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Research Article

Diabetes: A Continuous Challenge for Anesthesiologist

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Abstract

Diabetes mellitus is not a simple metabolic disorder but a worldwide emergent problem that has its implications both in patients in the Intensive Care Unit (ICU) and in the perioperative period. Preoperative evaluation, management and treatment of perioperative hyperglycemia is still an open question for anesthesiologists. Evaluation of decreased functions of various organs and compromised systems by diabetic pathology are mandatory, especially cardiac and renal function, musculoskeletal impairment related to predictive difficult intubation. A strict control of glycemia in order to reduce complications and reduce the incidence of wound infection is mandatory but an algorithm of the best insulin infusion unanimously shared is not reported. However the key of perioperative treatment is an intensive control of glycemic value to avoid extreme hyperglycemia but above all hypoglycemia.

Keywords: Anesthesia; Antidiabetic drugs; Diabetes; Hyperglycemia; Hypoglycemia; Insulin

Diabetes: A Pandemic Disease

Diabetes Mellitus (DM) is not only a metabolism disorder, but it is a real pandemic disease that interests all continents in this last decade. According to estimates of the International Diabetes Federation (IDF), 379 million people suffer from diabetes in the world in 2014 and 77% of them lived in low and middle income countries, but this number will increase to 205 million in 2035 [1]. For Center of Disease Control and prevention (CDC) in the United States 29.1 million people (9.3% of population) having diabetes in 2012, 27.8% of them are undiagnosed and it interests overall people of 65 years old or older, but the number of young diabetic people has increased in last years [2].

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Considering this data, complication from diabetes and the modern diagnostic and management technologies, we can estimate an increasing number of people undergoing surgery in the next years. Vitrectomy, cataract, wounds debridement, vessel repair microsurgeries, kidney transplant, vascular and cardiac surgeries are the most prevalent surgeries in patients with DM [3]. Unexpectedly large numbers of patients show abnormal glucose homeostasis before surgery: Hatzakorzian et al., in a prospective study of 500 patients undergoing elective non-cardiac surgery showed that more than 25% of them without a prior diagnosis of DM had preoperative increased Fasting Blood Glucose (FBG) level [4].

Definition and Classification

The term Diabetes defines a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both [5]. This chronic condition leads to long-term damage, dysfunction and failure of the heart, vessels, eyes, kidneys and nerves.

The classic classification in insulin-dependent and not-insulin-dependent is outdated. DM can be classified into four groups [6]:

1. Type-1 diabetes, with a genetic and immuno-mediate progressive pancreatic beta cell destruction and insulin deficiency;
2. Type-2 diabetes, that starts with periferic insulin resistance and relative insulin deficiency until a progressive insulin secretory defect;
3. Gestational Diabetes Mellitus (GDM), diagnosed in the second or third trimester of pregnancy,
4. Diabetes caused by other conditions, i.e., MODY, diseases of exocrine pancreas or drug-induced diabetes.

Criteria of diagnosis are: Fasting Blood Glucose (FBG) >125 mg/dl (7.0 mmol/L) or levels of HbA1C >6.4% or 2-hour plasma glucose ≥200 mg/dl (11.1 mmol/l) during an Oral Glucose Tolerance Test (OGTT) or a random plasma glucose in a patient with classic symptoms of hyperglycemia ≥200 mg/dl.

Hyperglycemia and Surgery

All types of DM are characterized by an important status of hyperglycemia that is per se an usual consequence of any type of surgery and depends on the site and duration of surgery [7]. Shricker et al., demonstrates that in fasting non-diabetic patients undergoing elective abdominal surgeries, blood glucose levels typically increase to 7-10 mmol/L. During cardiac surgery they exceed 10 mmol/L in nondiabetic patients and 15 mmol/L in diabetic patients [8].

During the perioperative period, there is a strong activation of the neuroendocrine system as a response to surgery stress, with release in blood of counter regulatory hormones, such as glucagon, epinephrine, and cortisol; these hormones provoke and maintain hyperglycemia by targeting liver capacity to take up gluconeogenic precursors, mobilization of glycogen stores and facilitation of glucose release by the liver [9], with a total overproduction of glucose of 30% during surgery [10].

Intraoperative hypothermia, overall during cardiopulmonary bypass, leads to hyperglycemia in response to stress hormones production, inflammatory mechanism and decrease of insulin production [11,12].

Usually, in elective surgery preoperative fasting starts the night before intervention to reduce risk of aspiration; but in many cases, such as for bowel preparation, fasting is long enough to deplete hepatic glycogen stores and increase gluconeogenesis, at the expense of tissue repair and postoperative recovery: few studies advise use of glucose solution ev overnight to prevent loss of insulin sensitivity [13,14] and to reduce hospital stay, but the usefulness of this recommendation is yet unclear [15].

Drugs using for anesthesia could raise glycemic blood levels: neuroaxial blockade reduces stress response to surgery and does not decrease insulin sensibility, rather than general anesthesia [16]; opioids in high-doses also diminish stress hormone levels and hyperglycemia, consequently [17]. Dexamethasone, a well established antiemetic, is frequently used for prevention of Postoperative Nausea and Vomiting (PONV); its use, even in small doses, has been shown to transiently increase blood glucose levels. Dysglycaemic patients receiving dexamethasone, or other steroid medications, should have appropriate monitoring of glycemic levels and correction of hyperglycemia as needed.

An important role is covered by insulin resistance, a state of decreased biological effect of any given dose of insulin, that is a characteristic of DM II type, but it is also present in the perioperative period. It has been associated with invasiveness and duration of surgery, bed rest and immobilization, postoperative nutrition and physical status [18-20]. The exact mechanism is not clear: poor perioperative nutrition, free fatty acid, inflammatory mediators, like TNF alpha and IL-6, could have a key role [21-24]. Consequences of hyperglycemia and poor glucose blood level control in the intra- and post-operative period are more evident in cardiac surgery, with higher rates of adverse cardiac events in postoperative days, such as IMA, TIA, stroke, wound site infection [25], long hospital stay and mortality [26-28]; but they are also remarkable in vascular surgery [29,30], neurosurgery [31], spine surgery [32], mastectomies [33], transplant surgery [34], hepato-biliary-pancreatic surgery [35], cholecystectomy [36] and orthopedic surgery [37]. For ambulatory surgery, recent studies demonstrate that perioperative hyperglycemia is not strictly associated with adverse outcomes, probably due to the short duration of intervention and anesthesia [38].

Control of blood glucose levels has primary importance for the anesthesiologist in diabetics and non-diabetics, even if several studies have shown that the risk of adverse outcomes and events, such as longer in-hospital stay, reoperation, infection rates are similar or worse in non-diabetic patients, probably due to underestimation of hyperglycemia and underuse of insulin in non-diabetic people [39-41].

Preoperative Evaluation

An optimal management of the perioperative period in diabetic patients starts with an optimal evaluation of patient status. A detailed history from the patient is necessary to know how well the blood glucose level is controlled, with a particular attention to:

- Type of diabetes
- When and how it was diagnosed
- Actual therapy that he is taking (oral medications or insulin)
- FBG and diet in the last period
- Report of diabetes consequences (previous cerebrovascular and cardiac accidents, i.e., TIA, strokes, IMA, renal failure, blood vessels and microcirculaton damage, glaucoma, cataracts, diabetic retinopathy, to evaluate glycemic control in the past) and last cardiac (ECG, echocardiogram), hepatic and renal exams
- Evaluation of associated risk factors for CVD in non-diabetic patients (i.e., sedentary lifestyle, obesity, smoking, hypertension, low HDL and high LDL cholesterol level, history of CVD). ADA recommends screening for DM in all adults at age 45 years and earlier in patients with BMI ≥25 kg/m^2 and one or more risk factors [6]. These patients could be considered in "prediabetic status": prediabetes is the term used for individuals with Impaired Fasting Glucose (IFG) and/or Impaired Glucose Tolerance (IGT) and indicates an increased risk for the future development of diabetes. Diagnosis of prediabetes is important for perioperative period, to identify people who need particular attention to hyperglycemia, but also for the patient himself, to prevent future damages due to DM. Overall, an accurate medical history is necessary to identify people with undiagnosed DM, who are at risk for greater rates of resuscitation, re-intubation and longer post-operative ventilation than healthy patients [42].

A complete physical examination is necessary to evaluate any damage or consequences of DM and presence of other risk factors: weight, blood pressure, heart and lung examination, vision defects, neurological sequelae, muscle-skeletal deficiency.

It is useful to predict intubation difficulties, too; severe limited joint mobility syndrome, or stiff joint syndrome, is reported in 10% of patients with long-time DM [43]: it is due to enzymatic glycosylation of collagen and its deposition in the joints, causing reduced mobility; it also involves the atlanto-occipital joint and limits adequate extension of head and neck during laryngoscopy, leading to intubation difficulties [44]. To detect this defect, the palm print test may be applied: collagen glycosylation involves inter-phalangeal joints too, then the ink impression on paper of the dominant hand provides information on the severity of joint interest with an high accuracy [45]. Another faster and older test is the "prayer sign": patients with diabetic stiff joint syndrome have difficulty in approximating their palms and cannot bend their fingers backwards, but it is less accurate to evaluate intubation difficulties [46].

Anesthesiologist must consider every system involved in diabetic damages:

Cardiac system:

- Be aware of silent ischemia and keep a high suspicion for myocardial disease
- Patients have to continue to take beta-blockers until the morning of surgery
- Autonomic neuropathy predisposes to dysrythmias and associated hypotension

Renal system:

- Maintain adequate hydration
- Hold a good renal perfusion and blood pressure

Neurologic system:

- Gastroparesis is common in chronic diabetic patients and risk of aspiration during intubation maneuvers is higher
- Consider peripheric neuropathies, that involves arms and legs, that occur as paresthesia, dysesthesia and difficulty of movement of articulation

Blood exams are fundamental to have a complete sight of glycemic control: they are not limited at FBG, urine glucose dosage, renal and hepatic function indices (creatinine, blood urea nitrogen, GOT, GPT, alkaline phosphatase) and electrolytic balance (sodium, potassium, calcium, magnesium, phosphate), but an increasing importance is covered in the last years by evaluation of HbA1C. It provides insight into glucose control over the preceding 3-4 months, to assess the identification and stratification of DM prior to surgery [47]: elevated values, greater than 7% according to ADA and Dronge and colleagues [48], 6.5% for Sato et al., [49] and 6% for Gustaffson and colleagues [50] are associated with increased rates of perioperative hyperglycemia problems, such as wound and systemic infection, postoperative length of stay, TIA, stroke, IMA and mortality. This evidence suggests performing HbA1C exams prior to surgery for diabetics and pre-diabetics patients also in ambulatory surgeries [51].

HbA1C is a routine test for patients with DM, approximately every three months, but ADA alerts its not absolute accuracy: conditions that affect red blood cell turnover (hemolysis, blood loss), recent transfusions and hemoglobin variants must be considered, particularly when the HbA1C result does not correlate with the patient's blood glucose levels. Sebranek underlines that there are not studies suggesting that delaying elective surgery to correct HbA1C levels control is useful [52]. However it allows to correct glycemic levels with eventual therapy or dietetic changes, with the precious help of other colleagues (such as endocrinologists, nutritionists) in a desirable multidisciplinary collaboration.

There are not univocal guidelines to management of oral antidiabetic drugs and insulin in preoperative assessment. For DM II types patients, in last years few studies, like NHS guidelines, suggests the maintenance of oral therapy until the morning of surgery, to avoid hyperglycemia spikes in intraoperative and early postoperative period [53], but several works underlined that in fasting patients undergoing surgery there is not postprandial hyperglycemia and blood glucose control is more sensible [54].

- Second-generation sulfonylureas should be discontinued 1 day before surgery, with the exception of chlopropramide, which should be stopped 2-3 days before surgery for its long half-life time (6-10 hours) and higher risk of hypoglycaemia [55];
- Meglitinides, that stimulate pancreatic secretion, may be stopped 1 day before surgery for risk of hypoglycaemia;
- Alpha-glucosidase inhibitors and Thiazolidindiones may be continued on the morning of surgery;
- Suspension of metformin and other biguanides is debated: it acts like an insulin sensitizer and inhibits gluconeogenesis. If given as the only therapeutic agent, it does not cause hypoglycaemia. The risk of lactic acidosis in patients taking metformin is very low [56], but is more likely in those with renal impairment [57].

To reduce this risk, many authors [51,58], guidelines from NICE [59] and the British National Formulary [60] advise the withdrawal of metformin one day before surgery.

On the contrary, NHS guidelines suggests assumption of metformin until the morning of surgery; in a retrospective study with 1200 patients undergoing cardiac surgery, Duncan demonstrated that metformin ingestion is not associated with increased risk of adverse outcome and showed less postoperative prolonged tracheal intubation, infection and overall morbidities [61]. In our experience, we suggest to withdraw metformin one day before surgery. This open debate underlines necessity of other studies to determine benefits and risks of metformin on the day of surgery, but all studies agree with the importance of FBG level continuous control not only the day of surgery, but also in earlier days.

All medications are resumed once oral intake is established.

For patients with DM type 1 and type 2 treated with insulin, adjustment of therapy is more difficult and personalized; it is based on FBG values, diet, insulin dosage and types (long, intermediate and fast-acting). Despite the importance of the problem, management of insulin therapy is often underestimated.

For minor surgery, Dagogo-Jack [55] suggests that patients treated with long-acting insulin should be switched to intermediate-acting forms 1-2 days before elective surgery for a better control of perioperative glycaemia, while SAMBA guidelines in 2010 prescribed only a reduction of 25-50% of long and intermediate-acting insulin on the day of surgery without an adjustment for short-acting insulin, if glycaemia is strictly controlled in night prior to surgery and there were not hypoglycaemia events [53].

For major surgery, NHS guidelines recommend that the usual dose of long-acting insulin should be given, morning or evening as appropriate, regardless of whether there is a short or long period of starvation [62]. Self-monitoring of blood glucose with capillary blood glucose levels should be maintained before meals and before bedtime the day prior to surgery and in the morning of intervention, maintaining target pre-prandial values of 80-120 mg/dl and bedtime values of 100-140 mg/dl [63].

Intraoperative Management

Considering night fasting and importance to maintain glycaemia within standard limits, surgery for diabetic patients should be programmed as first of the day, for children as well as adults [64].

Before going to the operating room, a capillary blood glucose exam is necessary to determine FBG level in the morning; dose of short acting insulin has to be omitted, while oral anti-diabetic drugs have to be taken as said before.

There is a strong recommendation to respect aseptic technique for every invasive procedure and antibiotic prophylaxis prior surgery, to decrease the incidence of postoperative infection; temperature control of the operating room is also essential, as hypothermia can lead to peripheral insulin resistance, hyperglycemia, increased stress hormones release and decreased wound healing: air or water heating systems must be used during surgery to avoid hypothermia.

For fluid therapy, international guidelines suggest balanced solutions (Ringer's lactate or Hartmann's solution), while some authors' advice use of saline solution without lactate, because it can cause exacerbation of hyperglycemia [54]. Solutions containing dextrose or glucose alone are not recommended, to avoid uncontrolled hyperglycemia. The ideal crystalloid solution in diabetic patients undergoing surgery should have sufficient glucose to minimise catabolism, contain potassium and be compliant with safety recommendations, be isotonic, and not lead to hyperchloremic acidosis [65]. Moreover, it is important to maintain an optimum water balance during surgery, whereas the greater water loss due to hyperglycaemia in these patients is during night fasting and surgery.

Peripheral pulsoxymetrie, blood pressure measurement every five minutes (non invasive or invasive method, depending of intervention and patient's comorbidities), continuous ECG have to be part of intraoperative monitoring: DM causes autonomic impairment of cardiac and neurologic systems, hypotension and bradycardia are frequent events during anesthesia induction, such as silent IMA during and after anesthesia. Moreover, diabetic neuropathy involving limbs must be taken into account during positioning: in particular cases, if possible, positioning should be realized before anesthesia induction to avoid possible neurologic damages in the anesthetized patient.

Plasma glucose levels should be measured every 1-2 hours with a capillary exam or better with hemogas analysis, to also evaluate electrolyte balance.

To correct hyperglycemia avoiding hypoglycemia, in last decades many solutions have been applied in the intraoperative period. Initially, in 1970's, infused insulin became more widely used in caring for the patient with critical illness [66]; Alberti and Thomas described a simple and safe method of achieving glycemic control whereby glucose, insulin and potassium were infused at a fixed rate. The "Alberti regimen" rapidly became established practice and the inclusion of Potassium, Glucose and Insulin in a same solution (GIK solution) was demonstrated safe [67]: GIK infusion consists of 500 ml of 10% glucose with 10 mmol/l of potassium chloride to which 10 units of rapid insulin (Actrapid) were added, at a rate of 100ml/hour, delivering 2 units insulin, 2 mmol KCl and 10 g glucose hourly. Glucose-Insulin-Potassium (GIK) solution was initially advocated for the treatment of acute myocardial infarction as a polarizing agent to promote electrical stability [68-70] and later as an agent to provide metabolic support. Further studies demonstrated that GIK solution leads to a moderate control of blood glucose level, reports of hypoglycemia are rare, blood lactate and cortisol level do not reach higher doses in respect to non-diabetic patients [71]. Overall, Straus in a cohort of 100 patients, demonstrated that GIK solution given to diabetic patients with CABG operations provides more stable intraoperative hemodynamic and better recovery of glycemic level [72]. GIK infusion has some limitations: with the 'Alberti regimen' neither glucose nor insulin could be varied independently and it does not consider that insulin requirements may fluctuate during surgery.

Then, in 1980's, with coming of electronic infusion pumps, authors investigated use of insulin infusion separately from glucose or other crystalloid solutions: they allow to regulate insulin infusion depending on plasma glucose concentration and this aspect attracted anaesthesiologists, which in the 1990's preferred this solution to GIK infusion [73,74]. Many protocols have been realized: Dagogo recommends infusion of an initial infusion of 0.5 unit/hour for women and 1 unit/hour for men, to be adjusted according to blood glucose measurement [55]; Goldberg identifies initial doses dividing initial blood plasma concentration (expressed in mg/dl) by 100 [75]; Rea suggests starting insulin infusion in diabetic patients if FBG > 100 mg/dl at 1 unit/hour, to be adjusted with subsequent measurements [76]; Subramaniam in vascular surgery applied continuous insulin infusion intraoperatively if blood glucose > 200 mg/dl [77]; Furnary showed superiority of insulin infusion respect of subcutaneous insulin in cardiac surgery [78].

In addition, computer based systems are available that calculate the continued dosing based on glucose concentration and rate of change: an example of such a system is the Glucommander. Initial parameters and baseline glucose values are entered and the program then recommends an insulin infusion rate and intervals to check subsequent glucose levels: the amount of insulin recommended is based on a simple equation: insulin per hour=0.02x(blood glucose-60) [79]. Although it is more manageable and flexible respect of GIK solution, insulin infusion revealed in some studies its dangerousness if not well regulated or done without strict monitoring blood glucose level, with a high risk of hypoglycemia; a particular attention is reserved to control of electrolytes during insulin infusion (hypokalemia, hyponatremia) [80]; overall, continuous infusion must be interrupted at the end of surgery or in recovery room, with an anaesthesiologists supervision, and it cannot be continued in wards, with a poorer control of glycemic status of the patient.

There are no studies that compare GIK solution infusion and continuous insulin infusion, so it is too difficult to suggest the better solution: the anaesthesiologist should choose his technique in according to his experience and the patient whom he is treating.

Glycemic Levels: Which Standard?

Despite the great number of clinical trials about diabetic patients in the perioperative period, a perfect range of blood glucose values is not clear. Although glycemic control has a key role for diabetic and non-diabetic patients and hyperglycemia's adverse effects are well-known, in the last years range of several values have been proposed.

In 2001, with a prospective study that involved more than 1500 critically ill patients (mainly during and after cardio-thoracic surgery) in the Leuven center, van den Berghe et al., demonstrated reduced mortality when blood glucose levels were maintained in the 80-110 mg/dl range as compared to 180-200 mg/dl (4.6% vs 8%), with an important reduction of sepsis and multiple organ failure rates [80].

This study opened the way to a series of trials that compared a tight control of glucose level, similar to FBG in patients not involving in surgeries, or liberal control, where intraoperative glycemia is greater than 150 or 180 mg/dl.

In a retrospective trial with 2600 patients undergoing cardiac surgery between 1987 and 2002, blood glucose levels less than 150 mg/dl have associated with lower in-hospital mortality and infection rates [78]. The prospective "Portland diabetic project" trial, including 5500 diabetic and non-diabetic patients undergoing cardiac surgery between 1987 and 2005, arrived at the same conclusion [81]. In 2006, van den Berghe published two other studies about this question: the first one, including 1200 ICU patients with and without DM, showed how blood glucose among 80-110 mg/dl is associated with less in-hospital stay, mortality and renal failure [82]; in the second study author analyzed data from two over mentioned trials, confirming the necessity to maintain blood glucose under 110 mg/dl in critical patients [83].

A few years later, NICE-SUGAR Study investigators refuted tight control of glycemia with an international multicenter prospective trial, involving 6100 ICU patients randomized in two groups: tight glycemic control (81-108 mg/dl) or conventional glucose control (109-180 mg/dl); results were unexpected, because mortality rate in first group was greater (27.5% vs 24.9%), while there was no difference in number of days in the ICU or days of mechanical ventilation [84].

Mortality was associated with a greater rate of hypoglycemia episodes in the tight control group.

In the last years, the question still remains open: a trial of Lazar et al., with 82 patients undergoing CABG surgery randomized in aggressive glycemic control (90-120 mg/dl) and moderate glycemic control (120-180 mg/dl), does not demonstrate superiority of the first regimen [85]; in a retrospective analysis of 4300 patients who underwent cardiac surgery between 2005 and 2007, a blood glucose < 140 mg/dl was associated with higher mortality rates and more hypoglycemic events [86]. A Cochrane meta-analysis of 2012, including 12 studies that randomized 694 diabetic patients undergoing major surgery to an intensive control group and 709 to conventional glycemic control group, confirmed same results [87].

Still in cardiac surgery, a prospective trial involving 212 patients underlines importance to maintain blood glucose between 120-160 mg/dl [88]; the society of thoracic surgeons in its guidelines recommends maintaining intraoperative and postoperative FBG between 120 and 180 mg/dl [89]. A metanalisis of Sathya of six studies substantiates an optimal blood glucose between 150-200 mg/dl [90].

Great care is then due to glycemic control and values of blood glucose to follow, that are difficult to standardize for any patient and any type of surgery. It is desirable that the anesthesiologist should understand the patients data during perioperative period in its entirely, not limited at FBG alone. For the intraoperative period, we suggest to maintain glucose level between 110 and 180 mg/dl, avoiding peaks of hyper or hypoglycemia through a strict initial, hourly and final control.

Postoperative Hyperglycemia Management

During the postoperative period, insulin requirements may fluctuate, depending on the metabolic impact of the procedure, glucocorticoid therapies, the presence of pain or infection and the adequacy of oral intake.

Until restarting an adequate oral intake, in non-ICU patients enteral or parenteral diet, a GKI infusion should be continued, with respect of maximum blood glucose of 180 mg/dl and a minimum of 80 mg/dl, as ADA, society of thoracic surgeons guidelines and the AACE/ADA consensus statement suggest [6,54]; the joint commission and the surgical care improvement project have also issued requirements that morning blood glucose on postoperative day 1 and 2 be < 200 mg/dL [91]. Prevention of hypoglycemia is equally as important to patient outcomes and is an equally necessary part of any effective glucose control program.

Thus capillary glucose measurements must be obtained every 6 hours and infusion has to be adjusted in according to glucose values. This attention has to be maintained also with alimentation's recovery, with control of fasting and pre-meal blood glucose, four times a day.

In past, both in type-1 and type-2 diabetic patients, a standard protocol was approved, using a monotherapy with regular human insulin, in according to blood glucose levels: the Sliding Scale Insulin (SSI) was applied to threat hyperglycemia in non-ICU wards [92,93]. It involved administration of subcutaneous insulin at fixed doses: more than 20 different types of SSI were realized (an example of protocol is presented by Donihi et al., [94]; prescribers decided in which group patient was including, low-dose or moderate or high dose scale, and a fixed dose of regular insulin was administered in according to BG levels) and they were associated with decreased prescribing errors and decreased frequency of hyperglycemia; but therapies were to be strictly controlled by prescribers and this method can not prevent hyperglycemia, but only treat it. Later studies showed that hyperglycemia is best managed using subcutaneous basal-bolus insulin regimens: modern insulin analogs offer more advantages than the older human insulin, because their time-action profiles more closely correspond to physiological basal and prandial insulin requirements, and have a lower propensity for inducing hypoglycemia than human insulin formulations. Long-acting basal insulin analogs (glargine, detemir) are suitable and preferred for the basal component of therapy; rapid-acting insulin analogs (aspart, lispro, glulisine) are recommended for bolus and correction doses [95], as the RABBIT-2 trial demonstrated in a prospective multicenter study including 130 diabetic patients [96].

Especially in first postoperative days, when oral intake is variable, a basal-bolus insulin regimen is more appropriate with the timing and doses of short-acting insulin adapted according to the patients carbohydrate and protein intake [97]. Umpierrez et al., [98] have compared three different subcutaneous insulin therapies in type-2 diabetic patients ("basal-bolus" regimen with insulin glargine once daily and glulisine before meals plus corrective doses of glulisine if BG > 140 mg/dl, a "basal plus" regimen with glargine once daily and supplemental doses of glulisine if BG > 140 mg/dl and a sliding scale insulin even if BG > 140 mg/dl), demonstrating that treatment with basal plus and basal-bolus regimens resulted in similar improvements in glycemic control, and both regimens resulted in better glycemic control and in a lower number of treatment failures than did SSI treatment. No differences were found in surgical or medical patients for hyperglycemia management [99].

Some authors suggests that the starting dose of basal insulin should be 50-80% of the prior IV insulin total daily dose, contained in GKI solution [100]; Schoenberger, in a recent review, proposed to begin with glargine insulin at 0.3 units/kg if blood glucose >160 mg/dl, adding rapid-acting insulin with meals beginning with 1/6 of the dose of glargine to maintain the same BG standard [101].

Whatever chosen protocol for hyperglycemia control, some key points should be remembered, as mentioned by Moghissi [102]:

- Apply a judicious treatment to prevent hyperglycemia, but also to avoid hypoglycemia;
- Intravenous insulin infusion is still preferred during and immediately after surgery, but subcutaneous basal insulin with prandial or correction doses should be used after the immediate post-operative period;
- Frequent and effective glucose monitoring is mandatory;
- Glucose targets near 140 mg/dl are recommended as being the most appropriate for all hospitalized patients;
- Prefer a individualized therapy, based on BG levels, that a standard protocol, because each patient has a personal response to insulin therapy, which can not be standardized in simple protocols;
- Glycemic control should not only be made with the administration of insulin, but correct and rapid recovery of food, when possible, is desirable, as the collaboration between several colleagues (anesthesiologist, surgeon, internist, nutritionist, physical therapist) is critical to faster discharge from hospital and patient wellness.

Conclusion

A significant number of known diabetic patients undergo major surgery because of the high prevalence of diabetes in the world population so this pathology presents a significant problem for anesthesiologists.

A special attention to preoperative evaluation and perioperative treatment should be given to diabetic patients. Neuropathic pain, silent myocardial ischemia, renal insufficiencies are all causes of increased postoperative complications, especially infections and cardiovascular complications. Another possible problem is the occurrence of a difficult intubation especially in subjects that are obese, have high neck circumference and stiff joint syndrome.

Diabetes treatment for the anaesthesiologist starts before surgery, with a optimal evaluation of the patient, with a detailed history, examination, blood exams, to adopt an intraoperative and postoperative patient-targeted regimen, because there were not standard methods for every patient to control glycemic levels, but it is mandatory to maintain a strict control of glycaemia before, during and after surgery not only for anaesthesiologists but also for other colleagues.

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