Metabolic and cardiac outcomes after acute myocardial infarction

Anuksha Gujadhur, Trisha Dunning, Frank Alford

Introduction

The original DIGAMI protocol recommended using intravenous insulin to manage myocardial infarction from first presentation followed by subcutaneous insulin for 3 months in patients with diabetes. This paper describes the metabolic and cardiac outcomes and barriers to implementing a protocol designed to match the DIGAMI principles across our emergency and cardiology departments. Patients managed using the revised DIGAMI protocol achieved better blood glucose control and had fewer reinfarcts than those managed without insulin. The major barrier to using the protocol appeared to be staff fear of causing hypoglycaemia.

People with diabetes have a high risk of cardiovascular complications including myocardial infarction (MI; Egede and Zheng, 2002). During an acute MI and myocardial damage a dramatic rise in free fatty acid (FFA) levels occurs that inhibits residual insulin release in patients with diabetes and leads to insulin resistance. Furthermore, the accumulation of toxic FFA metabolites induces further myocardial damage (Vetter et al, 1974; Aronson and Rayfield, 1997). Insulin is important to reduce these ‘toxic’ factors.

The DIGAMI study

The DIGAMI study described the outcomes of intensive control of hyperglycaemia with insulin infusions commenced on initial presentation to the emergency department, followed by subcutaneous insulin for at least 3 months, in patients with diabetes presenting with an MI.

The investigators showed a relative risk reduction of 52% at 3 months that was sustained at 12 months, and significantly fewer deaths after 1 year in the intensive insulin group than in the standard treatment group (Malmberg et al, 1997). However, it was not possible to determine whether the benefit accrued from insulin infusion during the acute event or from improved glycaemic control after discharge.

Implementing DIGAMI

A modified version of the protocol was initiated at St. Vincent’s Hospital in 1999 and involved collaboration between the emergency, cardiac, and endocrinology and diabetes departments to decide the processes to be followed, doses of insulin to be infused and the education that would be required for nurses and medical staff. An initial audit carried out during a month of detailed monitoring 3 months after implementation revealed that the protocol was followed in two-thirds of patients with diabetes and acute MI.

Aim of the study

A follow-up study was devised to assess adherence to the protocol 2 years after initial implementation; determine barriers to use of the protocol; and evaluate metabolic and cardiac outcomes in patients receiving insulin infusion compared with those not receiving an infusion and with unmatched historical controls.

Methodology

The sampling population consisted of a retrospective and a prospective group.

Retrospective group

The retrospective group consisted of 22 patients admitted between 1998 and early 1999 before the DIGAMI protocol was implemented. Eligible patients were identified by the medical records department. The retrospective group was included as an unmatched historical control for the prospective group in order to ascertain if there were any improvements in overall outcomes after implementation.
of the DIGAMI protocol, rather than as a direct comparison/control group.

**Prospective group**

Thirty-three patients with diabetes and a MI who were admitted to the coronary care unit (CCU) during the study period, August and September 2002, consented to participate in the study. Follow-up was at 3 months. Patients with inadequate English, those who were too ill or who declined to participate were excluded.

**Metabolic and cardiac data**

The diagnosis of myocardial infarction was based on the joint criteria of the European Society of Cardiology and the American College of Cardiology (2001). Patients with a documented diagnosis of diabetes and treatment for diabetes (diet, tablets or insulin) were recruited.

Major outcome measures consisted of:
- Metabolic control – HbA1c, lipids and average plasma glucose during admission.
- Cardiac enzymes (troponins, creatine kinase) and electrocardiogram results.
- Diabetes management regimen and during admission and on discharge.

**Statistical analysis**

Data were analysed using Microsoft Excel 2000 (Microsoft Corporation, Redmond, Washington). The significance of the difference between groups treated with and without insulin infusion was assessed using unpaired Student's t-test. The level of significance was set at 0.05 with 82% power to detect a difference between the groups.

**Results**

**Retrospective group (n=22)**

The retrospective and prospective groups were of similar ages (67.3 ± 11.1 vs 66.2 ± 1.4 years, P=0.5). There was a higher proportion of females (54.5 vs 39.4%) and a longer duration of diabetes (17.5 ± 11.1 vs 11.6 ± 10.9 years, P=0.01) in the retrospective group than in the prospective group. There was also a higher proportion of patients with hypertension (81.8%) and heart disease (72.7%) in the retrospective group.

Thirty-six percent of patients were on oral agents. Although intravenous insulin was not routine management at the time it was used in seven patients. The remaining 15 were maintained in hospital on their routine outpatient treatment. The majority

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**PAGE POINTS**

1. Thirty-three patients with diabetes and a MI who were admitted to the coronary care unit (CCU) during the study period consented to participate in the study.

2. Major outcome measures consisted of metabolic control, cardiac enzymes and electrocardiogram results and diabetes management regimen.
Table 2. Metabolic results of the combined retrospective and prospective groups

<table>
<thead>
<tr>
<th></th>
<th>No-infusion group</th>
<th>Infusion group</th>
<th>Mean difference</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length of hospital stay (days)</td>
<td>4.7±11.1 (1-14)</td>
<td>5.3±4.9</td>
<td>0.6</td>
<td>0.6</td>
</tr>
<tr>
<td>Average plasma glucose levels on admission (mmol/l)</td>
<td>11.3±2.4 (7.5-1.6)</td>
<td>9.3±1.6</td>
<td>2.0</td>
<td>0.0007</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.4±1.3</td>
<td>8.8±1.6</td>
<td>1.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Admission for another cardiac event 3 months after discharge</td>
<td>7.5/31 (16.1%)</td>
<td>2/24 (16.7%)</td>
<td>4ND</td>
<td>0.07</td>
</tr>
</tbody>
</table>

a= data are given as mean±sd (range); b= measured on admission only; c= results expressed as number of patients (% of total); d= not documented.

(68.2%) of patients were discharged on their preinfarct treatment.

The average glucose levels in hospital were significantly lower in the infusion group (23.4% lower, P=0.012). Five patients in the non-infusion group were admitted for another coronary event within 3 months of discharge compared with only two in the infusion group.

Prospective group (n=33)

By chance, the prospective group fell into two almost equal groups – an intravenous insulin infusion group (n=17) and a non-infusion group (n=16), which allowed outcomes to be compared. Age and duration of diabetes were similar in both groups, with a higher proportion of men in the infusion group (12 vs 9, P=0.03).

Table 1 compares the metabolic parameters of the infusion and non-infusion groups. The infusion group had a more adverse profile of clinical characteristics for coronary vascular disease than the non-infusion group, with a higher mean HbA1c and cholesterol levels. The average glucose during admission was lower by 20.6% in the infusion group than in the non-infusion group. The infusion group had a lower incidence of reinfarction in the 3 months after discharge.

A larger proportion of patients in the infusion group than the non-infusion group were on insulin before their infarct (10 vs 2). Five patients from the insulin infusion group commenced subcutaneous insulin for the first time when the infusion was ceased. A further two patients commenced insulin after discharge, while the majority remained on their preinfarct oral hypoglycaemic agents.

The frequency of self-reported hypoglycaemia was similar in both groups, but ten (58.8%) patients in the infusion group described their hypoglycaemia as severe, compared with three (18.7%) in the non-infusion group. The blood glucose levels documented on the blood glucose chart did not support patients' perceived hypoglycaemia. Blood glucose levels were tested every 2h during the infusion then every 4h as is standard practice in our hospital.

Combined group

The metabolic parameters of the seven patients from the retrospective and the 17 from the prospective intravenous insulin groups were combined to obtain a larger sample (n=24). There was a significantly lower blood glucose profile in the infusion group (9.3±1.6 vs 11.3±2.4 mmol/l, P=0.007) but higher HbA1c (8.8±1.6 vs. 7.6±1.3 %, P=0.03) than in the non-infusion group (n=33). Five patients from the non-infusion group were readmitted with another infarct compared with two from the infusion group (P=0.07). The combined metabolic results of the retrospective and prospective groups are shown in Table 2.

Barriers to the use of the insulin infusion protocol

Although the DIGAMI infusion protocol has been in use since 1999 it was not used
Table 3. Reasons given by the CCU registrars for not using the DIGAMI protocol

<table>
<thead>
<tr>
<th>Reason</th>
<th>Frequency of response</th>
</tr>
</thead>
<tbody>
<tr>
<td>To avoid hypoglycaemic episodes</td>
<td>7</td>
</tr>
<tr>
<td>Patients had adequate control with conventional treatment</td>
<td>3</td>
</tr>
<tr>
<td>Blood glucose levels were under control</td>
<td>3</td>
</tr>
<tr>
<td>Silent infarct during hospital stay</td>
<td>2</td>
</tr>
<tr>
<td>Patient refused to have insulin</td>
<td>1</td>
</tr>
</tbody>
</table>

Some registrars gave more than one reason.

In 16 of the 33 patients (48.5%) presenting with MI during the study. The reasons registrars gave for not using an insulin infusion are shown in Table 3.

**Discussion**

**Metabolic outcomes: infusion versus no infusion**

In-hospital metabolic control was significantly improved in patients who had an insulin infusion, despite the more adverse risk-factor profile (higher HbA1c levels, duration of diabetes), especially in the prospective group. This improvement may be due to the longer duration of the infusion after implementation of the protocol, closer monitoring of blood glucose levels and treatment titration after infusion was stopped. However, the average blood glucose in the prospective group during admission was not significantly lower than that in the retrospective group. This finding could be attributed to the fact that only half of the prospective group had received intravenous insulin, so that use of the protocol did not entail any considerable improvement in outcomes.

**Cardiac outcomes**

The number of episodes of reinfarction 3 months after discharge was markedly lower (although the difference was not statistically significant) in the infusion group than in the pooled group. The beneficial effects of intravenous insulin in improving regional myocardial function, promoting enhanced glucose utilisation by the cardiac muscles and reducing FFA metabolism in the early stages of MI have been documented (Jonassen et al, 2001; Marano et al, 2002; Sundell et al, 2002). Our study reinforces the findings of DIGAMI in that early tissue healing and long-term prognosis improves with intravenous insulin.

**Diabetic treatment**

Most patients were continued on their original outpatient treatment regimen on admission and at discharge in both the retrospective and prospective groups, despite the fact that patients require some treatment modification to counteract the effects of acute illness (Metchick et al, 2002). Furthermore, it is well established that after a first MI, patients with diabetes have an adverse long-term prognosis including increased rates of reinfarction and death and need more aggressive treatment after a cardiac event (Lomuscio et al, 1991). In fact, a recent audit in our hospital revealed that the majority of inpatient referrals to the diabetes nurse educators had cardiovascular complications and most were from the CCU. Therefore, it is of concern that compliance with recommended treatment was low despite the established DIGAMI protocol.

**Adherence to the DIGAMI protocol**

The results from this study and the 1999 audit clearly indicate that adherence to the agreed DIGAMI protocol gradually decreased over time, and the rate of insulin infusion use is nearly the same as it was in the pre-DIGAMI era. This suggests the need for continued monitoring and education because CCU registrars change every 2–3 years. Interestingly, a recent study indicated that using the DIGAMI protocol did not put additional workload on the staff but rather proved to be beneficial (Portogallo, 2001).
Criteria for using the protocol

The registrars based the decision to use insulin infusion on the severity of the myocardial infarction. This severity was assessed by the troponin levels and the degree of hyperglycaemia on presentation. Therefore, it can be postulated that the clinicians in our study used certain undefined clinical parameters to decide whether or not to use an insulin infusion, despite the agreed protocol. It seems likely that these decisions were based on biochemical, cardiac and metabolic parameters and/or perceived convenience to the patient or desire not to complicate the management further.

Hypoglycaemic risks as a barrier

The risk of causing hypoglycaemia was cited as the major barrier to using insulin infusion by the CCU registrars even though the intravenous route enables more rapid control of glucose levels than subcutaneous insulin administration, avoids insulin depots and is therefore less likely to produce unexpected hypoglycaemia. Although the incidence of hypoglycaemia in the infusion and non-infusion groups was similar, it must be pointed out that hypoglycaemic events were self-reported by patients and not substantiated by nursing documentation. Patients may have confused anxiety or illness with the symptoms of hypoglycaemia. In addition, the incidence of hypoglycaemia was lower in our study than in the DIGAMI study. The infusion doses used in our protocol were deliberately lower than those used in the DIGAMI study (Malmberg et al., 1997), which could explain the lower frequency of hypoglycaemia in our study. Our study demonstrated that low-dose insulin infusion is as effective as a high-dose infusion in terms of improved metabolic outcomes, and had fewer side-effects.

Limitations of the study

The retrospective and prospective groups, as well as the groups receiving and not receiving the intravenous insulin were not matched in any way and there may have been inherent differences between the groups. The small sample size could mean that the results might only apply to the population under study and we may not be able to extrapolate to the general population.

Conclusion

Intravenous insulin significantly improved metabolic and cardiac outcomes, in terms of better glycaemic control and less risk of reinfarction among patients with diabetes and MI. This study highlights the challenge of ensuring the timely initiation of subcutaneous insulin in patients with diabetes and a MI, and the opportunity to improve the implementation of insulin infusions and drugs that are known to be effective and beneficial in the acute and long-term treatment of MI in patients with diabetes.

There is a need for regular education and clinical discussion among the relevant departments, namely the emergency, cardiac, endocrinology and CCU departments. Appropriate education, especially among the CCU nurses and medical staff and a close collaboration between the CCU staff and the diabetes team can create an awareness of the long-term benefits of insulin use and hence ensure its optimum use.