Original articles

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

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Adverse effects; Glucose-insulin-potassium; Metabolism; Myocardial infarction; Reperfusion.

Background. **In ST-elevation myocardial infarction (STEMI) 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 into the magnitude of this effect. The aim of this article was to review randomized trials on adjunctive GIK infusion in STEMI.**

Methods. **Randomized trials comparing GIK with placebo or untreated controls in patients with STEMI 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. Thirteen trials, involving 4992 patients, were included.**

Results. **Overall, hospital mortality was 10.8% after GIK compared to 12.9% in controls (p = 0.02). GIK infusions were in particular effective when a high dose was used and if given as an adjunct to reperfusion therapy. 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.**

Conclusions. **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.**

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Introduction

Glucose-insulin-potassium (GIK) solution in the treatment of ST-elevation myocardial infarction (STEMI) has been a field of interest for many decades[1,2]. However, the results of early studies investigating the effect of GIK on clinical outcome after myocardial infarction were inconclusive and attention focused on reperfusion therapies. Furthermore, lack of financial interest of the pharmaceutical industry made it difficult to perform a large clinical trial[3]. Although early and sustained reperfusion is indeed the most important initial treatment of STEMI, agents that influence energy substrate metabolism in the reperfused myocardium may have additional beneficial effects. In a previous meta-analysis, mostly including trials conducted without any reperfusion therapy, it was shown that GIK has potential beneficial effects[4], particularly when a high-dose scheme is used. This potential dose-dependent effect of GIK was also observed before[5]. However, several additional randomized trials have been conducted to investigate GIK infusion as an adjunct to reperfusion therapies. Thus the aim of this article was to review currently available data concerning the clinical benefits and potential mechanisms of action of GIK.

Methods

We attempted to obtain results from all completed, published, randomized trials of GIK in acute myocardial infarction. The literature was scanned by formal searches of electronic databases (Medline) and informal searches for studies concerning the potential mechanisms of action of GIK. Since experimental and clinical studies have suggested a dose-re-

sponse 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 that used by Rackley et al.[6], 30% glucose (300 mg/l), 50 IU/l regular insulin and 80 mmol/l potassium chloride at 1.5 ml/kg/hour infusion rate (= a total of approximately 5 IU insulin/hour). 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. The RR and its 95% confidence interval (CI) were calculated for each trial and the grand totals.

Overview

Our search yielded 13 studies, involving 4992 patients. The meta-analysis of Fath-Ordoubadi and Beatt[4] included 9 studies, but did not include neither the DIGAMI study, in which GIK was studied in patients with hyperglycemia, nor three recently published trials. Baseline characteristics of all randomized trials are summarized in table I[1,2,7-17]. 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. The studies included in the meta-analysis of Fath-Ordoubadi and Beatt[4] had several other limitations. Mortality rates were generally very high in both the treatment and in placebo groups, with hospital mortality up to 28%[14]. Furthermore, only in the study by Satler et al.[10], including 17 patients, reperfusion therapy was given. The first randomized prospective trial in the era of reperfusion, the DIGAMI study, including only patients with hyperglycemia, found that the combination of insulin-glucose infusion with an intensive insulin treatment for at least 3 months after discharge resulted in a reduction in hospital mortality of 58% in patients without prior insulin use and a low cardiovascular risk profile[11]. In the DIGAMI study approximately 50% of the patients were treated with reperfusion therapy. The Estudios Cardiologicos Latinoamerica (ECLA) pilot trial was published in 1998 and also showed a trend toward a beneficial effect of GIK[12]. This effect was particularly observed in patients who received reperfusion therapy (62%, n = 252). Most patients were treated with thrombolysis as reperfusion therapy, whereas only 3% were treated with primary angioplasty. Hospital mortality in patients treated with reperfusion therapy was 5% in patients treated with GIK vs 15% in controls ($p < 0.01$), whereas no effect of GIK was observed in patients not treated with reperfusion therapy (9 vs 7%). After 1 year the beneficial effect of GIK was only present in reperfused patients treated with high-dose GIK. In 1999, the Polish-Glucose-Insulin-Potassium (Pol-GIK) trial was published, including 954 patients, of which 60% were treated with reperfusion therapy. Patients with insulin requiring diabetes were excluded. This trial demonstrated no differences in cardiac mortality at 35 days between GIK (6.5%) and control patients (4.6%)[17]. 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 STEMI patients all treated with primary angioplasty. High-dose GIK resulted in a non-significant reduction of mortality (4.8 vs 5.8%, $p = 0.50$). However, a significant mortality reduction was found in patients without signs of heart failure at presentation (1.2 vs 4.2%, $p = 0.01$)[13].

Table I. Glucose-insulin-potassium (GIK) trials and GIK doses used in acute myocardial infarction.

Study	No. patients	Glucose (%)	Insulin (IU/l)	Infusion rate (ml/kg/hour)	Infusion period (hours)
High-dose GIK					
Heng et al.[7], 1977	27	50	21	1.5	6-12 (11)
Stanley et al.[8], 1978	110	30	50	1.5	48
Rogers et al.[9], 1979	134	30	50	1.5	48
Satler et al.[10,] 1987	17	30	50	1.5	48
DIGAMI[11], 1995	620	5	80	0.7l/24h	24
ECLA[12], 1998	135	25	50	1.5	24
GIPS[13], 2003	940	20	50	3	12
Low-dose GIK					
Mittra[14]*	170	24	10 × 2	–	14 days
Pilcher[15], 1967*	102	24	10 × 2	–	14 days
MRC[1], 1968*	968	16	10 × 2	–	14 days
Pentecost et al.[2], 1968	200	10	30	1.5 l/24h	48
Hjermann[16], 1971*	204	20	16	–	10 days
ECLA[12], 1998	133	10	20	1.0	24
Pol-GIK[17], 1999	954	10	20	0.6	24

* glucose, potassium oral; insulin subcutaneous.

Time to treatment

Time between admission and initiation of GIK varied among the studies. Mittra[14] mentioned 10 hours, whereas in the MRC study[1] 70% of patients were treated within 30 min after inclusion. In the ECLA study, time from onset of symptoms till the initiation of GIK treatment was 10 to 11 hours[12]. 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[18].

Dose

The meta-analysis by Fath-Ordoubadi and Beatt[4] showed that use of high-dose GIK is most effective. This was also demonstrated in dose-response studies, showing that increasing doses were associated with more suppressed arterial free fatty acid (FFA) levels as well as increased myocardial glucose uptake[5,19]. Also the ECLA study confirmed that high-dose GIK was superior to low-dose[12]. In the Pol-GIK study, using a very low dose of GIK, no effect of GIK was observed[17]. 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. 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 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 (11 vs 13%, RR 0.8; 95% CI 0.7-1.0, p = 0.02) (Fig. 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

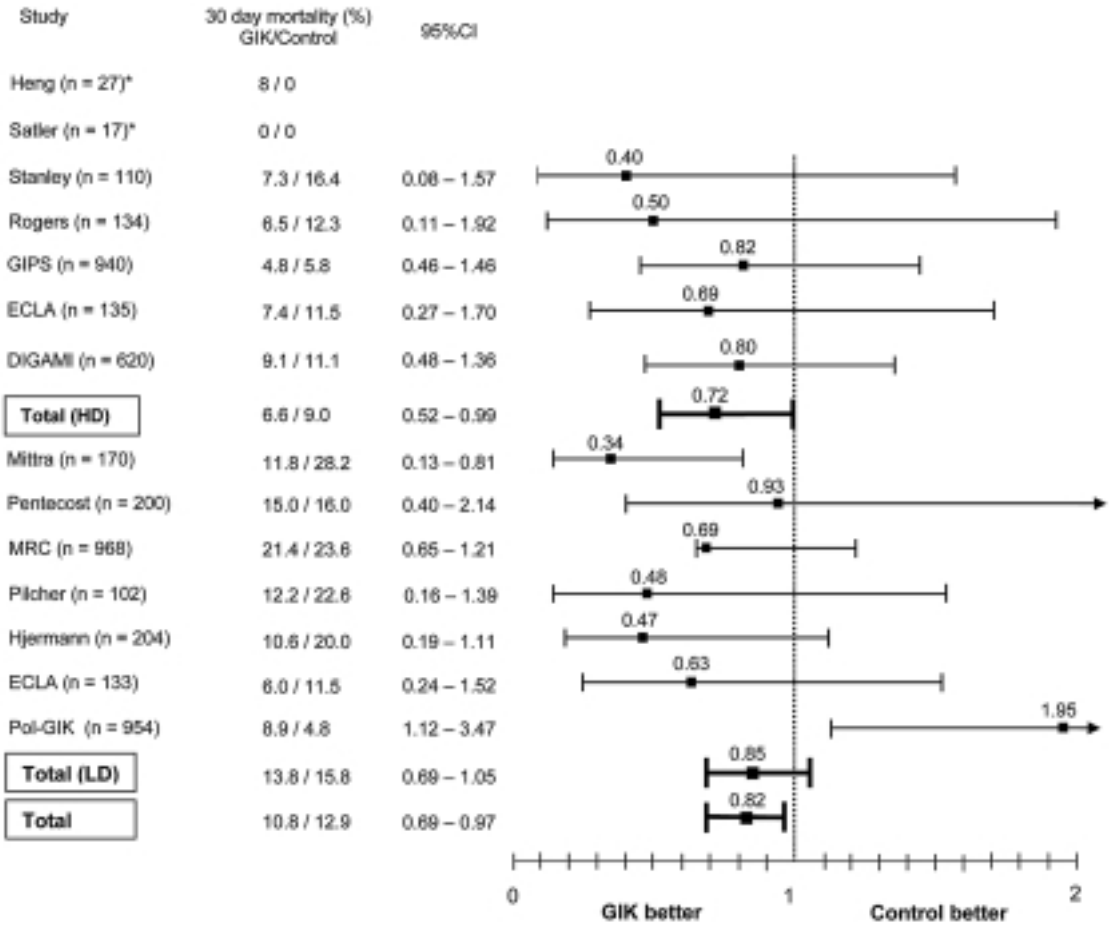

Figure 1. *Odds ratios and 95% confidence intervals (CI) of all individual trials and all trials combined. A stratified analysis with regard to glucose-insulin-potassium (GIK) dosage has been performed. HD = high dose; LD = low dose. * no calculation of the 95% CI possible.*

catheters, phlebitis was relatively common with percentages up to 15%[2], but severe phlebitis however was rare[14]. Infusion of large amounts of fluid may cause fluid overload. Some studies demonstrated a small increase of signs of congestive heart failure after GIK[16]. In the GIPS trial, there was a trend toward a higher mortality in patients with Killip class > 1 (n = 84) when treated with GIK (18 of 50 patients – 36% vs 9 of 34 patients – 27%), possibly due to volume overload[13]. In the DIGAMI study, 15% of the patients who received intensified therapy had a hypoglycemic event, compared to none in the control group[11]. In the Pol-GIK trial hypoglycemia occurred in 8% of the patients, whereafter the insulin dose was decreased[17]. They also found hyperglycemia in less than 1% in 585 patients with no differences between GIK and control group. With a blood glucose level > 16.8 mmol/l as criteria for interruption, only 1% was interrupted. This is not surprising since a low-dose GIK infusion was used. Hjermann[16] used a reduced dose of insulin, which prevented the occurrence of hypoglycemia.

Mode of action

There are several potential mechanisms by which GIK therapy might improve outcome after STEMI (Table II). Although the primary energy substrate for the non-ischemic myocardium are FFA, the myocardium uses various forms of energy substrates, including glucose[20]. During STEMI, circulating FFA levels are elevated and insulin sensitivity is reduced, limiting cellular uptake of glucose and promoting the use of FFA[21]. These FFA are thought to have a detrimental effect on ischemic myocardium through varying pathways. They are an energy supply which is associated with a relatively high oxygen consumption in comparison to the utilization of glucose[22]. Moreover, in contrast with glucose, FFA cannot be metabolized anaerobically. Indeed, experimental evidence suggests a negative influence of FFA on myocardial mechanical performance in the setting of hypoxia[23]. Furthermore, excess FFA metabolism increases susceptibility to ventricular arrhythmias and reperfusion injury due to disturbances in calcium homeostasis and accumulation of free radicals[24,25]. Administration of GIK lowers the circulating levels of FFA through the inhibitory effect of insulin on lipolyses[26]. This decrease in FFA levels, in combination with an increase in glucose and insulin availability, promotes the myocardial use of glucose over FFA[24]. Glucose is less oxygen-consuming and has beneficial effect on preservation of mechanical function and membrane stability[6,27,28]. Moreover, GIK therapy might also reduce arrhythmias after successful reperfusion[29]. As insulin itself induces coronary vasodilation, myocardial metabolism could further be improved through enhanced myocardial perfusion[30-32]. Single-photon emission computed tomography analysis showed that GIK infusion improved regional myocardial perfusion and function in segments adjacent to recently infarcted areas in human subjects[30]. Recent evidence suggests that insulin might also inhibit reperfusion injury by inhibiting apoptosis via activation of innate cell-survival pathways in the heart[18].

Table II. Mechanisms for beneficial effects of glucose-insulin-potassium in patients with acute myocardial infarction.

Anti-free fatty acid effects
Increased myocardial adenosine triphosphate production by anaerobic glycolysis
Improved myocardial reperfusion
Antiarrhythmic effects
Reduction of reperfusion damage through activation of innate cell survival pathways

Future glucose-insulin-potassium trials

Additional trials investigating GIK in acute myocardial infarction are underway. The DIGAMI-II will provide data on the effects of glycometabolic control in hyperglycemic patients. The combined ECLA-II/CREATE trial, investigating high-dose GIK in reperfused myocardial infarction patients, has already included a tremendous number of patients (> 27 000) and therefore has optimal statistical power. The OASIS-6 trial will include at least 10 000 patients with a myocardial infarction and has a side arm to investigate the effect of GIK infusion on short-term outcome. The GIPS-II trial will include 1044 patients without heart failure treated with reperfusion therapy. A GIK regimen with a reduced volume load, compared to GIPS-I, will be used in this study.

Conclusions

Of 13 published randomized trials, 12 studies reported mortality reduction after GIK. Most effects were observed when GIK was given in a high dose and when it was given as an adjunct to reperfusion therapy. Adverse effects were rare, however fluid overload may be a problem in patients with signs of heart failure at presentation. 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. The limited evidence currently available does not warrant GIK therapy to be applied in patients at the present time.

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