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THE EFFECTS OF PERIOPERATIVE DEXAMETHASONE ON GLYCEMIC CONTROL AND POSTOPERATIVE OUTCOMES

Rebecca A. Herbst, MD[1], Onala T. Telford, MD[1], John Hunting MPH[2], W Michael Bullock MD, PhD[2], Erin Manning MD, PhD[2], Beatrice D. Hong, MD[1], David A. D'Alessio, MD[1], Tracy L. Setji, MD, MHS.[1]

From: [1]Duke University Medical Center, Division of Endocrinology and Metabolism; [2]Duke University Medical Center, Dept of Anesthesia

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Corresponding author: Tracy L Setji M.D. M.H.S.

201 Trent Dr, Baker House Room 305, Box 3222,

Durham, NC 27710

Email: tracy.setji@duke.edu

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Summary statement: Perioperative dexamethasone is associated with transient post-operative hyperglycemia, but a shorter length of hospital stay in patients with and without diabetes, and a higher survival rate in patients without diabetes who undergo orthopedic surgery.

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Abstract

Objective: Perioperative glucocorticoids are commonly given to reduce pain and nausea in patients undergoing surgery. However, the glycemic effects of steroids, and potential effects on morbidity and mortality, have not been systematically evaluated. This study investigates the association between perioperative dexamethasone and post-operative blood glucose, hospital length of stay (LOS), readmission rates, and ninety-day survival.

Methods: Data from 4800 consecutive orthopedic surgery patients who underwent surgery between 2000 and 2016 within a health system were retrospectively analyzed.

Results: Patients with and without diabetes who were given a single dose of dexamethasone had higher rates of hyperglycemia during the first twenty-four hours after surgery as compared to those who did not receive dexamethasone (HR (95% CI) for diabetes cohort = 1.81 (1.46, 2.24); HR (95% CI) for non-diabetes cohort = 2.34 (1.66, 3.29)). LOS was nearly one day shorter in patients who received dexamethasone (GMR (95% CI) for patients with diabetes = 0.79 (0.75, 0.83); GMR (95% CI) for patients without diabetes = 0.75 (0.72, 0.79)), and there was no difference in ninety-day readmission rates. In patients without diabetes, dexamethasone was associated with a higher ninety-day overall survival (99.07% versus 96.90%; p=0.004).

Conclusions: In patients with and without diabetes who undergo orthopedic surgery, perioperative dexamethasone was associated with a transiently higher risk of hyperglycemia. However, dexamethasone treatment was associated with a shorter LOS in patients with and without diabetes, and a higher overall ninety-day survival rate in patients without diabetes, compared to patients who did not receive dexamethasone.

Abbreviations:
LOS = length of stay; **IV =** intravenous; **EMR =** electronic medical record; **ICD =** international classification of disease; **BMI =** body mass index; **POD =** post op day; **CAD =**

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coronary artery disease; **DM =** diabetes mellitus; **HR =** hazard ratio; **CI =** confidence interval; **GMR =** geometric mean ratios; **SD =** standard deviation; **IQR =** interquartile range.

Introduction

Perioperative steroids are now widely used in multimodal analgesic regimens to improve postoperative pain and nausea. Studies have repeatedly demonstrated that a single dose of intravenous (IV) dexamethasone, given at or near the time of surgery, reduces postoperative requirements for analgesics and anti-emetics. Furthermore, some studies have shown a significant correlation between perioperative glucocorticoids and shorter hospital length of stay,[1-3] less time spent in the post-anesthesia care unit,[4] and higher patient satisfaction scores.[5] However, glucocorticoids also cause hyperglycemia through the combination of increased insulin resistance and reduced pancreatic beta cell function.[6] The effects of dexamethasone-induced dysglycemia on post-surgical outcomes are unknown.

The impact of hyperglycemia in hospitalized patients has long been a target of investigation with little consensus on the overall significance on morbidity and mortality. Several recent studies suggest that hyperglycemia has an adverse effect on hospital mortality in non-cardiac surgery patients.[7-9] Other investigators describe perioperative hyperglycemia as a risk factor for poor wound healing and surgical site infections.[10-12] In critically ill patients, hyperglycemia is associated with increased mortality;[13] however, maintaining glucose < 150 mg/dl has not consistently demonstrated improvement in outcomes.[14] In cardiac surgery patients, intraoperative hyperglycemia is associated with higher mortality[15,16] and greater in-hospital morbidity,[17-19] including increased risk of wound infections.[20] Therefore, expert guidelines recommend perioperative blood glucose targets of 80-180 mg/dl for cardiac surgery patients,

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with more stringent targets (<140 mg/dl) if achievable without hypoglycemia.[21] Recommendations on the optimal glucose range in non-cardiac surgery patients remain debatable among expert panels.[22,23]

Several small prospective studies demonstrate a clear association between a single dose of perioperative IV dexamethasone and increased blood glucose levels; however, these studies did not evaluate the impact of hyperglycemia on clinically pertinent post-operative outcomes.[5,24-27] In a meta-analysis of forty-five studies of the effects of perioperative dexamethasone, Waldron and colleagues found that only three studies measured perioperative blood glucose. None of the studies evaluated glycemic effects in patients with diabetes.[28] Because perioperative steroids may drive blood glucose above generally-accepted inpatient goals, the risk of transient hyperglycemia, as compared to potential benefits of perioperative steroids, needs further clarification.

Because of the established anti-inflammatory and immunosuppressive effects of glucocorticoids, one important consideration is post-operative infection risk.[29] A recent study reported no difference in the incidence of post-operative periprosthetic joint infection in patients who received perioperative dexamethasone.[30] However, this study did not analyze postoperative blood glucose, and it was underpowered to account for diabetes status. Other studies of the risks of perioperative glucocorticoids have similar limitations: low power; short follow up periods; exclusion of patients with diabetes; and heterogeneity in type of surgery. In this study, we examine the association between perioperative dexamethasone and the rates and severity of post-operative hyperglycemia, readmission rates, duration of hospitalization, and mortality in patients with and without diabetes undergoing orthopedic surgery.

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Materials and methods

Study Population

This retrospective study used the electronic medical record (EMR) to identify men and women, aged 18 to 89 years, who underwent elective orthopedic joint surgery at Duke University Health System between January 2000 and August 2016. Demographic variables, relevant comorbid conditions, perioperative data (including medications and laboratory results), and readmission and death rates for 90 days following the index operation were collected. Potentially moderating comorbid conditions were defined by the presence of the respective International Classification of Disease (ICD) codes. Subjects were excluded from the study if postoperative glucose values were not available or if hyperglycemia was present during the hospital admission prior to the operation. Patients who received glucocorticoids other than dexamethasone and those who were treated with more than one dose of glucocorticoids during the index admission were excluded. The final study cohort included 4800 individuals. This study was approved by the Duke University Institutional Review Board.

The subjects were categorized into two groups: those who received perioperative dexamethasone (treatment group) and those who did not receive perioperative dexamethasone (untreated group). Perioperative dexamethasone was given at the discretion of the attending anesthesiologist. Patients were subdivided according to the presence or absence of diabetes.

Outcomes

The primary outcomes were hyperglycemia, readmission rate and survival. Hyperglycemia was defined as serum or point-of-care blood glucose greater than or equal to 180 mg/dl. The peak glucose values were summed for specified time periods (<24 hours, 24-48 hours, and >48 hours following the operation) for the primary analysis. Readmission was defined

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as an admission to Duke University Medical Center for any indication within 90 days of the index operation. Similarly, deaths were collected for members of the two study groups if they occurred from any cause within 90 days of operation. Hospital length of stay (LOS) was calculated as the difference between admission and discharge times (in hours) as documented in the EMR.

Statistical Analyses

Descriptive statistics were calculated for the entire cohort at baseline and compared between patients who received dexamethasone and those who did not. Continuous variables were reported as mean and standard deviation; categorical variables were reported as frequency and percentage. Continuous variables were tested for statistical significance with the Wilcoxon sum rank test. Categorical variables were tested for significance with either the Chi-squared test or Fisher's exact test depending on the distribution of the variable.

The three primary outcomes (hyperglycemia, mortality, and readmission) were investigated through time-dependent multivariable Cox proportional hazards modeling. For hyperglycemia, the time range began at the end of surgery and patients were censored at 72 hours after surgery. Mortality and readmission were censored at 90 days postoperatively. The analysis was stratified by diabetes status. Each model was built independently through either a-priori variable consideration or the univariate associations with the exposure of $p < 0.10$. The final survival model among subjects with diabetes included age, BMI, hyperlipidemia, gender, race, hypertension, coronary artery disease, anesthesia method, and procedure type. The final model among subjects without-diabetes included age, BMI, gender, race, hypertension, anesthesia method, and procedure type. Due to the low mortality rate, the survival models for the entire study population was reduced to age, coronary artery disease, and procedure type. The

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time-dependent exposure was introduced as a heavy side function with the patient required to receive dexamethasone prior to the minimum time of the blood glucose timeframe.

Postoperative peak blood glucose concentration was compared through multivariable linear regression between groups at 0-24 hours, 24-48 hours, and 48-72 hours. The models were independently built for patients with and without diabetes. The outcome variable, peak blood glucose concentration, was determined to be non-normal and thus was log-transformed for modeling and the beta coefficient exponentiated to report the geometric mean ratio. Additional variables were included into the multivariable model based upon either a-priori variable consideration or univariate associations with the exposure of $p < 0.10$. The final model among diabetics included age, hyperlipidemia, race, gender, hypertension, coronary artery disease, anesthesia method, and procedure type.

Length of stay was tested through multivariable linear modeling. Potential confounders were introduced based upon univariate associations with the exposure ($p < 0.10$), the outcome ($p < 0.10$), or a-priori consideration. The final model among patients with diabetes included age, gender, race, body mass index (BMI), hypertension, coronary artery disease, procedure type, and anesthesia method. Among patients without diabetes, the final model included age, gender, race, BMI, hypertension, coronary artery disease, hyperlipidemia, procedure type, and anesthesia method. Multivariable normality was determined to be violated, and so the outcome variable was log transformed for modeling and beta estimates exponentiated back and reported as geometric mean ratios (GMR). Statistical significance was determined by $p<0.05$. SAS version 9.4 (SAS Inc. Cary, NC) was used for all analysis

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Results

Patient Characteristics

Among the total cohort of 4800 patients, the mean (SD) age was 65.5 (11.1) years; mean (SD) BMI was 30.6 (6.33) m_2/kg; females represented 57% of the study population; and 60.1% were treated with a single 4 to 10 mg dose of dexamethasone in the perioperative period. Total knee replacement (46.83%) and total hip replacement (38.13%) represented the majority of the operations. Approximately 25% of the patients had diabetes: 21.7% in the dexamethasone group and 29.3% in the untreated group. Obesity rates and BMI were higher in the diabetes group as compared to the non-diabetes group (difference in average BMI was 3.34 m_2/kg). There were small but significant differences between the treatment and control groups for BMI, race, diabetes, type of surgery, and anesthesia (Table 1).

Glycemic Effects

Patients who received perioperative dexamethasone were significantly more likely to develop post-operative hyperglycemia (glucose > 180 mg/dl) as compared to those who were not treated with dexamethasone (Table 2). Among patients with diabetes, 61.18% of the dexamethasone group developed hyperglycemia as compared to 51.16% of the untreated group (HR 1.82; 95% CI 1.47, 2.25). In patients without diabetes, 6.2% of the dexamethasone group developed hyperglycemia as compared to 3.55% of the untreated group (HR 2.35 (1.66, 3.331).

Blood glucose values peaked within 24 hours after the operation in all patient groups (Figure 1). Mean peak blood glucose values during the first post-operative twenty-four hours were significantly higher in the dexamethasone group as compared to untreated group. In the diabetes cohort, the mean peak glucose in steroid-treated patients at POD one was 201 mg/dL as compared to 166 mg/dL for the group that did not receive steroids. In the non-diabetes cohort,

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the mean peak glucose in the steroid-treated patients at POD one was 135 mg/dl as compared to 121 mg/dL for the untreated group. On POD two (24-48 hours), glucose was lower in the steroid-treated patients with diabetes (GMR (95% CI) 0.98 (0.94, 1.01) and without diabetes (GMR (95% CI) 0.96 (0.95, 0.97) as compared to the respective cohorts that did not receive steroids. On POD three (48-72 hours), glucose was significantly lower in patients that were treated with steroids as compared to corresponding cohorts who did not receive steroids (GMR (95% CI) 0.95 (0.91, 0.998) for the diabetes group and GMR (95% CI) 0.98 (0.96, 0.999) for the non-diabetes group).

Length of Stay and Readmission Rate

Dexamethasone exposure was associated with a shorter LOS in patients with and without diabetes (Table 2). The median (IQR) LOS overall was 3.11 (2.20, 3.39) and 2.39 (2.11, 3.29) days for the diabetes and non-diabetes cohorts, respectively. When fully adjusted for baseline characteristics, procedure type and anesthesia method, LOS was 21% shorter for patients with diabetes who received dexamethasone as compared to patients with diabetes who did not receive dexamethasone (GMR (95% CI) 0.79 (0.75, 0.83). Patients without diabetes who received dexamethasone had a 25% shorter LOS as compared to patients without diabetes who did not receive dexamethasone (GMR (95% CI) 0.75 (0.72, 0.79).

Dexamethasone exposure was not associated with a statistically significant difference in ninety-day readmission rate in the diabetes or non-diabetes groups. The readmission rate for the entire study cohort was 15.77%. Patients with diabetes were more likely to be readmitted than patients without diabetes (19.63% versus 14.50%) but this did not correlate with glucocorticoid exposure.

Steroids and Mortality Rate

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Glucocorticoids were independently associated with higher 90-day survival rates (Figure 2; Table 2). There was a total of 89 (1.85%) deaths in the study. In the total cohort, 1.01% (n = 29) of the treated group died as compared to 3.13% (n = 60) of the untreated group (p = <0.001). Patients with diabetes who received dexamethasone had a lower mortality rate (1.28%) compared to patients with diabetes who did not receive dexamethasone (3.21%), but this did not reach statistical significance (p = 0.37). However, patients without diabetes were 55% less likely to die within 90 days of the operation if they received dexamethasone compared to those without diabetes that did not receive dexamethasone (0.93% versus 3.10% death; HR(95% CI) 0.45 (0.26, 0.78). Regardless of dexamethasone exposure, patients with diabetes were more likely to die (2.19%) than patients without diabetes (1.74%).

Discussion

Perioperative glucocorticoids improve post-operative nausea/vomiting and pain in a variety of surgical settings and are correlated with shorter LOS in the hospital and post-anesthesia care unit.[1-4] However, glucocorticoids may also cause hyperglycemia. Perioperative hyperglycemia is associated with adverse outcomes including increased morbidity, LOS and mortality. Patients that do not have a history of diabetes, often called stress hyperglycemia, have worse outcomes than those with a known history of diabetes.[7] Thus, it is important to understand the impact of steroids on glycemic control in the perioperative setting and to investigate potential adverse clinical outcomes. In a large cohort of consecutive orthopedic surgery patients with and without diabetes, we observed a transient effect of a single dose of dexamethasone to raise blood glucose. However, steroid-induced hyperglycemia resolved within 24-48 hours. Perioperative

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steroids were associated with shorter lengths of hospital stay in patient with and without diabetes, and lower 90-day mortality rates in patients without diabetes.

As expected, patients who received perioperative dexamethasone were more likely to develop post-operative hyperglycemia compared to patients who were not given dexamethasone. Similarly, regardless of diabetes status, mean peak glucose values were significantly higher in patients who received dexamethasone. However, the rate of hyperglycemia in steroid-treated patients without diabetes was low (6.2%), and considerably less than the 61.2% of steroid-treated patients with diabetes who developed hyperglycemia. Importantly, regardless of diabetes status, the glycemic effects of dexamethasone disappeared within 48 hours of the surgery. These findings indicate that a single dose of dexamethasone has minimal effect on glycemia beyond 24 hours and suggests that the immediate glycemic effects are modest in most patients, including patients with diabetes. The lower glucose values on POD two and three in the patients who were given dexamethasone relative to their untreated comparators suggests more intensive insulin treatment, likely due to the higher glucose values on POD one. Given the predictable rise in blood glucose during the first twenty-four hours after dexamethasone exposure, and the profound steroid-induced postoperative hyperglycemia in some patients, it is reasonable to monitor glucose intermittently over the first twenty-four hours after surgery. Formal glycemic protocols may be useful to optimize postoperative blood glucose while minimizing the risk for iatrogenic hypoglycemia.[31,32]

Our results demonstrate a significant association of perioperative dexamethasone treatment with shorter hospital LOS. After adjustment for potential confounding variables, patients with diabetes who received dexamethasone had a 21% shorter LOS, and patients without diabetes treated with dexamethasone had a 17% shorter LOS than corresponding cohorts who did

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not receive dexamethasone. This amounts to ~20 hours less time in the hospital for patients given steroids at the time of surgery. The shorter LOS may be attributed to improved post-operative pain and nausea, reduced symptomatic medication requirement, and perhaps, reduced opioid-related complications.[33,34] Notably, for the vast majority of patients, glycemic sequelae of steroid treatment was not a factor in LOS. This effect extended outside the hospital as well, with no difference in readmission rates in dexamethasone-exposed compared to unexposed groups. These findings add to the literature that a single dose of IV perioperative glucocorticoids may improve outcomes without increasing the risk of postoperative complications.[30,35,36]

Unexpectedly, we found a significant association of perioperative steroids with higher 90-day survival rates. Only about one third of the deaths in the study occurred in steroid-exposed patients (29 deaths in the dexamethasone-treated patients and 60 in the untreated patients). After adjustment for BMI, procedure type and coronary artery disease, this finding remained statistically significant in the non-diabetes group (HR (95% CI) 0.45 (0.26, 0.78). There was a numerically, but not statistically significant, lower rate of death in patients with diabetes who received dexamethasone as compared to patients with diabetes who did not receive dexamethasone (HR (95% CI) 0.67 (0.28, 1.61)). The cause of this association is unknown. Dexamethasone has anti-inflammatory effects[37] as well as potential positive impact on post-operative cognitive function.[38] Additionally, reduced opioid exposure and/or earlier post-operative physical therapy due to improved pain control may be playing a role. This association of reduced mortality with perioperative steroids is hypothesis generating and warrants further investigation.

There are several strengths to this study. The large cohort provided ample statistical power to analyze several clinically important post-operative outcomes without exclusion based

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on comorbid conditions. By focusing our analysis on a discrete group of procedures, joint replacement, confounding by different surgical and patient risk factors was minimized. Lastly, the high volume of orthopedic surgeries at our institution allowed for the inclusion of multiple surgeon/anesthesia teams which increases the generalizability of the findings.

There are also limitations of the study that merit consideration. These include the retrospective nature of the study which can only demonstrate associations and be hypothesis generating, rather than leading to conclusive evidence of cause and effect. In our analysis, we needed to exclude some patients due to missing glucose values. In addition, there was a potential for selection bias given the lack of standardized approach to patient selection for dexamethasone. The decision of who did and did not receive dexamethasone perioperatively was made by the anesthesiologist at the time of surgery, and based on individual provider preference. It is possible that patients with more labile diabetes did not receive dexamethasone in an effort to maintain better glycemic control. Further, there may have been unrecognized changes in practice and/or treatment protocols over time that we have not been able to capture in our analysis. Another limitation of the study is that it focuses on patients that only received a single dose of dexamethasone. More recently, some institutions have begun implementing a two-dose protocol of perioperative dexamethasone. Finally, since this was a single health system study, we cannot assure that all readmissions were accounted for. However, it is unlikely that we missed many deaths given the robust electronic medical record and its connection with most nearby hospitals.

In summary, patients who received a single dose of perioperative dexamethasone were more likely to develop hyperglycemia within the first twenty-four hours after surgery. However, this effect of dexamethasone did not persist beyond postoperative day one. As has been previously reported, our data demonstrates that dexamethasone is associated with a significantly

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shorter LOS. To the best of our knowledge, this is the first study to report an association of dexamethasone with improved postoperative survival and this is a topic worthy of further study in a prospective trial. Additional investigation into the effects of protocols that utilize more than one dose of dexamethasone is also warranted. Finally, this study supports the use of dexamethasone in orthopedic joint procedures with the recommendation that patients are monitored for post-operative hyperglycemia for the first twenty-four hours after the operation.

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Table 1. Patient characteristics.

	Total study population (N = 4800)	Dexamethasone-treated group (N = 2885)	Untreated Group(no steroids) (N = 1915)	P value
Age, mean (std)	64.45 (11.08)	64.87 (10.91)	66.33 (11.28)	<0.0001[1]
Female, n (%)	2735 (56.98%)	1645 (57.02%)	1090 (56.92%)	0.9454[2]
Race, n (%)				<0.0001[2]
Caucasian	3658 (76.21%)	2261 (78.37%)	1397 (72.95%)	
African American	966 (20.13%)	519 (17.99%)	447 (23.34%)	
Other	176 (3.67%)	105 (3.64%)	71 (3.71%)	
Diabetes, n (%)	1187 (24.73%)	626 (21.70%)	561 (29.30%)	0.0018[2]
Hypertension, n (%)	3341 (69.60%)	1958 (67.87%)	1383 (77.22%)	0.0013[2]
Hyperlipidemia, n (%)	1802 (37.54%	1131 (39.20%)	671 (35.04%)	0.0035[2]
CAD, n (%)	560 (11.67%)	322 (11.16%)	238 (12.43%)	0.1806[2]
Obesity, n (%)	2356 (49.23%)	1366 (47.40%)	990 (52.00%)	0.0018[2]
BMI, mean (std)	30.57 (6.33)	30.25 (6.18)	31.05 (6.53)	0.0001[1]
Procedure Type, n (%)				<0.0001[2]
Total hip	1830 (38.13%)	1251 (43.36%)	579 (30.23%)	
Total knee	2248 (46.83%)	1274 (44.16%)	974 (50.86%)	
Partial hip	205 (4.27%)	60 (2.08%)	145 (7.57%)	
Revision hip	203 (4.23%)	121 (4.19%)	82 (4.28%)	
Revision knee	314 (6.54%)	179 (6.20%)	135 (7.05%)	

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Continuous variables reported as mean (sd); categorical variables reported as frequency (percentage); BMI = Body Mass Index; CAD = coronary artery disease

[1]Wilcoxon Rank Sum, [2]Chi-Square, [3]Fisher Exact

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Table 2. Patient Outcomes.

Outcome	Total	Dexamethasone Group	Untreated Group	Adjusted Hazard Ratio (95% CI)	P value
Hyperglycemia					
Total, n (%)	858 (17.88%)	523 (18.13%)	335 (17.49%)		
Diabetes, n (%)	670 (56.44%)	383 (61.18%)	287 (51.16%)	1.81 (1.46, 2.24)	<0.001
No diabetes, n (%)	188 (5.2%)	140 (6.2%)	48 (3.55%)	2.34 (1.66, 3.29)	<0.001
Death (90-day)					
Total, n (%)	89 (1.85%)	29 (1.01%)	60 (3.13%)		
Diabetes, n (%)	26 (2.19%)	8 (1.28%)	18 (3.21%)	0.67 (0.28, 1.61)	0.37
No diabetes, n (%)	63 (1.74%)	21 (0.93%)	42 (3.1%)	0.45 (0.26, 0.78)	0.004
Readmission (90 day)					
Total, n (%)	757 (15.77%)	451 (15.63%)	306 (15.98%)		
Diabetes, n (%)	233 (19.63%)	126 (20.13%)	107 (19.07%)	1.12 (0.86, 1.46)	0.40
No diabetes, n (%)	524 (14.50%)	325 (14.39%)	199 (14.70%)	1.04 (0.87, 1.25)	0.66
Outcome	Total	Dexamethasone Group	Untreated Group	Adjusted Geometric Mean Ratio (95% CI)	P value
Length of Stay, median (days)					
Diabetes	3.11 (2.20, 3.39)	2.34 (1.48, 3.29)	3.25 (2.36, 4.20)	0.79 (0.75, 0.83)	<0.001 <0.001

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No diabetes	2.39 (2.11, 3.29)	2.28 (1.40, 3.21)	3.15 (2.29, 3.38)	0.85 (0.72, 0.79)	

Continuous variables reported as median (IQR); Categorical variables reported as frequency (percentage)

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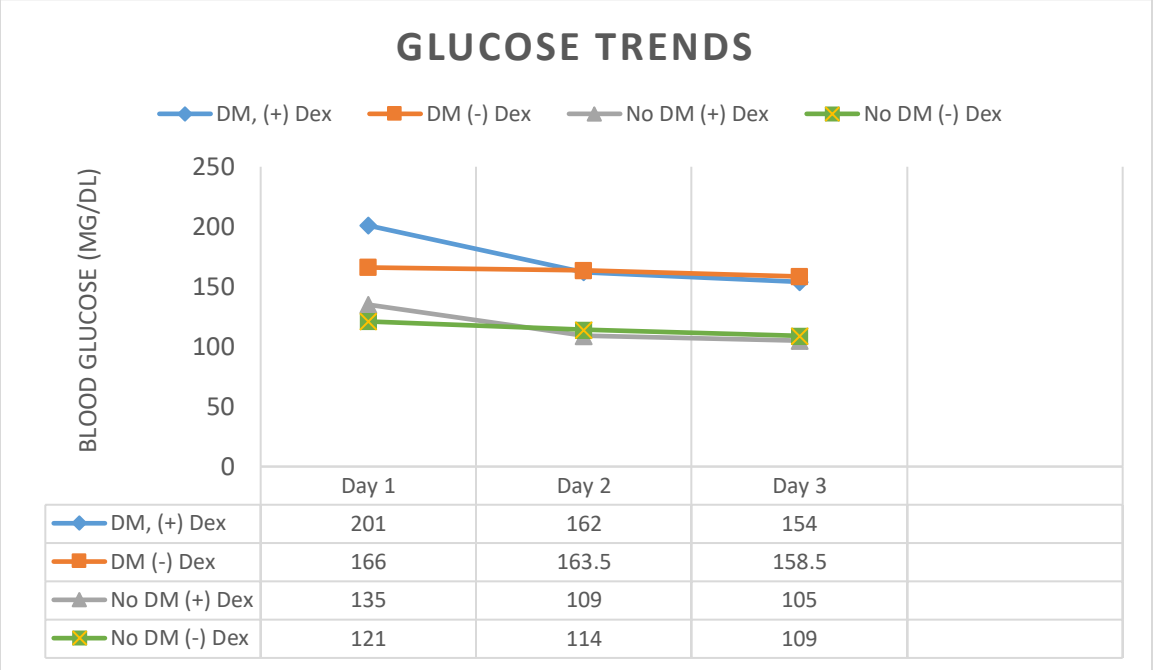
Figure 1. Glucose trends over time. Diabetes Mellitus (DM).



	Day 1	Day 2	Day 3	
DM, (+) Dex	201	162	154	
DM (-) Dex	166	163.5	158.5	
No DM (+) Dex	135	109	105	
No DM (-) Dex	121	114	109	

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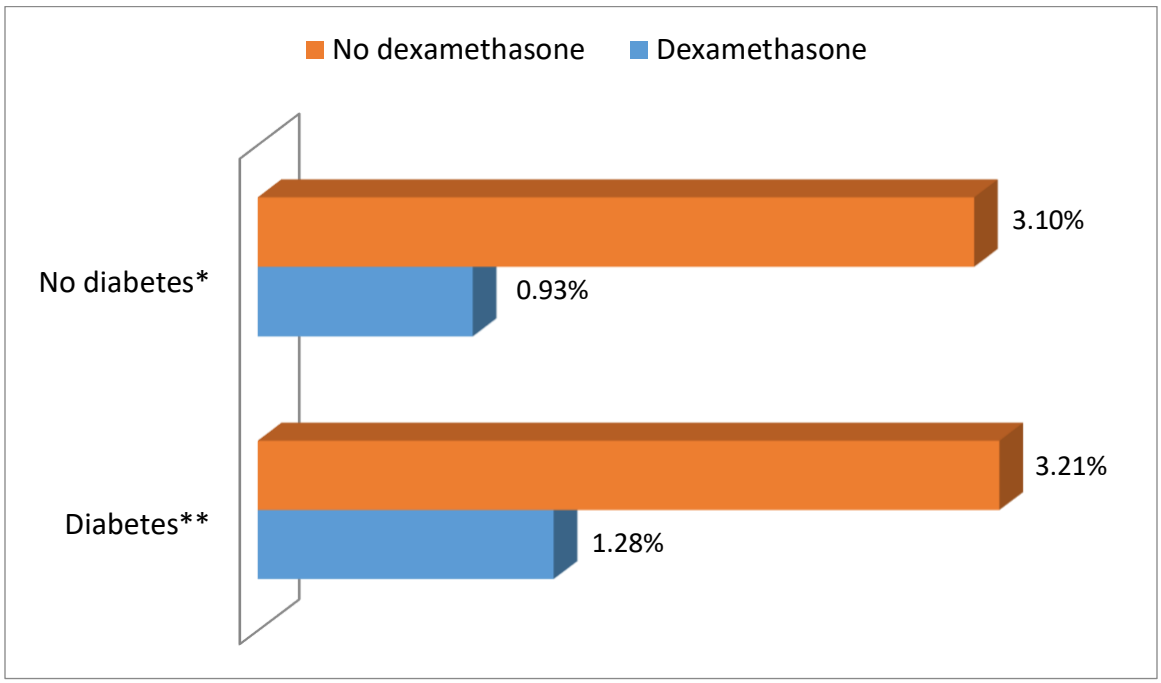
Figure 2. Rate of death within ninety days of index operation. *HR (95% CI) for patients without diabetes 0.45 (0.26, 0.78); **HR (95% CI) for patients with diabetes 0.67 (0.28, 1.61).



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