Early Post-operative Glucose Levels are an Independent Risk Factor for Infection after Peripheral Vascular Surgery. A Retrospective Study

T.M. Vriesendorp,1* Q.J. Morélis,1 J.H. DeVries,1 D.A. Legemate2 and J.B.L. Hoekstra1

Departments of 1Internal Medicine, and 2Surgery, Academic Medical Centre, Amsterdam, The Netherlands

Objective. To evaluate whether hyperglycaemia in the first 48 h after infrainguinal vascular surgery is a risk factor for post-operative infection, independent from factors associated with insulin resistance and surgical stress.

Design. Retrospective cohort study.

Patients and methods. Patients who underwent infrainguinal vascular surgery in our hospital between March 1998 and March 2003 were included. Glucose values until 48 h after surgery were retrieved from laboratory reports. Post-operative infections, treated with antibiotics, during hospital stay were scored until 30 days after surgery. Data were analysed with univariate and multivariate logistic regression analyses.

Results. At least one post-operative glucose value was retrieved for 211/275 (77%) patients. The incidence of post-operative infections was 84/275 (31%). When corrected for factors associated with insulin resistance and surgical stress, post-operative glucose levels were found to be an independent risk factor for post-operative infections (odds ratio top quartile versus lowest quartile: 5.1; 95% confidence interval: 1.6–17.1; P=0.007).

Conclusion. Post-operative glucose levels appear to be an independent risk factor for infections after infrainguinal vascular surgery. This finding requires confirmation in a prospective study.

Keywords: Peripheral vascular surgery; Infections; Post-operative hyperglycaemia.

Introduction

Infections after infrainguinal vascular surgery are associated with an increased risk of post-operative death and limb loss.1–4 Furthermore, post-operative infections lengthen in-hospital stay and increase in-hospital costs.5 Post-operative infections, especially wound infections, occur frequently after infrainguinal vascular surgery: the reported incidence of post-operative wound infections varies between 5 and 25%.5,6 Several risk factors for post-operative infections after peripheral vascular surgery have been described: duration of surgery was found to be an independent risk factor for post-operative wound and graft infection after peripheral surgery.7 Other factors reported to be associated with post-operative infection after infrainguinal vascular surgery are incision site, body mass index (BMI), female gender, age, chronic steroid use and diabetes mellitus.8–10

Recently, there has been increased interest in post-operative glucose metabolism and complications after surgery, both in patients with and without diabetes mellitus. Intensive insulin therapy, aiming for blood glucose values between 4.4 and 6.1 mmol/l, in a (cardio)surgical intensive care unit reduced morbidity and mortality.11 The reduction in mortality was mainly attributed to the reduction of deaths due to multi-organ failure with a septic focus, and the need for prolonged treatment with antibiotics was reduced in the group treated with intensive insulin therapy.11 Post-operative hyperglycaemia is an easily modifiable risk factor, unlike most other potential risk factors for post-operative infections. If post-operative hyperglycaemia proves to be an independent risk factor for infections after peripheral vascular surgery, intensive insulin therapy may reduce post-operative infection risk.

We investigated whether post-operative glucose levels are an independent risk factor for post-operative infections in a retrospective cohort of patients undergoing peripheral vascular surgery.

* Corresponding author. Titia Vriesendorp, MD, Department of Internal Medicine, Academic Medical Centre, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands.
E-mail address: t.m.vriesendorp@amc.uva.nl (T.M. Vriesendorp).

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Patients and Methods

Patients

All patients who underwent infrainguinal vascular reconstruction between March 1st 1998 and March 1st 2003 in the Academic Medical Centre in Amsterdam, a tertiary teaching hospital, were included. If there was more than one reconstruction during the study period, only the first procedure was included in the analysis. Patients who underwent surgery because of trauma induced vascular damage were excluded.

Data collection

Glucose values obtained in the first 48 h after completion of surgery were retrieved from laboratory reports. Glucose values were determined automatically with each blood gas analysis. It was thus possible that in the sickest patients more blood gas analyses were taken. To correct for this, all available glucose values were averaged per patient. Other possible risk factors for infections we considered were sex, age, history of diabetes mellitus, BMI, preoperative Fontaine classification, American Society of Anesthesiologists (ASA) classification, previous myocardial infarction, smoking habit, steroid use at admission, type and location of surgery, bypass graft used, duration of surgery and rank of surgeon. These data were retrieved from inpatients charts and surgical reports.

The occurrence of post-operative infection was scored from review of the inpatient charts. Infections were scored only when treated with antibiotics, and only when they occurred during hospital admission within 30 days after surgery. Post-operative infections included wound infections, graft infection, pneumonia, urinary tract infection, catheter related infection and sepsis.

Prophylactic antibiotic treatment

Standard prophylactic antibiotic treatment for all patients undergoing infrainguinal vascular surgery consisted of 2000 mg cefamandol on arrival in the operating room and in cases of vascular reconstruction with autologous material a further 1000 mg cefamandol after skin closure. If prosthetic material was used an additional 1000 mg cefamandol was given every 6 h for the first 24 h after surgery.

Analysis

Univariate logistic regression analysis was used to select potential risk factors for post-operative infections. Variables with $P<0.1$ in univariate regression analysis were considered to be potential risk factors for post-operative infections and were selected for multivariate logistic regression analysis. Multivariate regression analysis or ‘best model analysis’ was used to define the independent contribution of potential risk factors. A regression coefficient is determined by fitting a regression line adjusting for all other variables in the model. In logistic regression analysis, the antilogarithm of the regression coefficient equals the odds ratio.$^{12}$

Results

In total, 275 patients were identified. Patient characteristics and procedure details are summarised in Tables 1 and 2. At least one post-operative glucose value was retrieved in 211/275 (77%) patients, median 3 values per patient (interquartile range: 1–6). Mean post-operative glucose values were divided into quartiles because of non-parametric distribution. The median post-operative glucose level was 6.5 mmol/l (interquartile range: 5.7–8.4 mmol/l).

At least one post-operative infection occurred in 84/275 patients (31%). Most were wound infections (62/275; 23%), followed by pneumonia (20/275; 7.3%), urinary tract infections (5/275; 1.8%), sepsis (4/275; 1.5%) and graft infections (2 out of 186 patients undergoing bypass surgery; 1.0%). No catheter related infections were found. Median length of stay was 13 days (range 1–121).

In univariate logistic regression analysis, there was no association between the occurrence of post-operative infection and a history of myocardial infarction, smoking habit, type of graft used, preoperative steroid use and location of surgery (all $P>0.1$). In univariate logistic regression analysis, post-operative hyperglycaemia was associated with post-operative infection (odds ratio top quartile versus lowest quartile: 3.2; 95% CI: 1.4–7.6; $P=0.005$, (Fig. 1). Other variables associated with post-operative infection were: higher preoperative Fontaine classification ($P=0.001$), higher rank of surgeon ($P=0.005$), female sex ($P=0.021$), older age ($P=0.003$), longer duration of surgery ($P=0.033$), higher BMI ($P=0.005$) and presence of diabetes mellitus ($P=0.044$).

Parameters with a $P$-value $<0.1$ in univariate regression analysis (also including ASA category, $P=0.083$) were analysed with multivariate regression
Multivariate regression analysis showed that higher post-operative glucose levels were associated with an increased occurrence of post-operative infections (odds ratio top quartile versus lowest quartile: 5.1; 95% CI: 1.6–17.1; \( P = 0.007 \)).

**Discussion**

Our study indicates that in a cohort of patients undergoing infrainguinal surgery increased post-operative glucose levels are a risk factor for the occurrence of post-operative infections, independent of factors associated with insulin resistance, such as diabetes mellitus and BMI, and of duration of surgery as an indicator of surgical stress.

Patients with diabetes mellitus are twice as likely to develop a post-operative infection.\(^{13}\) It is unknown whether post-operative hyperglycaemia is responsible for this increased risk, or whether it is explained by diabetes related complications, such as microvascular damage, or insulin resistance per se. Interestingly, we found type 2 diabetes mellitus to be associated with fewer post-operative infections, when corrected for post-operative glucose levels (Fig. 2). So how can it be explained that hyperglycaemia was a risk factor for post-operative infections, whereas diabetes mellitus was not?

Patients without a diagnosis of diabetes mellitus are less likely to be treated with insulin for preoperative and post-operative hyperglycaemia.\(^ {14}\) Insulin has been reported to have an anti-inflammatory effect,\(^ {15}\) and it is thus possible that the reduced risk for infections in patients with type 2 diabetes mellitus, corrected for post-operative hyperglycaemia, reflects the beneficial effects of insulin therapy. It is debatable whether beneficial effects of aggressive glucose lowering with insulin therapy found in the intensive care unit can be attributed to lowering hyperglycaemia or to the anti-inflammatory effects of insulin therapy.\(^ {11}\) In a post hoc analysis, the improved survival and the reduction of prolonged inflammation was attributed to both lower glucose levels and higher insulin dosages.\(^ {16}\) This supports our hypothesis that hyperglycaemia is a risk factor for post-operative infections, but that insulin therapy may also have an independent beneficial effect in preventing post-operative infections.

A recent study found that longer duration of surgery was the only independent risk factor for post-operative wound and graft infections.\(^ {7}\) It can be argued that post-operative hyperglycaemia is just a secondary phenomenon caused by surgical stress and that there is no causal relationship between post-operative hyperglycaemia and post-operative infections.
infections. However, we found that high post-operative glucose levels predicted occurrence of post-operative infections independent of the duration of surgery.

Post-operative hyperglycaemia also was reported to be an independent risk factor for post-operative infections in patients with, and without diabetes mellitus who underwent coronary artery bypass grafting (CABG).\textsuperscript{17,18} However, one study reported only a significant trend in the occurrence of post-operative infections\textsuperscript{19} and two studies reported no relationship between post-operative hyperglycaemia and post-operative infections in patients undergoing CABG.\textsuperscript{20,21} The mechanisms by which acute hyperglycaemia increases the risk of post-operative infection risk are unclear. In vitro studies have shown that patients with diabetes mellitus may have an impaired immune response, and that abnormalities in immune function can partially be reversed by better glucose control.\textsuperscript{22–25} Furthermore, acute hyperglycaemia may

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Fig. 1. Results of univariate analysis. Percentage of patients with at least one post-operative infection per post-operative glucose quartile. $P$ for trend $= 0.003$; $P = 0.006$; $P = 0.28$; $P = 0.69$.

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Fig. 2. Results of multivariate analysis. ASA = American Society of Anesthesiologists.
aggravate tissue ischemia through a vasoconstrictive effect, mediated by free oxygen radicals.\textsuperscript{26}

Infections occurred frequently in our cohort, almost one-third (31\%) of all patients developed at least one post-operative infection. Wound infections accounted for most of the post-operative infections (in 23\% of patients). The reported incidence of post-operative wound infections after the introduction of perioperative prophylaxis with antibiotics varies between 5 and 25\%, with higher incidences reported after distal procedures.\textsuperscript{5,6} We also observed that more infections occurred in patients who underwent distal procedures, however, this was not statistically significant.

We have no secure explanation for the high incidence of post-operative infection in our cohort. Possibly patients with a worse clinical condition and more complicated vascular disease are referred to our tertiary teaching hospital. Infections were scored retrospectively and not by the official Centre of Disease Control (CDC) criteria, and this also may have influenced our results.

An important limitation of this study is the retrospective data collection. For a considerable number of patients no post-operative glucose values were available (23\%). However, patients with missing post-operative glucose values did not appear to have a different risk for post-operative infections (Fig. 1). Secondly, timing and number of post-operative blood glucose values were not standardised between patients, and this may have influenced our results. Thirdly, infections themselves can cause insulin resistance and subsequent hyperglycaemia. Theoretically, it is possible that we observed the inverse relationship: infections that occurred within 48 h after surgery may have caused hyperglycaemia. We have no information on the temporal relationship between glucose values and the occurrence of infections in our cohort. In a previous study on risk factors for wound and graft infections in infrainguinal surgery, the mean time to the onset of infections was reported to be 21 days (range 3–135 days),\textsuperscript{7} so we consider this inverse relationship unlikely. Furthermore, when we repeated our analysis with glucose values collected within 24 h after surgery, post-operative hyperglycaemia remained an independent risk factor for post-operative infections (odds ratio top versus lowest quartile 4.1; 95\% confidence interval 1.2–13.5; \textit{P}=0.02). Another limitation is the relatively small number of procedures included in the analysis, resulting in wide 95\% confidence levels, especially for categorical variables.

In conclusion, our data indicate that higher post-operative glucose levels are an independent risk factor for post-operative infections in peripheral vascular surgery, and that post-operative infections are a very frequent complication in this patient group. Post-operative hyperglycaemia is a modifiable risk factor and thus a potential target for treatment. Because of the limitations of a retrospective study, confirmation of these results in a prospective study seems warranted. If such a study confirms our findings, the next step would be a randomised clinical trial with intensive insulin therapy in patients who undergo peripheral vascular surgery, with the aim of reducing post-operative infection.

References


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