Blood glucose level on postoperative day 1 is predictive of adverse outcomes after cardiovascular surgery

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Received 17 October 2008; received in revised form 7 June 2009; accepted 12 June 2009
Available online 27 January 2010

Abstract

Aim. – Hyperglycaemia is now a recognized predictive factor of morbidity and mortality after coronary artery bypass grafting (CABG). For this reason, we aimed to evaluate the postoperative management of glucose control in patients undergoing cardiovascular surgery, and to assess the impact of glucose levels on in-hospital mortality and morbidity.

Methods. – This was a retrospective study investigating the association between postoperative blood glucose and outcomes, including death, post-surgical complications, and length of stay in the intensive care unit (ICU) and in hospital.

Results. – A total of 642 consecutive patients were enrolled into the study after cardiovascular surgery (CABG, carotid endarterectomy and bypass in the lower limbs). Patients’ mean age was 68 ± 10 years, and 74% were male. In-hospital mortality was 5% in diabetic patients vs 2% in non-diabetic patients (OR: 1.66, P = 0.076). Having blood glucose levels in the upper quartile range (≥ 8.8 mmol/L) on postoperative day 1 was independently associated with death (OR: 10.16, P = 0.0002), infectious complications (OR: 1.76, P = 0.04) and prolonged ICU stay (OR: 3.10, P < 0.0001). Patients presenting with three or more hypoglycaemic episodes (< 4.1 mmol/L) had increased rates of mortality (OR: 9.08, P < 0.0001) and complications (OR: 8.57, P < 0.0001).

Conclusion. – Glucose levels greater than 8.8 mmol/L on postoperative day 1 and having three or more hypoglycaemic episodes in the postoperative period were predictive of mortality and morbidity among patients undergoing cardiovascular surgery. This suggests that a multidisciplinary approach may be able to achieve better postoperative blood glucose control.

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Keywords: Diabetes; Hyperglycaemia; Hypoglycaemia; Mortality; Coronary artery bypass Grafting; Surgery; Post-surgery monitoring

Résumé

La glycémie à j1 postopératoire après chirurgie cardiovasculaire est un facteur prédictif de morbimortalité.

Objectif. – L’hyperglycémie a été reconnue comme facteur prédictif de morbidité et mortalité après un pontage aortocoronaire. Notre étude avait pour objectif d’évaluer la prise en charge postopératoire des glycémies chez les patients qui avaient subi une intervention chirurgicale cardiovasculaire et d’évaluer l’impact de ces glycémies sur la mortalité et la morbidité intrahospitalières.

Méthodes. – Étude rétrospective recherchant une association entre la glycémie postopératoire et les complications postchirurgicales, la mortalité et la durée du séjour aux soins intensifs et à l’hôpital.

Résultats. – L’étude a été réalisée sur 642 patients qui avaient subi une intervention chirurgicale cardiovasculaire (ex. pontage aortocoronaire, endartériectomie de la carotide, pontage artériel des membres inférieurs). L’âge moyen est de 68 ± 10 ans et 74 % des patients étaient de sexe masculin. La mortalité intrahospitalière a été de 5 % parmi les patients diabétiques et 2 % chez les non-diabétiques (OR 1,66, p = 0,076). Les taux de glycémies situés dans le quartile supérieur (≥ 8,8 mmol/L) à j1 postopératoire sont associés de manière indépendante avec la mortalité (OR 10,16, 95 % CI 3,20–39,00, p = 0,0002), les complications infectieuses (OR 1,76, 95 % CI 1,02–3,00, p = 0,04) et la durée du séjour aux soins

Abbreviations: CABG, Coronary artery bypass grafting; CAD, Coronary artery disease; CEA, Carotid endarterectomy; CSD, Cardiovascular surgery department; Day 1, Postoperative day 1; DM, Diabetes mellitus; ICU, Intensive care unit; IIT, Intensive insulin therapy.

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1262-3636/$ – see front matter © 2009 Published by Elsevier Masson SAS.
doi:10.1016/j.diabet.2009.06.008
1. Introduction

DM is associated with a threefold risk of cardiovascular complications [1]. CAD is estimated to be responsible for 75% of deaths in diabetic patients [2], and mortality following myocardial infarction is three to six times higher in such a population [3]. Diabetes is a recognized predictive factor of morbidity and mortality after CABG [4], and hyperglycaemia greater or equal to 9.7 mmol/L has been associated with similar outcomes after CABG [5]. Some reports suggest that DM patients benefit even more than non-DM patients from cardiovascular surgery because of their more diffuse atherosclerotic disease [6,7]. However, the evidence is controversial regarding CEA surgery [7,8]. Nevertheless, whatever the findings, close follow-up of diabetic patients is required.

Postoperative management of blood glucose levels is critical for positive outcomes following surgery. The Leuven study showed that IIT that maintained blood glucose at 4.1–6.1 mmol/L substantially reduced mortality by 40% in critically ill surgical patients admitted to the ICU [9]. On the other hand, a less stringent approach found a highly significant relationship between mortality and postoperative hyperglycaemia greater or equal to 9.7 mmol/L in patients undergoing CABG. Also, there was a 57% reduction of risk when blood glucose levels were maintained at 5.5–8.3 mmol/L, using continuous insulin infusion compared with subcutaneous insulin, and a glycaemic target less than 11.1 mmol/L [5]. The aim of the present study was to evaluate the postoperative management of blood glucose control in patients undergoing any type of cardiovascular surgery, and to assess the impact of hyperglycaemia and hypoglycaemia on in-hospital mortality and morbidity.

2. Patients and methods

2.1. Population

A retrospective analysis was carried out in 1612 patients admitted between 1st January 2004 and 31st December 2005 to the CSD of University Hospital Lausanne. Of these, 970 patients were excluded because of procedures not related to arterial occlusive disease (n = 928), a second cardiovascular surgery during the same period or repeat operation on the same site (n = 32) and hospitalization in another department after surgery (n = 10). For the remaining 642 patients enrolled in the study, the interventions were: CABG (n = 427, 67%), alone, or with valve surgery (n = 100) or some other intervention (n = 22); CEA (n = 155, 24%); and procedures of the lower extremities (endarterectomy and arterial bypass, n = 58, 9%). Patients were included regardless of the priority of their intervention (elective or urgent). Diabetes was defined according to World Health Organization criteria as either previous known DM (n = 181) or plasma glucose greater or equal to 11.1 mmol/L at the time of hospital admission (n = 6). Non-DM patients were defined as patients with plasma glucose less than 11.1 mmol/L (n = 455) at the time of admission.

Data were collected from existing medical records and a computerized database (MetaVision iMDsoft, Tel Aviv, Israel), and the following variables were recorded: age; gender; comorbidities; type of surgery; levels of glycaemia; postoperative complications; length of ICU stay, and length of hospital stay.

2.2. Blood glucose measurement

Arterial and venous blood glucose values were recorded from the first postoperative day (Day 1) in our computerized database, and the daily medians calculated for all values. Thereafter, patients were divided into quartiles according to their blood glucose levels. In the ICU, the data were extracted from the computerized information system. Blood glucose measurements were more frequent in the ICU (taken every 2 or 3 h), and intravenous insulin was administered to achieve a glycaemic target of 5–8 mmol/L. In the CSD, preprandial blood glucose was measured in particular, and subcutaneous or intravenous insulin injections (Actrapid®) were delivered in patients with blood glucose levels greater than 12 mmol/L. Unlike the CSD, the ICU had no standardized protocol for glucose management.

2.3. Outcome variables

Hypoglycaemia was defined as glycaemia less than 4.1 mmol/L, and hypertension as high blood pressure above 140/90 mmHg. Dyslipidaemia was defined as either previous known dyslipidaemia or previous treatment with a lipid-lowering agent. Chronic preoperative renal failure was defined as creatinine clearance less than 60 mL/min, as reported on charts, while acute postoperative renal failure was defined as a new increase in creatinine greater than 50 μmol/L or creatinine clearance less than 60 mL/min. Mortality referred to any in-hospital death after the start of surgery. Patients who were still using tobacco were considered smokers, as were those who had stopped within the past three years. Length of stay in hospital versus in the ICU was defined as the period of time from the day of admission to the CSD before surgery to the day of hospital discharge versus ICU discharge; for this calculation,
patients who were receiving acute treatment in another department or hospital were excluded. Adverse outcomes were defined as death, any complication occurring within 30 days of surgery (or during the same hospitalization) and a prolonged length of stay in either the ICU or hospital ward.

2.4. Surgical procedures

All heart and peripheral vascular procedures were performed under general anaesthesia with orotracheal intubation. All carotid endarterectomies were performed under locoregional anaesthesia using superficial cervical block with bupivacaine 0.25%. Heart operations were performed using either median sternotomy, aortoauricular cannulation or the standard technique of cardiopulmonary bypass with moderate hypothermia (30–32°C), and full 3-mg/kg heparinization followed by protamine reversal. Vascular procedures followed the standard surgical techniques with routine 1-mg/kg heparinization and no protamine reversal at the end of the procedure. All CEA were performed with open arteriotomy, selective neurologically based shunting and direct or selective synthetic-patch closure.

In the immediate postoperative phase, all patients were anti-coagulated with prophylactic intravenous heparin within 6 h of surgery in the absence of haemorrhage.

2.5. Postoperative complications

All complications reported on the discharge summary (n=297) were classified into the following groups, as defined in the US Society of Thoracic Surgeons database: cardiac (n=189); infectious (n=87); surgical (n=56); haematological (n=28); renal (n=26); neurological (n=22); respiratory (n=21); and thromboembolic (n=5). Cardiac complications included arrhythmias, acute coronary syndrome and pathologies resulting in low cardiac-output syndrome (cardiogenic shock, ventricular dysfunction, circulatory failure). Infections included pulmonary, urinary tract, local, leg-vein harvest-site and systemic infections. Surgical complications included haemorrhage, tamponade, pleural or pericardial effusion, pneumothorax, and pressure or other non-infectious sores.

2.6. Statistical analyses

Continuous variables, normally distributed, were expressed in means ± standard deviation (SD), and Student’s t test was used for analyses. Non-normally distributed continuous variables were expressed as medians within 25th–75th percentiles, and Wilcoxon’s test was used for statistical analyses. Categorical variables were expressed as frequency, and differences were based on the Chi² test. Logistic-regression analyses were

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<th>Table 1 Clinical characteristics and postoperative outcomes in diabetic and non-diabetic patients.</th>
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<td>Length of ICU stay (h) (n=440)</td>
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Data are expressed as n (%) or median (25th–75th percentiles). CAD: coronary artery disease; BMI: body mass index; CABG: coronary artery bypass grafting; CEA: carotid endarterectomy; ICU: intensive care unit.
performed to determine independent predictors of complications, mortality and length of ICU stay. Statistical analyses were performed using JMP 5.0 (SAS Institute, Cary, NC, USA), and a P value < 0.05 was considered statistically significant.

3. Results

3.1. Patients' characteristics

Patients' mean age was 68 ± 10 years and 74% were men. Altogether, 440 patients were admitted to the ICU (69%), and most had undergone CABG (95%); 187 patients (29%) were diabetic. The global in-hospital mortality rate was 3.0% (n = 19) and, of these cases, all had undergone CABG except for one CEA patient who had co-morbidities.

Differences between DM and non-DM patients are presented in Table 1, according to baseline characteristics and postoperative outcomes. The co-morbidities that were more frequently seen in diabetic patients were hypertension, obesity, peripheral vascular disease (grade IV) and a trend towards lower ejection fractions.

Median glycaemia on Day 1 was 7.9 mmol/L (range: 7.3–8.7) and was observed in 55% (n = 265) of patients. Patients were divided into quartiles of glycaemia: quartile 1 (4.4–7.2 mmol/L); quartile 2 (7.3–7.9 mmol/L); quartile 3 (8.0–8.7 mmol/L); and quartile 4 (8.8–18.9 mmol/L). Although these quartiles do not correspond to glycaemic targets, they provide further insight into the behaviour of our local population.

Almost all of the ICU patients benefited from continuous insulin infusion (98%), and a diagnosis of DM had no effect on its requirement (97% of DM vs 98% of non-DM). In the CSD, insulin infusion was delivered to 32% of the study population (77% DM patients and 14% non-DM patients).

A trend towards higher mortality was observed in DM compared with non-DM patients (5% vs 2%, respectively; P = 0.076). A total of 297 complications were registered, most of which were of cardiac (n = 189), infectious (n = 87), and surgical (n = 56) origin. Diabetic cases showed a trend towards more frequent complications than their non-DM counterparts (52% vs 44%, respectively; P = 0.10). They also suffered significantly more frequently from pressure sores (P = 0.007), infectious complications (P = 0.03)—particularly systemic infections (P = 0.03) and leg-vein harvest-site infections (P = 0.04)—and stayed longer in both the ICU (46 h vs 27 h in non-DM) and hospital (10 days vs 9 days in non-DM). However, cardiac, respiratory or renal complications and local or pulmonary infections did not differ between DM and non-DM patients.

A strong relationship between blood glucose levels on Day 1 and in-hospital mortality was observed (Fig. 1). Also, the incidence of in-hospital mortality increased significantly from quartile 1 to quartile 4—from 0.0% to 9.0%, respectively (P < 0.0001). A similar correlation with glycaemia on Day 1 was found for postoperative complications and length of stay. Patients in the highest (≥ 8.8 mmol/L) compared with the lower quartiles exhibited higher rates of low cardiac output (20% vs 3%, respectively; OR: 3.28, P < 0.0001), acute coronary syndrome (9% vs 3%, respectively; OR: 2.27, P = 0.02), acute renal failure (13% vs 3%, respectively; OR: 2.57, P < 0.0001) and infection (25% vs 15%, respectively; OR: 1.58, P = 0.01). In addition, these patients had a longer ICU stay (11 days vs 10 days, respectively; P < 0.0001) and hospital stay (73 h vs 26 h, respectively; P < 0.0001). To determine whether or not hyperglycaemia was predictive of adverse outcomes in patients without and with DM, separate analyses were performed in these two populations. In fact, hyperglycaemia on Day 1 in non-DM patients had a significant impact on mortality (11% with glycaemia ≥ 8.8 mmol/L vs 1% with glycaemia < 8.8 mmol/L; P < 0.0001), and complications (72% vs 55%, respectively; P = 0.04) such as acute coronary syndrome (13% vs 4%, respectively; P = 0.06), low cardiac output (24% vs 3%, respectively; P < 0.0001), infection (30% vs 1%, respectively; P < 0.0001), and acute renal failure (20% vs 3%, respectively; P < 0.0001). A similar relationship was found for a prolonged ICU stay (74 h vs 26 h, respectively; P < 0.0001) and hospital stay (12 days vs 10 days, respectively; P < 0.0006). These outcomes in hyperglycaemic patients were not related to the surgical procedure.

Indeed, not only glycaemia in the upper quartile range, but also those greater than the glucose median on Day 1 (7.9 mmol/L) were predictive of adverse outcomes: increased risk of mortality (P < 0.0001); cardiac complications (P = 0.005); acute renal failure (P = 0.05); cardiac tamponade (P = 0.03); and prolonged stays in the ICU (P < 0.0001) and in hospital (P = 0.0006).

Multivariable analyses were carried out to assess the impact of glycaemia in the upper quartile range on Day 1 after adjustment for baseline parameters (age, male gender and presence of previously diagnosed DM). Table 2 shows that glycaemia in the highest quartile (≥ 8.8 mmol/L) on Day 1 was strongly associated with death (OR: 10.16, P = 0.0002), infectious complications (OR: 1.76, P = 0.04), and length of ICU stay (OR: 3.10, P < 0.0001). In contrast, previously diagnosed DM was not independently associated with these outcomes, a finding that suggests that the level of postoperative glucose control on Day 1 was more strongly predictive of adverse outcomes than a diagnosis of DM itself. Also, when the ejection fraction was introduced into this model, it did not appear to be predictive of mortality and, similarly, obesity also did not appear to be predictive of infection.
Another analysis was performed to assess the consequences of having three or more hypoglycaemic episodes (<4.1 mmol/L) in the postoperative period. The majority of the 25 patients with three or more hypoglycaemias also had DM (60%), but 40% were non-DM patients. However, 44% of the latter had a median glycaemia ≥ 8.8 mmol/L on Day 1, revealing unstable glycaemia. In addition, the patients with vs without three or more hypoglycaemias during the postoperative period showed higher rates of in-hospital death (16% vs 1%, respectively; OR: 0.08, P < 0.0001) and complications (88% vs 44%, respectively; OR: 8.57, P < 0.0001)—especially cardiac complications (52% vs 28%, respectively; OR: 2.64, P = 0.01), myocardial infarction (12% vs 2%, respectively; OR: 6.03, P = 0.0007), low cardiac output (32% vs 4%, respectively; OR: 8.29, P < 0.0001), infection (44% vs 13%, respectively; OR: 4.94, P < 0.0001) and acute renal failure (32% vs 3%, respectively; OR: 10.99, P < 0.0001). These patients also stayed longer in the ICU (4 days vs 1 day, respectively; P < 0.0001) and in hospital (17 days vs 9 days, respectively; P < 0.0001). Among the patients who died, four (16%) presented with three or more hypoglycaemias; three died of cardiogenic shock, and one was due to haemothorax and haemorrhagic shock. All of these indicators remained significant on multivariate analyses that included classical factors such as previous diagnosis of diabetes, history of myocardial infarction and chronic renal failure. The multivariate analyses (Table 2) also showed that having three or more hypoglycaemias during the postoperative period was even more predictive of in-hospital mortality and infectious complications than glycaemia ≥ 8.8 mmol/L on Day 1. However, the latter was a stronger predictor of a prolonged ICU stay than the presence of hypoglycaemias.

The median glucose levels on Days 2 and 3 (postoperatively) were not predictive of outcome.

4. Discussion

The mortality rate after cardiovascular surgery is 3.0% if emergencies are included, and 0.5% more on including elective surgery. According to the US Society of Thoracic Surgeons database, the predicted mortality risk after CABG in 2003 was 3.0% [10]. In the present study, the overall mortality, including emergencies, was concordant with that in the literature. These rates can be explained by several factors, such as team experience, ICU management and postoperative follow-up. For this reason, it is difficult to analyze the influence of glucose control on its own. Nevertheless, we observed that blood glucose levels on postoperative day 1 was an independent predictor of mortality and morbidity in patients undergoing cardiovascular surgery, irrespective of previously diagnosed DM. In particular, a blood glucose level in the upper quartile range was associated with a 10-fold increase in mortality, twice the risk of infectious complications and a threefold risk of a prolonged stay in the ICU. In addition, having three or more hypoglycaemic episodes (<4.1 mmol/L) was a critical factor for the clinical prognosis, and revealed unstable glycaemic control in such patients.

Our multivariate analyses confirmed the importance of blood glucose control in influencing the risk of postoperative morbidity and mortality. Observational studies have found similar negative outcomes associated with postoperative hyperglycaemia greater or equal to 11.1 mmol/L [11–15]. Also, a recent study demonstrated that glucose levels greater or equal to 11.0 mmol/L on ICU admission following cardiothoracic surgery was predictive of higher rates of mortality as well as renal, pulmonary, and cardiac postoperative complications [16].

Interventional studies aiming to achieve postoperative glucose control have confirmed the importance of glucose management. However, there is a persistent lack of consensus regarding the delivery of intravenous insulin to critically ill ICU patients and in identifying those subgroups of patients who would most benefit from such treatment [17,18]. Various levels of postoperative blood glucose control have been assessed. The most restrictive has suggested maintaining blood glucose at 4.1–6.1 mmol/L, which achieved a 40% reduction in mortality among critically ill surgical patients [9]. However, milder approaches have also been proposed, with glycaemic
targets less or equal to 9.7 mmol/L and less or equal to 11.1 mmol/L [5,19,20]. A recent meta-analysis of critically ill patients compared 29 randomized, controlled trials of strict glucose control (very tight [≤ 6.1 mmol/L] and moderately tight [≤ 8.3 mmol/L]) with the usual care (7.8–11.1 mmol/L) [21]. Its findings did not support the benefits of strict glucose control reported by Van der Berge et al. [9], as in-hospital mortality did not differ with tight glucose control versus usual care, not even when stratified by glucose goal (very tight vs moderately tight). Interestingly, however, intermediate glycaemic targets (6.1–8.8 mmol/L) did not have higher complication rates. Therefore, we propose a need to find consensus on interventions for glucose control that are moderate—neither too strict nor too mild.

Furthermore, it is important to bear in mind that strict glucose control is associated with a higher risk of hypoglycaemia, which is a recognized independent risk factor for death in the medical ICU [22,23]. Indeed, all glucose-control studies have reported a fair number of hypoglycaemic episodes, and the data on associated hazards during IIT have been conflicting [18]. The increased incidence of hypoglycaemia during IIT was the justification for the interruption of two large-scale multicentre trials of tight glucose control—the German VISEP and the European Glucontrol studies. In addition, the recent results of the NICE–SUGAR study contrast starkly with those of preceding trials, with an absolute increase in the rate of death at 90 days with intensive glucose control (27.5%) versus 24.9% with conventional control (OR: 1.14, P = 0.02) [24].

In the presence of hyperglycaemia, lactate levels increase as a result of stimulated glycolysis that, in turn, means that lactate clearance depends on liver and kidney neoglucogenesis [25]. In haemodynamically unstable patients, hepatic and renal functions—including neoglucogenesis—may be hampered. The hypoglycaemia arising after hyperglycaemia seen during IIT in insulin-resistant patients may be the fate of a subset of particularly severely ill patients who have incipient or established organ dysfunction. In such cases, the impact of hypoglycaemia on outcome may be the result of the severity of the underlying organ dysfunction, which is difficult to identify early on using various clinical scores and which may not be the result of hypoglycaemia itself. Indeed, in our experience, most hypoglycaemias are without immediate clinical consequences.

According to a recent study, blood glucose levels should probably be maintained at less than 7.8 mmol/L in surgical and medical ICUs; however, the optimal glucose range for patients undergoing CABG is more debatable and may be higher—up to 8.9 mmol/L [26,27]. Considering these factors and the present study results, we propose a glycaemia target of less than 8.8 mmol/L during Day 1 following cardiovascular surgery.

Our present study has a few important limitations. As a retrospective study, it has the usual weaknesses associated with such a design. The number of included patients (n = 642) is relatively small for an evaluation of multiple parameters that might have an influence on morbidity and mortality. Also, the study is based on a single centre, and the lack of strict guidelines might be partly responsible for the inadequate postoperative metabolic control. On the other hand, an interesting finding is the lack of consensus on glucose control, and that an intermediate glycaemic target (6.1–8.8 mmol/L) was not associated with poorer outcomes. In addition, the present study highlights the deleterious impact of hypoglycaemia, thus contributing to better evaluation of the effects of systematic postoperative management of glucose.

In conclusion, postoperative glycaemia is an independent risk factor of adverse outcomes after any cardiovascular surgery, not only in patients undergoing CABG. In our relatively small patient sample, glycaemia on Day 1 was an important predictive factor of outcome. However, tight postoperative glucose control is not a benign process; this suggests that hypoglycaemia should be avoided, but not at the cost of worsening glycaemic control. A multidisciplinary team approach to glucose control might improve the postoperative prognosis. In addition, the present study suggests the adoption of an intermediate postoperative blood glucose target of less than 8.8 mmol/L, which is neither too strict nor too mild, but which nevertheless requires prospective validation in further studies.

Conflicts of interest

There has been no duplicate publication or submission elsewhere, and no ethical problems or conflicts of interest are declared. All authors have read and approved the manuscript.

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