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# Does glucose-insulin-potassium use make sense during postischemic reperfusion syndrome?

**It is well known, that postischemic reperfusion syndrome (PRS) is accompanied by arrythmias, myocardial contractility decrease, systemic hemodynamics and microcirculation impairment, and also apoptosis of cardiac myocytes in damaged area.**

In pathophysiology of PRS significant importance belongs to biochemical disturbances (biochemical shock wave effect), destructive processes, and destabilizing factors on levels of ions, enzymes, micro-and macromolecular compounds of myocardium. According to current concepts, pharmacotherapy of PRS should be based on principles of myocardial energetic support mechanisms and correction of ion transport in myocardial cells, membrane protection, and restitution of extra- and intracardiac mechanisms of cardiac function regulation.

Glucose-insulin-potassium (GIP) can be included into the group of drugs, that intensify ATP synthesis and regulate transmembrane transport of $K^+$, $Na^+$, $Ca^{2+}$ ions.

It`s been more than 50 years from the time, when D. Sodi-Pallares performed clinical research of GIP considering its efficiency in patients with acute myocardial infarction (MI) and found its positive effect on disease course and early survivance in such category of patients. Since that time clinical observations were actively performed, aiming to discover GIP efficiency in practical medicine. During the period since 1962 a lot of scientific works, that showed efficiency of GIP use in clinical cardiology were published. According to these publications data, polarizing solution administration in case of MI contributed to mortality decrease in 28-40%, it is important to note, that treatment efficiency depended on mixture ingredients, as well as on time of its administration. Authors associated the cause of mortality decrease with antiarrhythmic effect of potassium and positive influence of glucose on metabolic processes in cardiac myocytes. Normalizing effect of GIP was found in case of local myocardial contractility disturbances. That is why administration of GIK during treatment of patients with severe heart failure (HF) was considered as a promising.

Some works showed, that administration of GIK directly before coronary artery bypass surgery promotes significant heart index increase (by 40%), decrease of cardiac arrhythmias rate and risk of postoperative cardiogenic shock development.

**A prospective randomized study ECLA represents strong evidence of GIK positive effect on mortality rate decrease in patients with MI.**

Firstly, results of this study were demonstrated on XIX congress of the European Society of Cardiology (Stockholm, 1997). The general conclusion was impressive: it was registered that mortality rate decreased by 66% in patients with acute MI, who received intravenous therapy with GIK during 24 hours; in addition, one-year mortality in these patients was lower than in control group. In patients, who did not undergo non-surgical revascularization due to objective reasons, but were administered GIK, there was registered no mortality rate increase.

In the large randomized study CREATE-ECLA, which included more than 20,000 patients, there was detected no significant difference neither in total fatal cases number, nor in derived endpoints number: total cases of cardiac arrest, cardiogenic shock, recurrent MI. At the same time, it was registered smaller number of recurrent ischemia cases during the first 5 days after MI development (5.6 versus 6.5%) in group of patients, who received GIP. Confidence of differences in these patients remained till the 30$^{th}$ day (p=0.036). According to study OASIS-6 and database of united study CREATE-ECLA, no difference was found in HF incidence in treatment and control groups. However, during day to day analysis it was found that the most positive effect in group of GIK therapy was observed between the 4$^{th}$ and the 30$^{th}$ days - decrease of HF incidence (2.4 versus 3.1% in control group, RR 0.78; p=0.01), and also its association with mortality rate (4.1 versus 5.0%; RR 0.81; p=0.004).

Considering question about if polarizing solution can be predictor of early unfavorable events, CREATE-ECLA study demonstrated negative effect of GIK on disease course. Due to this it is worth pointing out, that 25% glucose solution was used in mentioned study, and infusion rate was 1.5 mL/kg/hour during 24 hours. Through experimental clinical studies it is known, that hypertonic glucose solution contributes to increase of blood cells aggregation properties, which can negatively affect microcirculation, perfusion ability and eventually electric stability and myocardial energy potential. By the way, in their conclusion authors actually place emphasize on possible negative consequences of hyperglycemia, hyperkalemia and volume overload in patients with acute MI. However beginning from the 4$^{th}$ day and during the next 6 month of observation it was not demonstrated any increase of mortality rate, HF, recurrent MI and stroke incidence. It is possible that one of the causes of mortality rate increase, especially during the first 3 days of observation can be high daily dose of glucose ( up to 2.5 L), that can negatively affect intracardiac hemodynamics. Additionally, administration of hypertonic glucose solution as an inductor of red blood cells and platelet aggregation can lead to coronary occlusion with erythrocytic and thrombocytic conglomerates and intensify myocardial ischemia. Results of ECLA study, which showed that mortality in group of treatment with GIK had dose-dependent nature, can become a confirmation of such thoughts.

30-years' experience of GIK use in infarction unit of Kyiv City Clinical Hospital No.3 in patients with acute MI shows positive effect of GIK therapy on disease course. We noted decrease of complications rate - cardiac arrhythmias and HF, in group of GIP-therapy (more than 8,000 patients with Q-MI). Considering mortality rate, it was 10.0% in treatment group (standard therapy+ GIK) and 11.8 in control group (standard therapy). It is satisfactory argument in favor, that GIK is not a predictor of early unfavorable events.

It is necessary to emphasize that in our long-term practice of GIK use, we used only 5% glucose solution and did not observe its negative effect on blood cells aggregation properties and myocardial perfusion ability.

So, most published scientific researches noted positive effect of GIK on decrease of MI complication rate.

**It was proved that glucose provision to myocardium contributes to shift of the energy production balance to glucose metabolism during ischemia. In this case polarizing solution acts as non-specific myocardial metabolism modulator.**

Does GIK use make sense during myocardial ischemia from pathophysiological point of view? It was experimentally and clinically proved, that in presence of myocardial ischemia glycolysis is not able to liquidate high-energy compounds deficiency, which are necessary to maintain adequate contractile function of cells and plastic processes there. Disbalance between glucose and higher fatty acids (HFA) oxidation towards HFA is basic factor of myocardial dysfunction and damage.

One of possible ways to optimize energy production in stunned myocardium is to provide it with glucose, as part of polarizing solution. This shifts the balance of energy production towards glucose metabolism. GIP is a non-specific modulator of myocardial metabolism, it contributes to glucose uptake and oxidation. In such conditions HFA concentrations significantly decrease, that positively affects structural and functional activity of cardiomyocytes.

Today some scientific works put in doubt relevance of potassium preparations use during myocardial ischemia. As an argument authors of abovementioned works use the fact, that $K^+$ cation level in plasma during myocardial ischemia is increased. It is worth noting, that extracellular potassium level increase during MI is primarily the result of its excretion disorder and to a lesser extent depends on transport function of electrogenic pumps. If $K^+$ excretion is normal its blood plasma level, generally, is normal. It is known that normal potassium blood plasma level in patients with metabolic acidosis can be a sign of intracellular potassium deficiency. Intravenous therapy with potassium chloride and insulin contributes to intracellular K+ level restitution, as well as to $Mg^{2+}$,$Na^+$, $Ca^{2+}$ balance, that positively affects electrical stability of heart and myocardial contractile ability.

**Finally it is necessary to say that GIP use upon condition of only 5% glucose solution use positively affects the nature and course of acute MI, including the phase of postischemic reperfusion, that is demonstrated as a decrease of arrhythmia, HF and mortality rate. GIP can be used in association with standard therapy in patients with acute MI.**

List of reference is in editors office