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Research Article

The Effect of Preoperative Metformin on Postoperative Hyperglycemia in Non-Diabetic Patients: A Randomized Clinical Trial

*Arash Peyvandi Yazdi[1], Ebrahim Golmakani[1], Veghar Hejazi[1], Andia Peivandi Yazdi[2], Mehryar Taghavi Gilani[1]**

[1]*Lung Disease Research Center, Mashhad University of Medical Sciences, Mashhad, Iran.*

[2]*School of Dentistry, Mashhad University of Medical Sciences, Mashhad, Iran.*

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ABSTRACT

Background: Blood glucose control during surgery can decrease the infection, disability, and death rate. The purpose of this study was to determine the effect of preoperative metformin on blood glucose levels in nondiabetic orthopedic surgery.
Methods: This clinical trial was conducted on 176 nondiabetic patients with ASA class I or II who were candidates for orthopedic surgery. The patients were randomly divided into two equal groups. The metformin group received 500 mg metformin tablet orally and the placebo group received placebo tablet 30 minutes before the surgery. Blood glucose was measured every 6-hour to 24 hours and blood urine nitrogen (BUN), creatinine was measured preoperatively and the day after surgery. The data was analyzed by SPSS v21 and P value<0.05 was significant.
Results: Demographic characteristics such as age, sex and body mass index (BMI) had no significant difference in two groups. Creatinine and BUN were similar in two groups. Preoperative blood glucose was 101.8±22.6 mg/dl in the metformin group and 109.7±24.8 mg/dl in the control group without significant difference (p=0.08). However, BS at hours 6, 12, showed a significant difference between the two groups (p<0.001, 0.022) and then blood glucose was similar in two groups (0.8, 0.12 respectively).
Conclusion: Preoperative metformin (500 mg) was effective for blood glucose control in nondiabetic patients undergoing orthopedic surgery. However, additional research is required to determine the efficacy of this therapy.

Introduction

Hyperglycemia is defined as fasting plasma glucose more than 7.0 mmol/L (126 mg/dL) or two hours after a mealtime greater than 11.0 mmol/L (200 mg/dL) [1]. An acute or severe illness or surgery can cause transient hyperglycemia, also known as stress-induced or hospital-related hyperglycemia [1-2]. The hyperglycemia depends to the exent of surgery and the type of anesthesia [3]. Also, anatomic location, invasiveness of the procedure, intraoperative fluids and nutritional support have been linked to hyperglycemia. General anesthesia is more associated with hyperglycemia than local or epidural anesthesia due to high catecholamines, cortisol and glucagon [4]. Hyperglycemia disturbs the function of neutrophils, causes excessive production of reactive oxygen radicals, free fatty acids and inflammatory mediators. These pathophysiologic changes contribute to direct cellular damage, vascular and immune dysfunction [5].

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*Corresponding author.
E-mail address: taghavim@mums.ac.ir

The studies have shown that postoperative blood glucose control can reduce the risk of infection, disability, and mortality, speed up wound healing, and shorten hospital stays [6-7]. Also, the studies have shown that nondiabetic hyperglycemia is more lethal than diabetic hyperglycemia [8].

Rationale and knowledge gap

Currently, insulin is the only treatment available for acute hyperglycemia [9]. Research studies have demonstrated the benefits of using insulin to reduce the side effects of hyperglycemia in various surgical procedures [10-13]. But, the hypoglycemia is a significant side effect [14]. Metformin, a first-line oral antidiabetic, prevents hyperglycemia by accelerating tissue sensitivity to insulin and glucose clearance without affecting insulin secretion [15]. Metformin decreases chronic inflammation and increases lifespan as shown in several large preclinical retrospective clinical studies [16-17]. The use of metformin by non-diabetic peoples can reduce inflammation, protect against cardiovascular disease and cognitive impairment, and minimize risk of cancer, and prolong life. It also prevents endothelial dysfunction, promotes fibrinolysis, reduces lipids and regulates blood pressure [18]. Recent studies on metformine have shown a similar protective effect in nondiabetic cancer patients. However, the results are controversial [19].

Objective

Studies on metformin in postoperative sugar control in non-diabetic patients are limited. Accordingly, in this study, we sought to determine the effect of preoperative Metformin on the control of postoperative hyperglycemia in nondiabetics.

Methods

After approval by university ethical committee NO: IR.mums.medical.rec.1399.289 and regidtered NO: IRCT20111212008384N9, this clinical trial was conducted in educational hospital in 2019. The patients with ASA class I or II aged 18-80 years whom were candidates for femur surgery were chosen. Also, exclusion criteria included Metformin contraindications and allergia, such as acute or chronic renal failure, complicated surgical outcome, hemodynamic instability, addiction, need for second surgery within 24 hours. After informed consent, the 176 patients were randomly divided into two equal groups. The metformin group received 500 mg metformin tablet orally and the placebo group received placebo tablet 30 minutes before the surgery. Blood glucose, BUN, and creatinine were measured the day before surgery. Blood glucose was measured at first and every 6-hour in 24 hours and BUN, creatinine was measured the day after surgery. If blood glucose was more than 150 mg/dl, a unit of regular insulin for every 30 mg above 150, was prescribed subcutaneously. Moreover, symptoms such as vomiting, bloating, diarrhea, and lactic acidosis, were recorded.

The sample size was determined using GPower software with 88 subjects in each group considering the statistical power of 95% and the effect size of 0.5 with the significance level of alpha 5%, type I error = 0.05, and type II error = 0.95. The data was analyzed by SPSS v21 and P value<0.05 was significant. The data was analyzed with t-test, chi-square test, Fisher exact test and Mann-Whitney test.

Results

In the present study 176 nondiabetic patients who were candidtes for femur surgery in two equal group were evaluated. Demographic parameters such as age, sex and body mass index (BMI) were same and had not significant difference in two groups (Table 1).

Preoperative Cr was 0.95 mg/dl in the metformin group and 0.71 mg/dl in the control group, and postoperative Cr was 0.86 mg/dl in the Metformin and 0.74 mg/dl in the control group, none of which showed no significant difference (p= 0.098 and 0.069, respectively). Moreover, preoperative BUN was 26.58 mg/dl in the metformin group and 24.36 mg/dl in the control group, and postoperative BUN was 26.71 mg/dl in the metformin group and 25.34 mg/dl in the control group, which showed no significant difference between the two groups (p= 0.177 and 0.399, respectively) (Table 2).

BS was 101.8±22.6 mg/dl at baseline in the metformin group and 109.7±24.8 mg/dl in the control group. There was no significant difference between the first BS measurement of the two groups (p=0.08). However, a comparison of BS at hours 6, 12, 18, and 24 after surgery showed a significant difference between the two groups (p<0.001, 0.022, 0.8, 0.12 respectively). (Table 3) shows the amounts of BS after surgery.

Insulin consumption in two groups is shown in (Table 4). At 6 and 12 hours, the amount of insulin used in the metformin group was lower than the control group and significant (P=0.005 and 0.008 respectively). But there was no meaningful difference in the other times.

Table 1- Demographic parameters in two groups

Background parameters	Metformin group	Control group	P value
Gender (male: female)	26/62	37/51	0.3
Age (mean,year)	58.1±12.3	53.3±16.4	0.45
BMI (kg/cm2)	25.01± 5.52	23.06± 5.29	0.058

Table 2- Changes of Cr and BUN after the surgery in the metformin group Mean± Sd

Parameters	Metformin group	Control group	P value
Creatinine before the surgery	0.95 ± 0.90	0.71 ± 0.18	0.098
Creatinine after the surgery	0.86 ± 0.41	0.74 ± 0.21	0.069
BUN before the surgery	26.58 ± 9.39	24.36 ± 7.53	0.177
BUN after the surgery	26.71 ± 9.41	25.34 ± 7.32	0.399

Table 3- Comparison of blood glucose in two independent groups Mean ± SD

BS mg/dl (hours after surgery)	Metformin group	Control group	P value
BS (0)	101.8±22.6	109.7±24.8	0.35
BS (6)	117.8±19.1	141.3±33.4	<0.001
BS (12)	113.2±16.3	140.4±26.5	0.022
BS (18)	105.7±21.1	130.7±21.3	0.80
BS (24)	97.6±14.9	110.1±17.9	0.12

Table 4- Insulin consumption in two groups. N (%)

Insulin usage time (hours)	Metformin group	Control group	P value
0	1(1.1%)	4 (4.5%)	0.059
6	6 (6.8%)	16 (18.3%)	0.005
12	1 (1.1%)	8 (9.1%)	0.008
18	1 (1.1%)	3 (3.4%)	0.154
24	1(1.1%)	1 (1.1%)	0.65

Discussion

This present study showed that preoperative oral administration of Metformin at a dosage of 500 mg caused a significant improvement in postoperative blood glucose. Moreover, the highest amount of BS was 141.3±33.4 mg/dl in the control group and 117.8±19.1 mg/dl in the metformin group after 6 hours.

Strengths and limitations

Although this study was one of the few examining hyperglycemia in nondiabetics undergoing orthopedic surgery, it had limitations. Our study was the absence of a comparison group receiving insulin. Thus, we recommend that future studies perform similar research on Metformin and insulin-receiving subjects with matched control and intervention groups in terms of background data. Our study population was small due to lack of time; if these cases are studied in a larger community in a study, it can significantly reduce the research error.

Comparison with similar researches

A few studies have evaluated the preoperative metformin administration in nondiabetic patients, and mainly the diabetic patients have been studied more. Ghods et al. studied the effects of insulin and metformin administration in nondiabetic patients before coronary artery bypass surgery. Their results showed that both insulin and Metformin significantly decrease post-surgical BS levels. Moreover, they showed no significant difference between two methods of hyperglycemia prevention. However, they used a dosage of 500 mg bid before the surgery, and the surgery in their study was different from present study [8]. Also, Mojtahedzade et al. compared the effects of insulin and Metformin in decreasing post-surgical hyperglycemia in nondiabetic critically ill patients. They showed that both methods effectively controlled postoperative blood glucose, but insulin was more effective than Metformin. In their study was seen any hypoglycemia, despite using insulin in their study [22]. In one study in 2011 was been showed that the highest BS was detected at 199.8 ± 43.2 in the control group at 6 hours post-surgery and 194.8 ± 41.2 in the insulin group at 4 hours post-surgery [23], but in our study was showed that the highest amount of BS was 141.3±33.4 mg/dl in the control group and 117.8±19.1 mg/dl in the metformin group after 6 hours. Nevertheless, considering the different backgrounds of the subjects and the operations in the two studies, this difference could not regard as significant. In other study on 2008, they reported that the incidence of hyperglycemia was 95% in nondiabetic patients after CABG. In this study the BS levels were 225.24 ± 44.26 mg/dl in the insulin group and 221.80 ± 39.76 mg/dl in the metformin group after transfer to the ICU without significant difference was between the two study groups [24]. Liao et al. showed that the BS level in nondiabetic CPB surgery patients was 194 ± 50 mg/dl and in our study the highest BS level in the metformin group was 170 mg/dl [25].

Explanations of findings

Postoperative hyperglycemia increases risk of complications. Therefore, in the perioperative period, blood glucose monitoring and treatment are advised, and adjusted with subcutaneous insulin usage, intravenous

insulin infusion, or insulin pumps. Additionally, glucocorticoids administration via intravenous or perineural routes is associated with higher blood glucose levels, and clinicians should weigh the risk-benefit ratio in surgical patients [20]. Recent trials have shown that strict control, per se, may aggravate complications, plus that strict fasting plasma glucose control did not result in a significant reduction in complications compared to the control groups [12-13]. Metformin is an oral biguanid agent, which reduces blood glucose level in non–insulin-dependent diabetes mellitus in Europe since 1957 and in the United States since 1995. In type 2 diabetic patients, metformin suppresses endogenous glucose production, gluconeogenesis in the liver, glucose absorption in the digestive tract, and also increases glucose uptake in the muscles and fat tissue, does not increase insulin secretion and its release from the pancreas. The antihyperglycemic action of metformin is due to suppression of endogenous glucose production in patients with type 2 diabetes [8]. Metformin also have beneficial effects on lipids, fibrinolysis, endothelial dysfunction, and blood pressure. Metformin effectively reduces patients' body weight and insulin demand, and also improves glycemic control without hypoglycemia [12]. The absolute contraindications to the metformin are renal insufficiency, severe heart failure, and metabolic acidosis. On the contrary, recent studies show that metformin ingestion may be beneficial for patients with isolated cardiac insufficiency [21].

Implications and actions needed

The use of metformin 500 mg in non-diabetic patients control blood glucose, especially in the first hours after surgery, and it can be used in patients with complex surgeries to reduce postoperative complications due to hyperglycemia.

Conclusion

In nondiabetic individuals undergoing orthopedic surgery, 500 mg metformin may be beneficial. As a result, metformin usage in this population of patients can be regarded as a therapy option for hyperglycemia management. However, further research is necessary to determine the effectiveness of this therapy.

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