Evaluation of the Effect of Metformin and Insulin in Hyperglycemia Treatment after Coronary Artery Bypass Surgery in Nondiabetic Patients

Abstract

Introduction: Insulin therapy is the most commonly used treatment for controlling hyperglycemia after coronary artery bypass surgery in both diabetic and nondiabetic patients. Metformin has been indicated for critically ill patients as an alternate for the treatment of hyperglycemia. This study evaluated the effect of metformin and insulin in hyperglycemia treatment after coronary artery bypass surgery in nondiabetic patients. **Settings and Design:** This study was a clinical trial comprising nondiabetic patients who had undergone coronary artery bypass surgery. Patients were randomly divided into the insulin group and the metformin group. **Methods:** Patients in the insulin group received continuous infusion of insulin while those in the metformin group received 500 mg metformin tablets twice daily. All the patients were followed up for 3 days after stabilization of blood glucose levels. **Statistical Analysis:** Data were analyzed using Chi-square test and Mann–Whitney U-test. **Results:** This study included a total of 56 patients. During the study period, the mean blood glucose levels decreased from 225.24 to 112.36 mg/dl (↓112.88 mg/dl) in the insulin group and from 221.80 to 121.92 mg/dl in the metformin group (↓99.88 mg/dl). There was no significant difference in the blood glucose levels of the patients between the two groups at any measurement times ($P > 0.05$). **Conclusion:** Using 500 mg metformin twice daily is similar to using insulin in nondiabetic patients undergoing coronary artery bypass graft. Therefore, the use of metformin can be considered as a treatment strategy for controlling hyperglycemia in this group of patients.

Keywords: *Coronary artery bypasses surgery, hyperglycemia, insulin, metformin*

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Introduction

Hyperglycemia is a common disorder in 77%–95% of patients during the first 24 h after undergoing bypass surgery.[1,2] The most important stimulus causing hyperglycemia in these patients is the stress of the surgery. Hyperglycemia due to stress is defined as an increase in plasma glucose by >126 mg/dl in a fasting state or >200 mg/dl (at any time of the day) in ill or hospitalized patients with or without diabetes.[3] Cardiac surgery is considered as highly invasive, and some patients undergoing this type of surgery may experience hyperglycemia because of stress response to awakening from anesthesia,[1] anesthesia technique,[4] and preoperative emotional stress.[5] The proposed mechanism involved in the onset of hyperglycemia after a cardiac surgery includes the release of hormones that affect blood glucose levels and cause significant changes in the metabolism of carbohydrates, increased hepatic gluconeogenesis, insulin resistance

in peripheral tissues, and the relative loss of insulin production.[6,7]

Hyperglycemia after surgery can increase the duration of hospitalization and result in prolonged intubation, stroke, renal failure, infection, sepsis, multiorgan failure, and increase in mortality in nondiabetic patients undergoing coronary artery bypass graft (CABG).[2,8] Hyperglycemia occurring in nondiabetic patients is more fatal than that in diabetic patients, because the mortality rate increases in nondiabetic patients with blood glucose levels >200 mg/dl after the surgery, whereas in diabetic patients, mortality usually occurs when the blood glucose levels increase above 300 mg/dl.[9]

Insulin therapy is the most commonly used treatment for controlling hyperglycemia after coronary artery bypass surgery in both diabetic and nondiabetic patients based on their blood glucose levels.[10,11] The recommendation by the Society of Thoracic Surgeons (STS) is one of the guidelines that has been used to manage

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blood glucose levels in patients after a cardiac surgery. This guideline suggests that the blood glucose level of such patients should be <180 mg/dl and includes insulin therapy as the primary means of glycemic control, which has been reported to produce complications.[12] Therefore, a less risky, easier, and more useful method is required to control hyperglycemia in patients undergoing a cardiac surgery.

Metformin has been indicated for critically ill patients as an alternative to insulin for controlling hyperglycemia.[13] Metformin regulates blood glucose levels without causing hypoglycemia in diabetic patients. One of the adverse effects of metformin is lactic acidosis, which has been a challenge in critically ill patients. Maxhera *et al.* reported that administration of metformin before cardiac surgery will not cause lactic acidosis after the surgery.[14] Sirvinskas *et al.* conducted a retrospective study and showed that the use of metformin will not cause lactic acidosis in people without any underlying disease.[15] Therefore, the use of metformin has no contradiction to control hyperglycemia after a cardiac bypass surgery in patients without an underlying disease. It has also been reported that metformin can control blood glucose levels of patients in the intensive care unit (ICU), thus decreasing the need for insulin doses; moreover, metformin was also found to be effective in reducing insulin resistance without causing lactic acidosis. In addition, it does not cause adverse effects such as hypoglycemia, hypokalemia, and hypomagnesemia.[12]

Patients undergoing cardiopulmonary bypass (CPB) heart surgery may suffer from injury to the myocardium because of the phenomenon of ischemia and reperfusion. In these circumstances, the use of metformin can reduce the risk of reperfusion injury.[16] Due to less complications of the use of metformin compared to insulin to control hyperglycemia resulting coronary artery bypass surgery, the investigators did not find a study to compare the two methods for the control of hyperglycemia of such patients. This study has been carried out to compare the effects of metformin and insulin in patients undergoing coronary artery bypass surgery.

Methods

This study was a prospective clinical trial comprising all nondiabetic patients who had undergone coronary artery bypass surgery from March 12, 2015, to October 19, 2016. The study sample consisted of those patients who met the following inclusion criteria: postoperative blood glucose level >150 mg/dl, elective coronary artery bypass surgery, the use of CPB (on pump CABG), and stable hemodynamics (blood pressure >90 mmHg and pulse rate between 50 and 110). The exclusion criteria were creatinine level >1.5 mg/dl, life-threatening arrhythmia, and the use of inotropic agents. The sample size was estimated at 95% according to the confidence level, 80% power, mean and standard deviation 145.1 ± 18 for insulin effect, and mean and standard deviation 131.6 ± 7.9 for metformin effect,[17]

17 people were assigned for each group. However, to increase the accuracy of the study, 25 patients were studied in each group.

All the patients participating in the study provided the informed consents the day before surgery. Accurate measurements of height, weight, blood sugar (BS), body mass index (BMI), and creatinine levels were performed and recorded an hour before surgery. Blood glucose levels were measured after the surgery and in the open heart ICU. Patients who met the inclusion criteria were randomly divided into the insulin group and the metformin group. Computerized block randomization was used to randomize. Those in the insulin group received continuous infusion of insulin as shown in Tables 1 and 2.[18] The starting dose of insulin was calculated based on Table 1 and continued based on Table 2.

Blood glucose was monitored every 1 h after starting insulin infusion, and insulin infusion was controlled according to Table 2. Blood glucose control was carried out up to 24 h and every 6 h to 3 days every 12 h after controlling blood glucose levels in the range of 150–180 mg/dl.

Patients in the metformin group received 500 mg metformin tablets twice daily (9 a.m. and 9 p.m.) for 4 days. Patients in both the study groups were monitored and followed up for 3 days after stabilization of blood glucose levels. To assess the metabolic acidosis phase, arterial blood PH and bicarbonate levels and base excess were measured and recorded immediately for patients in both the study groups

Table 1: Method of calculating the initial dose of insulin

Blood sugar	Regular insulin IV bolus	Infusion rate
151-200	No bolus	2 units/h
201-240	4 units	2 units/h
241-280	6 units	4 units/h
281-320	10 units	6 units/h

IV: Intravenous

Table 2: Method of calculating the continuous dose of insulin

Blood sugar	Therapeutic Action
<90	IV bolus with 1/2 amp 50% dextrose and stop infusion
91-110	Stop infusion; restart at 50% of previous rate once BS is <150
111-150	No change in infusion rate
151-200	Increase infusion rate by 2 units/h
201-240	IV bolus with 4 units and increase infusion by 2 units/h
241-280	IV bolus with 6 units and increase infusion by 2 unit/h
281-320	IV bolus with 10 units and increase infusion by 4 units/h
>320	Page house officer

IV: Intravenous, BS: Blood sugar

after their admission in the cardiac ICU and then every 12 h for 3 days. Finally, the obtained data were analyzed at a significance level of 0.05 using Chi-square test and Mann–Whitney U-test.

Results

A total of 207 patients, including 97 diabetic and 110 nondiabetic patients, underwent on pump coronary artery bypass surgery at this center at the time of sampling. Among the nondiabetic patients, 56 met the inclusion criteria. Six patients were excluded from the study during the sampling process because of life-threatening arrhythmia (one patient), use of inotropic agents (two patients), and unstable hemodynamic status (three patients), and finally, the data of 50 patients were analyzed [Figure 1]. The mean age of patients in insulin group was 60.40 ± 11.59 and in metformin group was 61.64 ± 9.17, and the majority of them were males in each group. The mean CPB time was significantly higher (112.12 ± 28.05 min) in the insulin group than that in the metformin group (93.24 ± 15.80 min) ($P = 0.028$). All patients need to ventilator support after CABG. The average BMI of the patients ranged from 25 to 26. The mean length of hospital stay was significantly higher (7.40 ± 1.29 days) in the insulin group than that in the metformin group (6.52 ± 0.77 days) ($P < 0.05$). The Mann–Whitney U-test also showed no significant difference in sex, hyperlipoproteinemia background, and hypertension background between the two groups ($P > 0.05$) [Table 3]. All patients in both groups were suffering from hyperglycemia after the surgery. The minimum blood glucose level was 180 mg/dl, and the maximum was 360 mg/dl.
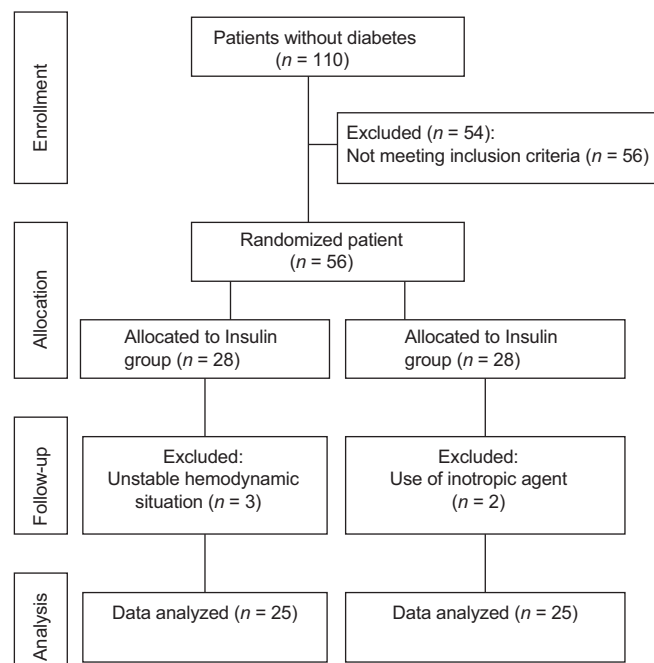
As shown in Figure 2, the mean blood glucose levels decreased during the 3 days of treatment from 225.24 to 112.36 mg/dl (↓112.88 mg/dl) in the insulin group and from 221.80 to 121.92 mg/dl in the metformin group (↓99.88 mg/dl). There was no significant difference in the blood glucose levels of the patients between the two groups at any measurement section ($P > 0.05$) [Table 4].

Discussion

In this study, the average BS was 102.92 ± 16.25 in the insulin group and 97.60 ± 15.21 in the metformin group before the surgery, with no significant difference between the two groups. A previous study by Székely *et al*. reported that the blood glucose levels of nondiabetic patients undergoing CABG ranged from 91.0 to 118.9 mg/dl.[9] Rassias also showed that the BS of the patients was <126 mg/dl before CABG.[19]

In the present study, all patients experienced some degree of hyperglycemia in the two groups. According to Azarafarin and Alizade (2008), the risk of developing hyperglycemia after CABG is 95% in nondiabetic patients. The mean BS levels of the patients were 225.24 ± 44.26 mg/dl in the insulin group and 221.80 ± 39.76 mg/dl in the metformin group immediately after admission in the ICU after the cardiac surgery. Therefore, the mean blood glucose levels increased by 123.24 mg/dl in the insulin group and 124.2 mg/dl in the metformin group. However, no significant difference was observed in the postoperative BS levels between the two study groups. Liao *et al*. showed that the mean BS level in nondiabetic patients who had undergone CPB surgery was 194 ± 50 mg/dl.[10] Azarafarin and Alizadeh-Asl reported that the mean BS level of nondiabetic patients who underwent CPB increased from 96.3 ± 8.4 to 194.8 ± 41.2 (↑98.5 mg/dl) in the intervention group and from 93.9 ± 10.3 to 199.8 ± 43.3 (↑105.9 mg/dl) in the control group.[11] It appears the higher postoperative BS levels and causes an increase in postoperative BS levels in the present study compared to those in other similar studies. The pattern of changes observed in the BS curve for the two study groups showed that the use of the
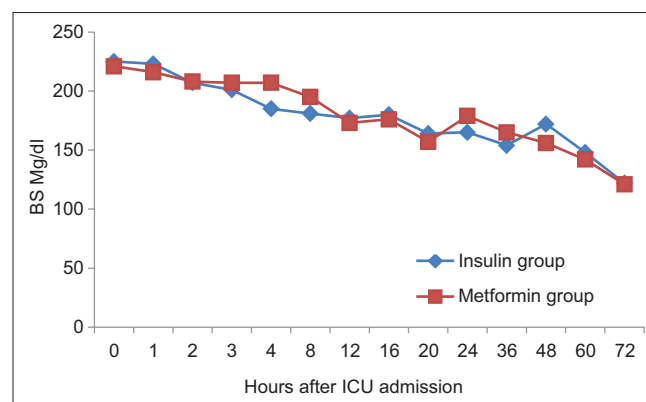

Figure 1: Flow of patients through the trial

Figure 2: Trend of blood sugar changes after treatment by insulin and metformin

Table 3: Background parameters of patients in the insulin and metformin groups

Background parameters	n	Insulin group (*n*=25)	Metformin group (*n*=25)	*P*
Age (year)		60.40±11.59	61.64±9.17	0.823
Gender (male/female)		19/6	21/4	0.363
BMI		26.06±4.88	25.48±3.93	0.985
Ejection fraction (%)		49.40±6.50	49.40±6.00	1.000
Length of stay in ICU		7.40±1.29	6.25±0.77	0.003
Operation time (min)				
CPB (min)		112.12±28.05	93.24±15.80	0.028
Ventilator support (yes/no)		25/0	25/0	1.000
Grafts number		4.04±0.61	3.80±0.76	0.251
CR before OR		1.02±0.19	1.01±0.17	0.921
CR 1 day after ICU admission		1.10±0.20	1.05±0.15	0.413
CR 2 day after ICU admission		1.18±0.23	1.09±0.11	0.234
CR 3 day after ICU admission		1.22±0.32	1.08±0.17	0.105
HTN history (yes/no)		4/21	8/17	0.160
HLP history (yes/no)		7/18	8/17	0.500
BS before OR (mg/dl)		102.92±16.25	97.60±15.21	0.165

Data shown as mean±SD or *n*. BMI: Body mass index, BS: Blood sugar, OR: Operation room, CR: Creatinine, ICU: Intensive care unit, SD: Standard deviation, CPB: Cardiopulmonary bypass, HTN: Hypertension, HLP: Hyperlipoproteinemia

Table 4: Blood sugar mg/dl changes after admission to the intensive care unit ward in insulin and metformin groups

BS mg/dL (hours after ICU admission)	Mean±SD		*P*
	Insulin group	Metformin group	
BS (0)	225.24±44.26	221.80±39.76	0.749
BS (1)	223.16±35.79	216.60±38.03	0.535
BS (2)	207.68±35.67	208.16±37.43	0.907
BS (3)	201.88±26.45	207.96±35.11	0.833
BS (4)	185.20±38.18	207.72±48.71	0.107
BS (8)	181.00±43.57	195.24±49.37	0.260
BS (12)	177.48±61.47	173.24±46.10	0.541
BS (16)	180.48±58.25	176.40±42.15	0.749
BS (20)	164.20±35.96	157.08±31.16	0.869
BS (24)	165.20±47.27	179.72±39.86	0.181
BS (36)	154.48±40.17	165.76±48.04	0.473
BS (48)	172.48±49.38	156.84±41.88	0.286
BS (60)	148.00±48.69	142.00±50.69	0.415
BS (72)	122.36±23.04	121.92±28.20	0.854

SD: Standard deviation, BS: Blood sugar, ICU: Intensive care unit

STS protocol and 500 mg metformin tablets twice daily can improve hyperglycemia occurring after CPB surgery during 72 h. This study also demonstrated that there was no significant difference between insulin therapy using the STS protocol and using metformin tablets in treating hyperglycemia after CABG. Mojtahedzadeh *et al.* compared the effects of insulin and metformin on blood glucose control in patients with severe injury and undergoing a major surgery, except abdominal surgery. They observed that hyperglycemia decreased significantly following the use of insulin and metformin. Nevertheless, the control of blood glucose levels by insulin and serum electrolyte control at an optimum level were achieved through expert nursing care and continuous monitoring.[20] Baradari *et al.* compared the effect of insulin plus metformin with that of insulin alone in patients undergoing CABG and reported that blood glucose can be controlled with insulin and metformin.[17] Mojtahedzadeh *et al.* compared the efficacy of three groups of treatment, namely, (1) insulin, (2) metformin, and (3) insulin in combination with metformin to control hyperglycemia occurring in medical and surgical patients. They divided 33 patients into three groups, including 11 patients in each group, as follows: Group A taking insulin, Group B taking metformin, and Group C taking metformin plus insulin. The results showed that blood glucose levels decreased in all the three groups, with a significant decrease in Groups A and B. An important observation was that the use of metformin decreased the dosage of insulin in severely ill patients. Moreover, metformin was found to be effective in reversing insulin resistance without causing lactic acidosis.[21] Székely *et al.* demonstrated that the success rate of using insulin in the treatment of hyperglycemia after CABG in diabetic patients is higher than that in patients without a history of diabetes.[9] The results also showed that the duration of hospitalization in the open heart ICUs was significantly less in the metformin group than that in the insulin group. Ouattara *et al.* showed that patients with uncontrolled blood glucose levels after a cardiac surgery had a longer duration of hospitalization.[22] It appears that the reduction in nursing care in patients who received metformin had persuaded the attending physician to discharge the patients earlier from the open heart ICU.

Conclusion

Using 500 mg metformin twice daily can be as useful as using insulin in nondiabetic patients undergoing CABG. Metformin can also reduce the duration of hospitalization

in these patients. Therefore, the use of metformin in this group of patients can be considered as a treatment modality for controlling hyperglycemia. However, further studies are required to ensure the efficacy of such treatment.

Conflicts of interest

There are no conflicts of interest.

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