Chapter 3

Glucose-insulin-potassium infusion as adjunctive therapy in myocardial infarction: current evidence and potential mechanisms

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Italian Heart Journal 2004;5:727-31
Metabolic interventions in acute myocardial infarction

Abstract

Background
In ST segment elevation myocardial infarction (MI) there is conflicting evidence that mortality, morbidity and infarct size is reduced by therapies influencing myocardial metabolism, such as infusion of glucose-insulin-potassium (GIK). Several clinical trials with GIK have already provided insight in the magnitude of this effect. Our aim was to investigate current evidence on the potential beneficial effect of GIK infusion in ST segment elevation MI.

Methods
Randomized trials comparing GIK with placebo or untreated controls in patients with ST segment elevation MI were identified by electronic and manual searches. A systematic analysis of all data was performed, with regard to inclusion criteria, dose of GIK and additional use of reperfusion therapy.

Results
Thirteen trials, involving 5009 patients, were included. Overall, hospital mortality was 10.7% after GIK compared to 12.8% in controls (P=0.02). GIK infusions were in particular effective when a high-dose was used and if given as adjunctive to reperfusion therapy. Low-dose GIK was less beneficial, and may even increase hospital mortality. Also in patients with heart failure on admission, GIK may have worse effects. In all analyzed trials, GIK infusion caused only mild adverse effects, although fluid overload may be a problem in certain patients.

Conclusion
GIK may reduce mortality in patients with STEMI, particularly if a high dose is used and when GIK is administered as an adjunct to reperfusion therapy. However, all studies had a relative small sample size and additional large randomized trials are certainly needed before a definite conclusion can be made. The limited evidence currently available does not warrant GIK therapy to be applied in patients at the present time.
Introduction

Glucose-insulin-potassium (GIK) infusion in the treatment of ST segment elevation myocardial infarction (MI) has been a field of interest for many decades. However, the results of early studies investigating the effect of GIK on clinical outcome after myocardial infarction were inconclusive and attention focussed on reperfusion therapies. Furthermore, lack of financial interest of the pharmaceutical industry made it difficult to perform a large clinical trial. Although early and sustained reperfusion is indeed the most important initial treatment of ST segment elevation MI, agents that influence energy substrate metabolism in the reperfused myocardium may have additional beneficial effects. In a meta-analysis of earlier randomised trials of GIK in ST segment elevation MI, it was shown that GIK has potential beneficial effects, but studies in the reperfusion era were lacking. Furthermore, the meta-analysis suggested that beneficial effects of GIK are particularly seen if high-dose GIK infusion was used. This potential dose dependent effect of GIK was also observed before. After the meta-analysis was published, several randomised trials have been reported, also with GIK as adjunctive therapy to reperfusion therapies. However, most trials had a relative small sample size. A meta-analysis or review of all relevant trials can provide sufficient power to demonstrate differences in outcome. This article will review the currently available data concerning the clinical benefits and potential mechanism of action of GIK. We also performed a stratified analysis of the effects of high and low dose GIK infusion, including all recently published trials.

Methods

We attempted to obtain results from all completed, published, randomised trials of GIK in acute MI. The literature was scanned by formal searches of electronic databases (MEDLINE) and informal searches for studies concerning the potential mechanism of action of GIK. Since experimental and clinical studies have suggested a dose-response curve of GIK, we performed stratified analyses of the effects of low and high dose of GIK. A high dose GIK was defined as an intravenous infusion of GIK in a dose equal to or higher than used by Rackley et al, 30% glucose (300 mg/L), 50 IU/L regular insulin and 80 mmol/L potassium chloride at 1.5 mL/kg per hour infusion rate. Our primary efficacy outcome of interest was hospital mortality. We calculated the relative risk (RR) for hospital death of patients treated with GIK as compared to those treated with placebo or no infusion. The RR and its 95% confidence interval (CI) were calculated for each trial and the grand totals.
<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Patients (N)</th>
<th>Glucose</th>
<th>Insulin</th>
<th>Potassium</th>
<th>Rate</th>
<th>Period</th>
<th>Mortality (%)</th>
<th>RR 95% CI</th>
<th>Time to Random, Treatment</th>
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<tr>
<td>ECLA</td>
<td>1998</td>
<td>135</td>
<td>25%</td>
<td>50 IU/L</td>
<td>80 mmol/L</td>
<td>1.5 mL/kg.h</td>
<td>24 h</td>
<td>10</td>
<td>0.69 (0.27-1.70)</td>
<td>11.4 (0.56)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>133</td>
<td>10%</td>
<td>20 IU/L</td>
<td>40 mmol/L</td>
<td>1.0 mL/kg.h</td>
<td>24 h</td>
<td>8</td>
<td>0.63 (0.24-1.52)</td>
<td>10.1 (0.53)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>139</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>16</td>
<td></td>
<td></td>
<td>10.6 (0.50)</td>
</tr>
<tr>
<td>Satler</td>
<td>1987</td>
<td>10</td>
<td>300 mg/L</td>
<td>50 IU/L</td>
<td>80 mEq/L</td>
<td>1.5 mL/kg.h</td>
<td>48 h</td>
<td>0</td>
<td>-</td>
<td>4.7 ± 2.7</td>
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<tr>
<td>Heng</td>
<td>1977</td>
<td>12</td>
<td>50%</td>
<td>0.3 IU/kg normal saline</td>
<td>0.15 mmol/kg</td>
<td>1.5 mL/kg.h</td>
<td>6-12 h</td>
<td>1</td>
<td>-</td>
<td>8 (4-11.5)</td>
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<td>Stanley</td>
<td>1978</td>
<td>55</td>
<td>300g</td>
<td>50 IU</td>
<td>normal saline</td>
<td>0.15 mmol/kg</td>
<td>48 h</td>
<td>9</td>
<td>0.40 (0.08-1.57)</td>
<td>7.5 (4-14)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>55</td>
<td>-</td>
<td>-</td>
<td>-</td>
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<td>9</td>
<td></td>
<td></td>
<td>7.0</td>
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<td>Rogers</td>
<td>1976</td>
<td>61</td>
<td>300g</td>
<td>50 IU</td>
<td>NaCl</td>
<td>0.15 mmol/kg</td>
<td>48 h</td>
<td>9</td>
<td>0.50 (0.11-1.92)</td>
<td>&lt;12</td>
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<tr>
<td>Pol-GIK</td>
<td>1999</td>
<td>494</td>
<td>10%</td>
<td>20 IU/L</td>
<td>80 mEq/L</td>
<td>1.5 mL/kg.h</td>
<td>48 h</td>
<td>4</td>
<td>1.95 (1.12-3.47)</td>
<td>5.0 (3.0-10.1)</td>
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<tr>
<td>Pentecost</td>
<td>1968</td>
<td>100</td>
<td>10%</td>
<td>30 IU</td>
<td>NaCl</td>
<td>0.15 mmol/kg</td>
<td>48 h</td>
<td>15</td>
<td>0.93 (0.40-2.14)</td>
<td>9.82</td>
</tr>
<tr>
<td>Mittra</td>
<td>1965</td>
<td>85</td>
<td>240 g or 2x10 Usc</td>
<td>52-78 mEq</td>
<td>-</td>
<td>-</td>
<td>14 d</td>
<td>0.34 (0.13-0.81)</td>
<td>11.94 ± 1.23</td>
<td>11.3 ± 1.26</td>
</tr>
<tr>
<td>MRC</td>
<td>1968</td>
<td>480</td>
<td>160 g or 2x10 Usc</td>
<td>52 mEq</td>
<td>in 1500</td>
<td>24 h</td>
<td>103</td>
<td>0.69 (0.65-1.21)</td>
<td>7.6 ± 1.21</td>
<td></td>
</tr>
<tr>
<td>Pilcher</td>
<td>1967</td>
<td>49</td>
<td>240 g or 2x10 Usc</td>
<td>52-78 mEq</td>
<td>-</td>
<td>-</td>
<td>6 d</td>
<td>0.48 (0.13-1.54)</td>
<td>unknown</td>
<td></td>
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<tr>
<td>Hjermann</td>
<td>1971</td>
<td>104</td>
<td>200 g or 16 IU placebo</td>
<td>55 mEq</td>
<td>-</td>
<td>-</td>
<td>10 d</td>
<td>0.47 (0.19-1.11)</td>
<td>11.8</td>
<td></td>
</tr>
<tr>
<td>DIGAMI</td>
<td>1995</td>
<td>306</td>
<td>5%</td>
<td>80 IU</td>
<td>-</td>
<td>0.7L</td>
<td>24 h</td>
<td>0.89 (0.67-1.19)</td>
<td>13 ± 7</td>
<td></td>
</tr>
<tr>
<td>GIPS</td>
<td>2003</td>
<td>476</td>
<td>20%</td>
<td>50 IU</td>
<td>160 mmol/L</td>
<td>1.5 mL/kg.h</td>
<td>8-12 h</td>
<td>4.8</td>
<td>0.82 (0.46-1.46)</td>
<td>2.5 (1.67-3.58)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>464</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>11.1</td>
<td></td>
<td></td>
<td>2.5 (1.75-3.9)</td>
</tr>
</tbody>
</table>

RR denotes relative risk. CI denotes confidence interval. h denotes hour. d denotes days. min denotes minutes. or denotes oral. Usc denotes units subcutaneous.
Overview of GIK studies in acute MI

Results

Our search yielded 13 studies, involving 5009 patients. The meta-analysis of Fath-Ordoubadi and Beatt including 9 studies did not include three recently published trials.\(^3\) They also excluded the Diabetes Mellitus, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) in which GIK (insulin-glucose) was studied in patients with diabetes mellitus or a glucose at admission of >11.0 mmol/L.\(^3\) Baseline characteristics of all randomised trials are summarised in table 1. The studies used GIK in different doses, and the time from onset of symptoms of myocardial infarction to treatment varied, with a large proportion of patients being treated after more than 6 hours from onset of symptoms. It is shown that in patients with ST segment elevation MI treated by primary coronary intervention, symptom-onset-to-balloon time is related to mortality.\(^8\) This study found that a symptom-onset-to-balloon time >4 hour was identified as independent predictor of one-year mortality. The studies included in the meta-analysis of Fath-Ordoubadi and Beatt had several other limitations.\(^3\) Firstly, randomization was not always optimal, resulting in significant differences in baseline clinical characteristics between the two treatment groups.\(^1;10\) Secondly, mortality rates were generally very high in both the treatment and in placebo groups, with hospital mortality up to 28%.\(^11\) Furthermore, only the study by Satler and colleagues including only 17 patients also received reperfusion therapy.\(^12\) The first randomised prospective trial in the era of reperfusion, the DIGAMI study including only patients with diabetes mellitus, found that the combination of insulin-glucose infusion with an intensive insulin treatment for at least three months after discharge resulted in a reduction in hospital mortality of 58% in patients without prior insulin use and a low cardiovascular risk profile.\(^8\) Potassium was added to the infusion when necessary. The Estudios Cardiologicos Latinoamerica (ECLA) pilot trial, was published in 1998 and also showed a beneficial effect of GIK.\(^6\) This effect was in particular observed in patients who also underwent reperfusion therapy. Hospital-mortality was 5.1% in patients treated with GIK versus 15.1% in controls (\(P<0.01\)). Most patients were treated with thrombolysis as reperfusion therapy, whereas only 3% were treated with primary angioplasty. In 1999, the Polish-Glucose-Insulin-Potassium (Pol-GIK) trial was published, including 954 patients.\(^5\) This trial demonstrated no differences in cardiac mortality or the occurrence of cardiac events at 35 days between GIK (6.5%) and control patients (4.6%). Total mortality at 35 days was even higher in the GIK group (8.9%) than in controls (4.8%, \(P<0.01\)). However, in this trial low-dose GIK was used. The most recent study, the Glucose Insulin Potassium Study (GIPS), included 940 ST segment elevation MI patients all treated with primary angioplasty as reperfusion therapy.\(^7\) High-dose GIK resulted in a non-significant reduction of mortality in GIK treated patients in the total patient group (4.8% versus 5.8%, \(P=0.50\)).
However, a significant mortality reduction was found in patients without signs of heart failure (1.2% versus 4.2%, \(P=0.01\)).

With regard to the presumed protective effect of GIK infusion on the myocardium, several studies were performed investigating the benefit of GIK infusion during cardiac surgery. Comparison of results is difficult because the studies differed in initiation of GIK (pre, during or post cardiac surgery), duration and dosing of GIK\(^{13-15}\) and end points (including enzymatic myocardial damage, need for inotropic support and mortality). Lazar et al. found a benefit of GIK in two small sized studies.\(^{16,17}\) However, many other trials, including a well sized randomised trial (\(N=1127\)), failed to show a clear benefit of GIK infusions in cardiac surgery.\(^{18,19}\) So, no definite conclusions about the use of GIK infusions in cardiac surgery can be drawn.

**Table 2. 30-day mortality in patients treated with high-dose GIK and low-dose GIK versus control patients of published trials**

<table>
<thead>
<tr>
<th>Trial (ref)</th>
<th>GIK patients</th>
<th>Control patients</th>
<th>GIK patients</th>
<th>Control patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Heng(^{38})</td>
<td>12</td>
<td>1 (8.3)</td>
<td>0 (-)</td>
<td></td>
</tr>
<tr>
<td>Stanley(^{39})</td>
<td>55</td>
<td>4 (7.3)</td>
<td>4 (7.3)</td>
<td></td>
</tr>
<tr>
<td>Rogers(^{10})</td>
<td>61</td>
<td>4 (6.5)</td>
<td>9 (12.3)</td>
<td></td>
</tr>
<tr>
<td>Satler(^{12})</td>
<td>10</td>
<td>0 (-)</td>
<td>0 (-)</td>
<td></td>
</tr>
<tr>
<td>ECLA(^{6*})</td>
<td>135</td>
<td>10 (7.4)</td>
<td>16 (11.5)*</td>
<td></td>
</tr>
<tr>
<td>GIPS(^7)</td>
<td>476</td>
<td>23 (4.8)</td>
<td>27 (5.8)</td>
<td></td>
</tr>
<tr>
<td>DIGAMI(^{8})</td>
<td>306</td>
<td>28 (9.2)</td>
<td>35 (11.1)</td>
<td></td>
</tr>
<tr>
<td>Total (high-dose)</td>
<td>1065</td>
<td>70 (6.6)</td>
<td>96 (8.9)</td>
<td></td>
</tr>
<tr>
<td>Mittra(^{11})</td>
<td>85</td>
<td>10 (11.8)</td>
<td>24 (23.5)</td>
<td></td>
</tr>
<tr>
<td>Pilcher(^{40})</td>
<td>49</td>
<td>6 (6.7)</td>
<td>12 (22.7)</td>
<td></td>
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<tr>
<td>Pentecost(^2)</td>
<td>100</td>
<td>15 (15.0)</td>
<td>16 (16.0)</td>
<td></td>
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<tr>
<td>MRC(^1)</td>
<td>480</td>
<td>103 (21.5)</td>
<td>115 (23.6)</td>
<td></td>
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<tr>
<td>Hjermann(^{21})</td>
<td>104</td>
<td>11 (9.6)</td>
<td>20 (20)</td>
<td></td>
</tr>
<tr>
<td>ECLA(^{6*})</td>
<td>133</td>
<td>10 (7.5)</td>
<td>16 (11.5)*</td>
<td></td>
</tr>
<tr>
<td>Pol-GIK(^6)</td>
<td>494</td>
<td>44 (8.9)</td>
<td>22 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Total (low-dose)</td>
<td>1445</td>
<td>199 (13.8)</td>
<td>225 (15.8)</td>
<td></td>
</tr>
<tr>
<td>Total (all)</td>
<td>2510</td>
<td>269 (10.7)</td>
<td>321 (12.8)</td>
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</table>

Data are number or number (%). Ref denotes reference. N denotes number of patients. ECLA = Estudios Cardiologicos Latinoamerica. GIPS = Glucose-Insulin-Potassium Study. DIGAMI = Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction. MRC = Medical Research Council. Pol-GIK = Polish Glucose Insulin Potassium. *In both comparisons the same control group is used; in the total of all patients this groups is accounted for once.
Time to treatment

Time between admission and initiation of GIK varied among the studies. Mittra mentioned 10 hours, whereas in the MRC study 70% of patients were treated within 30 minutes after inclusion.\textsuperscript{1,11} In the ECLA pilot trial, time from onset of symptoms till the initiation of GIK treatment was 10 to 11 hours.\textsuperscript{6} Whether the clinical effects of GIK on outcome are influenced by the time of initiation of treatment is not yet known. However, reperfusion may be obligatory as prolonged severe ischemia is followed by necrosis, even in the presence of GIK. Furthermore, GIK might not reach adequate concentrations in non-perfused myocardium. It would be logical to assume that GIK infusion would be most effective when initiated before reperfusion therapy has started, when glucose can temporarily salvage the severely ischemic myocardium and offer protection to possible reperfusion injury still to come.\textsuperscript{20}

Figure 1. Odds ratios and confidence intervals of high-dose and low-dose GIK trials

GIPS = Glucose-Insulin-Potassium Study. ECLA = Estudios Cardiologicos Latinoamerica. DIGAMI = Diabetes Insulin-Glucose in Acute Myocardial Infarction study MRC = Medical Research Council. Pol-GIK = Polish Glucose Insulin Potassium. In both comparisons of the ECLA the same control group is used; in the total of all patients this groups is accounted for once.
Dose

The above-mentioned meta-analysis showed that use of high-dose GIK is most effective.³ This was also demonstrated in dose-response studies, showing that increasing doses were associated with more suppressed arterial FFA levels as well as increased myocardial glucose uptake. Also the ECLA pilot-trial confirmed that high-dose GIK was superior to low-dose.⁶ In the Pol-GIK trial, using a very low dose of GIK, no effect of GIK was observed.⁵ Moreover, using this low dose regimen resulted in an increase in total mortality rate. We performed a stratified analysis according to GIK-dose, including all randomized trials investigating the influence of GIK on in-hospital mortality (table 2). Administration of high dose GIK resulted in a reduction of hospital mortality (6.6% versus 8.9%, RR 0.7; 95%CI: 0.5–1.0, P=0.04). Administration of low dose GIK versus placebo did not result in a significant difference of in-hospital mortality (13.8% versus 15.8%, RR 0.9; 95%CI: 0.7–1.1, P=0.13). Overall, GIK reduced statistically significant hospital mortality from 13% versus 11% (RR 0.8; 95%CI: 0.7-1.0, P=0.02) (figure 1).

Adverse effects

The reported adverse effects of GIK treatment were in general mild. Withdrawal because of side-effects was rare. As GIK was infused via peripheral intravenous catheters, phlebitis was relative common with percentages up to 15%, but severe phlebitis however was rare.¹¹ Infusion of large amounts of fluid in a short period may cause fluid overload. This potential adverse reaction was however, not reported in the meta-analysis. Possibly, because of inclusion of only few patients with Killip class >1 in earlier trials. Other studies demonstrated a small increase of signs of congestive heart failure after GIK.²¹ In the GIPS trial, there was a trend towards a higher mortality in GIK treated patients with Killip class >1 (36% versus 27%), possibly due to volume overload.⁷ A potential side-effect of GIK infusion is the induction of hypoglycemia.²² In the DIGAMI study, 15% of the patients who received intensified therapy had a hypoglycemic event (glucose <3.0 mmol/L), compared to none in the control group.⁶,²³ In the Pol-GIK trial hypoglycemia occurred in 8% of the patients, where after the insulin dose was decreased.⁵ They also found hyperglycemia in less than 1% in 585 patients with no differences between GIK and control group. In the GIPS hyperglycemia occurred also in the GIK group although the period was short-lived. With a blood glucose level >16.8 mmol/L as criteria for interruption in the Pol-GIK; only 1% was interrupted. This is not surprising since a low dose GIK infusion was used. Hjermann and colleagues used a reduced dose of insulin, which prevented the occurrence of hypoglycemia.²¹
Mode of action

There are several potential mechanisms by which GIK therapy might improve outcome after acute myocardial infarction. Although the primary energy substrate for the non-ischemic myocardium is free fatty acids (FFA), the myocardium uses various forms of energy substrates, including glucose. During an acute myocardial infarction, circulating FFA levels are elevated and insulin sensitivity is reduced, limiting cellular uptake of glucose and promoting the use of FFA. These FFA are thought to have a detrimental effect on ischemic myocardium through varying pathways. They are an energy supply which is associated with relatively high oxygen consumption in comparison to the utilisation of glucose. Moreover, in contrast with glucose, FFA cannot be metabolised without insulin. Indeed, experimental evidence suggests a negative influence of FFA on myocardial mechanical performance in the setting of hypoxia. Furthermore, excess FFA metabolism increases susceptibility to ventricular arrhythmia's and reperfusion injury due to disturbances in calcium homeostasis and accumulation of free radicals.

Administration of GIK lowers the circulating levels of FFA through the inhibitory effect of insulin on lipolysis. This decrease in FFA levels, in combination with an increase in glucose and insulin availability, promotes the myocardial use of glucose over FFA. Glucose is less oxygen consuming and has beneficial effect on preservation of mechanical function and membrane stability. Moreover, GIK therapy might also reduce arrhythmias after successful reperfusion. As insulin itself induces coronary vasodilation, myocardial metabolism could further be improved through enhanced myocardial perfusion. SPECT analysis showed that GIK infusion improved regional myocardial perfusion and function in segments adjacent to recently infarcted areas using in human subjects. Recent evidence suggests that insulin might also inhibit reperfusion injury by inhibiting apoptosis via activation of innate cell-survival pathways in the heart.

Conclusion

Of 13 published randomized trials, 12 studies reported mortality reduction after GIK. Despite the possibility of existence of a publication bias, i.e. small negative trials that not have been published, this seems promising. Most effects were observed when GIK was given in a high dose and when it was given as an adjunctive to reperfusion therapy. Adverse effects were rare, fluid overload may be a problem in certain patients, such as patients with signs of heart failure at admission. To achieve definite conclusions about the place of GIK in acute myocardial infarction, more randomized trials in which GIK is combined with optimal reperfusion therapy are needed. Currently large trials in different populations are undertaken and within a few years more evidence will be available. Possibly these data will change daily practice.
Metabolic interventions in acute myocardial infarction

References


