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Association between elevated pre-operative glycosylated hemoglobin and post-operative infections after non-emergent surgery

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HIGHLIGHTS

- This study reviews the impact of pre-operative HbA1c across many specialties undergoing elective surgery.
- The risk factors of post-operative infection are multiple and likely synergistic.
- Elevated serum HbA1c is not independently associated with an increased risk of post-operative infection.

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ABSTRACT

Background: A chronic state of impaired glucose metabolism affects multiple components of the immune system, possibly leading to an increased incidence of post-operative infections. Such infections increase morbidity, length of stay, and overall cost. This study evaluates the correlation between elevated pre-operative glycosylated hemoglobin (HbA1c) and post-operative infections.

Study design: Adult patients undergoing non-emergent procedures across all surgical subspecialties from January 2010 to July 2014 had a preoperative HbA1c measured as part of their routine pre-surgical assessment. 2200 patient charts (1100 < 6.5% HbA1c and1100 ≥ 6.5% HbA1c) were reviewed for evidence of post-operative infection (superficial surgical site infection, deep wound/surgical space abscess, pneumonia, and/or urinary tract infection as defined by Centers for Disease Control criteria) within 30 days of surgery.

Results: Patients with HbA1c < 6.5% and those with HbA1c ≥ 6.5% showed no statistically significant difference in overall infection rate (3.8% in the HbA1c < 6.5% group vs. 4.5% in the HbA1c ≥ 6.5% group, $p = 0.39$). Both linear regression and multivariate analysis did not identify HbA1c as an individual predictor of infection. Elevated HbA1c was, however, predictive of significantly increased risk of post-operative infection when associated with increased age (≥81 years of age) or dirty wounds.

Conclusions: The risk factors of post-operative infection are multiple and likely synergistic. While pre-operative HbA1c level is not independently associated with risk of post-operative infection, there are scenarios and patient subgroups where pre-operative HbA1c is useful in predicting an increased risk of infectious complications in the post-operative period.

1. Introduction

Studies have suggested that pre-existing diabetes mellitus (DM) and hyperglycemia are predictors of post-operative complications in patients undergoing cardiac, bariatric, vascular, orthopedic and colorectal surgery [1–5]. Commonly, these complications are infectious in etiology, with superficial surgical site infections (SSIs), deep wound infections and surgical space abscesses, urinary tract infections (UTIs), and pneumonia (PNA) accounting for a large percentage of these infectious complications [6].

It has also been suggested that optimizing a patient's pre-operative glycemic control (<7% glycosylated hemoglobin) may reduce post-operative infections in non-cardiac surgery patients [7]. And while tight post-operative control of a patient's blood glucose has been shown to reduce the incidence of infectious complications in post-operative patients, a review of pre- and post-

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operative glycemic control protocols concluded that there is still insufficient evidence to determine what role strict glycemic control plays in reducing SSIs and other relevant post-operative infections [8–10]. Subsequently, there continues to be some uncertainty regarding the risk of infection associated with patients with a known history of diabetes and derangements in peri-operative blood glucose levels and what should be done in the pre- and post-operative period to mitigate these risk factors.

A challenge often cited in determining the effectiveness of any protocol to optimize blood glucose is the transient nature of hyperglycemia and the multiplicity of factors and events that may influence blood glucose levels, especially in the post-operative period [11]. Alternatively, there has been long-standing interest in the use of glycosylated hemoglobin (HbA1c) levels for screening and the identification of patients with impaired glucose metabolism and diabetes mellitus (DM). In June 2009, an International Expert Committee issued a consensus report recommending that a HbA1c level greater than or equal to 6.5% be used to diagnose diabetes mellitus, and the American Diabetes Associated affirmed this recommendation [12].

What is known is that post-operative infections across all patient subtypes and surgical specialties increase morbidity, length of stay, and overall cost [13,14]. Additionally, there is evidence demonstrating that a chronic state of impaired glucose metabolism weakens multiple components of the immune system, and it has been postulated that these impairments of the immune system may contribute to the development of post-operative infections [15–17].

The present study was designed to assess the correlation between pre-operative HbA1c and the incidence of post-operative infections in surgical patients undergoing non-emergent operations. Our hypotheses were: diabetic patients (defined as those with a HbA1c $\geq$ 6.5%) are at increased risk of post-operative infection; elevated HbA1c is an independent risk factor for post-operative infections and higher pre-operative levels are associated with increased risk; and if HbA1c is not an independent risk factor, there are specific patient groups and/or scenarios where an elevated HbA1c increases the likelihood of a patient developing a post-operative infection.

2. Methods

This study was reviewed and approved by the Human Research Committee of the Institutional Review Board at Mount Sinai Beth Israel (IRB #178-14) as a retrospective study. Beginning in January of 2010, adult patients undergoing non-emergent procedures had a pre-operative serum hemoglobin A1c (HbA1c) level included in the routine pre-operative testing performed for each patient. Patients included in the study were those undergoing general surgery including vascular, orthopedic, gynecology, otolaryngology, urology, plastic surgery, ophthalmology, and neurosurgery procedures. Patients undergoing both inpatient and outpatient procedures were included.

That national rate of surgical site infection published by the Centers for Disease Control (CDC) of 1.9% across all surgical procedures, assuming a large percentage of elective procedures with clean wounds, was used as a hypothesized rate of infection seen in non-diabetic (pre-operative HbA1c < 6.5%) individuals presenting for non-emergent surgery. From previously published studies reporting the increased rates of SSI, UTI, and PNA in patients with DM (about a two-fold increase), we hypothesized a rate of infection near 4% for patients with a pre-operative HbA1c $\geq$ 6.5% and used these hypothesized rates in our power analysis before beginning this study [18,19].

Assuming 80% power, the hypothesized rates of infection suggested that 1100 patients in each of the <6.5% HbA1c group and the $\geq$6.5% group would be needed to appropriately compare the two groups and be able to draw valid comparative conclusions. Subsequently, the first 1100 consecutive patients in each group to undergo non-emergent surgery were recorded and included in the medical record review and analysis.

Charts were reviewed for details of the procedure, post-operative course, and evidence of post-operative infection during the 30 days following surgery. Pre-operative white blood cell count was also recorded and patient charts were reviewed for evidence of pre-existing infection. Patients believed to have had a pre-existing, pre-operative infection were excluded from the analysis. Also, if an attending physician acted on his or her own to optimize a patient's pre-operative HbA1c prior to the procedure, only the most recent pre-operative HbA1c was considered for this analysis.

Operative reports were reviewed and each procedure was assigned to a wound classification of either clean, clean/contaminated, contaminated, or dirty [20]. Recognizing the wide range of procedures within each surgical specialty, procedures were also grouped into low, medium, and high surgical risk classification according to the Modified Johns Hopkins Surgical Criteria [21,22].

Patient charts were further reviewed for evidence of post-operative infection in the 30 days following their procedure using the CDC criteria for nosocomial infections, specifically surgical site infection including both superficial and deep wound infection/surgical space abscess, urinary tract infection, and pneumonia [23,24]. Surgical site infection was considered positive with either the isolation of an organism in an aseptically collected culture or with documented purulence, pain, redness, tenderness, and/or swelling and suspicion of surgical site infection upon physical exam. Pneumonia was considered present with physical examination findings, including the onset of purulent sputum, consistent with PNA and the initiation of treatment for PNA and/or the isolation of pathogen from a sputum sample. PNA was also considered present if focal consolidation was identified on radiographic imaging. UTI required documented symptoms of UTI (either fever, urgency, frequency, dysuria, suprapubic tenderness) along with a positive urinalysis and/or positive urine cultures with 10^5 colony-forming units of no more than two different organisms. Deep wound/surgical space abscess required isolation of cultured organism upon drainage or re-operation.

Statistical analysis was performed using Stata release 14.0 (StataCorp (2015) *Stata Statistical Software: Release 14*. College Station, TX) and R Version 3.2.0 (The R Foundation for Statistical Computing (2015). Vienna, Austria). The overall impact of the effect of each of the major predictor variables was evaluated using logistic regression. The presence of any type of infection (SSI, deep wound infection/surgical space abscess, UTI, PNA) was modeled as a binary outcome against gender, wound type, surgical risk classification, age in years, and preoperative HbA1c [25].

3. Results

Medical record review and statistical analysis was completed for 2200 patients. In both groups, the vast majority of the procedures were classified as clean wounds (Table 1). Orthopedic procedures made up 69% of the procedures in the <6.5% group and 60% of the procedures in the $\geq$6.5% group. Other surgical services were generally equally represented between the two groups with the <6.5% group having a higher number of gynecologic surgery procedures and the $\geq$6.5% group having a much higher number of vascular procedures. The group with HbA1c $\geq$ 6.5% included significantly higher numbers of high-risk procedures, many of which were vascular operations. The higher number of moderate risk procedures in the <6.5% group was mostly due to the higher