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Metformin as an Adjunct to Insulin for Glycemic Control in Patients with Type 2 Diabetes after CABG Surgery: A Randomized Double Blind Clinical Trial

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Abstract: Perioperative hyperglycemia is common in patients with type 2 diabetes undergoing Coronary Artery Bypass Graft (CABG) surgery and there is a direct relation between postoperative hyperglycemia and mortality rate in these patients. The aim of the present study is to determine the efficacy of metformin on glycemic control in diabetic patients after CABG surgery. In a randomized double blind clinical trial, 100 patients with type 2 diabetes admitted in open heart ICU after CABG surgery in Mazandaran Heart Center were enrolled. They were randomly assigned to two intervention and control groups. Three hours after extubation, therapeutic antiglycemic regimens were applied in these two groups and continued for three days. Intervention group received regular insulin infusion along with two metformin 500 mg tablets per twelve hours while control group received regular insulin infusion with two placebo tablets per twelve hours. Blood glucose level and other parameters were measured and recorded in determined intervals. To analyze the data, independent T-test, paired T-test, Mann-Whitney and repeated measure ANOVA tests were employed. Mean blood glucose level was not significantly different in the two groups at the beginning of the ICU admission; however, mean glucose level in insulin-metformin group, twelve hours after the initiation of the study, was significantly lower than insulin group ($p<0.05$). In addition, mean doses of potassium and insulin demand as well as mean number of episodes of hyperglycemia, hypoglycemia and glucose levels out of the accepted range were significantly lower in insulin-metformin group ($p<0.05$). Alterations in mean levels of lactate, BE, pH and creatinine were not statistically significant in these two groups. It seems that adding metformin to insulin leads to a better glycemic control in type two diabetic patients undergoing CABG surgery without causing metabolic acidosis. Therefore, it might be a potential option in blood glucose control protocol in this group of patients.

Key words: CABG, metformin, glycemic control, insulin, diabetes

INTRODUCTION

Approximately 515,000 patients undergo coronary artery bypass graft surgery (CABG) annually in the United States. Almost thirty percent of these patients have known diabetes mellitus (Gandhi *et al*., 2005). These patients most commonly have type 2 diabetes and their number is continuously increasing (Lazar *et al*., 2009). Diabetes has been shown to be associated with some poor clinical outcomes including higher risk of infection, ischemic events, neurologic and renal complications, as well as higher mortality rate after cardiac surgery (Lazar *et al*., 2004; Ouattara *et al*., 2005; Zerr *et al*., 1997).

A direct relationship has been found between postoperative hyperglycemia and higher mortality rates in patients with type 2 diabetes undergoing CABG surgery (Menaka *et al*., 2007). In addition, studies have shown that perioperative hyperglycemia in patients with diabetes is associated with a higher infection rate, similarly in postoperative blood glucose > 200 mg dL^{-1}, there is a range of 17 to 86% rise in infection rate (Estrada *et al*., 2003). Several studies have stated that tighter control of

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blood glucose is associated with decrease in infection risk, mortality rate, hospital stays and improvement in survival rate of the patients, indicating the importance of glycemic control in diabetic patients undergoing CABG surgery (Lazar *et al*., 2009; Schmeltz *et al*., 2007; Lazar *et al*., 2004). Insulin is now considered as the main treatment for hyperglycemia (Estrada *et al*., 2003). However, issues such as insulin resistance and risk of hypoglycemia as well as possibility of insulin induced hypokalemia and hypomagnesaemia which might reinforce the insulin resistance, have led to some controversies in intensive insulin therapy. Obviously administration of high doses of insulin for aggressive glycemic control can cause this vicious cycle which might lead to some adverse effects (Lalau and Race, 2001; Mojtahedzadeh *et al*., 2008). Postoperative hyperglycemia in cardiac surgery patients usually requires considerable rise in insulin dose and sometimes even very high doses might be ineffective to reach the goal level of blood glucose (Doenst *et al*., 2005). On the other hand, it has been proved that administration of high doses of insulin is a risk factor for in-hospital mortality (Rady *et al*., 2005).

Metformin-a biguanide derived from guanidine-is one of the most commonly used hypoglycemic agents in treatment of patients with type 2 Diabetes Mellitus (DM). Unlike other hypoglycemic agents, metformin can reduce blood glucose level with a different mechanism, without causing severe hypoglycemia in diabetic patients (Knowler *et al*., 2002). A potential but rare adverse effect of metformin is lactic acidosis. Although lactic acidosis caused by metformin is a rare condition (Fitzgerald *et al*., 2009), it leads to contraindication of metformin in critically ill patients. During the last three decades, several studies have been conducted on metformin's role in causing lactic acidosis. Some researchers claim that it can't be definitely concluded that metformin is responsible for such a condition. Actually, the majority of patients developing lactic acidosis had serious underlying diseases such as cardiac, renal or liver diseases which all might result in lactic acidosis. Therefore the complication might be considered as a coincidence phenomenon (Lalau and Race, 2001). Furthermore, epidemiologic findings do not support the relationship between metformin and lactic acidosis (Kruse, 2001).

Recent studies have demonstrated that using metformin for glucose control in ICU admitted patients decreases the required insulin dose and it seems that this drug is effective in reducing insulin resistance without causing lactic acidosis. Besides, it does not lead to hypoglycemia, hypomagnesaemia and hypokalemia, complications which are almost common in insulin therapy and so it reduces nursing workload (Mojtahedzadeh *et al*., 2008; Ansari *et al*., 2008).

Overall, it seems that using agents like metformin can result in the reduction of gluconeogenesis and glycogenolysis as well as improvement in insulin receptors sensitivity through multiple mechanisms. Moreover, it doesn't show any complications such as hypoglycemia, so it can be considered as an effective option in glycemic control protocol of these patients. Therefore, this study is conducted to determine the effect of using metformin on blood glucose control in patients with type 2 diabetes mellitus admitted to cardiac surgery ICU after CABG surgery in Mazandaran Heart Center. If a positive effect is found, it will contribute to reducing complications and improving survival rate of these patients.

MATERIALS AND METHODS

One hundred patients with type 2 diabetes admitted in cardiac surgery ICU of Mazandaran Heart Center after CABG surgery were included in this clinical trial. Approval to conduct the study in human subjects was obtained from the Research Council and Ethics Committee of Mazandaran University of Medical Sciences. Patients were enrolled in the study after written informed consent. Inclusion criteria consisted of prior known diagnosis of type2 DM, elective CABG surgery, hemodynamically stable conditions (i.e., MAP>60 mm Hg, absence of life threatening dysrrhythmia and pulse rate of 50-110 per minute), age range of 35-75 years and use of cardiopulmonary pump during the surgery.

Those patients with a past medical history of liver disease (SGPT and SGOT level higher than 75 U L^{-1}), renal disease (serum creatinine higher than 1.5 mg dL^{-1} in two consecutive tests), cardiac disease (EF<30%) and history of administration of any kind of contrast agents or angiography during two days before the surgery were excluded from the study. Moreover, during the study, in any case of detecting a lactate level >45 mg dL^{-1} or a rise of more than 18 mg dL^{-1}, serum pH <7.25 or BE less than -6 mmol L^{-1}, arterial partial oxygen pressure <60 mmHg in two consecutive ABGs, K^+ level lower than 3 meq L^{-1}, nausea and vomiting, using medications that inhibit metformin metabolism such as amiodarone and cimetidine, administration of high doses of inotrope agents during three hours after extubation, prolonged intubation (more than 6 h after the surgery) and reoperation for any reason, the intervention would be stopped and the patients would be excluded from the study.

Patients who met these criteria were randomly assigned to two groups of insulin and insulin-metformin treatment each containing 50 patients.

Insulin therapy: Infusion of regular insulin according to the center's protocol with two placebo tablets (made in Pharmacology Laboratory of Mazandaran University of Medical Sciences) per 12 h.

Insulin-metformin therapy: Infusion of regular insulin according to the center's protocol with two metformin 500 mg tablets (Aria Co, Iran) per 12 h.

Therapy with metformin or its placebo was initiated three hours after extubation via oral administration if tolerated otherwise it was done through nasogastric tube. Other hypoglycemic agents were discontinued in all patients two days before the surgery and glucose control was performed by insulin with careful recording of the doses. The initiation of intervention and applying therapeutic protocols were simultaneous in both groups and their diets were similar (diabetic and cardiac according to hospital's routine). Interventional therapy protocols were performed for 60 h in all patients during which blood glucose, lactate level, pH and BE were measured every two hours and creatinine level was evaluated every 12 h. The study period was divided to five stages of 12 h and mean levels of the measured parameters were calculated for each stage.

This study was carried out double blinded and none of the patients, doctors, nurses and the laboratory staffs were aware of the type of therapy.

Glycemic control was the primary investigated outcome in this study. Blood glucose level between 100 to 150 mg dL^{-1} was considered acceptable. Hypoglycemia and acidosis were noticed as the two main complications. Data was analyzed using SPSS software version 16. Qualitative variables were assessed using chi-square test. After testing normal distribution in quantitative data using Kolmogorov-Smirnov test, comparisons between the two groups were performed by independent T-test. In order to compare the changes of measured parameters in each group and analysis of group interactions, repeated measure ANOVA test was used. Significancy was set at $p<0.05$.

RESULTS

A total of 100 patients entered the study, of which 50 were assigned to insulin therapy group and 50 to insulin-metformin therapy group. During the study seven patients were excluded and data from 93 patients were analyzed (Fig. 1).

Twenty two patients (46.8%) of the insulin group and 25 (54.3%) of the insulin-metformin group were men and the difference was not statistically significant. Moreover, no significant difference was found in the demographic and clinical characteristics of the two groups (Table 1).

Table 1: Demographic and clinical characteristics of patients in the two groups of insulin and insulin-metformin therapy

Characteristics	Insulin group (Mean±SD)	Insulin-metformin group (Mean±SD)	p-value
Age (year)	60.30±6.3	59.10±6.9	0.39
Body mass index (kg/m^2)	24.93±4.5	26.34±4.8	0.15
Mean arterial pressure (mmHg)	70.61±6.2	73.02±9.01	0.13
Ejection fraction (%)	45.53±8.54	48.10±7.27	0.12
Intubation time (h)	5.51±0.68	5.32±0.70	0.19

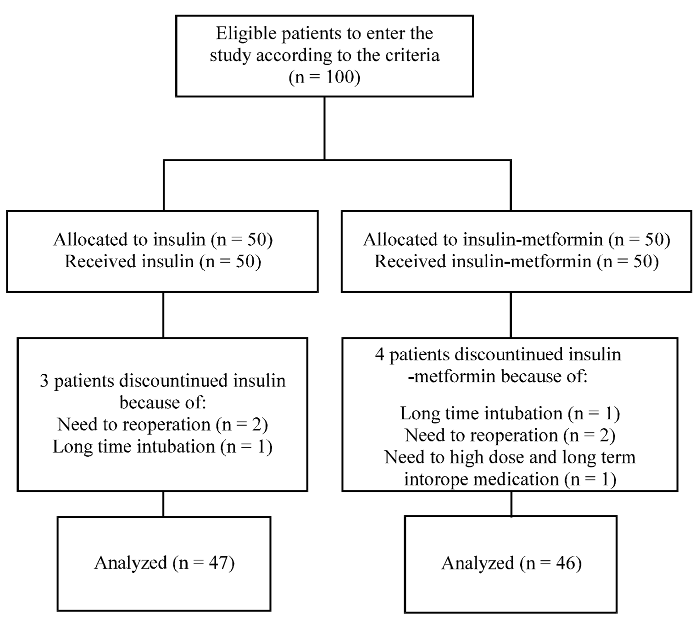

Fig. 1: Process of patient enrollment, random assignment and exclusion

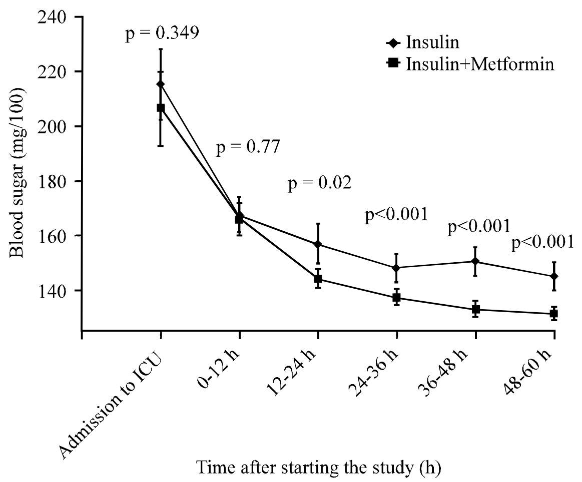

Fig. 2: Mean blood glucose level with 95% confidence interval in the two groups during the study period

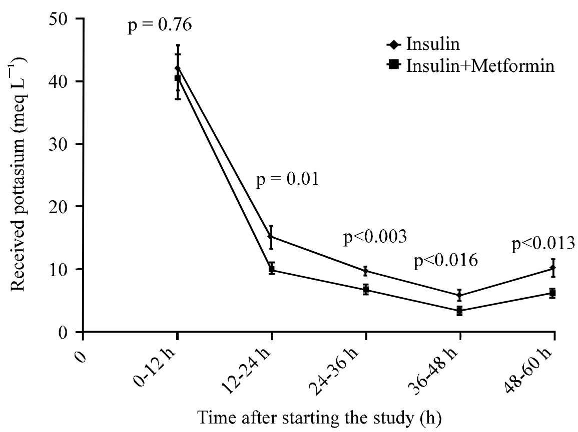

Fig. 3: Mean and standard error of mean potassium used in the two groups during the study period

At the beginning of the ICU admission, mean blood glucose was 215.4 (SD = 44.0) in insulin group and 206.8 (SD = 43.5) in insulin-metformin group ($p>0.05$). At the end of the study, mean blood glucose in insulin-metformin group was significantly lower than insulin group (145.1±18.0 vs. 131.6±7.9, $p<0.05$). As shown in Fig. 2, after twelve hours of the beginning of the therapeutic protocols, the patients' mean blood glucose levels were found significantly lower in insulin-metformin therapy group during the four subsequent stages. Moreover, scattering of blood glucose measures in insulin-metformin group was significantly lower than insulin group.

Twelve hours after the initiation of the study, results of the measurements demonstrated that during the proceeding four stages of the study, potassium level and insulin demand in insulin-metformin group were significantly lower than that of the insulin group (Fig. 3 and 4).

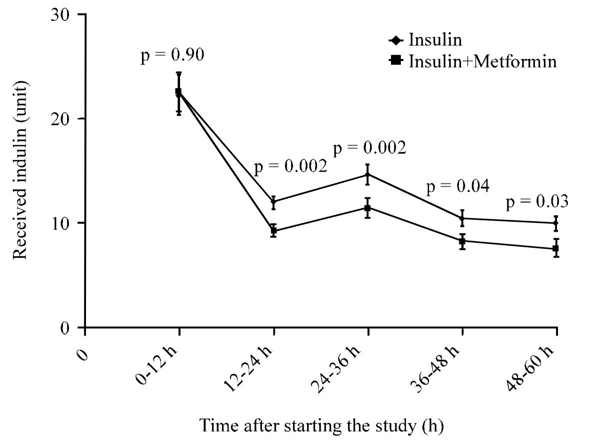

Fig. 4: Mean and standard error of mean insulin used in the two groups during the study period

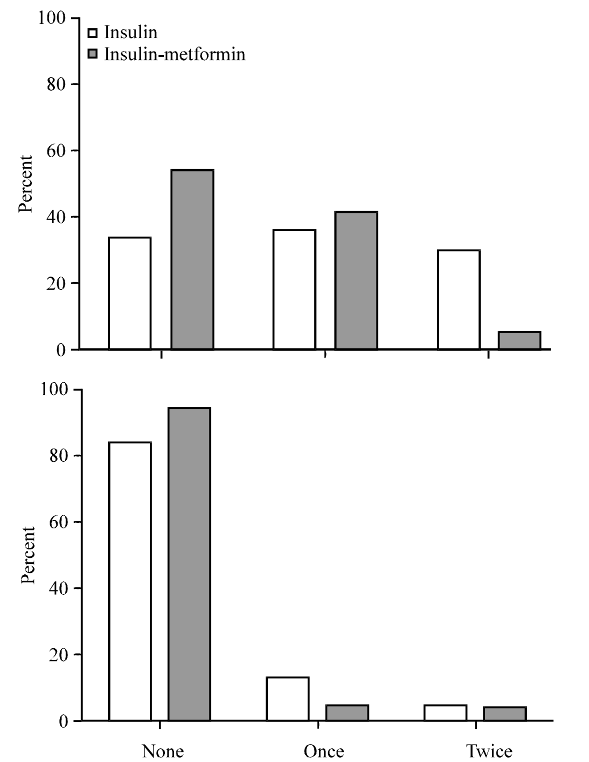

Fig. 5: Cases of hyperglycemia-higher than 200 mg dL^{-1}-(top) and hypoglycemia-lower than 75 mg dL^{-1}-(bottom) in the two study groups

As illustrated in Fig. 5, the mean number of hyperglycemic episodes (BS>200 mg dL^{-1}) detected in insulin group patients were significantly more than insulin-metformin group ($\chi^2 = 11.1$, $p = 0.004$). On the other hand, hypoglycemic episodes (BS<75 mg dL^{-1}) was detected in eight patients) 17%) in the insulin group while in insulin-metformin group, only three patients (6.5%) developed hypoglycemia ($p>0.05$).

Table 2: Comparison of the laboratory test results during the five 12-hour stages of the study in the two groups of insulin and insulin-metformin therapy

Tests	Group*	Firs stage	Second stage	Third stage	Fourth stage	Fifth stage	Group and time effect
Lactate	1	23.2±9.7**	21.9±9.7	19.7±9.7	16.8±7.2	19.7±5.9	$F_{(1,91)}$ = 0.031,
	2	24.0±9.7	22.5±10.1	20.4±9.6	17.6±6.7	19.9±6.1	p = 0.986
pH	1	7.35±0.038	7.39±0.047	7.42±0.049	7.42±0.037	7.41±0.046	$F_{(1,91)}$ = 0.190,
	2	7.35±0.037	7.39±0.050	7.42±0.048	7.42±0.037	7.42±0.042	p = 0.919
BE	1	-3.71±0.99	-0.94±1.2	-0.67±2.5	-0.36±2.4	-0.11±3.2	$F_{(1,91)}$ = 1.15,
	2	-3.63±1.01	-0.96±1.2	-0.93±2.37	-0.19±2.2	-0.32±3.0	p = 0.316
K^+	1	4.30±0.29	4.30±0.32	4.38±0.38	4.31±0.45	4.39±0.50	$F_{(1,91)}$ = 0.022,
	2	4.34±0.31	4.31±0.34	4.42±0.41	4.34±0.45	4.42±0.48	p = 0.993
Creatinine	1	0.89±0.19	0.94±0.26	1.0±0.19	0.98±0.24	1.0±0.23	$F_{(1,91)}$ = 0.126,
	2	0.91±0.19	0.94±0.26	1.0±0.21	1.0±0.23	1.0±0.24	p = 0.893

*Group 1: Insulin therapy; Group 2: Insulin-metformin therapy, **Data are presented as Mean±SD

Generally, the number of detected blood glucose levels out of the accepted range (100-150 mg dL^{-1}) was 8.4±3.6 in insulin group and 6.02±3 in insulin-metformin group for each patient and the difference was statistically significant (p = 0.001, t = 3.411). The mean measurements of k^+, lactate, pH, BE, creatinine performed during the study were not statistically significant (p>0.05) (Table 2). In the present study, the mean number of nursing interventions for controlling blood glucose, potassium and acidosis in insulin and insulin-metformin group for each patient were 46.9±8.4 and 43.5±6.2 times, respectively. Independent T-test also showed that the difference between the groups was statistically significant (p = 0.03, t = 2.21).

DISCUSSION

Findings of the present study indicate a better glycemic control in insulin-metformin group in comparison to insulin group. Furnary *et al*. (2003) conducted a follow-up study over 17 years on cardiac surgery patients and concluded that hyperglycemia is directly and significantly associated with increased mortality, deep sternum infection, hospital stays and costs. That is, for each 50 mg dL^{-1} rise in blood glucose level, there is a one-day increase in hospital stay (Furnary *et al*., 2004).

Present study was divided into five stages of twelve hours and mean glucose level and other measured parameters were determined for each of these stages in the two groups. The mean glucose level of the patients in the two groups for the first twelve hour period after the study initiation didn't differ significantly which seems logical considering the time needed for absorption and initiation of the therapeutic effect of metformin. However, during the next four stages, mean glucose level of insulin-metformin group was found to be significantly lower than the insulin group which might be due to reduced insulin resistance by metformin. In addition, scattering of blood glucose levels in insulin-metformin group was significantly lower in comparison to insulin group, reflecting metformin's efficacy in controlling the patients' glucose levels. Even when patients' glucose level is detected within the normal range, regardless of the glucose level, fluctuation of glucose level is found to be an independent predictor of mortality (Kavangh and McCowen, 2010).

Present results also showed that during all the stages of the study, except for the first twelve hour period, doses of insulin and potassium used in insulin-metformin group were significantly lower than insulin group; suggesting the positive effect of metformin. Since insulin therapy might result in hypokalemia and hypomagnesaemia via increased intracellular transportation of K^+ and Mg^{2+}, receiving lower doses of insulin might decrease these complications as well as the risk of hypoglycemia (Ansari *et al*., 2008). On the other hand, decreased blood levels of magnesium and potassium might promote insulin resistance (Huerta *et al*., 2005; Choi *et al*., 2001).

Consistent with our results, Mojtahedzadeh *et al*. (2008) found that a combination of insulin and metformin therapy results in significantly better glucose control and reduction in insulin usage compared to single insulin therapy and single metformin therapy in a study on general ICU patients.

In the present study, we found that hypoglycemia (BS<75 mg dL^{-1}) has occurred less frequent in insulin- metformin group than insulin group. In contrast to sulfonylurea, metformin does not increase insulin secretion and so hypoglycemia is not observed with its therapeutic doses even in non-diabetic patients (Giugliano *et al*., 1993; Campbell *et al*., 1996). In the study carried out by Ansari *et al*. (2008) the number of patients detected with mild hypoglycemia in insulin metformin group (n = 1) was less than insulin group (n = 3). Similarly, in this study hyperglycemia was significantly more common in insulin group than insulin-metformin group indicating metformin's positive effect in glycemic control of patients after CABG surgery. Considering the definition of the accepted range for blood glucose in this study (100-150 mg dL^{-1}), the number of blood glucose levels out of this range in insulin group was significantly higher than insulin-metformin group; supporting the advantageous effects of adding metformin to therapeutic regimen for glycemic control of patients after CABG surgery.

Another considerable finding was that the mean number of nursing intervention in order to check and control blood glucose and K^+ was significantly lower in insulin-metformin combination therapy leading to a lower nursing workload in this group. It was expected because the mean number of detecting hypoglycemia, hyperglycemia, blood glucose out of accepted range (100-150 mg dL^{-1}) and hypokalemia in insulin-metformin group were significantly lower than insulin group. Similarly in studies by Ansari *et al*. (2008) as well as Mojtahedzadeh *et al*. (2008) adding metformin to insulin therapy caused significant decrease in therapeutic interventions and nursing workload. High workload is a key job stressor of nurse in a variety of care setting, such as ICU (Hughes, 2008). Under a heavy workload, nurses may not have sufficient time to perform tasks which may bring about negative effects on patient safety (Ash *et al*., 2004).

During the study, changes in lactate level, pH and BE were not found to be significantly different between the two groups and no episode of lactic acidosis was recorded in any of the groups. In a study by Baradari *et al*. (2011) performed in patients undergoing CABG surgery and admitted in the open heart ICU, use of high-dose metformin (1,000 mg twice daily with insulin) didn't cause lactic acidosis in patients with type 2 diabetes. Mojtahedzadeh *et al*. (2008) also in their study investigating efficacy and safety of metformin in trauma patients admitted in ICU showed that there was no significant relation between metformin's plasma level, hypoglycemia, lactate level and pH in patients receiving metformin. No cases of lactic acidosis were detected during the study (Mojtahedzadeh *et al*., 2008). According to Ansari *et al*. (2008) study there wasn't any cases of lactate level rise or decrease in pH level in metformin-insulin therapy group. Metformin induced lactic acidosis is a rare complication with nearly 50% mortality rate. In order to decrease the risk, tight guidelines have been approved for metformin therapy (Duncan *et al*., 2007). Nevertheless, another study concluded that metformin causes the lactic acidosis since most of the patients having this complication during treatment with metformin had other underlying disorders such as cardiac, renal or hepatic failure which all might lead to lactic acidosis. Therefore they considered the lactic acidosis caused during metformin therapy as a coincident phenomenon with other underlying conditions (Lalau and Race, 2000; Kamber *et al*., 2008). In addition, this complication might not be a major concern in ICU patients, considering frequent continuous monitoring of all vital organs and compensations of any disturbances with intensive cares administered in these units (Ansari *et al*., 2008).

CONCLUSION

Given the better blood glucose control and no episodes of lactic acidosis in combined metformin and insulin therapy, lower doses of insulin and potassium used in this group and significant decrease in nursing workload, it seems that using metformin as an insulin sensitizing agent might be an appropriate option in postoperative glucose control protocols in diabetic patients undergoing CABG surgery.

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