

## Perioperative control of blood glucose

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### Abstract

This review mainly focuses on the management of type 2 diabetes in the preoperative setting with a special emphasis on intraoperative glycemic control. Some patients learn their diagnosis of diabetes just prior to the surgery. The prevalence of previously undiagnosed diabetes is reported to be 5.2-10% in literature. Treatment protocols must be tailored individually but evidence based approach in insulin administration and close monitoring of blood glucose are important in order to avoid both hyper and hypoglycemia

**Key words:** Diabetes Mellitus, Perioperative hyperglycemia, Preoperative care

### Introduction

Prevalence of diabetes is increasing worldwide (1). Management of diabetes in the perioperative setting is a challenge to physician. There are many different treatment protocols applied and yet the target glucose value is a matter of debate among practicing doctors. So, regular, updated and evidence based renewal of data is necessary in the field. This review mainly focuses on the management of type 2 diabetes in the preoperative setting with a special emphasis on intraoperative glycemic control.

### Perioperative hyperglycemia vs diabetes mellitus

Before going further with the perioperative management of diabetes, it is appropriate to explain the term: "perioperative hyperglycemia". This term refers to the hyperglycemia in surgical patients who are known to be non-diabetic (2). Hyperglycemia due to surgical stress is a result of a couple of metabolic changes in glucose utilization including release of counter-regulatory hormones and pro-inflammatory cytokines. Like diabetes, perioperative hyperglycemia is associated with adverse outcomes after surgery. Increased incidence of infections and increased mortality is reported in patients with perioperative hyperglycemia (3-5). Perioperative hyperglycemia is assumed to be associated with the degree of severity of the related stress. Further studies are needed to clarify if perioperative hyperglycemia directly contributes to the adverse outcomes and if its management prevents perioperative morbidities.

### Hyperglycemia and perioperative adverse events

Association between hyperglycemia and variable perioperative risks is well defined (6). Clinical studies showed increased morbidity and

mortality with hyperglycemia, after coronary artery bypass grafting (7-8). Diabetes is a well-known risk factor for postoperative infections (9), acute renal failure, ileus and prolonged hospital stay (10-11). These data show the importance of perioperative blood glucose control in diabetes. Current guidelines do not recommend routine preoperative screening for diabetes (12). Criteria for diabetes screening in general population are defined by American Diabetes Association (ADA). ADA suggests screening for all adults who are 45 years or older and for younger adults whose body mass index >25 kg/m<sup>2</sup> and have at least one additional risk factor. These risk factors are summarized in the table 1 (13).

**Table 1.** Summary of risk factors for diabetes

Physical inactivity
First degree relative with diabetes
High risk ethnicity
History of gestational diabetes
Hypertension
Dyslipidemia
Polycystic ovary syndrome
History of prediabetes
Conditions associated with insulin resistance (obesity, acanthosis nigricans)
Cardiovascular disease

### Preoperative care of the diabetic patient

Some patients learn their diagnosis of diabetes just prior to the surgery. The prevalence of previously undiagnosed diabetes is reported to be 5.2-10% in literature (14,15). These patients seem to have a higher risk of perioperative mortality when compared to patients who are aware of their diabetes (16).

Poor glycemic control is an established risk factor for perioperative morbidity. HbA1c is shown to be correlated with the risk. However it is not known whether surgery should be postponed until a better HbA1c value is achieved or not (17,18). It is difficult to estimate the real contribution of diabetes to perioperative morbidity since many diabetic patients have confounding factors like obesity or smoking history (19).

While preparing a diabetic patient to surgery, it is essential to take a detailed history of diabetes and its complications with a thorough list of medications. Guidelines advise prioritizing diabetic patient on the operating list (20). In general, it is suggested to continue the usual oral anti-diabetic medications until the day of surgery (21,22). Some oral anti-diabetics have specific effects so should be withheld at least 24 hours before surgery. Sulfonylureas are one of them. Sulfonylureas preclude the cardiac protection mechanism named "ischemic preconditioning" by closing the ATP dependent potassium channels (23). Metformin is supposed to increase the risk of lactic acidosis especially when renal dysfunction is present. So metformin is also stopped 24-48 hours before surgery. (24).

Dose adjustment is needed for patients who are already on insulin. Some authors suggest halving the dose of long acting insulin on the morning of surgery and changing the premixed insulin- which contains both short acting and intermediate acting insulin –to NPH insulin for that morning (25,26). If proper glycemic control is not achieved in a patient who is on oral anti-diabetics, basal-bolus insulin regimen is appropriate. In a study, 0.4-0.5U/kg/day of insulin is given to the patients undergoing general surgery, in divided doses; as 40-50% basal insulin and the remainder in pre-meal boluses and this regimen is found to be superior to sliding scale insulin (SSI) (27). SSI regimen is based on; not initiating insulin treatment until a predefined glucose value is exceeded. This method which was popular in seventies lost its importance by the introduction of new and superior methods for glycemic control. However it is still used in some institutions in a "non-evidence based" fashion (28, 29).

In short, withholding sulfonylureas and metformin a day before surgery and giving basal bolus insulin if necessary is suggested for good preoperative glycemic control.

#### **How to control blood glucose intraoperatively?**

Algorithms for perioperative control of blood glucose are variable. A traditional approach was to infuse insulin glucose and potassium named shortly as GIK (or Alberti regimen) (30).

Braithwaite algorithm uses a nurse implemented insulin infusion protocol guided by a standardized table which shows the rate of insulin infusion at a given blood glucose value (31). In this

approach, 100IU insulin in 100mL 0.09% NaCl is infused together with 100-200mL/hour 5% Dextrose in water (D<sub>5</sub>W). There are small studies showing the effectiveness of this approach (32,33).

Recently, variable rate intravenous insulin infusion is used to control blood glucose in the perioperative setting. In this approach, insulin is infused separately, ideally through an electronic infusion pump. This allows tight glycemic control and provides flexibility to the physician in changing doses (20).

United Kingdom guidelines advise implementing variable rate insulin infusion if glycemic control of the patient is not well. The authors suggest using 0.45% sodium chloride and 5% glucose with either 0.15 or 0.3% potassium chloride (as appropriate) as the substrate fluid of choice (20) together with insulin. Hourly measurement of capillary blood glucose to guide insulin infusion rate is recommended by the committee.

Studies looking into the intraoperative management of glucose are few. In a study, which looked into the association of intraoperative glucose values with predefined end points of death, infection, cardiac, neurological, renal, or pulmonary problems; every 20 mg/dl increase in glucose above 100 mg/dl was found to be associated with a 34% increase in experiencing a primary endpoint (34). A multivariate analysis in both diabetic and non-diabetic patients undergoing cardiac surgery showed that a high glucose level during the operation is an independent predictor of mortality in both groups (35). In another study, in which the effect of intraoperative glycemic control on cardiac bypass patients were evaluated, intraoperative insulin infusion was started if blood glucose exceeded 180mg/dl and infusion rate was adjusted according to the Portland protocol. Patients whose blood glucose exceeded 200mg/dl four times consecutively are defined as poor control group. The authors reported increased risk for severe postoperative complications in patients with poor glycemic control (36). Kohl et al, searched for the effect of intraoperative insulin infusion in to patients undergoing cardiopulmonary bypass surgery. They found a small but beneficial effect of insulin infusion on 30 day mortality in their study in which intraoperative insulin infusion was given to keep blood glucose <150mg/dL by the help of a standard protocol (37).

Administration of insulin glargine with dextrose solution for intraoperative glycemic control is tried in a small study and is found to be no different than GIK infusion (38). However changes in tissue perfusion and body temperature under anesthesia may result in unexpected variations in absorption of subcutaneous insulin. Indeed, insulin infusion is shown to be superior to subcutaneous injections in perioperative period in vascular surgery patients, regarding all cause death, myocardial infarction and congestive heart failure (39). Insulin infusion also

seems to decrease sternal wound infection and mortality in coronary artery bypass patients (40,41).

### Target blood glucose values

The study by van Den Bergh et al was a landmark in diabetes care (42). This was a prospective randomized controlled study conducted in the surgical intensive care unit (ICU). A total of 1548 patients were enrolled in the study. The patients were grouped as intensive (target blood glucose: 80-110 mg/dL) and conventional (insulin started if only blood glucose exceeds 215 mg/dL and target blood glucose 180-200 mg/dL) treatment groups. At 12 months mortality rate was significantly lower in intensive group than in conventional group (4.6% vs 8% respectively). However this exciting mortality benefit was not repeated in a study carried out by the same investigators in medical ICU setting (43).

Intensive insulin therapy is further questioned when the results of NICE SUGAR study are reported. In this multicenter study, 6104 patients from medical and surgical ICU were randomized to strict (81-108mg/dL) and conventional (144-180mg/dL) glucose control groups. Mortality was higher in intensive group than in the conventional group (27.5% vs 24.9% respectively, odds ratio for intensive control, 1.14; 95% confidence interval, 1.02 to 1.28; P=0.02) Increased incidence of hypoglycemia might have contributed to increased perioperative morbidity and mortality.

A meta-analysis of five studies comparing intensive and conventional insulin regimens found similar mortalities in both groups (44). Three of these trials failed to show a mortality benefit of intensive insulin treatment (target blood glucose: 70-179mg/dL) where insulin was begun before, during, or immediately after surgery and was continued for less than 24 hours after surgery. Due to these conflicting data, guidelines about perioperative management of diabetes state different target blood glucose values. European Society of Cardiology (ESC) guidelines rely on the results of NICE SUGAR study and advice a target of 144 mg/dL in ICU setting (45). American College of Physicians in ICU suggests keeping blood glucose between 140-200mg/dL in diabetic patients in surgical ICU (46). On the other hand, United Kingdom guidelines define a target glucose of 6-10 mmol/L (108-180mg/dL) for the diabetic patient undergoing surgery (20).

### Postoperative care of diabetic patient

After the operation, the patient's oral antidiabetics may be restarted, as soon as he/she is able to eat regular meals. For the patients on intravenous insulin infusion, basal bolus insulin regimen may be given postoperatively (47). Total daily dose can be estimated according to the total insulin dose infused in the preceding 6-8 hours.

About half of the calculated dose may be given as basal insulin and the remainder may be divided into three to be given before meals as short acting insulin. If regular insulin is given as a short acting insulin, insulin infusion should not be stopped for 1-2 hours after the first dose to cover the period between the time of subcutaneous injection of bolus and its initiation of action. A summary of insulin types and their properties is given in table 2 (48). Management of patients in ICU is beyond the scope of this review and the reader may see other reviews discussing this subject (49).

**Table 2.** Insulin types and their properties

Insulin type	Onset of action	Peak effect	Duration of action
Regular	30-60 min	2 h	6-8 h
Lispro	5-15 min	60-90 min	3-4 h
Aspart	5-15 min	60-90 min	3-4 h
Glulysine	5-15 min	60-90 min	3-4 h
NPH	2-4 h	6-7 h	10-20 h
Glargine	1,5 h	Peakless	24 h
Detemir	1 h	Peakless	17 h

### Conclusion

Proper management of diabetes in the perioperative setting is essential as effect of glycemic control on perioperative morbidity and mortality is well known. Treatment protocols must be tailored individually but evidence based approach in insulin administration and close monitoring of blood glucose are important in order to avoid both hyper and hypoglycemia. Further studies are needed to ascertain target blood glucose values in different surgical patients.

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