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Perioperative Management of Diabetic Patients

New Controversies

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Br J Anaesth. 2014;113(6):906-909.

Abstract and Introduction

Introduction

The prevalence of diabetes mellitus (DM) is increasing rapidly. In 2011, it was estimated that 366 million people worldwide had DM with a projected increase to 522 million by 2030. Diabetes is one of the most common non-communicable diseases and is ranked as one of the top five global causes of premature death. The costs of treating DM are an increasing burden on healthcare budgets. For example, the NHS annual spending on DM was £9.8 billion in 2012 with an expected increase to £16.9 billion in the next 25 yr (~17% of the total NHS budget).[1]

Diabetes affects 4–5% of the UK population. However, the recent National Diabetes Inpatient Audit (NaDIA) found an inpatient prevalence of DM ranging from 5.5% to 31.1% within the UK.[2] Diabetes was associated with increased in-hospital morbidity and consequently increased duration of hospital stay, regardless of medical speciality. This confirms previous work showing a significantly increased duration of hospital stay in diabetic patients undergoing surgery.[3]

The primary aim of perioperative management of the surgical diabetic patient is to decrease morbidity and hopefully reduce the duration of hospital stay. Two authoritative publications, one by the National Health Services Diabetes in the UK[4] and the other by the Society for Ambulatory Anesthesia (SAMBA) in the USA,[5] have provided clear guidelines that are intended to improve perioperative care. The former describes an ideal pathway for all diabetic patients undergoing elective surgery: primary care referral, surgical outpatients, preoperative assessment, hospital admission, theatre and recovery, postoperative care, and discharge. Although this pathway will be a valuable standard for elective surgery, there is limited recognition in the guidelines that urgent and emergency surgery constitute an increasing proportion of patients in many hospitals. It is notable that both guidelines provide limited supporting evidence due to the absence of studies in this field, thus they are largely based on expert opinion. They should be considered 'work in progress'.

It is now over 3 yr since the publication of these two guidelines, and with the publication of new evidence, the purpose of this editorial is to examine the following areas of clinical controversy: utility of preoperative glycated haemoglobin values ($HbA1_c$), metformin use perioperatively, dose of long-acting insulins before surgery, and ideal blood glucose range and measurement error. Editorials on choice of i.v. fluid and the use of dexamethasone in the diabetic patient have previously been published.[6,7]

Utility of Preoperative Glycated Haemoglobin Values ($HbA1_c$)

It is well established that diabetic patients undergoing major surgery, cardiac and non-cardiac, are at increased risk of mortality and morbidity.[8–10] Furthermore, the relationship between inadequate preoperative glucose control and adverse outcomes has also been found in several surgical specialities: orthopaedics,[11] colorectal,[12] spinal,[13] vascular,[14] and cardiac.[15] These studies included diabetic and non-diabetic patients and it is notable that many non-diabetic patients were found to have elevated $HbA1_c$ values (>6% or >42 mmol mol^{-1}). Thus, there is evidence to show that good preoperative glycaemic control, as determined by $HbA1_c$ concentrations, is associated with a lower incidence of systemic and surgical complications, decreased mortality, and shorter duration of hospital stay.

The importance of glycated haemoglobin was emphasized recently by its incorporation into guidelines for the diagnosis of DM in the UK,[16] following the recommendations of the WHO. An $HbA1_c$ value >6.5% or 48 mmol mol^{-1}, on repeated testing, is diagnostic of DM, with concentrations between 6.0% and 6.4% or 42 and 47 mmol mol^{-1}, indicating a high risk of diabetes. The non-diabetic reference range is 4.0–6.0% or 20–42 mmol mol^{-1}. Target $HbA1_c$ concentrations for diabetic patients are 6.5–7.5% or 48–58 mmol mol^{-1} with the higher concentrations accepted for patients at risk of hypoglycaemia.

We suggest that preoperative $HbA1_c$ values should be determined in all patients undergoing major surgery, and also in all elective surgical patients with diabetes. Not only will this strategy diagnose DM in some patients with undiagnosed DM, it may also influence the timing of elective surgery. Glycated haemoglobin values >8.6% or 70 mmol mol^{-1} were associated with a four-fold increase in mortality after cardiac surgery.[15] Delaying elective major surgery while glycaemic control is improved is predicted to decrease mortality and serious morbidity—an objective that patient and clinician will surely support!

Perioperative use of Metformin

Metformin is a key drug in the treatment of type 2 diabetes. It acts as an insulin sensitizer and also inhibits gluconeogenesis. If given as the sole therapeutic agent, it does not cause hypoglycaemia. The risk of lactic acidosis in patients taking metformin is very low, but is more likely in those with renal impairment. Guidelines from NICE,[17] the British National Formulary,[18] and the drug manufacturer's datasheet[19] all advise the withdrawal of metformin before surgery, even 48 h before operation in one instance.[19]

For patients undergoing surgery with a period of short starvation, the NHS guidelines advise the continuation of metformin throughout the day of surgery with the omission of the lunchtime dose if the drug is taken three times a day and provided certain criteria are fulfilled (no contrast medium is used, and the eGFR is >50 ml min^{-1} 1.73 m^{-2}).[4] The NHS guidelines are at variance with established practice but are supported by recent guidance from the Royal College of Radiologists. The Royal College of Radiologists recommend that there is no need to discontinue metformin after contrast in patients with serum creatinine within the normal reference range, eGFR >60 ml min^{-1}, or both, and in patients with impaired renal function, they suggest that any decision to stop it for 48 h should be made in consultation with the referring clinic.[20] The inconsistency highlights the confusion about the current use of metformin perioperatively.

The NHS guidelines admit that there is limited evidence to support the perioperative recommendations on metformin. However, in a retrospective survey of 1284 diabetic cardiac surgical patients, it was found that those who continued with metformin, often inadvertently, had improved outcomes compared with those patients who omitted metformin as instructed.[21] Whether such benefits may occur in general surgical patients has yet to be established. At present, a rational conclusion is to continue metformin throughout the perioperative period in all patients with normal renal function. This will enhance the activity of residual insulin secretion in type 2 diabetic patients.

Optimal Dose of Perioperative Long-acting Analogue Insulin

Insulin therapy has changed for many diabetic patients with the introduction of basal insulin formulations, such as insulin detemir and glargine, and short-acting analogues. This has enabled patients with type 1 DM to manage both the basal and postprandial insulin requirements and try to mimic the non-diabetic state. Long-acting insulin therapy is used increasingly in type 2 diabetes if glycaemic control is poor. Long-acting insulins are given either in the evening or morning.

The 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.[4] The SAMBA guidelines provide a similar recommendation for amubulatory surgery.[5] Both authorities acknowledge that the dose of long-acting insulin may need to be decreased in patients who snack in addition to regular meals ('grazing'), miss meals, or have large reductions in overnight blood glucose values. A decrease in the usual dose of long-acting insulin by a third is suggested in these circumstances.[4] In support of this proposal, the NHS guidelines at that time were only able to cite an abstract which reported no problems with glucose control when the usual dose of long-acting insulin was continued.

A recent detailed investigation tried to answer the question—'which dose of insulin glargine should be administered on the evening before surgery?'.[22] Four hundred and one types 1 and 2 diabetic patients who were undergoing elective non-cardiac surgery were studied. Three evening insulin glargine regimens were evaluated: take 80% of usual dose, ask the patient's physician for the dose, or a simple dose schedule derived locally. The primary endpoint was the attainment of a preoperative fasting blood glucose in the range 5.5–9.9 mmol $litre^{-1}$.

Target glucose concentrations were achieved more easily in patients taking insulin glargine only (type 2 DM) than in those taking glargine and bolus insulin. There were no significant differences between the three groups in the number of patients achieving glucose values between 5.5 and 9.9 mmol litre^{-1} in the insulin glargine only patients, but a notable difference in the preoperative dose: 80% in the 80% usual dose group, 64% in the ask physician group, and 54% in the local dose schedule group. Similarly, in the insulin glargine and bolus insulin patients, there were no significant differences in the number of patients achieving the target glucose range; the preoperative evening doses were 80% in the 80% usual insulin dose group, 69% in the ask physician group, and 81% in the local dose schedule group.

Hypoglycaemia was uncommon; only two patients had preoperative glucose values of 2.7 and 3.1 mmol litre^{-1}. Conversely, only two patients had severe hyperglycaemia (>22 mmol litre^{-1}), and in one patient, this was the result of a self-medication error. The main limitation of the study was the sole endpoint of preoperative glucose values. Further work is necessary to show whether adequate intra- and postoperative glycaemic control can be obtained with these dosing schedules. Nevertheless, this study is an important step in providing data on which to determine basal insulin dosage before surgery. Currently, 80% of the usual evening dose is a simple, safe, and effective schema.

Ideal Blood Glucose Range and Measurement Error

There is almost unanimity between the NHS guidelines and the American Association of Clinical Endocrinologists with the American Diabetes Association Consensus Statement[23] that the ideal glucose range in hospital for non-critically ill diabetic patients should be 6–10 mmol litre^{-1} (in the USA, the lower limit is 100 mg dl^{-1} or 5.6 mmol litre^{-1}). There is considerable evidence that good glycaemic control decreases perioperative infection, morbidity, and mortality.[9,10] The NHS guidelines state that a range of 4–12 mmol litre^{-1} is also acceptable.

We argue that this extended range should not be used. The upper limit of 12 mmol litre^{-1} is similar to the concentration that *in vitro* results in a variety of changes in endothelial function, expression of adhesion molecules, impaired neutrophil function, enhanced cytokine synthesis, and decreased complement activity which combine to exacerbate inflammation and increase the risk of infection.[24] The lower limit of 4 mmol litre^{-1} is close to glucose values that, in some diabetic patients, will induce hypoglycaemic symptoms. Furthermore, safe use of the extended range will be critically dependent on accurate measurements of blood glucose values.

It is salutary to note that the FDA in the USA allows a 20% error for glucose meters at concentrations above 100 mg dl^{-1} (5.6 mmol litre^{-1}) and a 15% error for values <100 mg dl^{-1}. Thus, a measured concentration of 4 mmol litre^{-1} will have an actual value between 3.4 and 4.6 mmol litre^{-1}, while a measured concentration of 12 mmol litre^{-1} will have an actual value between 9.6 and 14.4 mmol litre^{-1}. In addition, measurement of glucose values with assay strips and glucose meters and by arterial gas analysis overestimates concentrations at low values. Also many factors commonly found in surgical patients can affect the measurement: poor peripheral perfusion, anaemia, increased bilirubin and uric acid, and drugs such as paracetamol, dopamine, and mannitol.[25] The title of this last reference is particularly apposite to the control and measurement of glucose perioperatively—'The devil is in the details'.

In conclusion, there can be no doubt that the publication of guidelines will facilitate the care of surgical diabetic patients. Nevertheless, these important documents should not be accepted uncritically. There is a tendency for guidelines to be judged by the status of the supporting organizations rather than the scientific merit of the publication. In which case, the guidelines become an assertion of authority—a territorial imperative—that must not be questioned.[26] In this article, we have addressed several controversial new areas in the perioperative care of the diabetic patient where recent research challenges current accepted practice. We suggest that the guidelines will need to evolve rapidly in the next few years to remain relevant.

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Declaration of interest

In the last 4 yr, N.L. has received rail travel expenses to attend meetings, as part of the NHS Diabetes writing group for Management of adults with diabetes undergoing surgery and elective procedures: improving standards. April 2011. G.M.H. is an editor of *Anesthesia and Analgesia*.

Br J Anaesth. 2014;113(6):906-909. © 2014 Oxford University Press