dose of dexamethasone (ranging from 4 to 10 mg), and data on blood glucose levels were not collected. While dexamethasone use trended toward an increase in infection rates (1.7% vs 1.0%; $P = .177$), this was not statistically significant. However, the administration of dexamethasone was associated with a statistically significant increase in POD1 glucose levels.

While this study is the first to comment directly on the influence of dexamethasone administration on postoperative glucose levels and how this correlates with infection, there were a few limitations. First, this study was retrospectively performed at a single institution and, therefore, has inherent design limitations. Our method of using CPT codes to detect patients who underwent an additional surgery excludes superficial infections managed exclusively with antibiotics, patients who were treated nonoperatively, and patients who received further treatment outside of our institution although these numbers are likely low in comparison to the size of our cohort. Additionally, medical comorbidities associated with PJI including diabetic status could have been underreported. We attempted to accurately identify this patient population based on a medication and chart review as well as an evaluation of International Classification of Diseases 9 and 10 codes for diabetes. While our numbers trended towards an increase in infection rates with dexamethasone administration, our study was underpowered to determine statistical significance. A larger, multi-institutional prospective study is likely necessary. A power analysis was conducted and determined that approximately 8530 patients would be needed to detect an increase in PJI incidence from 1.0% to the 1.7% seen in this study with dexamethasone administration (1:1 enrollment ratio, alpha = 0.05, power = 80%). Our study was performed at a single institution, but the observed rates of PJI were similar to those in the studies performed at other institutions and suggest that our results would be generalizable to the population. Finally, given the >20-year period over which our data were collected, several protocol changes (anesthesia, antibiotics, etc.) took place that may have influenced the outcomes of our patients, and there is a possibility that changes in local bacterial epidemiology may have influenced our results over the study period.

Conclusion

Dexamethasone use caused significant increases in POD1 glucose levels. Dexamethasone use should continue to be closely monitored given the potential risks of elevated postoperative glucose levels and potential for periprosthetic infection.

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Conflicts of interest

S. M. Engstrom receives financial or material support from DJO Global Inc. and is in the advocacy committee of American Association of Hip and Knee Surgeons. G. G. Polkowski receives royalties from and is a paid consultant for DJO Global Inc. and is a board member of the American Association of Hip and Knee Surgeons. J. Ryan Martin is in the speakers' bureau of or gave paid presentations for DePuy Synthes and is a paid consultant for DePuy Synthes. The other authors declare no potential conflicts of interest.

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