Commentary

The benefits of insulin therapy following acute myocardial infarction revisited

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Introduction

The increased mortality and morbidity from cardiovascular disease associated with diabetes mellitus (DM) is well known.1 Patients with DM but no previous myocardial infarction (MI) have a risk of MI similar to that of non-diabetic patients with a previous history of MI,1 and mortality from acute MI in patients with DM is double that in non-diabetic individuals.2,3 Five-year mortality in patients with DM hospitalized with MI is 75%:3 higher than that for many malignant diseases. In spite of more aggressive and interventional therapies for MI, mortality remains significantly higher in patients with DM, compared with those without.4 There are several possible explanations for this increased mortality, including the presence of more severe, extensive and diffuse coronary artery lesions, diabetic cardiomyopathy, diabetic autonomic neuropathy, and the pro-thrombotic tendency in DM.5

The concept of infusing glucose together with insulin and potassium (GIK) to protect ischaemic myocardium was pioneered by Sodi-Pallares et al.6 more than 40 years ago. Many studies lacked statistical power to demonstrate a clear benefit of this intervention compared to controls, and many trials had poor randomization techniques.7 In the DIGAMI study, insulin-glucose intravenous infusion in an acute MI followed by intensive subcutaneous insulin therapy for 3 or more months improved long-term survival compared to the conventional treatment group, with a benefit lasting for at least 3 years.8 The absolute reduction in mortality was 11%, suggesting that one life was saved for every nine treated patients.8 In the DIGAMI study, the greatest mortality reduction was observed in the group that was classified as lowest risk, with an absolute reduction in mortality of 15%. In addition, higher mean glucose values were associated with increased mortality.8 This is in keeping with findings from a latter systematic review9 and another study.10 The clinical implications of the DIGAMI study were not clear; it was not known whether the benefit was related to the initial insulin-glucose infusion, the subsequent subcutaneous insulin treatment, or both. In addition, only half of the patients eligible for entry were randomized over the course of the study. As a result, opinion was divided as to whether the results should be implemented in hospital practice in full,11 or whether we should await the results of further studies.12

The DIGAMI 2 study

Subsequently, Malmberg et al. embarked on the DIGAMI 2 trial to further investigate their initial findings.13 This study was done in 48 hospitals in Sweden, Norway, Denmark, Finland, Holland and the UK. Patients with diabetes were randomized into three groups: (i) insulin-glucose infusion for

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24 h, followed by multi-dose subcutaneous insulin, aiming at a target fasting glucose of 5–7 mmol/l; (ii) insulin-glucose infusion for 24 h, followed by conventional therapy; and (iii) conventional therapy only. However, the study at close did not reach the full recruitment of patients. More significantly, the fasting blood glucose target was never reached in group (i) and mean HbA1c did not differ significantly among the three groups. There were no mortality or morbidity differences amongst the three groups, and neither 24-h insulin-glucose infusion nor administration of insulin in the days and months after acute MI appeared to influence the outcome after acute MI. Multivariate logistic regression analysis indicated that the severity of hyperglycaemia was an independent risk factor for adverse outcome.

Disappointingly, the DIGAMI 2 study did not discover whether the hospital insulin or subsequent multi-dose subcutaneous insulin treatment was important. This may have been due to the lack of significant difference in long-term blood glucose between the three arms of the study. Although, a statistically significant difference in blood glucose control was achieved between the first two groups and group three in the acute stage, this difference was smaller than expected, and may not have reached clinical significance. Low recruitment, leading to a 50% reduction in the study power and modifications in the entry criteria to improve recruitment (patients known to have type 2 diabetes and glucose concentration <11 mmol/l were included), may have also played a role. Importantly, the patients investigated in DIGAMI 2 differed significantly from those in the first DIGAMI study. Their levels of admission hyperglycaemia were lower, and this may be the reason for the reduced absolute level of mortality at the end of the study in the three groups. Thus the original DIGAMI trial findings are not entirely contradicted.

In other randomized controlled trials investigating the influence of intensive insulin therapy on the outcome of acutely ill patients in the context of intensive care and after cardiac surgery, where the variation in blood glucose control between different study arms was actually achieved, outcomes were indeed significantly better.7–9,14

Conclusions

In the DIGAMI 2 trial, patients with type 2 DM did not show improved survival following an acute MI from insulin treatment (either acutely introduced or long-term) compared with conventional management. However, several factors, mentioned above, may account for this outcome, which should be interpreted as ‘no result’, rather than a negative result.

In an intensive care study, Van den Berghe et al. indicated that it was the tight glycaemia control in particular, rather than the amount of insulin administered, that explained the mortality benefit in their intensive insulin therapy group.15 However, a role for insulin therapy, independent of its blood-glucose-lowering effect, cannot be completely ruled out.16–18 There is an increasing body of evidence to suggest that preventing hyperglycaemia and subsequent glucose toxicity is an effective, safe and practicable way of reducing mortality and morbidity in both post acute MI and other acutely ill patients.8,9,12,14,15 Due to funding and logistic difficulties, further multicentre randomized controlled trials are unlikely, at least in the near future. Nevertheless, there is a local need to develop protocols. With the current available evidence, out-of-hospital routine subcutaneous insulin may not be necessary, provided that the desired glycaemic control can be attained using lifestyle modifications and oral hypoglycaemic agents. However, in hospital, insulin-glucose infusion as per the DIGAMI protocol appears justified in patients with acute MI and blood glucose concentrations >11 mmol/l.

References


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