The Role of Glucose–Insulin–Potassium on ST Resolution in Acute Myocardial Infarction; A randomized clinical trial

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Abstract: Background: The effects of glucose–insulin–potassium in the treatment of ST segment elevation myocardial infarction are controversial. We aimed to evaluate the effect of this solution on ST segment resolution which is an early noninvasive marker of coronary reperfusion. Methods: From September 2008 to July 2009, this randomized clinical trial enrolled 74 patients who had myocardial infarction that was treated with 25% glucose, 50 unit of soluble insulin per liter, and 80 mille mol of potassium chloride per liter at 1 ml/kg/hour (case group) or normal saline (control group) as adjunct to thrombolytic therapy in Sabzevar ,Iran . ST-segment resolution was defined as complete (>70%), partial (30% to 70%), or none (<30%) and absent (<50%) or present (≥50%). Results: No difference was present between groups in ST-segment resolution (p=0.8). There was no difference in the rate of complete ST-segment resolution between groups at 120 min (P=NS).Left ventricular ejection fraction was significantly higher in patients who had complete ST-segment elevation resolution (44.6± 7.4%) than others (40.9± 9.2 %and 35.0± 9.2%). Conclusion: ST-segment resolution was similar in groups. A more degree of ST-segment elevation resolution was correlated with better ejection fraction.
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1. Introduction

The ST-segment resolution on electrocardiogram (ECG) has been shown to be a simple, indicator of reperfusion (1) (2) (3) (4), which is the most effective treatment in acute myocardial infarction(5).However, reperfusion itself may cause reperfusion myocardial injury and affect infarct size. Therefore, next step is limiting myocardial infarct size in order to improve clinical outcomes in patients with myocardial infarction(6). One of these strategies is treatment with glucose–insulin–potassium (GIK) which can shift myocardial free fatty acid metabolism towards glucose metabolism(7) , but the effects of glucose–insulin–potassium in the treatment of ST segment elevation myocardial infarction (STEMI) are controversial. Fath-Ordoubadi et al published a meta-analysis of GIK treatment and showed that GIK infusion could reduce in-hospital mortality (8), while in some studies, no benefit effects of GIK were observed(9) (10) (11).

However, studies about GIK effects are ongoing; the effects on ST-segment resolution have been used in a few studies. Hence we investigated the effect of administration of GIK on single-lead ST-segment analysis before and 120 minutes after thrombolytic therapy. In addition we used a different thrombolytic in this study (streptokinase) which is not investigated in previous studies.

2. Materials and Methods

This is a part of a study which evaluated the effects of GIK on STEMI.As soon as the university ethic committee approved the research, recruitment began. From September 2008 to July 2009, 74 consecutive STEMI patients were randomized to normal saline (N = 39) or GIK infusion (N = 35).two ECGs in the GIK group were not valid to include in the study. All consecutive patients who had ST elevation myocardial infarction according to AHA guildline, when admitted to the Coronary Care Unit of the vaseie general hospital (Sabzevar ,Iran) were recruited (12) (13). Details of study design and population are described elsewhere(14)

Patient with hypotension, congestive heart failure, creatinine >2.0 mg/dL and anemia (hemoglobin <11 g/dL), were excluded. Further exclusion criteria were unwillingness to participate. Informed consent was obtained from the participants or their legal guardians.

The study was randomized, prospective, and triple blinded. On admission, patients were randomized via block randomization and assigned to the respective group by a closed envelope system. In A group, patients received high-dose GIK infusion (25% glucose, 50 IU of soluble insulin per liter, and 80 mmol of potassium chloride per liter at 1 ml/kg/hour) as an adjunct to thrombolytic therapy (1.5 MU of streptokinase/30 to 60 minutes) [GIK group].In B group 1 L normal saline at 60 mL/h infused in addition to thrombolytic therapy (1.5 MU of streptokinase/30 to 60 minutes) [control group]. Neither the patients nor the researcher and investigator assessing the ECGs, nor the statistical consultant knew which group called A and which one called B group (triple blinded). GIK administered in the hospital that initiated the reperfusion therapy. All other medication was standard as ACC/AHA guidelines. (13)

In each patient, total CK and CK-MB level were measured on admission, 16 and 24 hours thereafter. In all patients, plasma concentrations of glucose and potassium were determined before and at 6 hour after administering therapy. Two-dimensional echocardiography was obtained in all patients after 72 hours of admission.

A standard 12-lead electrocardiogram with a speed of 25 mm/s and amplitude of 10 mm/mV were obtained before and within 120 minutes of starting treatment .ST-segment elevation was investigated by a single observer who was blinded to study groups with lens-intensified calipers. The single lead with the most prominent ST-segment elevation before treatment was identified, and ST-segment elevation was measured at 20 ms after the J point with the PR segment as reference baseline. The percent resolution of ST-segment deviation from baseline to 120 was calculated and categorized: complete (>70%) STRs, partial (30% to 70%) STRs, and no (<30%) STRes [5].Another classification was performed as present ST-segment resolution (STRes ≥50%) or absent ST-segment resolution (STRs <50%). A similar approach was used in recent studies (15) (16) (17). Patients were followed clinically for 7 days.

Data were analyzed thorough the Statistical Package for the Social Sciences (SPSS, version15). Continuous variables were expressed as mean ± SD and were compared using independent t tests and repeated measure ANOVA. Categorical data were analyzed by use of chi-square or Fisher exact test. The relation between ST segment resolution and left ventricular ejection fraction was made with 2-way analysis of variance. Assuming a power of 80% and α=5%, comparing ST segment resolution could be demonstrated with a sample size of 32 patients in each group. A p value <0.05 was considered to be statistically significant.

4. Results

74 Patients were enrolled into the study. There was no significant difference in basal data between two study groups.The time from chest pain onset to initiation of streptokinase was 4.66±3.81 hours. There was no significant difference in this interval between two study groups (P=0.16). Glucose level at Baseline was 149±61 mg/dL in the control and 168±83 mg/dL in the GIK group (P=0.25). Mean glucose level over 6 hours was higher in the GIK group (212± 139 mg/dL) than control group (142±46 mg/dL) (P=0.006).

No difference was present between two groups in ST-segment elevation resolution (p=0.8). Ejection Fraction (39% G vs41% C, p=0.34) was similar between the two groups.

In GIK and control group, complete resolution was registered in 8 patients (25%) vs 18 patients(46.2%), partial in 12 (37.5%) vs 14(35.9%), and absent in 12 (37.5%) vs 7(17.9%) , respectively(P=NS).A resolution ≥50% was observed in 56.3% of patients in GIK group, and in 71.8 % of control group (P=0.17).

Left ventricular EF was significantly higher in patients who had complete ST-segment elevation resolution (44.6± 7.4%) than in those who had partial resolution (40.9± 9.2 %,), and in patients who had absent resolution (35.0± 9.2%), (p=0.003).

There was no significant difference between groups regarding mean admission serum CK, peak CK, peak CK-MB levels and early peak of CK within 16 hour.

3. Discussion:

According to our data GIK therapy in patients who receive streptokinase ,offers no effect on ST-segment resolution, which is a sign of successful recanalization (18).

The simplest approach to analyze ST-segment resolution is to classify ST-segment elevation in different groups and to categorize the patient in these groups. One of these classifications is ST-segment resolution with the 50% cutoff as present or absent (15) (16) (19). We also used the other common classification with 70% and 30% thresholds, as complete, partial, or absent ST-segment elevation resolution, (20) .We found GIK ineffective according to both classification.

Previous studies have investigated the effect of GIK on ST-segment elevation resolution in animals. GIK has decreased ST-segment elevation in dogs with induced myocardial ischemia (21). Result of differences between animal studies versus our study can be due to thinner myocardium in animals which is more resistant to ischemia after myocardial infarction than in humans with thick myocardium. One study showed that GIK can decrease in free fatty acid

concentration and promotion of glycolysis. Therefore an ischemic cell needs less oxygen and produces less toxic intermediates of free fatty acid metabolism (7). However, while reperfusion therapy with streptokinase can rescue the ischemic myocardium effectively, treatment with GIK has less value. In a post hoc analysis, GIK results in a higher number of patients with partial or complete ST-segment elevation resolution but they suggested more prospective trial (22). In 32 ST-elevation MI patients treated with reteplase and alternately assigned to either GIK or saline with potassium chloride, GIK failed to decrease ST-segment elevation (23), which is corresponding to our study with enough sampling. Therefore at least at the present time, there is no role for GIK as adjunctive treatment with thrombolytic drugs.

In our study, ST-segment elevation resolution was related to a favorable outcome in EF according to both classification of ST segment resolution, which is corresponding to previous studies (15) (24) (25). We suggest the use of electrocardiogram to estimate left ventricular function. Or, in minimum ST-segment evaluation can be used to categorize outcome as acceptable or unacceptable.

We should mention some limitations of this study. We used easy-to-use method to analyze ST-segment resolution and using all ECG leads could have produced different results. However, this method has been used and validated in previous studies. (16) (26) (27) (28) And, recent studies failed to demonstrate advantages of more complex measurements. (26) (27).However, one of the advantages of this method is early decision making because we can evaluate it shortly after treatment. As far as there is no data about functional status before infarction, we could not recognize functional recovery, and we cannot exclude some degree of functional impairment in a patient with normal left ventricular EF.

In conclusion, in patients with STEMI, according to ECG finding, there is no role for GIK as adjunctive treatment with streptokinase, but a more degree of ST-segment elevation resolution remains a valuable predictor of effective reperfusion and left ventricular EF.

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Conflict of interest: None declared

5. References

1. Clemmensen P, Ohman EM, Sevilla DC, Peck S, Wagner NB, Quigley PS, et al. Changes in standard electrocardiographic ST-segment elevation predictive of successful reperfusion in acute myocardial infarction. The American journal of cardiology. 1990 Dec 15. 11-1407:(20)66.
2. Mauri F, Maggioni AP, Franzosi MG, de Vita C, Santoro E, Santoro L, et al. A simple electrocardiographic predictor of the outcome of patients with acute myocardial infarction treated with a thrombolytic agent. A Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-2)-Derived Analysis. J Am Coll Cardiol. 1994 Sep;24(3):600-7.
3. Doevendans PA, Gorgels AP, van der Zee R, Partouns J, Bar FW, Wellens HJ. Electrocardiographic diagnosis of reperfusion during thrombolytic therapy in acute myocardial infarction. The American journal of cardiology. 1995 Jun 15;75(17):1206-10.
4. de Lemos JA. ST-Segment resolution as a marker of epicardial and myocardial reperfusion after thrombolysis: insights from the TIMI 14 and in TIME-II trials. J Electrocardiol. 2000;33 Suppl:67-72.
5. Yellon DM, Hausenloy DJ. Myocardial reperfusion injury. N Engl J Med. 2007 Sep 13;357(11):1121-35.
6. Riksen NP, Hausenloy DJ, Yellon DM. Erythropoietin: ready for prime-time cardioprotection. Trends Pharmacol Sci. 2008 May;29(5):258-67.
7. Apstein CS, Opie LH. A challenge to the metabolic approach to myocardial ischaemia. Eur Heart J. 2005 May;26(10):956-9.
8. Fath-Ordoubadi F, Beatt KJ. Glucose-insulin-potassium therapy for treatment of acute myocardial infarction: an overview of randomized placebo-controlled trials. Circulation. 1997 Aug 19;96(4):1152-6.
9. Kloner RA, Nesto RW. Glucose-insulin-potassium for acute myocardial infarction: continuing controversy over cardioprotection. Circulation 2008 May 13;117(19):2523-33.
10. Mehta SR, Yusuf S, Diaz R, Zhu J, Pais P, Xavier D, et al. Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: the CREATE-ECLA randomized controlled trial. Jama. 2005 Jan 26;293(4):437-46.
11. Puskarich MA, Runyon MS, Trzeciak S, Kline JA, Jones AE. Effect of glucose-insulin-potassium infusion on mortality in critical care settings: a systematic review and meta-analysis. Journal of clinical pharmacology. 2009 Jul;49(7):758-67.
12. Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of ST-Segment Elevation Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J. 2008 Dec;29(23):2909-45.

13. Kushner FG, Hand M, Smith SC, Jr., King SB, 3rd, Anderson JL, Antman EM, et al. 2009 Focused Updates: ACC/AHA Guidelines for the Management of Patients With ST-Elevation Myocardial Infarction (updating the 2004 Guideline and 2007 Focused Update) and ACC/AHA/SCAI Guidelines on Percutaneous Coronary Intervention (updating the 2005 Guideline and 2007 Focused Update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. Circulation. 2009 Dec 1;120(22):2271-306.
14. HASHEMIAN M, VAKILI, A. & AKABERI, A. Effect of glucose-insulin-potassium on Plasma concentrations of C-reactive protein in Acute ST-Elevation Myocardial Infarction; A randomized clinical trial. Pak J Med Sci. 2011;27:673-6.
15. Matetzky S, Novikov M, Gruberg L, Freimark D, Feinberg M, Elian D, et al. The significance of persistent ST elevation versus early resolution of ST segment elevation after primary PTCA. J Am Coll Cardiol. 1999 Dec;34(7):1932-8.
16. Santoro GM, Antoniucci D, Valenti R, Bolognese L, Buonamici P, Trapani M, et al. Rapid reduction of ST-segment elevation after successful direct angioplasty in acute myocardial infarction. The American journal of cardiology. 1997 Sep 15;80(6):685-9.
17. Sciagra R, Parodi G, Migliorini A, Valenti R, Antoniucci D, Sotgia B, et al. ST-segment analysis to predict infarct size and functional outcome in acute myocardial infarction treated with primary coronary intervention and adjunctive abciximab therapy. The American journal of cardiology. 2006 Jan 1;97(1):48-54.
18. Schroder R, Zeymer U, Wegscheider K, Neuhaus KL. Comparison of the predictive value of ST segment elevation resolution at 90 and 180 min after start of streptokinase in acute myocardial infarction. A substudy of the hirudin for improvement of thrombolysis (HIT)-4 study. Eur Heart J. 1999 Nov;20(21):1563-71.
19. Feldman LJ, Coste P, Furber A, Dupouy P, Slama MS, Monassier JP, et al. Incomplete resolution of ST-segment elevation is a marker of transient microcirculatory dysfunction after stenting for acute myocardial infarction. Circulation. 2003 Jun 3;107(21):2684-9.
20. Schroder R, Dissmann R, Bruggemann T, Wegscheider K, Linderer T, Tebbe U, et al. Extent of early ST segment elevation resolution: a simple but strong predictor of outcome in patients with acute myocardial infarction. J Am Coll Cardiol. 1994 Aug;24(2):384-91.
21. Opie LH, Owen P. Effect of glucose-insulin-potassium infusions on arteriovenous differences of glucose of free fatty acids and on tissue metabolic changes in dogs with developing myocardial infarction. The American journal of cardiology. 1976 Sep;38(3):310-21.
22. van der Horst IC, De Luca G, Ottervanger JP, de Boer MJ, Hoorntje JC, Suryapranata H, et al. ST-segment elevation resolution and outcome in patients treated with primary angioplasty and glucose-insulin-potassium infusion. Am Heart J. 2005 Jun;149(6):1135.
23. Chaudhuri A, Janicke D, Wilson MF, Tripathy D, Garg R, Bandyopadhyay A, et al. Anti-inflammatory and profibrinolytic effect of insulin in acute ST-segment-elevation myocardial infarction. Circulation. 2004 Feb 24;109(7):849-54.
24. Angeja BG, Gunda M, Murphy SA, Sobel BE, Rundle AC, Syed M, et al. TIMI myocardial perfusion grade and ST segment resolution: association with infarct size as assessed by single photon emission computed tomography imaging. Circulation. 2002 Jan 22;105(3):282-5.
25. Nicolau JC, Maia LN, Vitola J, Vaz VD, Machado MN, Godoy MF, et al. ST-segment resolution and late (6-month) left ventricular remodeling after acute myocardial infarction. The American journal of cardiology. 2003 Feb 15;91(4):451-3.
26. Cooper HA, de Lemos JA, Morrow DA ,Sabatine MS, Murphy SA, McCabe CH, et al. Minimal ST-segment deviation: a simple, noninvasive method for identifying patients with a patent infarction-related artery after fibrinolytic administration. Am Heart J. 2002 Nov;144(5):790-5.
27. Schroder K, Wegscheider K, Zeymer U, Tebbe U, Schroder R. Extent of ST-segment deviation in a single electrocardiogram lead 90 min after thrombolysis as a predictor of medium-term mortality in acute myocardial infarction. Lancet. 2001 Nov 3;358(9292):1479-86.
28. Zeymer U, Schroder K, Wegscheider K, Senges J, Neuhaus KL, Schroder R. ST resolution in a single electrocardiographic lead: a simple and accurate predictor of cardiac mortality in patients with fibrinolytic therapy for acute ST-elevation myocardial infarction .Am Heart J. 2005 Jan;149(1):91-7.

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