Original Article

Impacts of insulin infusion protocol on blood glucose level and outcomes in acute coronary syndrome patients with diabetes mellitus

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Abstract

Background: Acute coronary syndrome is the most common disease in the world. Several studies suggest that hyperglycemia is associated with poor clinical outcomes in patients with coronary artery disease. The aim of this study was to investigate the impact of insulin infusion protocol and conventional therapy on the blood glucose level and outcomes in acute coronary syndrome patients with diabetes mellitus.

Materials and Methods: We studied 64 patients (32 in each group) with acute coronary syndrome and acute myocardial infarction, who were admitted to the coronary care unit in a hospital in Isfahan, Iran in 2012. Inclusion criterion was blood sugar (BS) of more than 180 mg/dl on admission. Patients in the intervention group received insulin with East Jefferson insulin infusion protocol for at least 4 h, and in the control group, the subjects received subcutaneous insulin (conventional therapy) for at least for 48 h. Independent *t*-test, Student's *t*-test, and Chi-square test were used to analyze the data.

Results: Groups were matched for baseline characteristics. Blood glucose was significantly reduced in the two groups ($P < 0.001$), and the mean blood glucose level in the interaction group was significantly less than in the control group ($P = 0.0002$). Hypoglycemia was 31.2% and 25% in the intervention and control groups, respectively. The frequency of hypoglycemia did not differ significantly between the two groups ($P = 0.75$). Time to reach target insulin level differed between the two groups (4.75 h in the intervention group and 36.93 h in the control group; $P < 0.001$).

Conclusions: Our research showed that use of insulin infusion protocol is better in maintaining glycemia control compared to subcutaneous sliding scale method. The protocol allows nurses to commence and maintain the infusion more effectively and safely compared to the traditional method.

Key words: Acute coronary syndrome, diabetes mellitus, insulin infusion systems, Iran, nursing

Introduction

Acute coronary syndrome is among the most common diseases that prevail in various societies nowadays. So, based on statistics, in the US, about 1.5 million people get affected by myocardial infarction (MI) annually, of whom a high percentage is hospitalized in health centers. It imposes huge economic burden to these societies due to partial disability of these patients.[1] In Iran, prevalence of coronary artery diseases and their mortality is increasing. Previous research showed the mortality rate of the patients due to cardiovascular disease was 25–45% in eastern Mediterranean and Middle East countries including Iran.[2] Cardiovascular diseases in Iran account for 45% of mortality, 26% of life years wasted, and 10.4% of disease burden.[3] Among the risk factors for cardiovascular diseases, hyperlipidemia, hypertension, and hyperglycemia are common.

Hyperglycemia due to diabetes is one of the major factors for increase in mortality and morbidity caused due to cardiovascular diseases.[4] Prevalence of diabetes among the hospitalized patients with MI is 10–20%[5] of which 30% accounts for undiagnosed diabetes and 35% for the individuals with glucose tolerance disorder.[6] In fact, 85% of the patients with acute coronary syndrome experience a degree of blood glucose tolerance disorder.[7] Therefore,

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diabetes mellitus is known to be the main cause for mortality due to high risk of atherosclerosis,[6] and thus, the risk of mortality in diabetic patients is twofold more than in non-diabetic individuals.[8] Acute MI, accompanied with hyperglycemia, leads to increase of necrotic area and prevalence of heart failure and mortality.[9] One of the factors that reduces the development and prevalence of microvascular complications including sclerosis is appropriate control of blood sugar. Nowadays, the interventions to improve the prognosis in MI patients are conducted through two methods of metabolic modulation and metabolic control. Previous studies conducted on metabolic modulation focused on the potentially useful effects of insulin and potassium during acute stress, regardless of the level of blood sugar. This strategy is based on infusion of a steady dosage of glucose-insulin potassium (GIK).[10]

On the other hand, metabolic control lies on the usage of insulin to reduce blood sugar level to an already determined level in order to decrease the negative effects of hyperglycemia and to make the best of the useful effects of insulin[11] which may be injected by intravenous or subcutaneous methods. Insulin prescription method should be performed with the lowest risk of hypoglycemia as it may lead to cardiac injury and dangerous arrhythmia.[12] The published guidelines of European Society of Cardiology (ESC) and European Association for the Study of Diabetes (EASD) suggest insulin infusion to control blood sugar in all patients with acute coronary artery syndrome with history of diabetes.[6] Hypoglycemia is a major complication of insulin infusion compared to subcutaneous insulin injection, but previous research showed that iatrogenic hypoglycemia is not accompanied with high risk of mortality in patients after insulin therapy.[7] Checking the blood sugar by the nurses and conducting continuous insulin infusion protocol concurrently result in ideal control of blood sugar among critical patients in Cardiac Care Unit (CCU), but subcutaneous insulin injection needs a longer time.[13] In the patients with insulin infusion, it is possible to return the patients to their former diet therapy (through modification of lifestyle, diet, and/or oral insulin agents) after acute period of the disease. Meanwhile, among the patients without appropriate control of blood sugar, subcutaneous insulin injection is needed not only during hospitalization but also after discharge. Therefore, the nurses in CCUs are responsible for preservation of patients' blood sugar level based on insulin protocol which starts with a physician order. In this protocol, the nurses are permitted to control patients' blood sugar with the lowest need of physician order. The research has also shown that it is possible to achieve ideal blood sugar level without incidence of hypoglycemia through comprehensive nursing care as well as appropriate nutrition.[13]

The American Association of Diabetes has emphasized on the importance of blood sugar control in diabetic patients and considers nurses' function essential in successful administration of protocols, taking medical orders, precise monitoring, and educational programs of blood sugar control.[14] Outcomes of hyperglycemia control through insulin infusion compared to conventional methods have been considered in various studies. Among these outcomes, mean blood sugar level at the time of beginning insulin infusion[15] and the level of hypoglycemia[11,13,15] can be mentioned. As the conventional method in CCUs in Iran is usage of a subcutaneous insulin injection chart as well as insulin infusion in acute period of the disease to achieve the aforementioned outcomes better and faster, the present study compared the effects of insulin infusion method to those of conventional method (subcutaneous insulin injection) on blood sugar control and the outcomes such as hypoglycemia, and on achieving the target blood sugar in diabetic patients with acute coronary syndrome in CCUs.

Materials and Methods

This is a clinical trial conducted on patients with acute coronary syndrome with history of diabetes mellitus and hospitalized in CCU of Saee Hospital in Khomeinishahr, Iran. The researchers used convenient sampling for selecting the patients. The patients were randomly assigned to two groups based on random numbers table. The patients were explained about the research, its goals, and conditions. Among the selected patients, those who were willing to attend entered the study after filling a written consent form. Inclusion criteria were age over 18 years and diagnosis of acute coronary syndrome at the time of admission to CCU with approval of a specialist. Not inclusion criteria were high-risk patients and unusual hypoglycemia (like known insulin secretion tumors or history of frequent and idiopathic hypoglycemia), pregnancy, renal and hepatic failure, or liver transplantation.

Exclusion criteria were imminent death (expected heart arrest within <24 h), patients' decision on withdrawal from intervention during the study, and not achieving the target blood sugar level 24 h after beginning insulin infusion.[8]

In the present study, the. Sample size was calculated by test power of 80% and confidence interval of 95%. The number of the subjects obtained was 32 in each group by confidence interval of 95%, test power of 80%, and $d = 0.7$ (after consultation with a statistician). Subject drop was considered with regard to the exclusion criteria, and each dropped out subject was replaced by another new subject. Five subjects were left out of the study due to expedition to a more equipped center, one patient due to

his withdrawal of taking part in the study, and two subjects as a result of not giving consent. The glucometer and the infusion pump were calibrated before sampling began. Just after patients' admission to CCU, their blood sugar was checked by an Accucheck glucometer device, and concurrently, a blood sample was sent to laboratory for random blood sugar check.

The patients with blood sugar >180 mg/dl were randomly assigned to the study group (insulin infusion) and control group (subcutaneous insulin injection). The earlier blood sugar control medications (metformin, *pioglitazone* etc.) of all patients were stopped before the study began. Insulin infusion was prescribed for the subjects based on East Jefferson protocol in the study, and subcutaneous insulin injection in the control group was administered by a cardiologist. For patients in the study group, a venous infusion solution made from 100 units human regular insulin and 100 ml normal saline (0.9%) at a ratio of 1:1 was administered. Insulin infusion was started from column 5 of the East Jefferson protocol.[16] Patients' blood sugar was checked each hour using the glucometer, and the protocol of insulin infusion level (units per hour) was changed based on the last measurement value of blood sugar based on the measured blood sugar level. In case of no reduction observed in the blood sugar level, compared to the latest measurement, the column was changed by one to right (e.g. from column 5 to column 6), and if blood sugar was less than 140 mg/dl, the column was changed by one to left (e.g. from column 5 to column 4), and infusion level was regulated based on the new column. When patients' blood sugar level was in the range of target value (140–180 mg/dl) and/or the blood sugar titer was less than the former one, insulin infusion was continued based on the same column. When patients' blood sugar was not in the target level (140–180 mg/dl) for at least 4 h, insulin infusion was changed to subcutaneous insulin injection two times a day or other blood sugar control methods. If the blood sugar was not in the target level for 24 h, insulin infusion was stopped and the patient was excluded from the study. The patients in the control group were on regular insulin sliding scale.[17] Blood sugar was checked four times a day in this group (three times before meals and one time before sleep). Based on patients' nutrition timetable in the hospital, patients' blood sugar was checked at 06:00 h, 12:00 h, 18:00 h, and 24:00 h for 48 h, and human regular insulin was injected to patients in this group through subcutaneous method based on their blood sugar level.

After 48 h, infusion was stopped based on the chart and changed to subcutaneous insulin injection twice a day or to other conventional methods of blood sugar control (blood sugar control with diet therapy or blood sugar lowering pills). In both groups, if blood sugar was less than 8 mg/dl, hypoglycemia guideline was used. Blood sugar (daily Fasting blood suger (FBS), BS) was checked every 12 h in all patients until discharge. All the obtained data (all the measured blood sugar levels for each patient and the nursing interventions conducted such as stopping infusion, interventions for hypoglycemia, etc.) were recorded for each patient separately by the researcher or the project cooperator in the data collection form.

Each data collection from yielded the time interval to reach target sugar level and the onset number of patients' hypoglycemia. Data were analyzed by descriptive and analytical statistical tests such as central indexes, dispersion index, frequency distribution, independent *t*-test, paired *t*-test, and Chi-square through SPSS.

Ethical considerations

The ethical and scientific contents of this study have been approved by Isfahan University of Medical Sciences.

Results

Both groups were identical concerning demographic characteristics based on Chi-square test and independent *t*-test [Table 1]. Mean patients' blood sugar was 289.6 (108.9) mg/dl in the insulin infusion group before intervention and 275.03 (77.5) mg/dl in the subcutaneous insulin injection group, which showed no significant difference ($P = 0.54$).

Mean patients' blood sugar was 153.6 (44.5) mg/dl in the study group and 180.7 (76.3) mg/dl in the control group after intervention. It was significantly less in the study group compared to the control group ($P = 0.04$). Mean

Table 1: Identical baseline characteristics of the patients in study and control groups

Variable	Study	Control	Test	*P* value
Sex (female) (No. (%))	(56.2) 18	(62.5) 20	Chi-square	0.61
Type of diseases (MI No. (%))	(37.5) 12	(31.2) 10	Chi-square	0.59
Age (mean (SD))	(10.48) 64.50	(10.74) 63.56	Independent *t*-test	0.72
BMI (mean (SD))	(3.5) 26.8	(4.9) 26.3	Independent *t*-test	0.67
Length of diabetes	(3.4) 8.8	(3.14) 9.06	Independent *t*-test	0.82

MI: Myocardial infarctio, BMI: Body mass index, SD: Standard deviation

blood sugar levels at the end of intervention compared to before beginning the intervention were significantly reduced in study ($P < 0.001$) and control ($P < 0.001$) groups, of which the reduction was significantly lower in the study group compared to control ($P = 0.04$). Mean patients' blood sugar during hospitalization period was 189.2 (25.5) mg/dl in the study group and 217.9 (65.25) mg/dl in the control group, which showed a significant difference ($P = 0.02$). Mean time interval to reach target blood sugar level was 4.75 h in the study group and 36.94 h in the control group, for which independent *t*-test showed a significant difference ($P < 0.001$) [Table 2]. Incidence of hypoglycemia was 32.2% in the study group and 25% in the control group, for which Chi-square test showed no significant difference ($P = 0.57$).

Discussion

Acute coronary syndrome patients with history of diabetes mellitus hospitalized in CCU were studied. Investigation showed that the mean blood sugar level during the entire hospitalization period (all blood tests except those of admission and discharge) was 189.2 (25.5) mg/dl in the insulin infusion group and 217.9 (65.1) mg/dl in the subcutaneous insulin injection group. Zimmerman (2004) showed that the mean blood sugar level in the insulin infusion group during hospitalization was 114 (66) mg/dl and it was 183 (39) mg/dl in the subcutaneous insulin injection group.[18] The subjects in Zimmerman's study had lower level of blood sugar during hospitalization compared to the present study, which can be a result of lower target level of blood sugar in Zimmerman's study (80–150 mg/dl), participation of the patients both with and without diabetes mellitus in his study, and usage of a different protocol. On the other hand, blood sugar level showed a significant difference during hospitalization after intervention in both groups in the above study, which is consistent with the present study. Balkin (2006) conducted a study on the patients hospitalized in CCU. Patients' mean blood sugar level in the study group was 253 (95.6) mg/dl before intervention and 133.5 (43.9) mg/dl after intervention,[19] which shows a significant effect of insulin infusion with protocol on the blood sugar level ($P < 0.001$). This finding is in line with that of the present study.

Table 2: Comparison of mean blood sugar levels at various time points in the two groups

Group Intervention Phase	Study	Control	*P* value
Before intervention	289.6±108.9	275.03±77.5	0.54
After intervention	153.6±44.5	108.7±76.3	0.04
Paired *t*-test	*P*<0.001	*P*<0.001	

In the present study, 31.2% of the patients in the study group and 25% of the patients in the control group developed hypoglycemia. In Dilkhush's study (2005) on 30 patients hospitalized in the ICU, frequency distribution of hypoglycemia was reported to be 0.4% in the study group.[20] But in Osborne's study conducted on the effect of evaluation of nurses' role on administration of insulin infusion column protocol among the patients hospitalized in the ICU, frequency distribution of hypoglycemia was reported as 0.9%.[21]

In NICE-SUGAR study (2009) on two different target blood sugar levels with insulin infusion and its outcomes in CCU patients, the frequency distribution of hypoglycemia among the patients in the insulin infusion group with target blood sugar level of 140–180 mg/dl was reported as 0.5% and in the other group with a target level of 81–108 mg/dl, it was reported to be 6.8%.[22] As observed, the frequency distributions of hypoglycemia obtained by studies conducted on these patients are different from those of insulin infusion group in the present study, which could have resulted from the difference in subjects' number, type of the used protocol, target blood sugar, environment, and the type of the disease between those studies and the present study. But there was no significant difference in the incidence of hypoglycemia in both groups in the present study. In Zimmerman's study, the incidence of hypoglycemia was reported to be 16.1% in the insulin infusion group and 98% in the subcutaneous insulin injection group.

In the above study, there was no significant difference between two groups ($P = 0.098$), which is consistent with the present study. In Zimmerman's study, there was also a significant difference between the two groups concerning the time interval to achieve target blood sugar ($P < 0.001$), which was 2.1 h in the study group and 9.4 h in the control group,[18] while they were 4.75 h versus 36.93 h in the present study. The difference can be due to patients' lower mean blood sugar in Zimmerman's study and the various protocols used in these studies. Goldberg *et al*. (2004) reported the mean time interval to achieve target blood sugar as 10.1 (4.6) h in insulin infusion, which could have resulted from lower target blood level in their study and the difference in the ward where the patients were hospitalized, as well as the protocols used in these two studies.[15] Meanwhile, there was a significant difference in the time interval to achieve target blood sugar in these studies just like that observed in the present study. With regard to the existing studies, it can be concluded that blood sugar control with use of insulin infusion protocol in acute coronary syndrome patients with history of diabetes mellitus is more efficient and effective. As appropriate control of blood sugar among CCU patients affects the length of their

hospitalization, treatment costs, and the disease outcomes, it is suggested to facilitate use of insulin infusion protocol in CCUs through education of nurses as the administrators of the protocol. One of the limitations of the present study was the short length of the study and conducting the study by just the researcher and her colleague. It is suggested that nurses in charge of the patients should conduct further studies after receiving education to investigate the effect of blood sugar control on the delayed outcomes.

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