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Hyperglycemia and risk of adverse outcomes following microvascular reconstruction of oncologic head and neck defects

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A R T I C L E I N F O

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A B S T R A C T

Introduction: Our aim is to examine the correlation between perioperative hyperglycemia and post-operative outcomes following microvascular reconstruction of head and neck defects.
Patients and methods: Retrospective review of a prospectively collected database of 350 consecutive patients who underwent microvascular reconstruction of malignant head and neck defects over a 2 year period. The relationship between perioperative hyperglycemia (≥ 180 mg/dL) and the incidence of the following complications was evaluated: flap loss, flap-related complications and surgical site infections (SSI). Sub-group analysis based on timing of hyperglycemia was also performed.
Results: We identified 313 patients (89.4%) in the normoglycemic group and 37 patients (10.6%) in the hyperglycemic group. Baseline demographics, tumor stage, operative variable were comparable. There were no significant differences in flap-related complications and overall mortality. SSI were significantly higher in the hyperglycemic cohort (48% *vs.* 28%, $p = 0.01$). On multivariate analysis, hyperglycemia [OR 2.07; 95% CI, 1.87–4.89], perioperative insulin administration [OR 4.805; 95% CI, 2.18–10.60], prolonged operative time [OR 1.003; 95% CI, 1.002–1.025] and higher Charlson co-morbidity indices [II: OR 2.286 & III: OR 2.284] were independent predictors of SSI. On sub-group analysis, only patients with early (POD 1) post-operative hyperglycemia had a significant OR for SSI (OR 1.88; 95% CI, 1.07–3.29).
Conclusion: Our findings suggest that perioperative hyperglycemia, specifically during the first 24 h post-operatively, is associated with SSI in microvascular head and neck reconstruction. This association highlights the need for strict screening of head and neck patients for hyperglycemia especially in the immediate post-operative period.

Introduction

Ample evidence of the deleterious effects of poor glycemic control on clinical outcomes following major surgical procedures have emerged over the past two decades [1]. Increased post-operative complications have been reliably associated with hyperglycemia in patients undergoing mastectomy [2], colon resection [3], vascular surgery [4], hernia repair [5] and cardiac surgery [6]. The literature is particularly robust with respect to the link between tight glycemic control and a decreased incidence of post-operative infections following cardiac surgery [7,8]. Equally noteworthy, is the fact that this relationship appears to be independent of a primary diagnosis of diabetes [1,5]. This is pertinent because (a) unrecognized insulin resistance is prevalent amongst surgical patients [1,9–11] and (b) the relationship between hyperglycemia and adverse clinical outcomes holds for both the early postoperative period (within 24–48 h of surgery) and entire hospitalization [12].

In the face of wide-spread recognition that hyperglycemia is a modifiable and sensitive predictor of poor post-operative outcomes [11], there is still limited data on its impact on the outcomes of patients who undergo major head and neck cancer operations – a population concomitant with a high burden of co-morbid conditions [13]. In particular, there is a dearth of information on the interaction between the timing of hyperglycemia i.e. *before* or *during* the post-operative period and the rates of microvascular and overall complications. Such an

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understanding will facilitate the development of precise instruments for risk-stratification [14] and outcomes optimization. We hypothesize that patients with perioperative hyperglycemia will experience higher rates of infectious and flap-related complications relative to their normoglycemic counterparts.

Patients and methods

A retrospective cross-sectional study was performed using a prospectively maintained database of all microvascular reconstructions performed at Chang Gung Memorial Hospital, a tertiary academic medical center in Taoyuan, Taiwan. We identified all patients who underwent microvascular reconstruction of a head and neck defect following oncologic extirpation between June 2013 and December 2014. Patients < 18 years of age, patients without a pre-operative glucose measurement and patients with incomplete medical records were excluded from analysis. Patients with preoperative infection (systemic or localized to the head and neck region) were also excluded from the study. Following the application of exclusion criteria, patients were assigned to two mutually exclusive groups and categorized as either normoglycemic, defined as a serum blood glucose level of less than 180 mg/dL or hyperglycemic, which was defined as a serum blood glucose level of greater than 180 mg/dL [11]. Our cut-off level for hyperglycemia is consistent with recommendations of the American Diabetes Association for ideal random blood glucose level in non-critically ill patients [15]. Designation to the perioperative hyperglycemia cohort was based on pre-operative fasting glucose measurements obtained prior to incision on the day of surgery [11], and/or the highest serum blood glucose obtained during the first 24 h after surgery.

The corresponding medical records were then reviewed for data related to patient demographics, perioperative variables and clinical outcomes. Patient-level data included age, gender, body mass index (BMI, kg/m^2), preoperative nutritional status (serum albumin, g/dL), active smoking history (< 4 weeks prior to surgery), clinical diagnosis of diabetes mellitus, preoperative glycosylated hemoglobin (HbA1c), history of radiation therapy (RT), and clinicopathologic characteristics (TNM, overall stage). Baseline co-morbidities were assessed and quantified according to the Charlson Comorbidity Index (CCI).

The operative records were abstracted to confirm the operative time, estimated blood loss (EBL), incidence of at least one intra-operative blood transfusion, flap size, ischemia time and type of free flap utilized. The specific types of free tissue transfer included the following flaps: Anterolateral thigh (ALT), Free Fibula (FF), Medial Sural Artery Perforator (MSAP), and other. Per institutional protocol, all patients received preoperative antibiotic prophylaxis, typically Cefazolin, one hour before surgical incision and were admitted to the intensive care unit (ICU) in the immediate post-operative period. Normothermia (36–38 °C) was maintained throughout the peri-operative period [5]. With regard to insulin use, a binary classification was used to identify patients as receiving perioperative insulin or not. In other words, patients are considered to have received insulin if they are administered insulin at any time point in the perioperative period. Detected episodes of hyperglycemia were promptly treated with a dose of soluble rapid-acting insulin and an endocrinology consult was ordered for prospective management. The dosage of administered insulin was proportionate to the degree of hyperglycemia i.e. sliding scale approach.

Our primary outcomes of interest were the following: acute flap loss within seven days of surgery [16], major microvascular flap-related complications (arterial or venous thrombosis, and recipient site hematoma) within seven days of surgery [16] and post-operative surgical site infections (SSI) as defined by clinical identification of erythema, purulent discharge or wound dehiscence at the recipient or donor site within the first 30 days after surgery [11]. Secondary outcomes included inpatient mortality, unplanned re-intubation, EBL, and length of stay (ICU and Hospital). Finally, sub-group analysis was performed in order to scrutinize the relationship between the timing of hyperglycemia, i.e. pre-operative versus early post-operative, and the incidence of SSI [11]. Pre-operative hyperglycemia was defined as within 24 h prior to the day of surgery while post-operative hyperglycemia was defined as within 24 h after surgery.

Continuous data are presented as means and standard deviations while categorical data are expressed as frequencies and percentages. Group comparisons were performed using Fisher's exact testing and Wilcoxon signed rank sum test for categorical and continuous variables, respectively. Logistic regression was used to determine whether certain co-variates (i.e. patient-level characteristics) were associated with the occurrence of wound infection, flap loss and acute microvascular, flap-related complications. All analyses were performed using SAS software, version 9.1 (SAS Institute Inc., Cary, NC). All p-values were two-sided and values < 0.05 were considered statistically significant. This study was approved by the Institutional Review Board (IRB) at Chang Gung Memorial Hospital, Taoyuan, Taiwan and performed in accordance with the ethical standards of the Helsinki Declaration.

Results

Demographics

The overall study cohort comprised of 350 consecutive patients with 313 patients (89.4%) in the normoglycemic group and 37 patients (10.6%) in the hyperglycemic group. Demographics and clinicopathologic characteristics of the two groups are summarized in Table 1. The two groups were comparable with respect to gender predominance, age, BMI, active smoking history, pre-operative hemoglobin, pre-operative albumin, tumor location, overall stage, and pre-operative RT. Greater prevalence of ASA III/IV (94.6% *vs.* 77.3%, $p = 0.014$), pre-existing diagnosis of diabetes (83.8% *vs.* 18.2%, $p < 0.001$) and a higher CCI on admission ($p < 0.001$) were noted in the hyperglycemic cohort. Lastly, the pre-operative HbA1c value was significantly higher in the hyperglycemic cohort (8.53 ± 2.12 *vs.* 6.05 ± 1.05, $p < 0.001$).

Operative variables

Operative characteristics of the two groups are summarized in Table 2. There were no statistically significant differences noted between the two groups with respect to flap size, operative duration, EBL, flap type and frequency of intra-operative blood transfusions. The fasciocutaneous ALT was the most common donor site in both the normoglycemic (65.3%) and hyperglycemic (67.6%) cohorts.

Clinical outcomes

Morbidity with respect to incidence of flap complications, unplanned re-intubation and length of stay (ICU/hospital) was not significantly different between the two groups (Table 2). The incidence of SSI for the entire study cohort was 29.4% (n = 106). Of note, there were no donor site infectious complications noted. Therefore, all SSI occurred at the head and neck recipient bed. A significantly higher incidence of SSI was appreciated in the hyperglycemic cohort (48% *vs.* 28%, $p = 0.01$) (Fig. 1a). A pattern of sustained hyperglycemia was also observed among those patients who developed SSI. The rates of arterial occlusion, venous occlusion, neck hematoma and acute flap loss were comparable between the two groups (Fig. 1b). On multivariate analysis evaluating the effect of perioperative glycemic control (see Table 3), hyperglycemia, perioperative insulin requirement, operative duration, and Charlson index scores of 2 and 3 were identified as independent risk factors for a postoperative SSI. No risk factor associations were identified on regression analysis for flap loss and acute flap complications, although prolonged operative duration exhibited a trend towards significance for predicting acute flap loss ($p = 0.058$).

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