Editorial

The battle against perioperative glycaemic control: Hard to win?

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In spite of so many advancements in the medical sciences, precise control of hyperglycaemia has always been a tough challenge for anaesthesiologists and intensivists. The battle to achieve euglycaemia in the intensive care unit (ICU) and operation theatres with newer oral and injectable drugs has witnessed varied results. Perioperative hyperglycaemia, especially a plasma glucose level above 180 mg/dl, is an independent marker of poor clinical and surgical outcomes in both, the known diabetic and non-diabetic population.[1] The unwanted outcomes include delayed wound healing, an enhanced rate of wound infection, postoperative pulmonary complications, prolonged hospital stay and higher postoperative mortality. Hyperglycaemia (plasma glucose levels above 140 mg/dl) is common, with an occurrence of 20–40% in patients undergoing general surgery and the highest incidence of 80–90% in the cardiac surgical population.[2]

THE PERIOPERATIVE GLYCAEMIC CHALLENGE

The molecular mechanisms and pathophysiology of perioperative hyperglycaemia are now fairly well understood. The preoperative anxiety, stress of surgery, sympathetic response to intraoperative pain, hypoxia, hypercarbia, blood loss and low arterial pressure lead to decrease in insulin secretion and the peripheral utilisation of glucose. This produces an increase in gluconeogenesis and glycogenolysis, thus leading to perioperative hyperglycaemia, and the resultant increased production of pro-inflammatory cytokines and osmotic diuresis that can produce fluid and electrolyte imbalance. All this can lead to the early development of ketoacidosis, immune deregulation, insulin resistance and an inflammatory state which can play havoc with patient recovery after surgery.[3] A study has shown that marked insulin resistance can develop in surgical patients during upper abdominal surgery even when the endocrine response is minimal.[4] Lengthy preoperative fasting and inability to take oral feeds postoperatively add to the difficulties in the management of perioperative blood glucose.

Perioperative stress reduction and allaying of preoperative anxiety have been an all-time favourite of researchers.[5-7] The comparison of the effect of different anaesthesia techniques on the perioperative glycaemic level has also been a topic that has been often researched upon. Studies have shown that inhalational agents such as sevoflurane and isoflurane increase the blood glucose levels by affecting the neuroendocrine surgical response to stress, and there is not much difference between the two.[8] Also, propofol produces lesser rise in blood glucose levels than inhalational agents like sevoflurane.[9]

It is clear that blood glucose levels 1–2 days preoperatively and postoperatively are associated with

postoperative complications and mortality, and it is necessary to optimise them. However, are we always able to achieve 100% success in this endeavour?

PREOPERATIVE GLUCOSE CONTROL

Our own national guidelines on preoperative investigations mention that preoperative blood glucose estimation is not recommended in American Society of Anesthesiologists (ASA) grade I and II patients without a known history of diabetes undergoing any type of surgery.[10] However, several authors say that screening for diabetes is recommended in every patient being planned for surgery.[11] The preoperative assessment of diabetes control is done using glycosylated haemoglobin (HbA1c), and higher HbA1c values are closely related to morbidity, cardiac injury, postsurgical infection and mortality. The optimum level of HbA1c and the cut-off point for the postponement/cancellation of elective surgery are still not clear. Nevertheless, preoperative HbA1c levels in the range of 5%–9% are considered optimal, and elective surgery has to be delayed if HbA1c level is ≥9% and random plasma glucose level is >216 mg/dl.[12] When to order an endocrine consult is another question. As suggested in Chinese guidelines, endocrine consultation is recommended for patients with preoperative acute/chronic complications of diabetes mellitus and for high-risk patients.

PERIOPERATIVE GLYCAEMIC TARGETS

In most elective and emergency perioperative patients, maintaining the blood glucose in the range of 140–180 mg/dl with the aim of preventing both hypoglycaemia and severe hyperglycaemia is a reasonable goal. The recommendation by the American Diabetes Association (ADA) is to keep perioperative glucose in the range of 80–180 mg/dl and 140–180 mg/dl for most critically ill and non-critically ill patients, respectively.[13] The target intraoperative blood glucose level is generally 108–180 mg/dl for long- and medium-length surgeries, with a slightly higher target range for cardiac and neurosurgery. For minimally invasive surgery, which is most commonly done nowadays, the target blood glucose levels are 90 mg/dl–129 mg/dl. Postoperative blood glucose levels have been found to be highest on the first postoperative day than at any other perioperative time-point, after which they usually decrease.[14] The postoperative target level is 216 mg/dl for all kinds of surgery. However, for those in the postoperative ICU or on mechanical ventilation, the target blood glucose level is 126 mg/dl–144 mg/dl with a higher range up to 216 mg/dl in those with cardiovascular/cerebrovascular disease.[12]

CONTEMPORARY RESEARCH

In a randomised controlled study being published in this issue of the Indian Journal of Anaesthesia (IJA), the authors have compared the effect of sevoflurane and desflurane on hourly intraoperative blood glucose levels in non-diabetic patients undergoing intracranial surgery. The study concludes that sevoflurane causes a gradual increase in intraoperative glucose, whereas desflurane produces an initial rise followed by a decline in glucose level.[15] These changes, though statistically significant, remained clinically insignificant. Propofol, remifentanil and regional anaesthesia techniques including spinal anaesthesia and thoracic-epidural have been reported to improve intraoperative glucose homeostasis in both diabetics and non-diabetics.[16,17]

Glucovigilance is required in non-diabetic persons undergoing anaesthesia as well. In a randomised double-blind controlled trial involving 150 non-diabetic patients being published in this issue of the IJA, ASA physical status I or II subjects were administered a single dose of IV dexamethasone 0.15 mg/kg following intubation. It was found that even a single dose of dexamethasone in non-diabetic adults causes statistically significant and higher, earlier and prolonged postoperative hyperglycaemia up to 72 hours.[18]

Nevertheless, in studies related to perioperative blood glucose, one has to keep in mind that several factors such as temperature, altitude, oxygen concentration in the blood, plasma uric acid and triglyceride levels, patient haematocrit and medications such as acetaminophen and vasopressors can affect the capillary blood glucose (CBG) readings. Getting a capillary blood sample can be difficult in the presence of perioperative hypotension and hypothermia. Hence, all these factors need to be standardised in the study subjects and considered while designing the studies.[19,20]

ENSURING PERIOPERATIVE EUGLYCAEMIA: THE ANAESTHESIOLOGIST'S DOMAIN

A modification of the insulin and oral hypoglycaemic agent regimens for the perioperative care of diabetic patients undergoing elective surgery is commonly done.[21] A basal dose of insulin at all times is

recommended in persons with Type 1 diabetes at all times, unless the patient is hypoglycaemic. The different types of insulin preparations, strengths, delivery devices, their route, infusion rate and regimens add to the confusion over which one to choose. The frequency of measurement of the CBG is another matter of debate. Usually, CBG measurements are taken hourly at the beginning of the infusion, every 1–2 hours intraoperatively, every 2–4 hours postoperatively and more frequently in case of unstable or fluctuating glycaemia.[3] Nevertheless, each anaesthesiology unit should have its own insulin stewardship protocol, similar to those used for antibiotic stewardship.[22]

The guidelines regarding older hypoglycaemic drugs and their anaesthetic concerns are already well-established. Almost all oral hypoglycaemic agents except metformin are omitted on the day of surgery. However, all of us need to get ourselves familiarised with the newer oral hypoglycaemics. The newer oral hypoglycaemic drugs can be categorised under sodium-glucose cotransporter-2 inhibitors (gliflozins), glucagon-like peptide 1 receptor agonists (GLP-1RAs) and glimins. There are multiple drugs under the umbrella of gliflozins. The mechanism of action is sodium-glucose cotransporter-2 inhibition. These are a new class of oral antihyperglycaemic agents that promote glycosuria by blocking renal glucose reabsorption. The most used agents in the world are canagliflozin, dapagliflozin, and empagliflozin. Their distinct mode of action is unrelated to beta-cell function. The key feature of these drugs is that they have additional extra-glycaemic cardiovascular benefits including weight loss, reduction of blood pressure and a reduction in cardiovascular mortalities. The gliflozins must be discontinued two to three days prior to surgery. They cause problems which are likely to influence the anaesthetic management such as coincident volume contraction, a higher incidence of euglycaemic ketosis, hyperkalaemia and postoperative fluid imbalance. The glycaemic control should be achieved with perioperative insulins after discontinuation.[23]

In a letter to the editor being published in this issue of the IJA, the authors have reported the occurrence of euglycaemic diabetic ketoacidosis (EuDKA) in a 42-year-old female posted for bariatric surgery and on empagliflozin. The drug was omitted on the day of surgery, but EuDKA occurred towards the end of surgery and was corrected within 72 hours.[24]

Another class of drugs is GLP-1RAs. These drugs come as both oral and parenteral preparations. Injectable dulaglutide, lixisenatide and liraglutide as well as oral semaglutide are available in India. Nausea, vomiting and diarrhoea are the most often reported gastrointestinal adverse effects with GLP-1RAs. Reports indicate that these side effects are more common in the early weeks of initiation. The changes in milieu like alkalosis and electrolyte disturbances should be kept in mind when anaesthetising such patients. There are reports of better cardiovascular outcomes in patients receiving these drugs. The key factor is that the drug administration may be only once a week, and the withdrawal of drug seems impractical. Hence, it is ideal to continue and watch for any side effects and act accordingly.[25]

Imeglimin is a novel oral agent under investigation for the management of type 2 diabetes. Stimulation of muscle glucose uptake and reversal of pancreatic beta cell function are the possible described mechanisms of glucose control with imeglimins.[26] Imeglimin may also have the potential to address essential diabetes-related complications such as cardiac dysfunction and nephropathy. Till now, no deleterious effects have been detected in terms of cardiovascular safety, and current clinical data also demonstrate a lack of QT prolongation. There are no real data regarding their use and perioperative outcomes so far.[27] This is a topic for future research.

THE WAY FORWARD

Nonetheless, the area of perianaesthesia glucose control opens up newer vistas of research. Universal and latest Indian guidelines for pre-, peri- and postoperative glycaemic management are the need of the hour. It is known that ethnic differences in insulin resistance and glucose metabolism exist, and hence, prospective studies related to perioperative glucose in the Indian population need to be encouraged. Currently, though we have an ever-increasing choice of drugs and strategies to tackle hyperglycaemia, the question that lingers foremost in our minds is 'Have we been successful in mastering perioperative glucose control?'

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