Role of Insulin in Reducing Mortality in the Perioperative Period

12

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12.1 General Principles

Hyperglycaemia is a frequently diagnosed metabolic abnormality in the inpatient setting, either related to the case of known diabetes, previously undiagnosed diabetes or as a result of the acute or exacerbation of presenting chronic illness [1, 2]. Stress hyperglycaemia may also be induced by medications including steroids, inotropic agents, immunosuppressants and nutritional support via the enteral or parenteral route [1, 2]. Preoperative glycaemic imbalance and perioperative elevations of blood glucose are directly associated with poor prognosis [1–4], including increase in mortality, decrease in cardiovascular event-free survival, increase in resource utilisation and decrease in quality of life. Hyperglycaemia significantly influences hospital morbidity, including increase in the risk of infections, renal failure, prolonged mechanical ventilation and anaemia requiring blood transfusions, which subsequently extends the length of hospital stay [1–4].

Perioperative glycaemic control and mortality have been recently addressed during two Consensus Conference: the first included 340 physicians from 65 countries and covered interventions affecting mortality in cardiac anaesthesia and intensive care [5], while the second Consensus Conference – devoted to all surgical aspects of mortality reduction in the perioperative setting – included more than 1,000 physicians from 77 countries [6, 7].

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12.2 Main Evidences

In the first randomised study, in critically ill surgical subjects published in 2001, Van den Berghe et al. [8] revealed that intensive insulin therapy (IIT) (i.e. maintenance of blood glucose at a level 80–110 mg/dL) was more effective compared with conventional therapy (i.e. blood glucose 180–200 mg/dL) in reducing short-term mortality (RR = 0.58, 95 % CI 0.38–0.78; $p = 0.01$). In 2006, Van der Berghe et al. [9] published the results of a second randomised study performed in medical ICU subject. They found no impact of IIT on mortality, but in subgroup analysis of patients with an ICU stay longer than 2 days ($n = 386$), IIT was associated with a moderate decrease in mortality (from 53 to 43 %; $p = 0.009$).

Since then, the above-mentioned observations have not been confirmed in further well-designed studies performed in both medical and surgical intensive care settings. A meta-analysis published in JAMA in 2008, covering 29 randomised studies, revealed that short-term mortality did not differ between tight and usual glucose control in medical and surgical intensive care patients and also after stratification by glucose target or intensive care unit (ICU) setting [10]. Another meta-analysis of 21 trials including ICU and non-ICU hospitalised subjects found no benefit associated with IIT on short-term or medium-term mortality [11]. Finally, investigating perioperative outcomes in patients with diabetes, Sathya et al. in their meta-analysis revealed that moderate glycaemic control (150–200 mg/dL) compared to a liberal target (>200 mg/dL) was associated with reduced postoperative mortality (OR 0.48; 95 % CI 0.24–0.76, $p = 0.004$) and stroke (OR 0.61, 95 % CI 0.38–0.98, $p = 0.04$) and with no differences in atrial fibrillation (OR 0.54; 95 % CI 0.17–1.76, $p = 0.31$) or wound infection (OR 0.25; 95 % CI 0.01–5.20, $p = 0.04$) [12]. In addition, no significant differences in postoperative outcomes between moderate versus strict (i.e. 100–150 mg/dL) perioperative glycaemic target were found [12].

The successive multicentre NICE-SUGAR study, the largest included into above-mentioned analyses (including 2,232 surgical subjects), showed even an increase in mortality in subjects with a target glucose level of 80–108 mg/dL when compared with those with blood glucose <180 mg/dL (RR = 1.14, 95 % CI 1.02–1.28; $p = 0.02$) [13]. A post hoc analysis corroborated the results showing that moderate (blood glucose of 41–70 mg/dL) and severe hypoglycaemia (≤40 mg/dL) were associated with an increased risk of death (adjusted HR 1.41; 95 % CI 1.21–1.62, $p < 0.001$ and 2.10; 95 % CI 1.59–2.77, $p < 0.001$, respectively) [14]. In addition, two randomised trials were stopped prematurely for safety reasons due to high incidence of severe hypoglycaemia and serious adverse events. In the GLUCONTROL trial covering surgical and medical ICU patient, an increased incidence of hypoglycaemia was associated with increase in mortality (hypoglycaemia rate of 8.7 % and mortality of 17.2 % in the strict glucose control compared with 2.7 % and 15.3 %, respectively, when more liberal control was applied; $p < 0.001$) [15].

Additional evidence is given for critically ill neurosurgical and neurological patients, in whom a meta-analysis of nine studies also found no association between tight glycaemic control and mortality [16], but there was an eightfold higher risk of hypoglycaemia in IIT group.

In cardiac surgery setting, in a meta-analysis of seven randomised trials, Haga et al. [17] revealed that compared to liberal approach, keeping the blood glucose lower than 180 mg/dL reduced early mortality (OR = 0.52, 95 % CI 0.3–0.91; $p < 0.02$). A bit contradictory findings were published more recently by Hua et al. in 2012 [18] who found no association between more intensive insulin regimen (than those in a study by Haga) and the outcome. Moderate glycaemic control (127–179 mg/dL) was also superior to tight (≤126 mg/dL) or liberal (≥180 mg/dL) glycaemic control in a study of 4,658 cardiac surgery patients with perioperative hyperglycaemia [19], with a short-term mortality rate of 2 %, 2.9 % and 3.4 % ($p = 0.02$), respectively, for moderate, tight and liberal management. In 2015, Umpierrez et al. revealed no significant differences in the composite of complications between cardiac surgery patients randomised into an intensive (blood glucose of 100–140 mg/dL) or conservative (i.e. 140–180 mg/dL) treatment (42 vs. 52 %, $p = 0.08$). There were also no differences in complications among patients with diabetes treated with intensive or conservative regimens (49 vs. 48 %, $p = 0.87$), but a significant lower rate of complications in patients without diabetes treated with intensive treatment regimen (34 vs. 55 %, $p = 0.008$) [20].

More to the point, in nearly all large-cohort interventional trials (including NICE-SUGAR and two Van der Berghe trials), the impact of IIT on mortality was lower among diabetics than among nondiabetic individuals [21]. The association between increasing median or mean blood glucose and mortality was found to be much stronger among nondiabetics than diabetic ICU patients [21].

12.3 Pharmacologic Properties

Human insulin is polypeptide secreted by beta cells of pancreatic Langerhans islets containing two chains, a 21-aa A chain A and a 30-aa B chain, linked by two disulphide bonds [22]. Its secretion is triggered by the closure of ATP-dependent potassium channels caused by the increase of glucose level in blood. The translation of insulin initially results in synthesis of pre-proinsulin, which is then cleaved into proinsulin in endoplasmic reticulum and subsequently lysed into insulin by removing the somatomedin-like C-peptide in the Golgi network [23]. In response to secretion stimuli, both insulin and C-peptide are released, and thus, the concentration of the latter particle is the indicator of internal source of circulating insulin.

Insulin acts by binding to the extracellular portion of the alpha subunit of the cell-membrane insulin receptor, which activates the intracellular kinase domain [24]. This part of insulin receptor triggers further signal transduction via kinase pathway, which eventually leads to increased peripheral glucose uptake associated with activation of GLUT-4 glucose transporter, predominantly in fat tissue and muscles, promotion of glycolysis and hepatic glycogenesis (glycogen synthesis) and simultaneous inhibition of gluconeogenesis, glycogenolysis, lipolysis and proteolysis. This causes a rapid reduction in serum glucose concentration.

12.4 Therapeutic Use

In the operating room setting, glucose level should be controlled by means of a continuous intravenous infusion of regular human insulin or, in selected cases, of fast-acting insulin analogues. However, this rule does not apply to ambulatory minor surgical procedures performed on noncritically ill subjects, in whom target glucose level can be attained by means of repeated subcutaneous injections, preferably using rapid-acting insulin analogues [25, 26]. Because of the stacking risk of subcutaneous injections of insulin, additional doses should not be administered until the time to peak effect has passed [27].

The target for preoperative glycaemic control is fasting glucose level of 100–120 and 140–160 mg/dL 2 h after food intake. In patients with post-prandial glycaemia >200 mg/dL and HbA1c >9.0 %, surgery should be postponed to allow proper glycaemic control, except for urgent and emergent instances.

12.4.1 Insulin Solutions

Most of insulin formulations have 100 units of insulin per mL; however, 40 and 500 units/mL solutions can also be found. For intravenous (IV) use, recombinant human insulin (or fast-acting analogues) should be used at concentrations ranging from 0.05 to 1.0 IU/mL in infusion systems with 0.9 % sodium chloride.

12.4.2 Pharmacokinetics

Intravenous insulin has an average elimination half-life of less than 10 min, while action half-life is approximately 40 min. Liver and kidneys deactivate insulin (see Table 12.1).

12.4.3 Perioperative Therapy, Route of Administration and Dosing

In the direct preoperative period, patients with diabetes type 1 should follow their usual regimen, while patients with type 2 diabetes should be bridged to intensive insulin therapy (with the exception of patients successfully treated with diet together with metformin and on condition of minor procedures, such as tooth extraction, abscess incision, small amputation, cataract surgery). Oral hypoglycaemic agents (OHA) should be withdrawn 48 h before the surgery. Total daily intake (TDI) of insulin should be equal to 0.3–0.7 IU/kg. Long-acting insulin is expected to cover 40–50 % of daily dose (NPH injected twice daily at 8:00 a.m. and 10:00 p.m. or a single injection of long-acting analogue before sleep). Pre-prandial rapid-acting insulin is recommended to be given 3 times daily before meals according to proportions of 50–20–30 and should represent approximately 50–60 % of TDI [25].

Table 12.1 Pharmacokinetics of various insulin formulations

Route of administration	Insulin	Onset of action	Peak of action	Effective duration of action
Subcutaneous	Regular human insulin	30–60 min	2–3 h	4–6 h
”	Rapid-acting analogues (aspart, lispro, glulisine)	15 min	30–90 min	3–4 h
”	Isophane insulin (NPH)	1–4 h	6–10 h	10–16 h
”	Detemir	1–4 h	Slight peak after 6–14 h	12–20 h
”	Glargine	1–4 h	No peak activity	24 h
”	Degludec	30–90 min	No peak activity	40 h
Inhaled	Short-acting inhaled insulin	15 min	30–90 min	4–6 h
Intravenous	Regular human insulin or rapid-acting analogues	<10 min	Elimination half-life of 40 min (columns 4–5)	

The American Association of Clinical Endocrinologists and the American Diabetes Association 2009 consensus recommends that in the intensive care setting, target glucose level should be ≤180 mg/dL (10 mmol/L) and that glycaemia should be maintained in the range between 140 and 180 mg/dL (7.8–10 mmol/l). For surgical patients, a pre-prandial glucose concentration <140 mg/dL (7.8 mmol/L) and a random glucose concentration <180 mg/dL (10 mmol/L) are recommended [25]. The Society for Ambulatory Anesthesia Consensus Statement advocates to maintain intraoperative blood glucose levels between 100 and 180 mg/dL (5.5–10 mmol/L) [28]. The American College of Physicians 2014 updated guidelines for the management of inpatient hyperglycaemia recommend a target blood glucose level of 140–200 mg/dL (7.8–11.1 mmol/l) when insulin therapy is used in medical or surgical intensive care unit patients. Clinicians should avoid targets less than 140 mg/dL (<7.8 mmol/L) because harming risk increases with lower blood glucose targets. Moreover, they strongly recommend not using intensive insulin therapy to normalise blood glucose in patients with or without diabetes [29]. The Society of Thoracic Surgeons 2009 guidelines regarding blood glucose management in cardiac surgery recommend maintenance of blood glucose lower than 180 mg/dL (10 mmol/L) [30]. In patients who spend ≥3 days in ICU, require an intra-aortic balloon pump/inotropic/left ventricular assist device support, receive antiarrhythmic drugs or are on dialysis/continuous veno-venous hemofiltration, a blood glucose level of ≤150 mg/dL (8.3 mmol/L) is recommended [30].

Wilson et al. [31] reviewed and described 12 different insulin infusion protocols and found significant variations in initiation and titration of insulin, use of bolus dosing and calculations used for insulin dose adjustment. In clinical setting, however, two major well-recognised intraoperative algorithms of blood glucose control exist. The first algorithm is based on intravenous pump infusion of 50 IU of insulin dissolved in

Table 12.2 Rate of insulin and glucose infusion depending on the blood glucose level

Glycaemia [mg/dL]	10 % glucose infusion [mL/h]	Insulin delivery (IU/h)
<100	100	Stop infusion for 15–30 min
100–140	100	3–4
140–180	80	3–4
180–250	80	4–6
250–300	Stop the infusion until glycaemia decreases below 180 mg/dL	4–6

50 mL 0.9 % saline and a separate infusion of 10 % glucose. In this protocol, 1 g of exogenous glucose is used every 0.3 IU of insulin. The rate of both simultaneous infusions is adjusted according to actual blood glucose level (Table 12.2). The second scheme is based on a single infusion drip with 500 mL of 5–10 % glucose containing approximately 8–16 IU of insulin and 10–20 mEq of potassium chloride administered at the rate of 80 mL/h. The amount of insulin in the solution should be higher (>20 IU) in case of obesity, cardiothoracic surgery, concomitant infection, hypothermia or initial glucose concentration >180 mg/dL. Conversely, the contents of insulin should be less than 12 IU in patients with low body mass index and previously treated with OHA. The amount of insulin in the solution should be increased by 2 IU for every 30 mg/dL increase of blood glucose above the threshold of 180 mg/dL and decreased by 4 IU if the blood glucose level falls to 100 mg/dL.

During intravenous administration of insulin, blood glucose level should be measured every 1 h using bedside or nearby stat laboratory monitoring. Of note, point-of-care testing can be disputed in the situation of hypoglycaemia, when it tends to overestimate blood glucose level [32]. Accordingly, higher alert value for hypoglycaemia (e.g. <70 mg/dL) should be implemented to trigger early glucose supplementation so as to allow time for prevention of symptomatic hypoglycaemia, which usually occurs at blood glucose levels of 45–55 mg/dL [33].

12.4.4 Side Effects and Toxicity

Insulin promotes intracellular potassium shift, possibly leading to hypokalaemia. Since perioperative IV insulin administration has a rapid onset of action, glucose and potassium levels must be strictly monitored.

Excessive doses of insulin can cause symptomatic hypoglycaemia (blood glucose level <45–55 mg/dL) manifested by sweating, tachycardia, mydriasis, pallor, weakness, nausea, confusion, aggressive behaviour, seizures, loss of consciousness, convulsions, brain damage and demise. Yet, this symptomatology is absent in patients under general anaesthesia, barring tachycardia and excessive sweating. This supports the need for hourly glucose monitoring.

Other side effects of insulin therapy include allergic reactions, lipodystrophy and weight gain.

12.5 Summary Table

Clinical summary					
Drugs	Indications	Cautions	Side effects	Dosage	Notes
Insulin in intravenous infusion (regular human insulin or short-acting analogue)	Perioperative management of hyperglycaemia in patients with diabetes type 1/2 and excessive intraoperative hyperglycaemia in patients without previous history of diabetes	Severe risk of hypoglycaemia and hypokalaemia	Hypoglycaemia	Initial insulin infusion of 0.5–1 IU/h, then 0.3 IU/h increments or decrements depending on blood glucose level	Target intraoperative blood glucose level is 140–180 mg/dL
		Glucose level should be checked directly before surgery and every 1 h during and after the procedure	Hypokalaemia		Minor ambulatory procedures in diabetes type 2 can be performed without IV insulin
		[K+] should be verified before and after the procedure	Allergic reactions		In patients with a well-controlled diabetes type 2 treated with diet or oral agents, IV insulin is not obligatory
			Weight gain		
			Lipodystrophy		

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