

# Glycaemic Control and Anaesthesia

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Evidence has mounted in long term studies such as the United Kingdom Prospective Diabetes Study (UKPDS) that protracted hyperglycaemia is the fundamental cause of diabetic microvascular complications,<sup>1</sup> and that it is strongly associated with macrovascular complications such as stroke, amputation and myocardial infarction. Aggressive treatment has become the recommended approach of diabetes associations across the world for long-term management of blood glucose.

A core philosophy of traditional teaching on the management of glucose during anaesthesia has been the avoidance of hypoglycaemia. Hypoglycaemic brain injury, whilst rare, is a serious complication of insulin therapy and most anaesthetic regimes are designed to avoid this at all costs. But, how much attention should anaesthetists pay to preventing hyperglycaemia during surgery?

This paper reviews the evidence for improved outcome with “tight” glycaemic control in various settings relevant to anaesthesia and critical care. What follows is a summary of published studies that hopefully will provide some guidelines for what blood glucose level will provide optimal outcomes in various situations. There have been many difficult issues associated with trying to provide this summary, as many published studies are insufficiently powered or have unusual endpoints. Others demonstrate an association (usually of diabetes rather than hyperglycaemia) with adverse outcomes, rather than determining if control of blood glucose will produce a better outcome. Most commonly, in many studies the groupings of patients make it hard to identify what the ideal blood glucose is.

Despite common fears, no study in the adult population has shown a blood glucose that was too low and resulted in worsened outcomes. The “ideal” upper limit for blood glucose in some studies is still high (e.g. <12 mmol/l), particularly in older studies (before 2000) where this band was simply the lowest group analysed. It is quite possible that normoglycaemia produces the best outcomes in many situations, but this has not been addressed in most studies to date.

## **Does short-term intervention make a long-term difference?**

Control of blood glucose in cardiac surgery has been shown to make a difference to both short-term complication rates and long-term outcomes. In a prospective randomised study by Lazar et al,<sup>2</sup> patients undergoing coronary artery bypass surgery were assigned to an active glucose-insulin-potassium regime or to standard therapy without active intervention in blood glucose management. The mean blood glucose in

the active group was 7.6 mmol/l versus 14.4 mmol/l in the standard group. Those in the active group showed fewer complications in the early postoperative period and had improved survival. This survival benefit was seen at two years post-surgery, although the period of treatment began before anaesthesia and continued only until 12 hours postoperatively.

The full significance of hyperglycaemia in the acute setting has only recently been appreciated. There is now a growing body of evidence that tight glycaemic control, for even short periods of time, in certain settings makes substantial differences to outcome in the long term.

### **Glycaemic Control in Critical Care**

The management of glycaemic control in the critically ill has changed substantially in the last four years. In 2001, van den Berghe et al<sup>3</sup> published a large (n=1548) randomised prospective controlled study looking at the effects of maintaining blood glucose in the physiological range (4.4-6.1 mmol/l) versus standard treatment which allowed higher levels (10.0-11.1 mmol/l). They showed significant benefits in maintaining physiological glucose levels. Independent results from Krinsley et al<sup>4</sup> (amongst others) appear to confirm the profound benefits of physiological glucose levels shown in the landmark van den Berghe study. The evidence for tight glycaemic control reducing peri-operative sepsis is now quite compelling.

### Mortality

Reduction in mortality may be substantial. Van den Berghe et al noted a 34% reduction in all-cause hospital mortality with lower glucose levels. Krinsley et al demonstrated a 29.3% reduction in hospital mortality after commencing an insulin protocol in 800 patients, compared to the immediately preceding 800 patients in an ICU. Remarkably, this benefit was associated with only a small reduction in mean blood glucose, from 8.4 mmol/l to 7.2 mmol/l.

### Reduced ICU Costs

Duration of ICU stay was reduced by 10% in one study. Decreases have also been found in transfusion requirements (18% in the Krinsley study; 40% in the van den Berghe study), in the incidence of acute renal failure (reduced by 75% in one study) and in the need for dialysis (by 50% in the original study by van den Berghe et al).

### Mechanism of benefit

Multivariate analysis by van de Berghe et al<sup>5</sup> revealed that the reduction in blood glucose, rather than in the amount of insulin given, was associated with improved outcome, which was originally noted to be in reduction of death from sepsis. In one study in a paediatric ICU, specifically excluding diabetics, a similar strong association between both the peak glucose level and the duration of hyperglycaemia and mortality was seen.<sup>6</sup> Hyperglycaemia was noted to be an independent predictor of mortality in this paediatric study. It remains unclear whether the high incidence of sepsis in the less tightly controlled groups is due to a direct effect of hyperglycaemia on bacteria, impairment of the immune response, or some other mechanism. However, the causal role of hyperglycaemia is now well established.

### Role of diabetes

It is also clear that hyperglycaemia appears to be the significant risk factor in diabetes, rather than the disease itself.

### **Myocardial Injury**

There is strong evidence that elevated blood glucose levels are independent predictors of poor outcome following acute myocardial infarction and other ischaemic syndromes, even in the non-diabetic patient.<sup>7</sup> It is difficult to determine whether or not any treatment for this may be effective.

The management of blood glucose in the peri-infarct setting has been influenced strongly by studies such as the DIGAMI study by Malmberg et al.<sup>8</sup> This prospective randomised controlled study showed significant reduction in mortality with the use of glucose and insulin following myocardial infarction. The subgroup who were given glucose and insulin and continued to use insulin post-infarct had significantly lower blood glucose levels. Survival was considerably higher in this subgroup. The greatest benefits were seen in those patients who had not had previous insulin treatment and who were considered to be at low cardiovascular risk before their infarcts. The benefits of this treatment did not dissipate over time. Follow up was continued to five years post-intervention and a 30% reduction in mortality was seen.

The question of whether the insulin therapy itself or treatment of hyperglycaemia results in the predominant benefit has not yet been fully answered in this setting. The DIGAMI 2 study,<sup>9</sup> which compared three different insulin/glucose strategies, failed to achieve significant outcome differences in its three subgroups. However, this study did not achieve its target blood glucose of 5-7 mmol/l (the mean glucose levels for the three groups were 8.0, 8.3 and 8.6 mmol/l) and epidemiological analysis confirmed that blood glucose levels remained a strong independent predictor of outcome post-myocardial infarction. These findings are consistent with the concept that the absolute blood glucose level is the key determinant in survival, even with other interventions such as revascularisation.<sup>10</sup> Persistent hyperglycaemia is associated with residual left ventricular dysfunction.<sup>11</sup>

### **Neurological Injury**

There is a growing body of evidence that neurological injury is worsened in the presence of hyperglycaemia. Work in animal models shows that hyperglycaemia increases the size of infarction, but the evidence in humans is more limited.<sup>12</sup> In animal models, it has been shown that hyperglycaemia in ischaemic stroke will produce brain oedema, intracellular acidosis, accumulation of glutamate in the extra cellular space and, ultimately, disruption of the blood brain barrier with increased tissue damage and risk of secondary haemorrhage. The underlying pathophysiology of hyperglycaemia has been demonstrated with functional MRI scanning in acute stroke in humans. MR spectroscopy demonstrates that hyperglycaemia increases the production of lactic acid in the under-perfused brain. This leads to a reduction in recovery in tissue where hypo-perfusion is present. This appears to increase infarct size and worsen functional outcome.<sup>13</sup>

The evidence for diabetes and hyperglycaemia being independent predictors of poor outcome in stroke has been demonstrated in many studies.<sup>14</sup> Generally speaking, diabetes predicts worsened outcomes in ischaemic stroke, with greater residual disability and prolonged admissions. Thus, diabetes itself is a recognised risk factor in

ischaemic stroke, but the role of hyperglycaemia has only been demonstrated more recently. Recovery from ischaemic reperfusion injury appears to be critically dependent on normoglycaemia. Blood glucose levels above 7.7 mmol/l are associated with poor reperfusion outcomes, many times worse than those in normoglycaemic patients following reperfused ischaemic stroke.<sup>15</sup> Beneficial outcomes persist for months after the initial injury.

Large scale randomised studies into whether altering glucose levels improves outcome are not yet available. Small prospective trials have shown mild improvements in some outcomes with tight control (BSL <7.0 mmol/l).<sup>16</sup> These studies are probably too small in size to show a major outcome benefit.

In summary, there is no doubt that diabetes in general, and hyperglycaemia specifically, are independent predictors of a worse outcome in humans with ischaemic stroke. The underlying pathophysiology of hyperglycaemia in neuronal ischaemia is well understood and readily explains these findings. To date, no clinical trials of sufficient size have demonstrated that reducing blood glucose will dramatically improve outcomes, but small studies do suggest benefit.

### **Trauma**

Several studies have shown hyperglycaemia to be strongly predictive of poor outcome in the setting of trauma. The majority of these studies have looked at neurological trauma and outcomes including length of stay, mortality and residual neurological deficits. Non-survivors of traumatic injury tend to have higher blood glucose levels for longer periods than survivors.<sup>17</sup> The hyperglycaemic response that is associated with worse outcomes is a stress response and is not necessarily related to diabetes. In the younger patients typically seen in trauma studies, significant differences in outcomes have been demonstrated at high blood glucose levels (e.g. poorer outcomes with blood glucose >11 mmol/l).<sup>18</sup> The benefits of reducing blood glucose below 10 mmol/l have not been shown in any large trauma study to date. Nonetheless, it should be noted that there is no evidence of harm in maintaining blood glucose under 8 mmol/l in these studies. Given the known poorer outcomes in brain ischaemia where blood glucose exceeds 8 mmol/l, this seems a reasonable target level pending larger studies in the trauma population.

### **Glycaemic Control and Perioperative Outcomes**

#### Cardiac Surgery

Control of blood glucose is of particular significance in cardiac surgery. In part, this is because high blood glucose affects outcome from surgery. It is also because diabetes, and poorly controlled diabetes in particular, is a major contributor to coronary artery disease. The reported incidence of diabetes in the cardiac surgical patient is higher than the population average (approximately one in six patients undergoing bypass surgery).<sup>19</sup> Typically, by the time that cardiac surgery is considered, patients have had diabetes for a long period of time — in one study the mean duration was 10 years at the time of surgery.<sup>20</sup> In this large, but retrospective, study, a significant difference was seen between those who had elevated blood glucose levels post-operatively and those who did not. Of particular interest, there was an increase in adverse outcomes (death, myocardial infarction, stroke or sepsis) of 17% for every mmol/l that blood glucose rose above 6.1, a similar level to that shown in the study by van den Berghe et al in the ICU population.

While the van den Berghe study mainly demonstrated an increase in sepsis, this cardiac surgery study found an increased risk of other (non fatal) adverse outcomes, such as stroke and myocardial infarction, with hyperglycaemia. The differences in blood glucose on the second and subsequent days were not shown to be significant, although the overall outcomes were. This again points to the role of tight control of blood glucose early in the peri-operative period as being the important determinant in outcome after cardiac surgery.

There is evidence for benefit in open chamber as well as coronary artery surgery. In a large (n=4864) prospective but non-randomised study by Furnary et al<sup>21</sup> of diabetics undergoing open-heart surgery, the use of a continuous insulin infusion for three days post-operatively, with a target blood glucose of <8.3 mmol/l, was shown to produce significant benefits. There were clinically and statistically significant reductions in mortality (57% reduction,  $P<0.0001$ ) and deep sternal wound infections (66% reduction,  $P<0.0001$ ), as well as a reduction in length of stay and hospital costs.

The exact role of glycaemic control versus combined glucose-insulin-potassium (GIK) treatment for ischaemic preconditioning is not fully defined, as there may be some role for insulin (plus supportive glucose and potassium) independent of its effect on blood glucose. In the previously mentioned study of diabetic patients by Lazar et al, patients receiving GIK infusion treatment with an average blood glucose of 7.6 mmol/l had significantly better outcomes than those using a subcutaneous insulin protocol with an average blood glucose of 14.4 mmol/l. Atrial fibrillation post-operatively was decreased from 42% to 16%. Postoperative stay was decreased from 9.2 to 6.5 days. Similar to the findings of other studies, wound infections were reduced from 10% to 1% in the group that had the lower blood glucose. The extent to which these impressive gains were attributable to insulin versus normoglycaemia is not yet fully defined, although the GIK regime is clearly associated with a marked reduction in blood glucose compared to standard therapy, and both groups received insulin.

### Transplantation

Hyperglycaemia has been demonstrated to modulate the immune response to transplanted cadaveric kidneys.<sup>22</sup> A blood glucose below 11 mmol/l was associated with a 11% rejection rate, compared with a 58% rejection rate in those above this level. In addition, in the subgroup with higher blood glucose (23 patients, n=50), all the patients developed postoperative infections. Whilst the exact rejection rate is dependent on many factors, it seems clear that high blood glucose levels are strongly associated with an increased risk of transplant rejection. In addition, in immunosuppressed patients undergoing surgery, a high blood glucose would appear to significantly increase the risk of perioperative infection. The optimal blood glucose in immunosuppressed patient is not yet established, but is clearly below 11 mmol/l. In consideration of the poor outcomes from sepsis demonstrated in the critical care setting, a blood glucose below 8.0 mmol/l, and possibly as low as 6 mmol/l, is a reasonable target until more extensive studies have been performed.

### Burns

The association between hyperglycaemia and burns is complex, in that hyperglycaemia is common in thermal injury and is a part of the hypermetabolic stress syndrome of a severe burn. The association between hyperglycaemia and mortality

appears clear, and in one study this association was seen independently of the surface area of the burn.<sup>23</sup>

### Other areas

There are many studies that show an association between diabetes and poor outcomes in a number of surgical settings, but very few actually have looked at blood glucose levels. Most have been retrospective analyses, where the presence of a diagnosis of "Diabetes" has been one of many variables analysed with respect to outcome.

These studies have two obvious limitations in their applicability to management in the perioperative period. Firstly, many patients are diabetic for a number of years before the diagnosis is made and will be missed by such studies, as they have not yet been labelled as "diabetic". Secondly, a diagnosis of "Diabetes" does not provide a good basis for treatment, whereas a blood glucose level does. Thus, until appropriate studies are done, the treatment strategies for hyperglycaemia in the perioperative setting are best based on objective data taken from related areas, such as intensive care, cardiology, emergency medicine and neurology where better evidence exists.

### **Hyperglycaemia in Paediatric Patients**

Whilst prospective randomised outcome data is not yet available, several studies in the paediatric intensive care setting have demonstrated a similar relationship between hyperglycaemia and poor outcome as that seen in adults. In one series of neonates with necrotizing enterocolitis, a blood glucose greater than 11 mmol/l was associated with a mortality of 29% versus 2% in the group whose glucose level was below this level.<sup>24</sup> In another observational study in the paediatric critical care setting, a worse outcome was seen with hyperglycaemia. Mean glucose in non-survivors was significantly higher than in survivors (17.3 mmol/l versus 11.4 mmol/l).<sup>25</sup> In another retrospective<sup>26</sup> series of non-diabetic children with severe burns, those with blood glucose levels above 7.8 mmol/l over 40% of the time had a significantly lower percentage of successful skin graft take. In this group, hyperglycaemia was associated with a non-significant increase in positive blood cultures (particularly yeasts) and a large, but again non-significant, increase in mortality (27% versus 4%). (The study was not powered sufficiently to identify significant differences in mortality.)

However, the case against hyperglycaemia in neonates is not entirely clearcut. One long-term follow up study<sup>27</sup> on arterial switch surgery (chosen because of being a relatively standard procedure not especially associated with neurological syndromes) showed that high glucose levels were not associated with poor neuro-developmental outcomes up to eight years after surgery. On the other hand, low glucose levels were associated with seizure like activity on EEG.

Overall, hyperglycaemia appears to show a similar association with poor outcomes in the critically unwell infant in the setting of sepsis. However, the case for poor myocardial and neurological outcomes is not yet established for the paediatric population and the findings in adults may not always be accurately applied in paediatrics. Further research in this area is necessary.

### **Hyperglycaemia and Anaesthesia**

The choice of medication or therapy based on glycaemic control is not well established in the literature, as it has only recently become evident that major

improvements in outcome can be achieved by tightly controlling blood glucose levels. However, some studies have been reported which are of interest in relation to glycaemic control in anaesthesia.

One interesting study from Canada used isotope labelled glucose tracers during anaesthesia.<sup>28</sup> In this study, both glucose production and clearance were measured before and during surgery. Surgery itself was shown to be a cause of decreased glucose clearance, which will tend to promote hyperglycaemia. However, a regional anaesthetic plus intravenous general anaesthesia reduced the production of glucose and had a nett effect of balancing the reduced clearance. Blood glucose rose in this group a statistically, but not clinically, significant amount — from 5.0 to 5.2 mmol/l. With isoflurane anaesthesia, a significant increase in blood glucose was seen due to an increase in glucose production, in addition to the decreased glucose clearance found with surgery. Blood glucose rose from 5.2 to 7.2 in this group.

In one recent study, the use of clonidine IV was shown to reduce plasma insulin and increase blood glucose levels.<sup>29</sup> In the control group, blood glucose was 5.7 mmol/l versus 6.8 mmol/l in those who received 1 mcg/kg clonidine prior to induction of anaesthesia. Clonidine also appeared to reduce the plasma noradrenaline and cortisol response compared to controls.

It appears that the changes in blood glucose due to choice of agents in anaesthesia are not well known at present. What can be said is that regional anaesthesia, even in the presence of general anaesthesia, appears to improve glucose handling during surgery and significantly reduces the hyperglycaemic response to surgical stress. Certain agents appear to have a small negative effect on blood glucose control. Isoflurane and clonidine both cause a rise in blood glucose to a small degree. The degree of glucose rise is not significant in healthy patients. In the setting of critical illness, where hyperglycaemia is common and worsens outcome, the use of these agents may still be reasonable. However, their use should prompt closer monitoring of blood glucose and consideration of insulin therapy at an earlier stage during surgery.

## **Summary**

### Critical Illness and Sepsis

There is sufficient evidence that glycaemic control impacts on outcome. This mandates tight blood glucose control intraoperatively under certain circumstances. The ideal blood glucose level is not yet established in all situations, but it would appear that, in the sickest of patients, there is evidence that better outcomes are achieved when physiological range (4-6 mmol/l) blood glucose levels are maintained.

### Myocardial Injury and Cardiac Surgery

There is clear evidence that myocardial injury has a worse outcome in the presence of hyperglycaemia. There appears to be significant evidence that control of hyperglycaemia improves outcome and that benefits are seen in reducing blood glucose below 8 mmol/l, and possibly to below 6 mmol/l. The duration of this tight control should be at least until one day post-injury, and possibly as long as three days in diabetic patients where prolonged hyperglycaemia is likely.

### Neurological Injury

Clear evidence exists that ischaemic neurological injury has a worse outcome in the presence of hyperglycaemia. The pathophysiology associated with this has been

demonstrated to a reasonable extent in human and animal models. The evidence for benefit from tight control of blood glucose is not fully established. However, the combination of some evidence for benefit, along with a sound scientific explanation for why hyperglycaemia causes injury, suggests that control of blood glucose in the presence of a neurological injury is a standard of care. This view may be altered by large prospective outcome studies. At present, the best evidence available suggests that a blood glucose below 8.0 mmol/l will produce better outcomes in these cases.

### Other Trauma & Burns

Clear evidence exists that hyperglycaemia is predictive of adverse outcome in the setting of trauma. There are no large trials to demonstrate if control of blood glucose will alter outcome. However, given the evidence from non-trauma patients, it is reasonable to maintain a blood glucose below 6-8 mmol/l, particularly if there are clinical grounds for suspecting neurological injury, myocardial injury or sepsis. There appears to be a clear association between hyperglycaemia after burns and poor outcome and a target blood glucose below 8 mmol/l appears to be justified, whilst awaiting outcome studies.

### Anaesthesia

Despite the large number of studies from many specialties, there are few large prospective randomized trials that look at the effect of blood glucose control on outcome in the anaesthetic setting. With the weight of evidence available, it is clear that such a study is needed urgently. In the interim, the routine adoption of tight blood glucose control peri-operatively, particularly in the subgroups outlined above, should be strongly considered by all anaesthetists.

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