Myocardial infarction and glucose-insulin-potassium infusion: an overview

Summary

Background: Mortality and infarct size in ST segment elevation myocardial infarction (STEMI) may be reduced by therapies influencing myocardial metabolism, such as infusion of glucose-insulin-potassium (GIK). Although several clinical trials with GIK have been performed, the effect of GIK on outcome is still uncertain. In this article a review of all randomised trials on GIK infusion in STEMI is given.

Methods and Results: We identified randomised trials comparing GIK with placebo or controls in STEMI patients by electronic and manual searches. Thirteen trials were included with a total of 4992 patients. Overall, hospital mortality was lower after GIK (10.8% vs 12.9%, p = 0.02). Particularly high-dose GIK infusions were effective and if given as adjunctive to reperfusion therapy. GIK may have worse effects in patients with heart failure on admission. GIK infusion caused only mild adverse effects. Fluid overload may be a problem in certain patients.

Conclusions: GIK may reduce mortality in patients with STEMI. GIK is particularly effective when a high dose is used and when administered as adjunctive to reperfusion therapy. However, definite conclusions cannot be made and additional large randomised trials are needed.

Key words: glucose-insulin-potassium; acute myocardial infarction; reperfusion; dose; metabolism; adverse effects

Introduction

Glucose-insulin-potassium solution (GIK) in the treatment of ST segment elevation myocardial infarction (STEMI) has been investigated for many decades [1, 2]. However, the results of early studies on the effect of GIK on clinical outcome were inconclusive and attention focused on reperfusion therapies. Large clinical trials were difficult to perform due to lack of financial interest of the pharmaceutical industry [3]. Early and sustained reperfusion is the most important initial treatment of STEMI, but agents that influence energy substrate metabolism may have additional beneficial effects. In a previous meta-analysis it was shown that GIK has potential beneficial effects [4], particularly when a high dose scheme is used. A dose-dependent effect of GIK was also observed before [5]. Several additional randomised trials have been conducted to investigate GIK infusion as adjunct to reperfusion therapies since the last meta-analysis was published. We aimed to review currently available data concerning the clinical benefits and potential mechanism of action of GIK.

Methods

We attempted to obtain results from all completed, published, randomised trials of GIK in STEMI. The literature was scanned by formal and informal searches in medical databases for studies concerning the potential mechanism of action of GIK. We performed a 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, which is approximately 5 IU insulin/hour [6]. 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 controls. The RR and its 95% confidence interval (CI) were calculated for each trial and the grand totals.

**GIK trials**

Our search yielded 13 studies, involving 4992 patients. The meta-analysis of Fath-Ordoubadi and Beatt included 9 studies. However, neither the DIGAMI study, in which GIK was studied in patients with diabetes or hyperglycaemia, nor three other recently published trials were included [4]. Baseline characteristics of the randomised trials are summarised in table 1. The time from onset of symptoms of myocardial infarction to treatment varied between the studies and different doses of GIK were used. The studies included in the meta-analysis of Fath-Ordoubadi and Beatt had several other limitations. Mortality rates were generally very high in both the treatment and in placebo groups, with hospital mortality up to 28% [7]. Furthermore, reperfusion therapy was infrequently given [8]. The DIGAMI study, including only patients with hyperglycaemia, 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 [9]. The Estudios Cardiologicos Latinoamerica (ECLA) pilot trial, was published in 1998 and also showed a beneficial effect of GIK [10]. This effect was particularly observed in patients who received reperfusion therapy. Hospital-mortality was 5% in patients treated with GIK versus 15% in controls (p <0.01). In 1999, the Polish-Glucose-Insulin-Potassium (Pol-GIK) trial was published, including 954 patients. This trial demonstrated no differences in cardiac mortality at 35 days between GIK (6.5%) and control patients (4.6%) [11]. Total mortality at 35 days was even higher in the GIK group than in controls (8.9% vs 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 STEMI patients all treated with primary angioplasty as reperfusion therapy. High-dose GIK resulted in a non-significant reduction of mortality (4.8% vs 5.8%; p = 0.50). However, in patients without signs of heart failure at presentation a significant mortality reduction was found (1.2% vs 4.2%; p = 0.01) [12].

**Time to treatment**

There were large differences between the studies with regard to the time between admission and initiation of GIK. Ranging from 30 minutes to 10 hours after inclusion [1, 7]. 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 ischaemia is followed by necrosis, even in the presence of GIK. Furthermore, GIK might not reach adequate concentrations in non-perfused myocardium. Probably, GIK infusion would be most effective when initiated before reperfusion therapy has started, when glucose can temporarily salvage the severely ischaemic myocardium and offer protection to possible reperfusion injury [13].

**Table 1**

<table>
<thead>
<tr>
<th>Study</th>
<th>publication year</th>
<th>patients (n)</th>
<th>glucose (%)</th>
<th>insulin (IU/l)</th>
<th>infusion rate (ml/kg/h)</th>
<th>infusion period (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Satler</td>
<td>1987</td>
<td>17</td>
<td>30</td>
<td>50</td>
<td>1.5</td>
<td>48</td>
</tr>
<tr>
<td>Heng</td>
<td>1977</td>
<td>27</td>
<td>50</td>
<td>21</td>
<td>1.5</td>
<td>6–12 (11)</td>
</tr>
<tr>
<td>Stanley</td>
<td>1978</td>
<td>110</td>
<td>30</td>
<td>50</td>
<td>1.5</td>
<td>48</td>
</tr>
<tr>
<td>GIPS</td>
<td>2003</td>
<td>940</td>
<td>20</td>
<td>50</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>Rogers</td>
<td>1979</td>
<td>134</td>
<td>30</td>
<td>50</td>
<td>1.5</td>
<td>48</td>
</tr>
<tr>
<td>DIGAMI</td>
<td>1995</td>
<td>620</td>
<td>5</td>
<td>80</td>
<td>0.7 l/24 h</td>
<td>24</td>
</tr>
<tr>
<td>ECLA</td>
<td>1998</td>
<td>135</td>
<td>25</td>
<td>50</td>
<td>1.5</td>
<td>24</td>
</tr>
<tr>
<td>ECLA</td>
<td>1998</td>
<td>133</td>
<td>10</td>
<td>20</td>
<td>1.0</td>
<td>24</td>
</tr>
<tr>
<td>Pol-GIK</td>
<td>1999</td>
<td>954</td>
<td>10</td>
<td>20</td>
<td>0.6</td>
<td>24</td>
</tr>
<tr>
<td>Pentecost</td>
<td>1968</td>
<td>200</td>
<td>10</td>
<td>30</td>
<td>1.5 l/24 h</td>
<td>48</td>
</tr>
<tr>
<td>Mittra*</td>
<td>1965</td>
<td>170</td>
<td>24</td>
<td>10×2</td>
<td>–</td>
<td>14 days</td>
</tr>
<tr>
<td>MRC*</td>
<td>1968</td>
<td>968</td>
<td>16</td>
<td>10×2</td>
<td>–</td>
<td>14 days</td>
</tr>
<tr>
<td>Pilcher*</td>
<td>1967</td>
<td>102</td>
<td>24</td>
<td>10×2</td>
<td>–</td>
<td>14 days</td>
</tr>
<tr>
<td>Hjermann*</td>
<td>1971</td>
<td>204</td>
<td>20</td>
<td>16</td>
<td>–</td>
<td>10 days</td>
</tr>
</tbody>
</table>

* glucose, potassium oral; insulin subcutaneous
**Dose of GIK**

The meta-analysis by Fath-Ordoubadi and Beatt showed that use of high-dose GIK was most effective [4]. This was also demonstrated in dose-response studies, showing that increasing doses were associated with increased myocardial glucose uptake and more suppressed arterial FFA levels [5, 14]. Also the ECLA study confirmed that high-dose GIK was superior to low-dose [10]. In the Pol-GIK study, using a low-dose of GIK, no effect of GIK was reported [11]. Moreover, using this regimen resulted in an increase in total mortality rate. We performed a stratified analysis according to GIK-dose, including all randomised trials investigating the influence of GIK on in-hospital mortality. Administration of high-dose GIK resulted in a reduction of hospital mortality (7% vs 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 (14% vs 16%, RR 0.9; 95%CI: 0.7–1.1; p = 0.13). Overall, GIK significantly reduced hospital mortality from 13% to 11% (RR 0.8; 95%CI: 0.7–1.0; p = 0.02) (fig. 1).

**Side effects**

The reported adverse side effects of GIK treatment were in general mild and withdrawal because of side-effects were rare. Peripheral phlebitis was relatively common with percentages up to 15% [2], but severe phlebitis however was rare [7]. Infusion of large amounts of fluid may cause fluid overload. Some studies demonstrated a small increase of signs of congestive heart failure after GIK [15]. In the GIPS trial, there was a trend towards a higher mortality in GIK treated patients with Killip class >1 (36% vs 27%) [12]. In the DIGAMI study, 15% of the patients who received intensified therapy had a hypoglycaemic event, compared to none in the control group [9]. In the Pol-GIK trial hypoglycaemia occurred in 8% of the patients, whereafter the insulin dose was decreased [11]. Hjermann et al. used a reduced dose of insulin, which prevented the occurrence of hypoglycaemia [15].

**Mode of action**

GIK therapy might improve outcome after STEMI through several potential mechanisms (table 2). The non-ischaemic myocardium uses various forms of energy substrates including free fatty acids (FFA) and glucose [16]. During STEMI, circulating FFA levels are elevated and insulin sensitivity is reduced promoting the use of FFA [17]. These FFA are thought to have a detrimental effect on ischaemic myocardium. They are an energy supply which is associated with a relatively high oxygen consumption in comparison to the utilisation of glucose [18]. Moreover, in contrast with glucose, FFA can not be metabolised anaerobically. Experimental evidence suggests a negative influence of FFA on myocardial mechanical performance in the setting of hypoxia [19]. Furthermore, excess FFA metabolism increases susceptibility to ventricular arrhythmia’s and reperfusion injury [20, 21]. Administration of GIK lowers the circulating levels of FFA through the inhibitory effect of insulin on lipolyses [22]. This decrease in FFA levels, in combination with an increase in glucose and insulin availability, promotes the myocardial use of glucose over FFA [20]. Glucose is less
oxygen consuming and has beneficial effects on preservation of mechanical function and membrane stability [6, 23, 24]. Moreover, GIK therapy might also reduce arrhythmia’s after successful reperfusion [25]. As insulin itself induces coronary vasodilation, myocardial metabolism could further be improved through enhanced myocardial perfusion [26–28]. SPECT analysis showed that GIK infusion improved regional myocardial perfusion and function in segments adjacent to recently infarcted areas [26]. Recent evidence suggests that insulin might also inhibit reperfusion injury by inhibiting apoptosis via activation of innate cell-survival pathways in the heart [13].

**Future GIK trials**

The combined ECLA-II / CREATE trial, investigating high-dose GIK in reperfused MI patients, has already included a very large number of patients (>27 000) and therefore has optimal statistical power. The DIGAMI-II will provide additional data on potential effects of glycometabolic control in diabetic patients. The OASIS-6 trial will include at least 10 000 patients with an MI and will investigate the effect of GIK infusion on short term outcome. The GIPS-II trial will include 1044 patients treated with reperfusion. Extensive laboratory and angiographic data and measurement of residual left ventricular function in the GIPS-II will provide additional insight into the therapeutic mechanisms of GIK.

**Conclusions**

GIK may reduce mortality in patients with STEMI. Most effects are observed when GIK is given in a high-dose and as an adjunctive to reperfusion therapy. Fluid overload may be a problem in patients with signs of heart failure on admission. Definite conclusions cannot be made and additional large randomised trials need to be awaited.

**Références**


