Original Article

The Effect of the Tight Glycemic Control Coupled with the Use of a Continuous Glucose Monitoring System on the Outcome of Acute Myocardial Infarction.

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Abstract:

Objective: To investigate whether lowering blood glucose to <120mg/dl with an insulin infusion in STEMI will improve myocardial function, reduce hs-CRP and CK concentrations and lower the incidence of major adverse cardiac events (MACEs). We also investigated the effectiveness of continuous blood glucose monitoring in the setting of STEMI. **Methods:** 50 patients with STEMI receiving thrombolytic therapy within 6 hours of developing symptoms, were randomized into 3 groups: intensive insulin infusion therapy (IIT); glucose-insulin-potassium infusion (GIK), with both groups targeting a glucose of 80-120 mg/dl and a control group targeting glucose concentrations of 140-150 mg/dl. Blood glucose concentrations were monitored using a capillary blood glucometer 2 hourly or a continuous glucose monitoring (CGM) device. **Results:** The improvement of LVEF and WMSI in both IIT and GIK groups at 3 and 30 days after admission was greater than that in the control group. The hs-CRP and peak CK concentrations and the incidence of MACEs were significantly lower in IIT and GIK groups than those in the control group, ($p<0.001$, 0.05 & 0.015). The percentage of in-target glucose concentrations was significantly higher in the patients monitored using the CGM than that in patients having 2 hourly glucometer readings (56.85±12.04%, 82.92±5.77%, $p<0.001$). The incidence of hypoglycemia was significantly lower in patients monitored using CGM ($p = 0.007$). **Conclusions:** Tight glycemic control in ITT and GIK groups resulted in a significantly reduced peak CK and CRP concentrations, less myocardial dyskinesia, an improved ejection fraction and a lower incidence of MACE in patients with STEMI when compared to controls. CGM facilitated the attainment of tight glycemic control with a decreased incidence of hypoglycemia.

Keywords: Tight Glycemic Control – CGM- Acute Myocardial Infarction

Introduction:

Admission hyperglycemia (> 140mg/dl) in patients with acute myocardial infarction (AMI) is associated with increased morbidity and mortality.[1,2] while a decrease in glucose concentrations following admission have been shown to be associated with a reduction in mortality and morbidity.[3,4] Hyperglycemia exerts potent pro-inflammatory, pro-thrombotic and pro-apoptotic effects,[5-13] while an insulin infusion exerts potent anti-inflammatory, anti-platelet, pro-fibrinolytic and anti-apoptotic effects in addition to lowering blood glucose concentrations. [14-22]

In spite of the potentially beneficial effects of insulin in acute myocardial infarction (AMI), the outcomes from the insulin infusion trials have been variable. In most of these studies, a fixed dose of insulin was infused with a high dose of glucose and potassium [23, 24]. This often led to hyperglycemia and fluid overload.. Some trials have infused insulin in

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hyperglycemic patients to reduce glucose but never to <140mg/dl. [25-27]

We, therefore, investigated whether the restoration and maintenance of euglycemia (blood glucose target < 120mg/dl) with insulin either given alone or as a GIK infusion in patients with STEMI would exert a beneficial effect on myocardial function and on post-AMI increases in plasma CK and hsCRP concentrations when compared to patients with blood glucose concentrations between 140-150mg/dl. Furthermore, we investigated whether hypoglycemia could be avoided while maintaining blood glucose concentrations <120 mg/dl by using a continuous blood glucose monitoring system.

Patients:

The present study included 50 patients admitted to the Alexandria Main University Hospital from the 1st of June 2008 to January 2009 with the following criteria: Acute ST segment elevation myocardial infarction (STEMI) for the first time, diagnosed by symptoms consistent with AMI ≥ 20 minutes in duration, and new ST elevation at the J-point in two contiguous leads with the cut-off points: ≥0.2 mV in men or ≥0.15 mV in women in leads V2, V3 and/or ≥0.1 mV in other leads.[28] Killip class I-II, presenting within 6 hours of symptoms onset. An informed consent was obtained from all subjects or their first degree relatives.

Methods:

This is a prospective, randomized, controlled, open label study. All subjects received Streptokinase (1.500.000U+100 ml of 5% glucose) intravenously over one hour. They were also given aspirin, clopidogrel, a β-blocker, an ACE inhibitor and a statin, according to a protocol adopted by the Alexandria Main University Hospital (AMUH) consistent with the AHA/ACC guidelines. [29]

The patients were randomized into 3 groups:

Intensive insulin therapy (IIT) group: 20 patients received IIT in the form of continuous intravenous insulin infusion targeting normoglycemia (80-120 mg/dl) for 72 hrs post MI. The insulin infusion was initiated before thrombolytic therapy. We chose a target glucose of 80-120mg/dl since AMI patients with post admission glucose of 80 to 130mg/dl have the lowest mortality. [30]

Glucose-insulin-potassium (GIK) with Tight Glycemic control group: 15 patients received a high dose GIK infusion[31] for the first 24 hours of admission in addition to a continuous intravenous insulin infusion to maintain glucose between 80-120mg/dl for 72 hrs post MI. An Intravenous infusion of 1 liter 25% glucose + 40 U Insulin (ActRapid) + 80 meq Potassium, was started prior to thrombolytic therapy in a large peripheral or central vein,[32] at a rate of 1 ml /kg /hour. Additional intravenous insulin infusion was started, if required to maintain blood glucose between 80-120mg/dl. We used a high dose GIK infusion as a low dose (1U/h) GIK infusion has not been shown to be beneficial in AMI.

Control Group: 15 patients received subcutaneous doses of Regular insulin every 6 hrs to maintain glucose below 150 mg/dl for 72 hrs post MI, according to a sliding scale protocol. A glucose target of below 150mg/dl is in accordance with the American Heart Association's scientific statement on hyperglycemia and acute coronary syndrome. [33]

In all groups, the other anti-diabetic medications were withdrawn for 72 hrs in subjects with known diabetes

Insulin Infusion protocol in the IIT and GIK group to maintain tight glycemic control:

In the GIK and the IIT groups, blood glucose (BG) concentrations were maintained by following a protocol, modified from the LEUVEN Protocol[34]. 50 Unit Insulin (ActRapid) was added to 50 ml normal saline and infused by a syringe pump.

i. If BG was > 220 mg/dl on admission, insulin 2-4 U/h was started.

ii. If BG was 120-220 mg/dl on admission, insulin 1-2 U/hour was started.

iii. If BG was 80-119 mg dl on admission, insulin was initiated depending on the next RBG value one hour later.

iv. Insulin dose was adjusted according to the blood glucose values measured two hourly:

v. If BG was > 140 mg/dl, insulin was increased by 1-2 U/hour.

vi. If BG was 120-140 mg/dl, insulin dose was increased by 0.5-1 U/hour.

vii. If BG was 90-119 mg/dl, insulin was adjusted upon the next BG value after 2 hours.

viii. If BG fell between 60-89 mg/dl insulin was reduced by half and blood glucose was measured after 30 minutes after assuring adequate baseline glucose intake.

ix. If BG was <60 mg/dl, insulin was stopped, 10 g Glucose IV bolus was administered and BG was re-measured after 30 minutes.

In the Control group blood glucose target was maintained < 150mg/dl for 3 days post admission with the use of a sliding scale every 6 hours. (Appendix 1)

Monitoring of Glycemic Control:

All patients were randomized for their BG monitoring into:

1) BG was measured by a glucometer "AccuCheck / Go – by Roche" every 2 hours for 3 days.

2) RBG measured by continuous blood glucose level monitoring device "GUARDIAN System-by Medtronic / USA" for 3 days. [35]

For statistical comparison and to reduce bias of readings between the different groups, capillary testing was done in all patients, even those monitored by the Guardian system. Between scheduled capillary readings, if the Guardian system alerted the physician about potential hypoglycemia or out of target glucose, changes to caloric intake and/or insulin infusion rate were made, until the next capillary testing and confirmation. Physicians were allowed to confirm the Guardian readings by capillary testing at any time.

Serum CK was measured on admission, 90 minutes, 6 hours, 12 hours and then every 12 hours for 3 days. High sensitivity C - reactive protein (CRP) was measured on admission and at 48 hours.

To assess reperfusion success, myocardial function and cardiac complication the following were monitored:

a) ECG/ Symptoms/ CK: Resolution of ST elevation more than 50% on ECG performed within 90 minutes of reperfusion therapy/the absence of electrocardiographic Q waves. Chest pain resolved during or just after (within 90 minutes) of reperfusion therapy; Reperfusion arrhythmia during reperfusion therapy in the form of accelerated idioventricular rhythm (rate equal or below 100 b/min) or sinus bradycardia (below 55 beats/min) in inferior MI; Creatinine Kinase (CK) peak level. [36, 37]

b) A two dimension trans-thoracic Echo was done on admission, day 3 and at one month for: assessment of: Left ventricular ejection fraction using the Simpson's method and Wall motion score index calculated with the 16-segment model of the American Society of Echocardiography. [38]

In hospital and 30 day Major Adverse Cardiac Events (MACEs) were defined as a composite of:

1. Cardiac death defined as any death from cardiac causes or when a cardiac cause could not be excluded.

2. Re-infarction defined as recurrence of severe ischemic chest discomfort that lasted more than 20 minutes and was accompanied by recurrent ST-segment elevation of 0.1 mV in 2 contiguous electrocardiographic leads.

3. Serious arrhythmias (ventricular fibrillation and/or tachycardia).

4. Severe heart failure defined as Killip's class,[39] >II (pulmonary edema and cardiogenic shock) during hospitalization or New York Heart Association class,[40] >II after discharge.

In hospital MACE events were excluded from 30 day MACE events. Each individual MACE event was counted even if it occurred in the same patient.

Patients follow up after discharge:

All patients were seen at one month to assess LVEF and WMSI by echo and to be evaluated for MACE.

Statistical analysis of the data:

Qualitative data of the groups was analyzed using: Chi square test, Fisher Exact test, Monte Carlo test.

Normally distributed quantitative data was analyzed using: F-test (ANOVA) and Post HOC test (LSD).

While not normally distributed quantitative data was analyzed using non parametric test:

Kruskal Wallis test and Mann-Whitney test. Correlations between different parameters were done using Pearson and Spearman coefficients. P value < 0.05 was considered as significant. Statistical analysis was carried out using SPSS version 15.

Results:

There were no significant differences in baseline demographics between the 3 studied groups (table I)

Glucose Concentrations:

Glucose concentrations were similar at admission between the 3 groups; 183, 214 and 192 mg/dl at admission, in the control, IIT and GIK groups respectively. Glucose concentrations were significantly lower in IIT and GIK groups versus the Control group at 24, 48 and 72 hours after admission (table II). The reduction in glucose from the baseline was also significantly greater in these two groups after 24 hours (p=0.04), 72 hours (p=0.003), and on the mean of the 3 days (p=0.004).

The percentages of in-target RBG readings were 67.01 ± 14.61 in the Control group, 74.76 ± 17.02 in the IIT group and 68.80 ± 15.79 in the GIK group, with no statistically significant difference between the three groups (p=0.327) in terms of achievement of targets. The percentage of readings in the targeted glycemic range was significantly higher in the patients monitored using the CGM than patients monitored using 2 hours glucometer reading in all the three studied groups (56.85±12.04 [2 hrs. glucometer], 82.92±5.77 [CGM], p <0.001).

Incidence of Hypoglycemia

The incidence of hypoglycemia, defined as a blood glucose concentration below 60 mg/dl,-and severe hypoglycemia, defined as RBG below 40 mg/dl was not significantly different between the three groups.

However, there was a highly significant lower incidence of hypoglycemia in patients monitored using CGM versus those monitored every 2 hrs with a glucometer (2 in the former versus 10 in the latter, p = 0.007). The incidence of severe hypoglycemia was also significantly lower in the CGM monitored group (0 in the former and 4 in the latter group, p = 0.046). Table III)

Insulin dose:

The mean insulin dose over the three days of the study, was significantly different in the IIT and the GIK group versus the Control group (1.66 ± 0.82 units/hr [Control], 5.70 ± 3.30units/hr [IIT], 6.15 ± 3.06 units/hr [GIK], p<0.001). There was no significant difference between the insulin dose given in the IIT and the GIK group (p=0.633).

Success of thrombolytic therapy

There was no significant difference in relation to the success of thrombolytic in the three groups (p=0.928); 9 patients (60%) had successful reperfusion in the Control group, 14 patients (70%) in the IIT group and 10 patients (66.7%) in GIK group. (p=0.928). A recovery of ST elevation more than 50% on ECG performed within 90 minutes of reperfusion therapy in combination with relief of pain and the absence of electrocardiographic Q waves were considered signs of reperfusion success.

Echocardiographic Indices:

Wall Motion Score Index (WMSI) was 1.79, 2.01and 1.92 at admission, in the control, the IIT and in the GIK group respectively, with no significant difference between the 3 groups. (p=0.416). The percentage decrease in WMSI from baseline after 4 weeks was significantly greater in IIT and GIK groups than that in controls. (p=0.01) (Table IV).

Left Ventricular Ejection Fraction (LVEF%) was 38.07 ± 7.04, 36.80 ± 6.15, 36.67 ± 5.15 at admission in the control, the IIT and in the GIK group respectively, with no significant difference between the 3 groups. (p=0.76). LVEF was significantly greater after 4 weeks (p=0.003) in the IIT and GIK (p=0.037) group than in controls. The percentage increase in LVEF from baseline in both IIT and GIK groups after 72 hours (p=0.049) [data not shown] and 4 weeks (p=0.002) was significantly greater than that in control group (Table IV).

Plasma hsCRP Concentrations:

Plasma hsCRP concentrations was 1.98±0.69 mg/L, 1.98±0.68 mg/L and 2.08±0.74 mg/L in the control, IIT and GIK groups respectively, at admission (p=0.898). CRP concentrations were significantly lower at 48 hrs in IIT and GIK groups than those in the control group (p<0.001). The increase in hsCRP from the baseline was also significantly

lower in IIT and the GIK groups versus the control group (p<0.001). (Table V).

Plasma creatinine kinase (CK) Concentrations:

On admission serum CK levels; 518.20±485.08 mg/L in the control group, 349.50±386.88 mg/L in the IIT group and 316.57±201.10 mg/L in the GIK group. (p =0.303). There was a statistically significant increase in the peak CK value in the control group versus the IIT and the GIK group (p = 0.03), with no significance between the IIT vs the GIK group (p=0.730). (Table V)

Major adverse cardiac events (MACEs)

The incidence of in-hospital MACE was significantly different between the three studied groups (p=0.05), with a higher incidence in the control versus the IIT group, (p=0.022). (Table VI).

The incidence of in-hospital serious arrhythmias (ventricular fibrillation and/or tachycardia) and severe heart failure were significantly higher in the control versus the IIT group (p = 0.027). There was no difference between the incidences of in-hospital re-infarction and cardiac death between the three studied groups (Table VI).

There was also a significant difference between the three studied groups in the incidence of 30 day MACEs (p=0.015), with a significantly higher incidence in the control versus the IIT group and the GIK group (p=0.022, 0.035, respectively).

At 30 days, the incidence of severe heart failure was significantly higher in the control versus the IIT and the GIK group (p = 0.022, 0.035, respectively). There were no significant differences in the incidences of 30 day serious arrhythmias, re-infarction and cardiac death between the three groups. (Table VI).

Comparing IIT and GIK

When comparing the IIT and the GIK group, we found no benefit from the infusion of 25% Glucose in the GIK group. The incidence of hypoglycemia (p=0.7) and severe hypoglycemia (p=1.0) showed no statistically significant difference between the two groups. At the clinical level, there were no significant differences at 4 weeks on the incidence of MACE (p=1.0), improvement of the myocardial contractility (WMSI p=0.448 & EF% p=0.421), the attenuation of the increase of hsCRP (p=0.944).

Table I: Studied Groups Characteristics

	Control (n=15)		IIT (n=20)		GIK (n=15)		p
	No.	%	No.	%	No.	%	
Gender							
Male	10	66.7	12	60.0	9	60.0	0.906
Female	5	33.3	8	40.0	6	40.0	
Weight	83.93 ± 13.01		82.80 ± 13.81		84.40 ± 17.74		0.888
Smokers	7	46.7	10	50.0	8	53.3	0.936
Diabetics	8	53.3	10	50.0	9	60.0	0.840
Hypertensive	5	33.3	12	60.0	7	46.7	0.293
Anterior MI	5	33.3	6	30.0	5	33.3	0.970
Extensive Ant. MI	4	26.7	7	35.0	5	33.3	0.865
Lateral MI	5	33.3	7	35.0	6	40.0	0.924
Inferior MI	6	40.0	6	30.0	4	26.7	0.714
Pain to needle time (mins) Mean ± SD	224.33 ± 1.06.43		235.35 ± 95.38		227.00 ± 99.46		0.951
Door to needle time (mins) Mean ± SD	30.33 ± 15.29		31.35 ± 14.48		28.67 ± 12.60		0.833

IIT: Intensive Insulin Therapy group
GIK: Glucose Insulin Potassium Group
MI: Myocardial Infarction

Table II: Comparison between the different studied groups according to random blood glucose (RBG) (mg/dl) on admission, mean 1st, 2nd, 3rd and three days, mean Insulin dose over first 24 hours (U/hr), and over 72 hours (U/hr), IV Glucose 1st 24h (g/hr), incidence of hypoglycemia and severe hypoglycemia.

	Control (n=15)	IIT (n=20)	GIK (N=15)	p	p_{1a}	p_{1b}	p_2
RBG (mg/dl)							
On admission	182.73 ± 81.19	214.30± 108.12	192.40 ± 84.58	0.782	0.494	0.740	0.714
Mean 1st day	146.60 ± 12.89	118.02 ± 19.79	118.79 ± 17.41	<0.001	<0.001	<0.001	0.9
Mean 2nd day	145.57 ± 12.47	106.90 ± 13.57	110.57 ± 15.45	<0.001	<0.001	<0.001	0.45
Mean 3rd day	143.07 ± 9.61	108.93 ± 13.40	111.56 ± 19.12	<0.001	<0.001	<0.001	0.6
Mean 3 days	145.08 ± 9.14	111.29 ± 13.45	113.64 ± 15.11	<0.001	<0.001	<0.001	0.601
Insulin 1st 24h (U/hr)	1.59 ± 0.79	5.08±3.09	7.87±2.85	<0.001	<0.001	<0.001	0.019
Insulin 72 h (U/hr)	1.66 ± 0.82	5.70 ± 3.30	6.15 ± 3.06	<0.001	<0.001	<0.001	0.633
IV Glucose 1st 24h (g/hr)	0.42 ± 0.39	1.70± 0.85	21.1±5.5	<0.001	<0.001	<0.001	<0.001
Hypoglycemia	2 (13.3%)	5 (25.0%)	5 (33.3%)	0.506	0.672	0.390	0.712
S. hypoglycemia	0 (0.0%)	2 (10.0%)	2 (13.3%)	0.543	0.496	0.483	1.000

IIT: Intensive Insulin Therapy group

GIK: Glucose Insulin Potassium Group

RBG: Random Blood Glucose

S. hypoglycemia: severe hypoglycemia

p: p value comparing between the three studied groups

p1a: p value comparing between Control group and the IIT group.

p1b: p value comparing between Control group and the GIK group.

p2: p value comparing between IIT group and the GIK group.

Table III: Comparison between the two methods of monitoring random blood glucose (RBG) according to the percent of in target RBG readings, incidence of hypoglycemia and severe hypoglycemia

	2 hrs	CGM	p
% of In-Target RBG Readings	56.85±12.04	82.92±5.77	<0.001
Hypoglycemia	10 (41.7%)	2 (7.7%)	0.007
S. hypoglycemia	4 (16.7%)	0 (0%)	0.046

2 hrs: Method of monitoring random blood glucose using capillary blood glucometer device every 2 hours interval.

CGM: Method of monitoring random blood glucose using continuous glucose monitoring device.

RBG: Random Blood Glucose

S. hypoglycemia: severe hypoglycemia

Table IV: Comparison between the different studied groups according to ejection fraction (EF %) & wall motion score index (WMSI)

	Control	IIT	GIK	p	p_{1a}	p_{1b}	p_2
EF%							
On admission	38.07 ± 7.04	36.80 ± 6.15	36.67 ± 5.15	0.76	0.484	0.566	0.932
At 72 hours	44.33 ± 8.42	49.85 ± 9.02	47.50 ± 7.77	0.174	0.064	0.321	0.432
After 1 month	43.87 ± 11.27	55.65 ± 11.01	52.57 ± 10.23	0.009	0.003	0.037	0.421
% of change after 1 month	15.92 ± 24.00	53.00 ± 31.35	44.34 ± 30.39	0.002	0.001	0.009	0.285
WMSI							
On admission	1.79 ± 0.46	2.01 ± 0.51	1.92 ± 0.47	0.416	0.188	0.472	0.577
At 72 hours	1.56 ± 0.39	1.46 ± 0.40	1.49 ± 0.41	0.785	0.491	0.672	0.822
After1 month	1.55 ± 0.38	1.33 ± 0.44	1.34 ± 0.38	0.117	0.059	0.131	0.448
% of change after 1 month	-12.32 ± 10.83	-31.15 ± 20.27	-28.81 ± 17.78	0.013	0.010	0.010	0.753

IIT: Intensive Insulin Therapy group
GIK: Glucose Insulin Potassium Group
p: p value comparing between the three studied groups
p1a: p value comparing between Control group and the IIT group.
p1b: p value comparing between Control group and the GIK group.
p2: p value comparing between IIT group and the GIK group.

Table V: Comparison between the different studied groups according to High sensitivity C-reactive protein measurement (hsCRP) (mg/L), Creatine Kinase (CK) levels (mg/L).

	Control (n=15)	IIT (n=20)	GIK (n=15)	p	p_{1a}	p_{1b}	p_2
hsCRP(mg/L)							
On admissions	1.98 ± 0.69	1.98 ± 0.68	2.08 ± 0.74	0.898	0.998	0.696	0.678
After 48 hours	11.31 ± 2.95	4.76 ± 0.82	4.79 ± 0.76	<0.001	<0.001	<0.001	0.944
% of change	-10.15 ± 27.55	-40.90 ± 20.98	-34.01 ± 23.48	<0.001	<0.001	<0.001	0.506
CK (mg/L)							
On admissions (mean)	518.20 ± 485.08	349.50±386.88	316.57 ± 201.10	0.303	0.201	0.161	0.805
On admissions (median)	376	251	301	0.461	0.25	0.351	0.714
Peak value (mean)	3136.2 ± 902.29	2393.70±868.38	2495.79±732.24	0.034	0.013	0.047	0.730
Peak value (median)	3154	2595	2198.5	0.05	0.029	0.04	0.806

IIT: Intensive Insulin Therapy group
GIK: Glucose Insulin Potassium Group
hs CRP: High sensitivity C-reactive protein
CK: Creatine kinase
p: p value comparing between the three studied groups
p1a: p value comparing between Control group and the IIT group.
p1b: p value comparing between Control group and the GIK group.
p2: p value comparing between IIT group and the GIK group.

Table VI: Comparison between the different studied groups according to incidence of in-hospital major adverse cardiac events (MACEs) & discharge to 30 days follow up MACEs

		Control (n=15)		IIT (n=20)		GIK (n=15)		p	p_{1a}	p_{1b}	p_2
		N	%	N	%	N	%				
IN HOSPITAL MACEs	**Serious arrhythmia**	6	40.0	1	5.0	2	13.3	0.028	0.027	0.215	0.565
	Heart Failure	6	40.0	1	5.0	2	13.3	0.028	0.027	0.215	0.565
	Re-infarction	0	0.0	0	0.0	0	0.0	-	-	-	-
	Death	0	0.0	0	0.0	1	6.7	0.598	-	1.000	0.429
	All MACEs (subjects)	7	46.7	2	10.0	4	26.7	0.05	0.022	0.45	0.367
Discharge to 30 days follow up MACEs	**Serious arrhythmia**	0	0.0	0	0.0	0	0.0	-	-	-	-
	Heart Failure	7	56.7	2	10.0	1	7.1	0.015	0.022	0.035	1.000
	Re-infarction	1	6.7	0	0.0	0	0.0	0.591	0.429	1.000	-
	Death	1	6.7	0	0.0	0	0.0	0.591	0.429	1.000	-
	All MACEs (subjects)	7	46.7	2	10.0	1	7.1	0.015	0.022	0.035	1.000

IIT: Intensive Insulin Therapy group
GIK: Glucose Insulin Potassium Group
p: p value comparing between the three studied groups
p1a: p value comparing between Control group and the IIT group.
p1b: p value comparing between Control group and the GIK group.
p2: p value comparing between IIT group and the GIK group.

Appendix 1: Sliding Scale Protocol with Regular Insulin SC:

RBS (mg/dl)	Low Dose Scale	Moderate Dose Scale	High Dose Scale	Next Glucose Check
Below 60	**administer 100cc G10% IV bolus and re-measure after 30 mins.**			30 mins
60-130	0 units	0 units	0 units	6 hours
131-180	2 units	4 units	8 units	6 hours
181-240	4 units	8 units	12 units	6 hours
241-300	6 units	10 units	16 units	6 hours
301-350	8 units	12 units	20 units	6 hours
351-400	10 units	16 units	24 units	6 hours
Above 400	12 units	20 units	28 units	6 hours

Discussion:

Our data show clearly that in patients with STEMI, tight glycemic control (BG < 120mg/dl) with continuous insulin infusion either administered as insulin alone or in combination with high dose GIK leads to a greater improvement in the absolute ejection fraction at 30 days, than that in subjects with BG > 140mg/dl. In addition, the wall motion index, reflective of myocardial systolic function, was also improved more in the

intensively insulin treated patients than that in controls. These observations are consistent with a significant reduction in myocardial injury and probably a reduction in the size of the infarct. Consistent with this, there was a smaller magnitude of increase in CK concentrations in the IIT and GIK groups when compared to the controls. In addition, the patients in the IIT and GIK groups had smaller increases in plasma hsCRP concentrations which have previously been shown to be related to myocardial injury [41-43]. At the clinical level, intensively treated patients had fewer MACE including dysrythmia and cardiac failure. Thus, intensive insulin treatment exerted anti-inflammatory and cardio-protective effects while improving clinical outcomes. These effects are consistent with the observations recently published by Chaudhuri et al. [44].

Our study also demonstrates for the first time that with higher rates of glucose and insulin infusion as in the GIK group, if blood glucose concentrations are maintained between 80-120 mg/dl, there is a reduction in the magnitude of increase in CK and hsCRP concentrations along with an improvement in ejection fraction when compared with controls. These results were similar to those observed in the IIT group and are also consistent with those reported by Chaudhuri et al. [44]

In view of the absence of overt benefit from fixed high dose insulin and glucose regimes in the past, as in the CREATE-ECLA study, [24] the critical factor necessary for obtaining benefit with all such regimes appears to be the maintenance of euglycemia. In the CREATE-ECLA study, the institution of the GIK regime resulted in the induction of hyperglycemia consistent with the large amounts of glucose (25-30 g/h) infused: glucose concentrations increased from 162 mg/dl to 182 mg/dl at 6h and remained higher than that in controls throughout the period under study (24h). It is also of interest that in a re-analysis of the CREATE-ECLA study, it was clear that there was an excess of mortality and cardiac failure in the first 3 days of admission in the GIK arm while there was a reduction in mortality and cardiac failure between days 3-30. This is consistent with the detrimental effects of induction of hyperglycemia and fluid overload immediately after admission with insulin related benefits appearing in the later phase (days 3-30). In a further analysis of the data from this study, it was shown clearly that for any given concentration of glucose, the group given insulin had lower mortality when glucose concentrations were higher than 144mg/dl [45].In other previous regimes using high glucose and insulin infusion rates also, no effort was made to maintain euglycemia. In our study, we were able to maintain mean glucose concentrations at 108 mg/dl in the IIT arm and at 112 mg/dl in the GIK arm when compared to 143 mg/dl in the control arm.

Our data also show that blood glucose concentrations greater than 140 mg/dl are detrimental in patients with AMI. These observations are consistent with that of the HI-5 Study. [25] In the HI-5 study, there was a 50% reduction in the incidence of cardiac failure and re-infarction; however, there was no reduction in the rate of mortality in the insulin infused group. This was probably related to the minimal difference in blood glucose concentrations between the two groups: 8.3 ± 2.2 mmol/L (149.4 ± 39.6 mg/dl), in the insulin infusion group, and 9.0 ± 2.8 mmol/L (162 ± 50.4 mg/dl) in the control group (p=NS). When the data were analyzed on the basis of mean blood glucose concentrations achieved during the first 24 h, mortality was lower among patients with a mean blood glucose concentration of ≤ 8 mmol/L (144 mg/dl), compared with patients with a mean blood glucose concentration of >8 mmol/L (2 vs. 11% at 6 months, p = 0.02). Our observations are also consistent with that of Marfella et al [46] who have shown that in patients with first AMI, undergoing coronary bypass surgery, tight glycemic control (blood glucose 80-140 mg/dl) with insulin for three days before surgery, reduces oxidative stress and inflammation, reduces apoptosis and remodeling in the peri-infarct zones . These effects are associated with a reduction in myocardial infarct size and an improved left ventricular ejection fraction.

These observations may explain why there was no difference in mortality between the three groups in the DIGAMI-2 study(26). In that study, all groups had mean glucose concentrations greater than 140 mg/dl and the decrease in glucose concentrations achieved in the insulin infused arms was not significant. In contrast, in the DIGAMI 1 study, (27) which

showed a benefit of insulin infusion, there was a significant reduction in glucose concentrations in the insulin treated group compared to controls.

The present study also demonstrates for the first time that the continuous glucose monitoring system can be used effectively in studies investigating the effect of tight glycemic control on clinical outcomes in AMI. The percentage of in-target glycemic readings was significantly higher in the patients monitored using the CGM than patients monitored using glucometer readings (56.85±12.04 [2hours glucometer], 82.92±5.77 [CGM], p <0.001). Patients monitored using the CGM system reached a significantly lower glycemic level in the first 24 hours (134.44 ± 22.31 [2hours Glucometer], 120.39 ± 18.62 [CGM], p=0.02) This lower glycemic level was maintained when computing the mean glycemic level for 72 hours (130.41 ± 19.80 [Glucometer], 115.13 ± 17.16 [CGM], p=0.006) (data not shown) .Indeed, in our study, we achieved the best glycemic levels of any study investigating the effects of insulin infusion in patients with AMI.

Increased incidence of hypoglycemia is a major concern when implementing tight glycemic control. In our study there was a highly significant reduction in the incidence of hypoglycemia in the CGM group (10 [2 hrs GlucoCheck], 2 [CGM], p = 0.007). Furthermore, none of the patients monitored using the CGM system encountered any episode of severe hypoglycemia The reduction in hypoglycemia with CGMS is an important observation since recent studies, like the NICE-SUGAR study(47), tight glycemic control in the ICU was shown not to be beneficial. In this study there was a significantly higher incidence of severe hypoglycemia in the intensive glucose control (6.8%) versus the conventional control group (0.5%), As hypoglycemia is associated with adverse clinical outcomes and is also a pro-inflammatory and prothrombotic stimulus (48-50) higher incidence of hypoglycemia in the intensive group may have neutralized the benefits of insulin infusion and tight glycemic control in these studies. Thus, it is important that in any trial investigating the benefits of tight glycemic control, hypoglycemia is avoided. Continuous glucose monitoring allows easier treatment of hyperglycemia and the prevention and the prompt treatment of hypoglycemia. It should, therefore, be possible in the future to conduct such studies effectively, safely and in a simpler fashion by using CGMS to monitor glucose.

Conclusion: intensive insulin infusion treatment along with continuous glucose monitoring allowed us to maintain blood glucose concentrations at around a mean of 108 mg/dl in the IIT group and 112 mg/dl in the GIK group compared to 143 mg/dl in the control group over a period of 3 days without significant increase in the hazard of hypoglycemia. This resulted in significantly reduced incidence of MACE (dysrhythmia and cardiac failure), less myocardial dyskinesia and an improved ejection fraction, and lower CK and CRP concentrations in patients with STEMI. Future large multicenter trials need to be conducted with such insulin regimens targeting tight glycemic control using continuous glucose monitoring to confirm our findings in patients with STEMI and to establish the use of intravenous insulin infusions in the treatment of patients with this condition.

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