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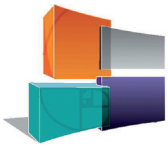

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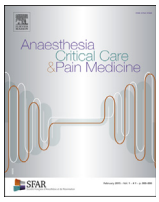

Guidelines

Perioperative management of adult diabetic patients. Intraoperative period

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ABSTRACT

Perioperative hyperglycaemia (> 1.80 g/L or 10 mmol/L) increases morbidity (particularly due to infection) and mortality. Hypoglycaemia can be managed in the perioperative period by decreasing blood sugar levels with insulin between 0.90 and 1.80 g/L but it may occur more frequently when the goal is strict normoglycaemia. We propose continuous administration of insulin therapy via an electronic syringe (IVES) in type-1 diabetes (T1D) and type-2 diabetes (T2D) patients if required or in cases of stress hyperglycaemia. Stopping a personal insulin pump requires immediate follow on with IVES insulin. We recommend 4 mg dexamethasone for the prophylaxis of nausea and vomiting, rather than 8 mg, combined with another antiemetic drug. The use of regional anaesthesia (RA), when possible, allows for better control of postoperative pain and should be prioritised. Analgesic requirements are higher in patients with poorly controlled blood sugar levels than in those with HbA1c < 6.5%. The struggle to prevent hypothermia, the use of RA and multimodal analgesia (which allow for a more rapid recovery of bowel movements), limitation of blood loss, early ambulation and minimally invasive surgery are the preferred measures to regulate perioperative insulin resistance. Finally, diabetes does not change the usual rules of fasting or of antibiotic prophylaxis.

Perioperative hyperglycaemia is associated with an increase in morbidity and mortality in diabetic and non-diabetic patients. It results in delayed healing and an increase in the frequency of infections. Correction of hyperglycaemia improves the prognosis of these patients and objectives for the best benefit/risk ratio should be determined.

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1. Consequences of perioperative hyperglycaemia

1.1. Transversal data

Most studies in this area have been conducted in cardiac surgery or intensive care units (ICUs). A significant positive relation has been found between maximal perioperative hyperglycaemia and perioperative mortality [1], as well as a 10-times higher risk of complications when postoperative glycaemia was > 2.5 g/L (13.5 mmol/L) [2]. In a retrospective study in 409 patients (20% diabetics), Gandhi et al. [3] concluded that perioperative hyperglycaemia was an independent risk factor for perioperative complications including mortality and infection and that an increase in glycaemia of 0.2 g/L (1.1 mmol/L) above 1 g/L (5.5 mmol/L) increased the risk of postoperative complications by 34%. Ouattara et al. found that in 200 diabetic patients who underwent cardiac surgery, uncontrolled perioperative hyperglycaemia (> 2 g/L or 11 mmol/L) was associated with a 7-fold higher risk of postoperative complications [4]. In non-cardiac surgery, a prospective study comprising 20% diabetic patients also found this link [5].

Perioperative hyperglycaemia is an independent risk factor for postoperative morbidity/mortality [1,6]. In patients with undiagnosed diabetes, hyperglycaemia was associated with an increased risk of infection, re-interventions and intra-hospital mortality [7,8].

In particular, a correlation exists between perioperative hyperglycaemia and the frequency of infections in diabetic patients. In cardiac surgery, there is an increase in sternal bone infections in patients with mean preoperative blood sugar levels > 2 g/L (11 mmol/L) [9]. For Zerr et al., patients developing postoperative mediastinitis presented mean blood sugar levels that were significantly higher during the 48 h post-surgery (2.1 vs 1.9 g/L, $P < 0.003$) (11.4 vs 10.5 mmol/L) [8].

The prognosis of hyperglycaemia appears to be different depending on whether it is stress hyperglycaemia or chronic imbalance in a patient with pre-existing diabetes. In a cohort of patients undergoing non-cardiac surgery, Krinsley et al. [10] reported a different glycaemia threshold above which mortality was significantly increased, whether the patient was diabetic (i.e. 1.8 g/L or 10 mmol/L) or not (i.e. 1.4 g/L or 7.8 mmol/L). Many studies have reported that perioperative stress hyperglycaemia, at a same level of glycaemia, was potentially less harmful to a patient who was previously known to be diabetic [7,11].

The prognostic impact of perioperative hyperglycaemia justifies its early detection by performing regular measurements of blood sugar levels, and its correction, particularly in at-risk surgical patients (age > 60-years, existence of a metabolic syndrome, previous history of transitory hyperglycaemia, cardiovascular history) [12].

1.2. Glycaemic objectives: observational studies

Furnary et al. [6] showed in 4051 aortocoronary bypass patients studied between 1987 and 2001 that the management of hyperglycaemia in the perioperative period of the 26% of patients with diabetes decreased the mortality to a level comparable to that of non-diabetic patients. The management of hyperglycaemia evolved during the study from management that was uniquely postoperative then perioperative, to perioperative until 3 days post-surgery, including continuous administration of insulin with regularly reduced glycaemic objectives (1.5–2 g/L or 8.25–11 mmol/L, then 1–1.50 g/L or 5.5–8.25 mmol/L). The mean blood sugar levels decreased to 1.77 g/L (9.73 mmol/L) compared to 2.14 g/L (11.8 mmol/L) in the historic group. The mortality rate decreased by 36% compared to the expected value, and by 57% compared to the historic group (2.4 vs. 4.0%), reaching that of non-diabetics (which remained stable during the study). The decrease in mortality included mortality of cardiac origin and a correlation was shown between the degree of hyperglycaemia and mortality. Comparable results were found in retrospective studies where the incidence of mediastinitis and mortality was decreased by 37% and 29%, respectively, in groups with a glycaemic objective of < 2 g/L (11 mmol/L) [8,13]. In a retrospective case-control study, D'Alessandro et al. [14] concluded that control of blood sugar levels between 1.5 and 2 g/L (8.25 to 11 mmol/L) is beneficial, but only in patients with a EUROSCORE > 4.

An initial meta-analysis study in 2004 reported a 15% decrease in mortality in ICU when glycaemia was controlled by insulin therapy [15]. In diabetic patients in the perioperative period, a reduction of blood sugar levels to < 1.8–2 g/L (10–11 mmol/L) decreased morbidity, in particular bone infections, duration of hospital stay and mortality of cardiac origin, particularly in patients with blood sugar levels > 1.75 g/L (9.6 mmol/L) [6].

Studies comparing different blood sugar levels in surgery regarding strict vs. moderate control, such as the retrospective study of 4658 diabetic patients by Bhamidipati et al. demonstrated that patients with blood sugar levels between 1.26 g/L and 1.79 g/L (7–10 mmol/L) had a better prognosis than patients with levels < 1.26 g/L (7 mmol/L) during aortocoronary bypass [16]. Similarly, moderate control of glycaemia (< 1.8 g/L or 10 mmol/L) decreased the number of hypoglycaemic episodes compared to strict control (0.8–1.2 g/L or 4.4–6.6 mmol/L) without any differences in morbidity/mortality in cardiac surgery [17,18].

1.3. Glycaemic objectives: randomised interventional studies

In a randomised study, Lazar et al. reported a significant decrease in morbidity when comparing infections at the cardiac operative site (0% vs. 13%, $P < 0.01$), in the treated group (glycaemic objective between 1.2 and 1.8 g/L or 6.6 and 10 mmol/L) compared to the untreated group (glycaemic objective < 2.50 g/L or 13.7 mmol/L). The mean blood sugar levels of the two groups were 1.38 g/L (7.6 mmol/L) and 2.26 g/L (12.4 mmol/L), respectively [19]. Tight perioperative glycaemic control started before induction of anaesthesia and continued until the twelfth hour post-surgery (1.26–2.00 g/L or 7–11 mmol/L), improved perioperative haemodynamic control. Follow-up five years later demonstrated a beneficial effect on long-term mortality [19].

The studies mentioned above have determined the upper limit for the glycaemic objective, but does normoglycaemia carry a supplementary benefit? In 2001, van den Berghe et al. published the first randomised study (1558 patients in surgical ICUs; 60% in cardiac surgery, 13% diabetic patients) to compare the strict objective (0.8–1 g/L or 4.4–5.5 mmol/L) versus the conventional objective (1.8–2 g/L or 10–11 mmol/L), demonstrating a decrease in mortality of 8% and a decrease in morbidity (including septicaemia and duration of antibiotic therapy) [20]. van den Berghe et al. conducted a second study in a medical ICU (same randomisation model, same objective) but did not find any benefit of intensive treatment upon mortality and septicaemia. The mortality decreased only in patients with a hospital stay > 3 days, except for diabetics who represented approximately 17% of the population. In terms of morbidity, they noted a decrease in the rate of renal failure, much earlier withdrawal of ventilation, a shorter stay in the ICU and earlier discharge from hospital [21].

The VISEP study [22] in septic shock, and the Glucontrol study [23] in ICUs were stopped early due to more frequent severe hypoglycaemias in the group receiving intensive treatment. The NICE-SUGAR [24] multicentre, randomised study

carried out on 6104 patients in surgical and medical ICUs (20% diabetic patients), comparing two glycaemic objectives: 0.81–1.08 g/L (4.4–6 mmol/L) vs. ≥ 1.8 g/L (10 mmol/L), showed the absence of benefit in terms of morbidity. In contrast, mortality was increased (+2.8%) as well as the number of severe hypoglycaemias in the group receiving intensive treatment. The mean blood sugar levels obtained in the two groups were 1.15 g/L (6.3 mmol/L) vs. 1.44 g/L (8 mmol/L), respectively. In 2008, a meta-analysis [25] of the largest randomised studies concluded not only that there was no benefit of intensive management in ICUs but also that there was an increased risk of hypoglycaemia.

It should be pointed out that in the most recent randomised studies (NICE-SUGAR in particular), the group receiving conventional treatment had mean blood sugar levels that were clearly less than 2 g/L (11 mmol/L). Intensive treatment was not superior to conventional treatment but enabled blood sugar levels to be maintained at < 1.8 g/L (10 mmol/L), at the levels obtained during establishment of the protocol in older studies that demonstrated a benefit on morbidity/mortality.

Finally, in a randomised study of 300 patients undergoing aortocoronary bypass, Umperriez et al. [26] compared different glycaemic objectives including strict control (1.1–1.4 g/L or 6–7.7 mmol/L) and moderate control (1.4–1.8 g/L or 7.7–10 mmol/L) of glycaemia. No differences in morbidity, sternal infection rate, mortality and duration of hospital stay were found, but hypoglycaemic episodes were more frequent in the group receiving intensive treatment.

1.4. Overall, what glycaemic objectives are proposed?

Hyperglycaemia (> 1.80 g/L or 10 mmol/L) in the perioperative period increases morbidity (in particular infections) and mortality. The control of glycaemia should start in the preoperative period and be continued in the early days after the operation. Patients benefit from a reduction in glycaemia rather than intense insulin therapy and the objective of normoglycaemia (0.80–1.20 g/L or 4.4–6.7 mmol/L) increases the rate of severe hypoglycaemia and possibly mortality. Moderate glycaemic control (1.40–1.8 g/L or 7.7–10 mmol/L) appears, to be the best compromise resulting in a decrease in morbidity/mortality without increasing the frequency of hypoglycaemia.

Maintaining stable blood sugar levels between 1.40 and 1.80 g/L (7.7–10 mmol/L) requires complex protocols employing IV insulin and these are difficult to execute, in the absence of a computer programme.

A broader objective is desirable: glycaemic control between 0.90 and 1.80 g/L (5–10 mmol/L), a cut-off leading to therapeutic adjustment, to avoid hypoglycaemia and to maintain glycaemia below 1.80 g/L (10 mmol/L).

(Practical sheets G, H, J, K, L, O).

2. Perioperative management of glycaemia

2.1. General principles (Practical Sheets O, G, H, J, K)

In the preoperative period, we recommend that management of diabetic patients be based on the following principles [27–30]:

- avoid prolonged fasting: schedule the diabetic patient for surgery as early as possible in the morning;
- have a glycaemic objective of 5–10 mmol/L (0.9–1.8 g/L). There is no consensus on the optimum glycaemia threshold in the perioperative period, but a target blood sugar level of < 1.8 g/L (10 mmol/L) will help to avoid hypoglycaemia [31–35];
- if insulin is required: ultra-rapid short-acting analogues are preferred, administered continually, by IVES [36–38]; always given in association with IV glucose (equivalent of 4 g/h) and electrolytes depending on the requirements and being careful to avoid hypokalaemia induced by insulin. There is great variability depending on the protocols used preoperatively for insulin therapy, without any evidence that one is superior to the others;
- if the patient is using a personal insulin pump, it should be removed with mandatory immediate follow-on with IVES insulin at the start of the intervention;
- monitoring of glycaemia by repeated measurement of blood sugar levels every 1–2 hours and control of kalaemia every 4 hours in the perioperative period under insulin. Measurements should be carried out in arterial or venous blood rather than in capillary blood using glycaemia readers, which overestimate blood sugar levels, especially in the presence of vasoconstriction and in hypoglycaemia [39]. Thus, a value of 0.7 g/L (3.8 mmol/L) on glycaemia readers should be considered as hypoglycaemia and impose corrective action and verification of the value by measurement in a laboratory;
- all solutes may be used in the perioperative period, including Ringer lactate;
- perioperative glycaemic control is conditioned by three parameters: the type of diabetes, the preoperative glycaemic control and the type of surgery (practical sheets G, H, J, K, L).

2.2. Protocol for IVES insulin therapy (practical sheet O)

We propose a protocol for IVES insulin therapy developed by the working party that can be used preoperatively and perioperatively in a continuous surveillance unit or ICU (Fig. 1). It can be used in all T1D and T2D patients or in cases of stress, hyperglycaemia in patients without diagnosed diabetes.

3. Additional principles of management

3.1. Prophylaxis of nausea and vomiting

The prevention of nausea and vomiting is an essential part of the perioperative strategy. It is particularly more so in a diabetic patient, taking into account the importance of the rapid resumption of feeding. In this context, it is valid to propose an anaesthesia strategy that minimises the risk of nausea/vomiting (propofol rather than halogenated agents, avoid N_2O, avoid reversal of neuromuscular blocking agents with neostigmine, favour RA) as well as broad-spectrum antiemetic therapy. Among the powerful antiemetic drugs that have been validated in the perioperative period, dexamethasone carries the risk of hyperglycaemia. In a recent retrospective study, the authors evaluated the risk of hyperglycaemia according to the dose of dexamethasone used. As expected, a dose of 8–10 mg was associated with an increased risk of hyperglycaemia when compared to a lower dose and the difference in blood sugar levels was still significant in this group during the first 24-h [40]. A dose of 8 mg dexamethasone is considered to be more antiemetic than a dose of 4 mg [41] but exposes the patient to a higher risk of hyperglycaemia. We recommend the use of 4 mg dexamethasone in association with another antiemetic, such as droperidol or a 5-HT3 antagonist drug.

3.2. Treatment of pain

The effective management of postoperative pain is important. Poorly controlled pain is a risk factor for hyperglycaemia. The usual

- Use ultra-rapid insulin only, diluting it to a concentration of 1 IU/mL.
- Always include simultaneous glucose infusion (100-150 g/day) except if hyperglycaemia > 16.5 mmol/L (3 g/L). Example: D10 % W: 40 mL/h.
- Perioperative glycaemic objectives: 5 mmol/L -10 mmol/L (0.9 -1.8 g/L).
- Administer a direct IV loading bolus depending on starting blood glucose level then maintain by IV insulin infusion.
- Measure blood glucose level every 2 h if stable glycaemia, every hour after each change of insulin flow rate and after 15-30 min in the case of hypoglycaemia.
- Adapt IV insulin infusion flow rate depending on glycaemic control according to the following scheme:

Glycaemia		0.4 g/L / 2.2 mmol/L	0.6 / 3.3	0.9 / 5	1.1 / 6	1.8 / 10	2.5 / 14	3 / 16.5
Initiation IV insulin infusion	IV Bolus	0	0	0	0	3 IU	4 IU	6 IU
	IV insulin infusion flow rate	0	0	0	1 IU/h for T1D 0 IU/h for T2D	2 IU/h	3 IU/h	4 IU Inform clinician
Frequency of blood glucose measurement		15 min	30 min	1 h	1 h / 2 h	1 h	1 h	1 h
Adaptation of insulin infusion flow rate		Stop	Stop	- 1 IU/h	-1 IU/h / idem	+ 1 IU/h	+ 2 IU/h	Bolus 6 IU Inform clinician
		Resume at 1/2 rate when : - glyc. > 5 mmol/L in T1D - glyc. > 10 mmol/L in T2D						
D30 % W		2 amp. (6 g) Inform clinician	1 amp. (3 g)					

- Prefer measurement of glycaemia in whole blood (arterial or venous taken from the opposite side to the glucose infusion) rather than capillary blood and if possible use a blood gas machine (rather than a glycaemia test strip)
- Monitoring of potassium blood concentration : objective 4-4.5 mmol/L. Measure every 4 h if concentration is stable and 1 h after each change of insulin flow rate.

Fig. 1. Practical sheet O – protocol for continuous IV insulin therapy. General principles. T1D: type 1 diabetes; T2D: type 2 diabetes; G30%: 30% glucose; Gly: glycaemia; IVD: intravenous, direct; IVES: intravenous electronic syringe; IU: international units.

analgesics do not affect glycaemic control and can be used without any modification of indication or dose. It has recently been demonstrated however that diabetic patients with poor glycaemic control (as measured by HbA1c level) have higher analgesic requirements than those with HbA1c < 6.5% [42]. The use of RA should be favoured, when possible, as it is associated with better control of postoperative pain.

3.3. Additional measures

The degree of preoperative glycaemic control evaluated by HbA1c, the cessation of usual anti-diabetic treatments and preoperative fasting in the diabetic patient will all play a role in the perioperative glycaemic imbalance. Modulation of perioperative insulin resistance is a major therapeutic goal as it helps to significantly reduce the duration of postoperative hospital stay [43]. The prevention of hypothermia, the use of RA and multimodal analgesia (which will enable more rapid resumption of bowel movements), the limitation of blood loss, early ambulation and mini-invasive surgery are all measures to prefer.

The dogma of prolonged preoperative fasting has recently been called into question by studies reporting the beneficial effects of preoperative carbohydrate administration on postoperative insulin resistance in non-diabetic patients [43]. Finally, diabetes does not alter the usual rules for antibiotic prophylaxis.

Disclosure of interest

The authors declare that they have no competing interest.

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