Perioperative management of hyperglycemia: the diabetologist’s point of view

M. Boscolo (*), L. Barvais (**), E. Engelman (***) and F. Féry (*)

INTRODUCTION

Dimensions of the problem

The prevalence of diabetes is increasing worldwide, reaching epidemic proportions in most developed countries. The International Diabetes Federation estimated that 382 million people were living with diabetes in 2013, half of which still remained undiagnosed (1). In Europe, 56 million individuals are estimated to have diabetes, reaching a prevalence of nearly 7% of the general population, one of three being undiagnosed (1). Estimates suggest that 5% of adults aged 20-79 years in Belgium had diabetes in 2011 (2). Because diabetes is on the rise worldwide and diabetes-related complications often require many surgical procedures in a patient’s lifetime, the number of people with diabetes undergoing surgery is expected to increase substantially.

The burden of perioperative diabetes

Diabetes is associated with an increased rate of perioperative complications, longer hospital stays, higher morbidity rates and higher inpatient costs (3, 4). The perioperative mortality rate among diabetics is reported to be up to 50% higher than that of the population without diabetes (3). These adverse outcomes have multifactorial origins but are primarily related to the control of perioperative glucose levels and include hypoglycemic events, untreated hyperglycemic peaks, and inappropriate use of intravenous (IV) or subcutaneous (SC) insulin due mainly to poor knowledge of diabetes among the care delivering staff and to lack of institutional guidelines (5). Comorbid conditions are another important factor. Vascular and/or neurological complications increase patient susceptibility to hemodynamic instability, silent myocardial ischemia and cardiac arrhythmia in the postoperative period (6, 7). A large body of evidence also indicates that diabetic patients are at increased risk of postoperative nosocomial infections (6), which become prominent at a glycemic threshold of 200 mg/dL (3, 8).

Hyperglycemia in non-diabetic patients

Hyperglycemia, a common response to critical illness and stress (9, 10), is associated with poorer outcomes in critically ill patients regardless of their diabetic status (3, 4, 11-13). Some data even suggest that the development of hyperglycemia in hospitalized patients without a known history of diabetes is associated with poorer clinical outcomes than in those with a previous history of diabetes (3). During the acute phase of a disease, however, the distinction between hyperglycemia caused by stress and pre-existing diabetes is not feasible without information in the patient’s medical record, which is not always available. The only way to identify stress-induced hyperglycemia is to measure the level of glycosylated hemoglobin A1c (HbA1c) at admission. As long as conditions interfering with HbA1c measurement have not occurred (hemolysis or blood transfusion), HbA1c levels < 6.5% (48 mmol/mol) in a patient with hyperglycemia is suggestive of a transient hyperglycemic response (9, 14). The current guidelines of the American Diabetes Association recommend the same clinical treatment for stress-induced hyperglycemia and pre-existing diabetes.

HYPERGLYCEMIA AND SURGERY

Impact of hyperglycemia on outcomes

Hyperglycemia is an independent risk factor for morbidity and mortality in the perioperative
period (15-18). Several observational studies have shown that poor intraoperative glycemic control is associated with high in-hospital morbidity and mortality in patients undergoing cardiac surgery. A significant correlation between postoperative hyperglycemia and mortality has been demonstrated in a large cohort of more than 14,000 patients undergoing cardiac surgery (19). Doenst and coworkers reviewed the outcomes of 6280 patients undergoing surgery for coronary artery bypass grafting (CABG) and found increased morbidity and mortality in patients presenting hyperglycemia during the surgical procedure in both diabetic and non-diabetic patients (17). Ouattara et al. showed that, in a population of patients undergoing cardiac surgery, four consecutive intraoperative blood glucose (BG) levels > 200 mg/dL were associated with an adjusted odds ratio for postoperative severe morbidity of 7.2 compared to patients without hyperglycemia (18). In a population of more than 400 patients undergoing cardiac surgery, an increase of 20 mg/dL in the mean intraoperative BG level was associated with a 30% increase in the risk of adverse outcomes (16). Unfortunately, studies of the effects of perioperative hyperglycemia outside the diabetic cardiac-surgery population are less common. One retrospective cohort study found elevated postoperative glucose levels to be an independent risk factor for infection in patients undergoing infra-inguinal vascular surgery (20).

Fruch and colleagues analyzed the impact of hyperglycemia on a large cohort of more than 3100 patients undergoing general non-cardiac surgery. Both preoperative and postoperative hyperglycemia were associated with a significant increase in morbidity and mortality rates. A substantial rise in mortality was observed for a glycemic threshold of 200 mg/dL (3). The association between hyperglycemia and mortality was greater in patients without a history of diabetes before admission compared with patients with known diabetes. All these studies suggest that maintaining BG levels < 200 mg/dL in a setting of critical illness may improve clinical outcomes.

Does glycemic control improve outcomes?

Many studies have shown that perioperative glycemic control is associated with decreased rates of infection and improved survival (16, 18, 19). The vast majority of such studies were conducted during the postoperative period in intensive care units (ICUs). Data on the impact of hyperglycemia during surgery or the immediate postoperative period are largely lacking.

Furnary and colleagues have shown that insulin infusion to control BG levels on the day of surgery and during the first two postoperative days reduced absolute mortality by nearly 60% in a large population of diabetic patients undergoing CABG surgery (19). Sternal and wound infections remain a significant source of morbidity and mortality in diabetic patients undergoing cardiac surgery (7). A prospective, randomized trial with 140 diabetic patients undergoing CABG surgery has shown that intraoperative treatment of hyperglycemia with a target BG level of 125-200 mg/dL improved survival and decreased ischemic events and wound complications (21). A prospective study conducted on more than 750 cardiac surgery patients demonstrated that maintaining glucose levels between 120 and 160 mg/dL in the immediate postoperative period significantly decreased the incidence of wound infections in diabetic patients (22). Interestingly, a recent retrospective study suggested that the degree of preoperative diabetic control could also affect surgical outcomes. Patients with HbA1c levels > 8.0% had longer hospital stays than control patients, but patients with HbA1c levels of 6.5-8.0% did not (23).

What are the optimal glycemic targets?

Hyperglycemia has been clearly identified as a major risk factor for poorer perioperative outcomes, and glucose control has proven to decrease morbidity and mortality, but the most appropriate target BG level is still a matter of debate (24, 25). Most studies analyzing the impact of tight BG control on outcomes in the postoperative phase have been conducted in a critical-care setting. A landmark study in 2001 led by Van Den Berghe et al. in a single Belgian surgical ICU reported a decrease in overall mortality > 30% in patients under intensive insulin treatment (target BG level of 80-110 mg/dL) compared to a conventionally treated group (target BG level < 215 mg/dL) (26). Initial enthusiasm for tight glycemic control began to wane as new data showed an increased rate of hypoglycemia and mortality. Indeed, none of the subsequent large clinical prospective trials comparing an intensive versus a standard glycemic target (27-30) were able to reproduce the initial findings. The NICE-SUGAR study even attested an increased mortality rate in the intensively treated group. Tight BG control has been associated with an increased rate of hypoglycemic events, and hypoglycemia has been strongly associated.
with mortality, suggesting that a glycemic target of 140-180 mg/dL is safer than a lower BG target in ICU settings (31). The conclusions of all studies on postoperative glycemic control are controversial, due to many factors such as the design of the study, glycemic objectives and the nurse-to-patient ratio. To summarize, current evidence indicates that patients receiving intensive insulin treatment in the postoperative period gain no real benefit in terms of mortality. Moreover, tight postoperative BG control is significantly associated with a higher rate of severe hypoglycemic events (32, 33). Hypoglycemia is particularly dangerous in the perioperative setting, where symptoms may be masked by anesthesia or by an altered neurological state.

Fewer clinical trials have focused on the intraoperative period. A randomized trial with 400 patients undergoing cardiac surgery showed no improvement in outcomes for intensive intraoperative treatment (target BG level of 80-100 mg/dL) compared to standard therapy (target BG level < 200 mg/dL). An increase in mortality and stroke was observed in a group with tight glycemic control (34). More recently, Cochrane reviewed all existing evidence of the effects of perioperative glycemic control for diabetic patients undergoing surgery (35), including twelve randomized trials comparing intensive versus conventional glycemic targets in more than 1400 patients. Mortality from all causes and infectious complications were not significantly different between the two groups. A post-hoc evaluation indicated that targeting intensive glucose control increased the risk of hypoglycemic events (35). In conclusion, hyperglycemia is clearly harmful in the perioperative period, but insufficient evidence is currently available to support the routine use of tight glycemic control (target BG level of 80-110 mg/dL) in the operating room.

**TRANSLATING THEORY INTO PRACTICE**

International guidelines indicate that insulin should be used to control in-hospital hyperglycemia at a starting threshold of 180 mg/dL (14, 36, 37). Once insulin treatment has begun, BG levels should be maintained between 140-180 mg/dL for the majority of critically ill patients. Lower glucose targets may be appropriate in selected patients. For non-critically ill patients, a fasting target of 100-140 mg/dL may be appropriate, with random BG levels < 180 mg/dL. HbA1c levels should be assessed in all inpatients with hyperglycemia or previously diagnosed diabetes.

**How can the international guidelines be safely implemented in a setting of standard care?**

For effective and safe in-hospital BG control, a guidance protocol must be developed for each center (5). These protocols should be as simple as possible, accounting for every situation that can be encountered during hospitalization, but also for staff availability and allowing a smooth transition from acute to standard care.

In the intraoperative and early postoperative periods, during which patient care is provided by anesthesiologists or intensive-care physicians, glycemic control is usually maintained by an IV infusion of insulin. Several protocols of such IV control have been published. In contrast, the transition from IV insulin infusion to SC insulin injections is far less standardized and more difficult to implement, due to a number of factors such as the use of various postoperative fluid regimens, postoperative nausea and vomiting, rapid changes in insulin sensitivity and lack of expertise of the nursing staff outside the endocrinology department. For all these reasons, the use of insulin in patients with hyperglycemia is fraught with problems and is often incorrect or ineffective. Several guidelines have been published, but no consensus of an optimal strategy has been reached. An example of a clear and practical protocol is that of the Joint British Diabetes Societies Inpatient Care Group, commissioned by the British National Health Service, resulting from a collaboration of anesthetists, surgeons and diabetes specialists (5). This document proposes a pathway of care for patients undergoing elective surgery, from primary care referral to hospital discharge. The strength of this protocol is that each stage of the pathway is analyzed in detail, with discussion of controversial areas and supporting references. The importance for each center to develop a local strategy to improve standards of care for diabetic patients undergoing surgery is strongly emphasized. We have thus developed, in collaboration with anesthesiologists, a simple and practical flowchart to be used in our institution.

**A practical flowchart (Table 1)**

Some practical issues should be highlighted.

1. All patients, with or without a previous diagnosis of diabetes, should have their BG levels measured on admission.

2. Identification of patients with type 1 diabetes is crucial because they completely lack endogenous insulin production and have an absolute
requirement for insulin therapy to suppress gluconeogenesis and ketone production. Patients in this category always require continuous SC insulin infusion or a basal bolus insulin regimen before and after surgery even when fasting. In the absence of basal insulin administration, a type 1 diabetic patient will rapidly develop severe hyperglycemia and/or ketoacidosis (36, 38).

3. Type 2 diabetic patients with good or fair metabolic control (HbA1c levels < 8.0%) treated with oral antidiabetic agents or noninsulin injectables (GLP-1 receptor agonists) can be advised to continue their usual routine of antidiabetic medication until the morning of surgery, except for metformin, to be stopped 24 hours before surgery. The biguanide compound metformin is known to increase the risk of lactic acidosis, a potentially fatal metabolic condition, whenever substantial tissue hypoperfusion and hypoxia exist. Therefore, metformin is contraindicated in conditions that may be associated with tissue hypoperfusion, such as surgery, cardiovascular, renal, and liver disease (39). As a practical example, a patient with type 2 diabetes treated with metformin and sulfonylurea and whose

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Table 1
Pre- and postoperative glycemic management chart

<table>
<thead>
<tr>
<th>GENERAL MEASURES</th>
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<tbody>
<tr>
<td>• Measure fasting glucose level in every patient before a planned surgery</td>
</tr>
<tr>
<td>• Measure HbA1c level in all diabetic patients and in those with fasting BG levels ≥ 100 mg/dl</td>
</tr>
<tr>
<td>• For all patients</td>
</tr>
<tr>
<td>- Avoid long periods of fasting and try to schedule surgery for the morning</td>
</tr>
<tr>
<td>- Monitor capillary BG level before meals and at bedtime or every 6 h</td>
</tr>
<tr>
<td>- Maintain BG level between 140 and 180 mg/dl</td>
</tr>
</tbody>
</table>

**IN THE IMMEDIATE PREOPERATIVE PERIOD**

For a previously unknown diabetic patient with a random BG level > 180 mg/dl
Start regular injections of human insulin before each meal according to the algorithm in Table 2

For a previously diagnosed diabetic patient on oral medications and/or GLP-1 receptor agonists
• For HbA1c levels < 8% and/or fasting BG levels < 140 mg/dl, maintain the same treatment until the day before surgery (except metformin to be stopped 24 h before surgery)
• For HbA1c levels ≥ 8% or fasting BG levels ≥ 140 mg/dl, stop usual treatment immediately upon admission (oral medications and/or GLP-1 receptor agonists) and shift to insulin as follows:
  - Basal NPH insulin: 0.15 U/kg twice a day at 12-h intervals
  - Before each meal: regular human insulin at 0.1 U/kg + a correction dose if needed

For a previously diagnosed diabetic patient on insulin
Continue treatment as usual until the day before surgery (evenings included) and optimize glycemic control with insulin supplements according to the algorithm in Table 2

**DURING THE EARLY POSTOPERATIVE PERIOD**

From the day of surgery and postoperatively until resumption of a normal diet, shift all patients (including those receiving IV insulin during surgery) on a regimen of basal-prandial insulin as follows:
• two injections of basal insulin at 12-h intervals at:
  - 100% of the usual dose for patients on glargine (to be delivered as 2 × 50%)
  - 70% of the usual dose for all other basal insulins to be replaced by NPH (2 × 35%)
  - 0.2 U/kg for patients who were started on insulin the day before surgery (2 × 0.1 U/kg)
• + four injections of regular insulin every 6 h at correction doses according to the algorithm in Table 2

Patients treated with a continuous subcutaneous infusion (pump) of insulin
• Continue with the pump at a basal infusion rate until the morning of surgery
• 3 h before surgery, inject NPH insulin at a dose corresponding to 35% of their 24-h basal needs
• 1 h before surgery, stop and remove the pump
• Thereafter, manage identical to other patients

Correction of glycemic drifts the morning before surgery
• BG level > 180 mg/dl: inject regular human insulin according to the algorithm in Table 2
• BG level of 100-180 mg/dl: simple monitoring
• BG level of 60-100 mg/dl: start a 5% glucose infusion at a rate of 125 ml/h
• BG level < 60 mg/dl: give an IV bolus of 10 g glucose, increase the infusion rate to 200 ml/h and check BG level after 30 min

For intervention in the afternoon, recheck BG level at noon and adopt the same protocol as for the morning surgery

**AT FOOD RESUMPTION**
• Upon resumption of feeding, continue with the two basal insulin injections and start regular injections of human insulin before each meal (to prevent postprandial hyperglycemia) in addition to the corrective doses
• Return to the usual treatment (including the pump) as soon as possible

BG: blood glucose; IV: intravenous; HbA1c: glycosylated hemoglobin; NPH: neutral protamine Hagedorn.
HbA1c level is of 6.3% will stop metformin 24 hours before surgery. Sulfonylurea will be stopped on the day of surgery and replaced by regular insulin at correction doses (Table 2) until resumption of a normal diet. Patients with HbA1c levels ≥ 8.0% should discontinue their oral antidiabetic drugs and/or GLP-1 receptor agonists and be started on insulin upon admission. As a practical example, a patient on metformin and sulfonylurea whose HbA1c level is of 9% will stop usual treatment and will be started on basal NPH (neutral protamine Hagedorn) insulin at a starting dose of 0.15 U/Kg twice daily, and regular human insulin at 0.1 U/Kg before each meal. Even though most type 2 diabetic patients retain some capacity of endogenous insulin secretion, they are generally not able to fully compensate for insulin resistance induced by surgical stress. Insulin requirements usually change rapidly during the first few days of the postoperative period, due to decreasing medical stress, tapering medications with hyperglycemic effects (inotropes and corticosteroids), and unpredictable food ingestion with periods of fasting for technical investigations. Some patients may develop renal or heart failure, hypoperfusion, and hemodynamic instability, thereby preventing the use of oral drugs. For all these reasons, as recommended by the Endocrine Society (36), insulin therapy seems the simplest, safest, and most reasonable option for patients with type 2 diabetes in the early postoperative period.

4. For type 2 diabetic patients previously treated only by dietary adjustments and for previously undiagnosed diabetic patients with random BG levels > 180 mg/dL, correction insulin injections alone may be used as an initial insulin regimen or as a strategy for establishing the correct dose. Indeed, patients with new-onset hyperglycemia should be treated as if they had diabetes, because they appear to constitute an especially high-risk group (3). Unless used for occasional ‘coverage’ for short periods of time, the regular insulin sliding scale should not be used as the only form of treatment (40, 41).

No specific clinical trials have examined the best way to shift from IV to SC insulin therapy. For patients requiring SC insulin, rapid-acting and long-acting insulin must be injected 1-2 and 2-3 h, respectively, before discontinuation of the IV insulin infusion to allow for time interval overlap. The estimated total daily dose of insulin is based on several factors, including patient sensitivity to insulin, weight, and age. The initial total daily dose of SC insulin at the time of transition can be extrapolated from the dose required hourly and calculated from the preceding 6 h, multiplied by a factor of 20 (not 24 to avoid hypoglycemia) (5). The total dose should be administered by a combination of equivalent doses of basal and bolus insulin (5).

As previously mentioned, a SC insulin regimen involves the administration of three components: i) long-acting insulin to meet the basal needs between meals and overnight, ii) short-acting insulin administered in scheduled doses to control postprandial glucose spikes and iii) correction doses of short-acting insulin to correct hyperglycemic drifts. Prolonged use of sliding-scale insulin must be avoided due to the increased risk of ketoacidosis and to poorer glycemic control (40, 41). This outdated approach of treating hyperglycemia after it has occurred instead of preventing it leads to a saw-toothed curve of glucose levels, exacerbating both the hyperglycemia and hypoglycemia. In a study of 211 general-surgery patients with type 2 diabetes randomly assigned to receive either a basal bolus insulin regimen or a sliding-scale insulin protocol, glycemic control and patient outcomes were significantly better with the former treatment (40). Errors in insulin prescription are very common, and insulin has been identified as one of the five highest-risk

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Table 2

<table>
<thead>
<tr>
<th>Blood glucose level (mg/dl)</th>
<th>≤40 units of insulin per day or oral treatment</th>
<th>40-80 units of insulin per day</th>
<th>&gt;80 units of insulin per day</th>
</tr>
</thead>
<tbody>
<tr>
<td>150-199</td>
<td>+2</td>
<td>+4</td>
<td>+6</td>
</tr>
<tr>
<td>200-249</td>
<td>+4</td>
<td>+6</td>
<td>+8</td>
</tr>
<tr>
<td>250-299</td>
<td>+6</td>
<td>+8</td>
<td>+10</td>
</tr>
<tr>
<td>300-349</td>
<td>+10</td>
<td>+12</td>
<td>+12</td>
</tr>
<tr>
<td>350-399</td>
<td>+12</td>
<td>+14</td>
<td>+16</td>
</tr>
<tr>
<td>&gt;400</td>
<td></td>
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</table>

medications for inpatients (5). Rapid- and long-acting insulin analogs have some theoretical advantages (e.g. a more physiological profile), but a single type of insulin is easier to manage to avoid confusion and errors. Due to its delayed onset of action, regular human insulin may be more appropriate than rapid-acting analogs in ill patients who start out by eating slowly and may have slow gastric emptying, as some authors suggest (42, 43). A multicenter trial has shown that analogs were not superior to human insulin for controlling BG levels and the frequency of hypoglycemia in nonsurgical hospitalized type 2 diabetic patients (43). We therefore propose the use of regular human and neutral protamine Hagedorn insulins, except for patients already treated with the long-acting analog glargine, which offers a peakless and better diurnal coverage. Basal insulin is administered by two injections at 12-h intervals to ensure the best possible coverage. The suggested doses in the algorithms in Tables 1 and 2 are approximations derived from guidelines (36, 45-47); actual doses will depend on patient sensitivity to insulin and are partly determined by the severity of the underlying illness, caloric intake, use of IV substrate solutions, and glucocorticoid therapy.

All data for BG levels and insulin administration should be noted on a summary chart to ensure good communication among the various caregivers. Assessment of the patient’s response to therapy will anticipate further dose adjustments. If, for example, correction doses are frequently required, a trained specialist or diabetes nurse should increase the scheduled insulin doses the following day.

At discharge

Before the patient is discharged, the insulin regimen may need to be simplified or stopped and oral anti-diabetics (re-)introduced. This step necessarily requires the intervention of a diabetologist who assesses the situation and decides, in agreement with the patient, his/her family and, ideally, the general practitioner, the kind of therapy the patient will receive. If insulin is maintained in a patient who had not been taking insulin prior to hospitalization, a hospital diabetes educator dedicated to this function begins a basic education program for the patient, focused mainly on insulin injections and techniques of BG measurement, and on the signs and symptoms of hypoglycemia. The patient receives a log book for recording glycemic capillary measurements, and a telephone number if any help or advice is required. At our institution, an outpatient follow-up visit with a certified diabetes educator is organized within 10 days after discharge for all patients who have been started on insulin during their hospital stay.

Conclusions

Hyperglycemia is a well-recognized risk factor for increased morbidity and mortality in hospitalized patients. According to current guidelines, BG levels should be regulated at a starting threshold of 180 mg/dL. The glycemic targets considered most appropriate are still controversial, especially in the perioperative setting. Tight glucose control (BG target level of 80-110 mg/dL) is not supported by sufficient evidence. A glycemic target of 140-180 mg/dL appears safe and acceptable for the majority of critically ill patients in the perioperative setting. We propose a practical flowchart for perioperative glycemic management in our institution, focusing on the delicate postoperative transition phase to SC insulin.

References


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