Perioperative Hyperglycemia Increases Rates of Infection in Lumbar and Cervical Spine Surgery: A Case Control Study

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Abstract:

Background/Aim: Hyperglycemic changes can occur after surgery as a response to physiological stress or medication effects. Its association with surgical site infections (SSI) has been studied in other surgical specialties but it has not been looked at in spine surgery. This study aimed to evaluate the correlation of postoperative hyperglycemia with SSI in post-operative spine surgery patients, irrespective of diabetes.

Materials and Methods: We retrospectively reviewed 100 patients at our hospital who underwent spine surgery with SSI and compared them with 111 controls (2010-2020). Independent variables included average postoperative glucose (<100, 100-119, 120-139, ≥140), surgical approach, use of allograft, ASA class, and diabetes mellitus. A multivariate logistic regression analysis using the significant univariate variables was performed to calculate the odds ratio and corresponding 95% confidence intervals to identify patient demographics and surgical characteristics that were associated with development of SSI.

Results: Univariate analysis revealed stand-alone ALIF and lateral transpsoas approach to interbody fusion procedures were associated with a decreased risk of SSI while average serum glucose 120-139 mg/dL and ≥140 mg/dL were at increased risk. Diabetes alone was not a significant risk factor. Multivariant analysis revealed average serum glucose levels ≥140 mg/dL within five days after surgery was found to be a risk factor for SSIs relative to an average serum glucose <100 mg/dL.

Conclusions: Postoperative serum glucose levels ≥140 mg/dL were associated with an increased risk of SSI when compared to glucose levels <100 mg/dL. The role of postoperative hyperglycemia as a risk factor for SSI should be investigated further.

Key words: infection; spine; hyperglycemia; fusion; lumbar; complications

Introduction

Surgical site infections (SSI) are common postoperative complications with potentially catastrophic consequences in spinal surgery. Previous studies report incidence ranging from 0.2% to 16.7% [1,2]. SSIs after spinal surgery can result in significant morbidity, including pseudoarthrosis, chronic pain, deformity, neurologic deficits, and even death in severe cases [3]. Identification of risk factors for SSIs is essential for developing effective preventative strategies.

In the current literature, there are many patient-related and surgical risk factors for infection, such as prior infection, age, diabetes mellitus,

smoking, malnutrition, obesity, prolonged operative time, trauma, hypothermia, blood transfusion, inadequate skin preparation, and hyperglycemia, among others [4,5]. Minimizing risk factors, especially those that are modifiable, has the potential to reduce infection burden. Elevated postoperative glucose levels, irrespective of diabetes mellitus (DM) status, have been associated with an increased risk of SSI across in the orthopedic joint literature [6]. These findings are supported by several studies outside the field of orthopedics [7,8].

The association of hyperglycemia with postoperative infections after spine surgery, irrespective of a DM diagnosis, is not well understood. To our knowledge, there has been minimal examination of immediate postoperative glycemic control to establish an optimal threshold for lowering the incidence of SSIs. The present study aims to understand if postoperative hyperglycemia, irrespective of DM, is an independent risk factor for postoperative infection after spine surgery and to determine a threshold that surgeons should target following spine surgery.

Materials and Methods:

Study Design and Population:

Using Deep 6 Artificial Intelligence (AI) software (Pasadena, California, USA), we performed an AI driven search analyzing a complete database of patients at our level 1 trauma medical center since the incorporation of Epic (Epic Systems Corp.) electronic health record software in 2009. A detailed explanation of Deep 6 is described below. A combination of keywords and Current Procedural Terminology (CPT) codes were used to identify all patients, aged 18 years or older, who underwent either a cervical or lumbar spinal laminectomy, discectomy, or spinal arthrodesis from 2010 to 2020 (**Supplemental Table 1**). A combination of keywords and International Classification of Diseases Ninth (ICD-9) and Tenth Revision (ICD-10) codes were used to exclude patients undergoing operations for intraspinal abscess, osteomyelitis, and surgical site infections (**Supplemental Table 1**).

Laminectomy/Discectomy	CPT-63001, CPT-63005, CPT-63012, CPT-63015, CPT-63017, CPT-63020, CPT-63030, CPT-63035, CPT-63040, CPT-63042, CPT-63043, CPT-63044 CPT-63045, CPT-63047, CPT- CPT-63048, CPT-63050, CPT-63075, CPT-63076
Spinal Arthrodesis	CPT-22533, CPT-22534, CPT-22551, CPT-22552, CPT-22554, CPT-22558, CPT-22585, CPT-22600, CPT-22612, CPT-22614, CPT-22630, CPT-22632, CPT-22633, CPT-22634
Intraspinal Abscess	ICD-9-CM-324.1, ICD-10-D-G06.1, ICD-10-D-G06.2
Osteomyelitis	ICD-9-CM-730.08, ICD-9-CM-730.18, ICD-9-CM-730.28, ICD-10-D-M86.18, ICD-10-D-M86.60, ICD-10-D-M86.9
Surgical Site Infection	ICD-9-CM-998.5, ICD-9-CM-998.51, ICD-9-CM-998.59, ICD-10-D-T79.2XXA, ICD-10-D-T81.4XXA

Legend: CPT, Current Procedural Terminology; ICD-9-CM, International Classification of Diseases Ninth Revision; ICD-10-D, International Classification of Diseases Tenth Revision

Supplemental Table 1: International Classification of Diseases Ninth and Tenth Revision codes and Current Procedural Terminology codes used for inclusion and exclusion criteria.

Eligible surgeries were restricted to those performed by an orthopedic or neurological spine surgeon and patients with at least one year of follow-up. A retrospective chart review was then performed of all patients identified by Deep 6 AI to have had a postoperative SSI (infection cohort). The Center for Disease Control and Prevention definition for SSI was adopted for this study: infection that occurs at or near the surgical incision within 30 days of the procedure (where day 1 is the procedure date) and involves the skin and subcutaneous tissue of the incision [9]. In a similar fashion, a second cohort of patients, over the same period, were identified (controls) by Deep 6 AI and individually matched to the infection cohort based upon age, sex, American Society of Anesthesiologists (ASA) class, DM, and smoking status using propensity score matching

Outcomes Measures

The primary outcome was to evaluate postoperative fasting blood glucose levels as an independent indicator for infection risk irrespective of patient age, sex, diabetes status, steroid use, and operation performed. Blood glucose levels during the perioperative period were obtained via daily morning fasting labs. Of note, several medical societies have published guidelines for perioperative glucose management and provide a general recommendation for patients without diabetes [7,10,11], often defining >140 mg/dL as a risk factor for complications. To identify a stricter threshold at which there is an increased risk for SSIs in patients undergoing spine surgery, we elected to evaluate average blood glucose levels over 5 days after surgery (<100 mg/dL, 100-119 mg/dL, 120-139 mg/dL, and ≥140 mg/dL).

In addition to fasting blood glucose levels, the following secondary variables were also measured to evaluate SSI risk: surgical approach, spinal segment operated upon, bone graft use, vancomycin powder use, drain use, ASA class, duration of surgery, pre-incision antibiotics, DM, smoking, sliding scale insulin postoperative, transfusion, and obesity.

Lastly, patient demographic information and past medical history were gathered.

Perioperative Management:

A standard perioperative management protocol applied in our institution was followed. All patients fasted overnight 6-8 hours before surgery. In the operating room, patients were placed under a forced air-warming blanket to prevent hypothermia throughout the duration of the surgery. Patients received a single dose of weight-based cefazolin or equivalent antibiotics prior to the skin incision. General anesthesia was administered after orotracheal intubation. No prophylactic antibiotics were prescribed postoperatively. Standard morning fasting labs were obtained for all patients after surgery.

Statistical Analysis:

All data was analyzed using IBM SPSS statistics, version 27.0. Descriptive statistics, such as Student's t test and Chi-Squared analyses, were used to compare patients with an SSI to those without. A multivariable regression model using the significant univariate variables was created to identify associations between preoperative patient demographics and surgical characteristics with the development of SSIs. Odds ratios (OR) with 95% confidence intervals (CI) are reported. The threshold for statistical significance in the model was 0.05.

Deep 6 AI Search Platform

Deep 6 AI platform uses a variety of AI and machine learning to identify both unstructured and structured key terms in a center's electronic medical database to perform precise matching of search terms rather than relying on a single algorithm. During a search query, over a hundred different clinical ontologies are combined to accurately recognize clinical concepts from unstructured or semi-structured data sources, such as progress notes, consult notes, and operation notes. A set of annotators then

parses all source data then it labels and stores clinical concepts in a graph database. At this step, different clinical notes or fields are turned into a multidimensional vector that can represent a patient, which then becomes a node in the network. Machine learning then integrates and helps disambiguate concepts, detect negations and hypotheticals, and reconcile different concepts. The results are then ranked based on a multifactor confidence score. A user can further query the results by creating searches against indexed patient graphs. Once a final query list has been generated, the user can then perform a detailed chart review of each patient queried from the software.

100 infection and 111 control patients were included in the final analysis. There were no differences between cohorts regarding patient age (p=0.45), sex (p=0.63), ASA class (0.13), DM diagnosis (p=0.25), smoking status (p=0.27), and vancomycin powder use (p=0.33) (Table 1). In the infection cohort, 84% (84/100) had a posterior surgery, 10% (10/100) had an Anterior Lumber Interbody Fusion (ALIF) with posterior instrumentation, 4% (4/100) had a stand-alone ALIF, and 2% (2/100) had a lateral transpsoas approach to interbody fusion. In the control cohort, 73% (81/111) had a posterior surgery, 6% (7/111) had an ALIF with posterior instrumentation, 13% (14/111) had a stand-alone ALIF, and 8% (9/111) had a lateral surgery (Table 2).

Results:

N (%)	Infection n=100, 47.3	Control n=111, 52.6	Total n=211	P-value
Age (year)	66.5 (±14.5)	67.9 (±14.0)	67.3 (±13.9)	0.45
Sex				0.63
Male	40 (40)	48 (43.2)	88 (41.2)	
Female	60 (60)	63 (56.8)	123 (58.3)	
BMI	30.3 (±6.9)	26.7 (±6.05)	28.4 (±6.7)	<.001
ASA class	2.7 (±0.5)	2.6 (±0.6)	2.45 (±0.6)	0.13
DM	17 (17.0)	26 (23.4)	43 (20.4)	0.25
Smoking	11 (11.0)	18 (16.2)	29 (13.7)	0.27

Legend: BMI, Body Mass Index; ASA, American Society of Anesthesiologists

Table 1: Patient Demographic Characteristics

Number of Patients N (%)	Infection (n=100, 47.3)	Control (n=111, 52.6)	Total (n=211)	P value
Surgical Approach				
Posterior	84 (84.0)	81 (73.0)	165 (78.1)	0.35
Stand-alone ALIF	4 (4.0)	14 (6.6)	18 (8.5)	0.01
ALIF with posterior instrumentation	3 (3.0)	7 (6.3)	17 (8.0)	0.14
Lateral transpsoas approach to interbody fusion	2 (2.0)	9 (8.1)	11 (5.2)	0.02
Spine Region				
Lumbar	84 (84.0)	100 (90.1)	184 (87.2)	<.001
Cervical	16 (16.0)	11 (5.2)	27 (12.7)	.46
Revision	77 (77.0)	0 (0)	77 (36.5)	<.001
Vancomycin Powder	10 (10.0)	7 (7.2)	17 (8.1)	0.33

Legend: ASA, American Society of Anesthesiology; BMI, Body Mass Index; DM, diabetes mellitus; ALIF, Anterior Lumbar Interbody Fusion

Table 2: Baseline Clinical and Surgical Characteristics

Univariate analysis showed that stand-alone ALIF procedures (OR 0.28, 95% CI 0.08-0.81, p=0.03) and lateral transpsoas approaches to interbody fusion (OR 0.21, 95% CI 0.03-0.86, p=0.05) were associated with a significantly decreased risk for surgical site infections (Table 3). On the other hand, average serum glucose levels between 120-139 mg/dL (OR 3.29, 95% CI 1.07-11.55, p=0.05) and ≥140 mg/dL (OR 8.12, 95% CI 2.67-28.21, p<0.001) within five days after surgery relative to an average serum glucose <100 mg/dL were found to be associated with a significantly greater risk for surgical site infections.

	OR (95% CI)	P-Values
Average Post-Op Glucose (mg/dL)		
<100	NA	NA
100-119	1.34 (0.46-4.49)	0.60
120-139	3.29 (1.07-11.55)	0.05
≥140	8.12 (2.70-28.22)	<0.001
Surgical Approach		
Posterior	NA	NA
Stand-alone ALIF	0.28 (0.08-0.81)	0.03
ALIF with posterior instrumentation	1.38 (0.50-3.96)	0.54
Lateral transpsoas approach to interbody fusion	0.21 (0.03-0.86)	0.05
Use of Allograft	1.08 (0.60-1.96)	0.80

ASA Class		
ASA 1	NA	NA
ASA 2	3.41 (0.55-66.11)	0.27
ASA 3	7.85 (1.29-150.61)	0.06
ASA 4	6.00 (0.38-182.92)	0.22
DM	1.94 (0.99-3.90)	0.06
Smoking	2.00 (0.90-4.59)	0.09
pRBC Transfusion	1.13 (0.48-2.66)	0.79
Legend: OR, odds ratio; CI, confidence interval; mg, milligram; dL, deciliter; ASA, American Society of Anesthesiology; DM, diabetes mellitus; pRBC Transfusion, packed red blood cell transfusion; ALIF, Anterior Lumber Interbody Fusion		

Table 3: Odds ratios with 95% confidence intervals comparing clinical and surgical Characteristics and risk of surgical site infection.

Multivariate logistic regression analysis using the significant univariate variables showed that average serum glucose levels ≥140 mg/dL within five days after the operation were found to be most predictive of surgical site infections (OR 7.68, 95% CI 1.85-37.76, p=0.01). A diagnosis of DM alone was not a significant risk factor (OR 0.63, 95% CI 0.25-1.56, p=0.32), as well as stand-alone anterior and lateral transpsoas approaches to interbody fusion (Table 4).

n (%)	Control (N = 111)	Infection (N = 100)	Adjusted OR (95% CI)	Adjusted P Values
Average Post-Op Glucose* (mg/dL)				
<100	17 (15.5%)	5 (5.0%)	NA	NA
100-119	56 (50.5%)	27 (27.0%)	1.02 (0.27-4.42)	0.97
120-139	21 (18.9%)	23 (23.0%)	2.83 (0.69-13.43)	0.16
≥140	17 (15.3%)	45 (45.0%)	7.68 (1.85-37.79)	0.01
Surgical Approach**				
Posterior	81 (72.9%)	84 (84.0%)	NA	NA
Stand-alone ALIF	14 (12.6%)	4 (4.0%)	0.37 (0.08-1.34)	0.15
ALIF with Posterior Instrumentation	7 (6.3%)	10 (10.0%)	2.45 (0.68-9.31)	0.18
Lateral transpsoas approach to interbody fusion	9 (8.1%)	2 (2.0%)	0.23 (0.03-1.12)	0.10
Use of Allograft	84 (76.6%)	66 (66.0%)	2.31 (0.74-8.01)	0.16
ASA Class*				
ASA 1	6 (5.4%)	1 (1.0%)	NA	NA
ASA 2	51 (45.9%)	29 (29.0%)	1.48 (0.20-31.13)	0.73
ASA 3	52 (46.8%)	68 (68.0%)	4.83 (0.69-99.39)	0.17
ASA 4	2 (1.8%)	2 (2.0%)	1.80 (0.07-75.55)	0.73
DM	17 (15.3%)	26 (26.0%)	0.63 (0.25-1.56)	0.32
Smoking	11 (9.9%)	18 (18.0%)	2.48 (0.90-7.17)	0.08
pRBC Transfusion	16 (14.4%)	24 (24.0%)	1.57 (0.64-3.88)	0.32
Legend: OR, odds ratio; CI, confidence interval; mg, milligram; dL, deciliter; ASA, American Society of Anesthesiology; DM, diabetes mellitus; pRBC Transfusion, packed red blood cell transfusion; ALIF, Anterior Lumber Interbody Fusion				
*OR relative to blood glucose < 100 mg/dL.				
** OR relative to posterior approach.				
*** OR relative to ASA 1.				

Table 4: Adjusted odds ratios with 95% confidence intervals comparing clinical and surgical Characteristics and risk of surgical site infection.

Discussion:

The present study demonstrated that an elevated postoperative serum glucose ≥140 mg/dL was associated with an increased risk of SSI compared to patients with serum glucose less than 100 mg/dL. Postoperative serum glucose levels between 100-119 mg/dL and 120-129 were not associated with increased risk of infection compared to patients under 100 mg/dL. Additionally, we found that DM alone was not a significant risk factor for SSI on univariate analysis. The present study adds to the body of literature of perioperative glycemic control and gives a unique perspective on the importance of glucose control in patients undergoing spine surgery, irrespective of DM status [6,12–15].

Historically, orthopaedic literature has focused on DM as a risk factor for SSI, using glycosylated hemoglobin (HbA1c) as a biomarker to assess glycemic control in the preoperative setting [16-18]. Yet, studies found that using diabetes status alone or HbA1c thresholds, as a proxy to predict hyperglycemia, are of poor predictive value [19–22]. Instead, it has been suggested that hyperglycemia, and a postoperative measure, may be a stronger predictor of SSIs than DM itself or HbA1c levels, especially when other factors are considered in multivariable analyses [23]. Furthermore, in patients without DM, HBA1c levels are infrequently checked, which hinders the utility of these studies to the average spine patients undergoing surgery. The role of postoperative fasting blood glucose levels has gained attention across other surgical subspecialties. In

the joint arthroplasty, general surgery, and cardiothoracic surgery literature, hyperglycemia has been shown to be associated with an increased risk for perioperative infection, with postoperative values being more closely related to infection risk than preoperative values [6,8,24,25].

In this study, we found that elevated serum glucose in the postoperative setting increased the risk of SSI. Considering the impact of SSI on patient morbidity and healthcare costs, it is critical to understand and describe a safe target range of glucose levels for those undergoing spine surgery. Kheir et al. [6] performed a retrospective review of 24,857 primary total joint arthroplasties between 2001 and 2015 and found that the relationship between postoperative blood glucose levels and periprosthetic joint infections increased linearly, with an optimal cutoff of 137 mg/dL. In this study, our cutoff was identified to be ≥140 mg/dL. Similarly, Upadhyaya et al. identified glucose levels ≥140 mg/dL placed patients at a more than two-fold increase (OR 2.19; 95 % CI 1.13, 4.25) in the likelihood of revision surgery for infection [26], however the study did not stratify glucose levels in greater detail.

Our findings, and those from the joint arthroplasty literature [6], suggest that immediate and strict postoperative glycemic control may play an important role in reducing postoperative SSIs after orthopaedic procedures, irrespective of DM status. However, despite our findings, target glucose ranges can depend upon the patient and their comorbidities in the context of their operation and the implications of overtreating glycemic levels. Many studies have reported that anterior approaches are at lower risk for SSI [27]. A recent systematic review and meta-analyses found that the incidence of SSI in posterior approach surgery was more than twice anterior approach surgery (5.0% vs. 2.3%) [27]. In this study, we found that anterior and lateral approaches had a lower risk for SSI in the univariant analysis but lost statistical significance in the multivariant analysis. Additionally, previous studies have investigated the efficacy of adjunctive vancomycin powder and found that it lowers the risk of SSI [27,28]. In this study, no difference between groups was found. Notably the use of vancomycin powder was infrequent (overall incidence: 8.1%), significantly underpowering our findings. Future well-designed randomized controlled trials are warranted to investigate the effect of implementing various postoperative glucose strategies post spine surgery.

This study has inherent limitations, which should be considered in the context of our findings. First, the present study is a single-center retrospective study, which not only depends on the quality, availability, and accuracy of existing medical records, but also carries its own inherent biases that may not be generalizable to the general population. Second, it is important to realize that glucose measurements represent a snapshot in time in the perioperative setting, rather than the course of the patient's inpatient stay. However, glucose values in this study were obtained via routine fasting blood chemistry each morning at 0600. Third, preoperative HbA1c data was not included in our analyses because values were only available in patients with DM and the focus of this study was on postoperative hyperglycemia irrespective of DM diagnosis. Lastly, while propensity score matching can control for measured confounding variables, it cannot adjust for unmeasured variables, which may bias the estimated outcome. Using larger matched cohorts could increase the statistical power of our study, potentially improving the robustness of our findings. While our study was designed to have adequate power to detect small to medium effect sizes, it may lack the sensitivity to detect larger treatment effects. Nonetheless, we believe our findings are strengthened by the fact that cohorts are similar in terms of age, sex, ASA score, DM diagnosis, and smoking status. Furthermore, the strength of our study is its applicability to the average patient undergoing spine surgery. It does not require any additional preoperative testing. With our findings,

actionable changes can be implemented to reduce one potential risk factor for surgical site infections.

Conclusions:

Postoperative blood glucose levels ≥140 mg/dL increased the risk of SSI compared to those with postoperative blood glucose <100 mg/dL, in the setting of spine surgery independent of a DM diagnosis. DM diagnosis itself is not found to be a significant independent risk factor for SSI during spine surgery in this series. The present study suggests that perioperative glycemic control may play an important role in reducing postoperative infections for patients after spine surgery highlights the importance of tight glycemic control in the immediate perioperative setting.

Disclosures:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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