The Effect of Glucose-Insulin-Potassiurn on In-Hospital Events following Acute Myocardial Infarction

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A. Study Purpose and Rational

Despite significant improvements in the diagnosis and management of acute myocardial infarction (AMI), it continues to be a major public health problem in the U.S. As of 1996, approximately 1.5 million people suffer from AMI yearly, and the death rate is about one-third. Though most of this mortality occurs prior to arriving to the hospital, the death rate in the hospital is still considerable.[1/] Further treatment to decrease mortality would be welcome.

There have been theories on the usefulness of glucose alone, or as part of a combination with insulin or insulin and potassium, in the treatment of AMI since the early 1900s. Investigators have been gathering data in attempt to support these theories since the 1960s. The basic premise is that the metabolic conditions during an AMI can affect a patient's outcome.

The normal fuel source for the myocardium is primarily fatty acids (FFA), and secondarilly glucose. There is no anaerobic metabolism of FFA, only of glucose. During an AW the affected areas of the heart have little or no oxygen supply, and therefore metabolism of FFA is impaired.[2/] At the same time, an increase in the level of catecholamines (adrenaline) during the AMI leads to an increased release of FFA from their stores and a decreased release of insulin from its stores. The decrease in insulin decreases the ability of the heart to metabolize glucose. FFA that accumulate may affect a variety of channels of the heart cells and the their membrane, which can precipitate arrhythmias.[3/] Glucose seems to preserve the normal electrical activity in the ischemic cells to some degree, thereby decreasing the frequency of arrhythmias.[4/] FFA levels in patients with ANG have been correlated with the development of arrhythmias clinically. [5/] Data also suggests that the increased FFA may increase the amount of heart damaged by the ischemia, an effect that may be improved by the increased use of glucose as an energy source during the acute insult.[3,4/] Thus, a person with an AMI may benefit from therapy that increases the use of glucose as fuel for the heart in place of FFA.

There is clinical data to suggest that glucose-insulin-potassium (GIK) is a beneficial treatment for AMI. GIK has been shown in one randomized trial to decrease the number of ventricular ectopic beats after an AMI, suggesting it may help stabilize the electrical activity of the heart.[6/] This study also demonstrated that the volume infused due to the treatment had no ill-effect on the hemodynamics of the heart. Actually, there was a nonsignificant decrease in the number of patients who developed heart failure among the treatment group. To account for this, data suggests GIK may improve the mechanical function of the heart after an AMI.[7/] Because most of the studies using GIK in the treatment of AMI have been small, they have not been able to show a significant benefit in mortality. A recent meta-analysis of many of the studies using GIK suggests that it can improve mortality in AMI.[8/] Though the authors attempted to use only those studies of highest quality, considerable variation did exist, and they were all at least 10 years old.

Recently, 2 studies have been done outside the U.S. with GIK in AMI. One was done in diabetics only, and did not use potassium in the treatment. They showed that glucose-insulin IV for 24 hours and tight glucose control for the subsequent 3 months can reduce overall mortality in the treatment group significantly.[9/] The other study used GIK for 24 hours in addition to standard practice in South America, and showed that among patients who had reperfusion (95% by thrombolysis) and GIK, in-hospital mortality improved significantly.[10/] This new data suggests that GIK may be beneficial in the treatment of AMI.

This data needs to be repeated here in the U.S., given that there is likely some differences in the standard treatment of AMI among different countries. For example, the effectiveness of GIK is likely to

be enhanced with reperfusion, the rate of which may be higher here than in other countries. It would also be useful to know how feasible it will be to use GIK, given that patients may be receiving many other intravenous medications for AMI. If it does offer the benefit suggested by the present data, GIK, which is a cheap and , for the most part, benign treatment, should be added to the standard therapy for AMI.

B. Study Design and Statistical Analysis

This study will take place at the Columbia Presbyterian Hospital. All patients presenting to the hospital with AMI will be asked to participate in the treatment arm of the study. Inclusion criteria will be similar to that for thrombolytic therapy: an AMI (chest pain or its equivalent for >20 min and either ST segment elevations on the EKG in 2 contiguous lead or a new left bundle branch block pattern) with onset of symptoms less than 12 hours from the time of enrollment. They will be treated with a solution of 25% glucose, 50IU insulin/liter, and 80meq of potassium/liter in water at a rate of 1.5ml/kg per hour for 48 hours. The control group will consist of data on patients who were admitted during the year prior to the start of the study with a diagnosis of AMI. These patients will be selected to match the treatment group, if necessary, for age, sex, risk factor profile, size of AMI, location of AMI, and treatment received. There will be no identifiers used in either group.

The 2 groups will be compared on in-hospital events, including arrthythmias (ventricular tachycaridia of >10 beats, ventricular fibrillation), congestive heart failure (Killip class >2 = crackles > 50% of lung fields), size of MI by peak enzyme level, and mortality.

Statisical comparison of the groups will be made using the student's t-test, and the chi-squared test. Power analysis dictates that to find a decrease in mortality form 15% to 5% with a power of 80% and an alpha of .05, 160 patients will be needed in each arm.

C. Study Procedures

The only procedures necessitated by the study is the placement of an intravenous (IV) line and blood draws. The patient may require 1-2 intravenous lines above normal for the duration of the study. The blood draws may exceed the usual number for the patient's care by about 3-6. The patient will be treated with the study medication for 48 hours, a time that will definitively be less than his/her total hospital stay.

D. Study Drugs

Glucose, insulin, and potassium are the study medications. All other medications will be decided upon by the treating physician. All of these drugs are FDA approved. GIK has been used in many prior studies for this purpose, with only a few side effects. Insulin can cause hypoglycemia that, if severe, can cause confusion, lethargy, and eventually coma. Glucose, in diabetic patients, can lead to hyperglycemia, with a theoretical risk (which is virtually impossible given that insulin is being administered simultaneously) of ketoacidosis or coma. Potassium can raise the potassium level too high and cause arrhythmias. It is extremely unlikely in patients with normal kidney function. The risk increases as kidney function worsens. Patients with kidney disease or high levels of potassium at enrollment will be excluded. Potassium intravenously can lead to inflammation of the vein, which can be painful. It may require removal of the IV and placement of another. This side-effect is more common with small IV lines.

E. Medical Devices

The patient will have a heart monitor during his/her hospital stay. This is routine care for a patient with an ANH for the first 2-3 days at least. In this study, the monitoring will occur for the length of the hospital stay. There is no risk incurred.

F. Study Questionnaire

The patients enrolled will be asked questions pertinent to their disease. There will not be a questionnaire.

G. Study Subjects

All patients presenting to the hospital with an ANH (as defined above) within 12 hours of its onset will be asked to participate in the treatment arm. Exclusion criteria are: unable to give consent, serum creatinine (a marker of kidney disease) > 1.8 or a serum potassium > 5.0 on admission.

H. Recrutiment of Subjects

All patients arriving to the hospital with an AMI will be approached for enrollment in the study. Most such patients will come through the emergency room. Contact will likely be made through a medical resident or cardiology fellow. The patient's primary physician will be contacted if possible. However, the timing of the therapy will on occasion make this contact impossible. Patients will then be made aware of the study by a member of the team of treating doctor's, and will be offered a chance to have a second doctor's opinion if desired.

I. Confidentiality of Study Data

The patient's names will not be used, and any record linking the patient and his/her data will be kept confidential by the principal investigators.

J. Potential Conflict of Interest -

None

K. Location of the Study -

Columbia Presbyterian Medical Center

L. Potential Risks

The risks to the patient are : inflammation at the site of the IV line, hypoglycemia from the insulin, and arrthytmia from high potassium levels. Only the first of these is at all common. If it occurs, it would necessitate removal of the affected line and placement of another. IV line placement is a common procedure performed by nurses, doctors, and IV technicians.

M. Potential Benefits

The patient may benefit from the treatment if it improves his/her outcome following the AMI, as previous data indicates. If the treatment is shown to be beneficial, then it may lead to a large, randomized, controlled, blinded trial to prove its benefit, allowing us to add it the therapy of AMI.

N. Alternative Therapies

All standard therapy will be available to the patient.

O. Compensation to Subjects

None.

P. Costs to Subjects

None.

Q. Mors as Research Subjects

None.

R. Radiation or Radioactive Substances

None.

S. References

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