Original Article

The Effect of Perioperative Magnesium Sulfate on Blood Sugar in Patients with Diabetes Mellitus Undergoing Cardiac Surgery: A Double-Blinded Randomized Study

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Abstract

Objective: The aim of the present study was to evaluate the perioperative effect of magnesium infusion on blood sugar level in patients with diabetes mellitus undergoing cardiac surgery. **Design:** This was a double-blind randomized study. **Setting:** The study was conducted at cardiac center. **Patients:** The study included 122 adult patients. **Intervention:** Group M – The patients received a continuous infusion of magnesium sulfate (without a loading dose) at 15 mg/kg/h. The infusion rate was started 20 min before induction maintained during surgery and the first postoperative 24 h. The medication was prepared by adding 5 g magnesium sulfate in 50 ml syringe. Group C – The patients received equal amount of normal saline. **Measurements:** The monitors included heart rate, mean arterial blood pressure, central venous pressure, urine output, blood levels of magnesium, sugar, and potassium. **Results:** The blood sugar level and the required insulin significantly decreased with Group M than Group C ($P < 0.05$). There were minimal changes in the potassium level in Group M, but potassium decreased in patients of Group C ($P < 0.05$). The amount of urine output was too much higher in Group M than Group C ($P < 0.05$). The pharmacological and mechanical support significantly decreased with Group M than Group C ($P < 0.05$). The hospital and Intensive Care Unit length of stay significantly decreased with Group M than Group C ($P < 0.05$). **Conclusion:** The magnesium sulfate produced a better-controlled effect on the blood sugar level. It decreased the requirement of insulin infusion and minimized the changes in the blood level of potassium.

Keywords: *Blood sugar, cardiac surgery, diabetes mellitus, insulin, magnesium sulfate, potassium*

Introduction

Hyperglycemia is a frequent complication during cardiac surgery with cardiopulmonary bypass (CPB). The causes of hyperglycemia may be related to many factors; first: the reduced levels of blood insulin as a result of nonpulsatile flow during CPB and hypoperfusion of some vital organs such as the pancreas, thereby reducing the production and release of insulin by pancreas;[1] second: the adsorption of insulin to the CPB circuit;[2] and third: the insulin resistance.[3]

Magnesium is one of the cofactors that regulate blood glucose control by improving the insulin response and action as a result of the increased affinity of insulin to its receptors.[4-6] Hypomagnesemia is associated with insulin resistance and hyperglycemia.[5-8]

Perioperative factors that lead to hypomagnesemia such as the renal loss of magnesium (diuretics and digitalis), preoperative proton-pump inhibitors hemodilution, blood loss, blood transfusions, administration of large doses of calcium, the catecholamines that cause chelation of magnesium, intracellular shifts induced by the extracorporeal circulation, and the hypothermia during surgery.[9-11]

The aim of the present study was done to evaluate the perioperative effect of magnesium infusion on blood sugar level in patients with diabetes mellitus undergoing cardiac surgery.

Outcomes

The primary outcome was the efficacy of magnesium infusion in reducing the blood glucose levels. A secondary outcome was the requirement for insulin infusion in addition to the safety of the study medication, which was assessed by the occurrence of any adverse events.

Sample size calculation

Power analysis was performed using the Chi-square test for independent samples

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on the frequency of patients associated with elevated perioperative blood glucose levels because it was the main outcome variable in the present study. A pilot study was done before starting this study because there are no available data in the literature for the perioperative effect of magnesium infusion on blood sugar level in patients undergoing cardiac surgery. The results of the pilot study (16 patients in each group) showed that the perioperative blood sugar level increased in 31.25% of magnesium group and 56.25% of the control group. Taking power 0.8, alpha error 0.05, and beta 0.2, a minimum sample size of 61 patients was calculated for each group.

Patients

After obtaining informed consent and approval of local ethics and research committee, a double-blinded randomized study included 122 diabetic patients undergoing cardiac surgery using CPB. The inclusion criteria were adult patients with diabetes mellitus, ejection fraction >40%). Exclusion criteria included patients with congestive heart failure, acute myocardial infarction, emergency, redo cases, malfunctioning artificial heart valve, obstructive cardiomyopathy, heart rate <50 bpm, pericardial disease, and renal or hepatic impairment. The patients were randomly allocated into two equal groups (n = 61 each). The concealment of allocation was done using random numbers generated through Excel. The study medications were prepared in 50 ml syringe and the infusion started by the staff nurse according to the study protocol and the anesthetist was blinded to the contents of the syringe and the name of the medication infused by the syringe pump.

- Group M – (Magnesium sulfate group). The patients received a continuous infusion of magnesium sulfate (without a loading dose) at 15 mg/kg/h. The infusion rate was started 20 min before induction maintained during surgery and the first postoperative 24 h. The medication was prepared by adding 5 g magnesium sulfate in 50 ml syringe
- Group C– (Control group). The patients received equal amount of normal saline.

Anesthetic technique

For all patients and under local anesthesia, a radial arterial cannula and central venous line were inserted before operation to enable continuous hemodynamic monitoring. Induction was done by intravenous fentanyl (3–5 μg/kg), etomidate (0.3 mg/kg), and rocuronium (0.8 mg/kg). The anesthesia was maintained with oxygen/air (50%), sevoflurane (1%–3%), fentanyl infusion (1–3 μg/kg/h), and cisatracurium (1–2 μg/kg/min). CPB was established with cannulation of the ascending aorta and right atrium. Hemofiltration was done before weaning from CPB to induce hemoconcentration. At the end of surgical intervention, the patients were prepared for weaning from CBP. If there was difficulty to wean from CPB, pharmacological support (dopamine, epinephrine or norepinephrine, nitroglycerine) or mechanical support intra-aortic balloon pump (IABP) was started. During anesthesia, the elevated blood sugar (>10 mmol/L) was controlled by insulin infusion (insulin infusion was started 2 units/h and the dose was modified every 30 min), and if the blood sugar levels decreased below 10 mmol/L, the insulin infusion was discontinued. At the end of surgery, the patients were transferred to cardiac surgery Intensive Care Unit (ICU) with full monitoring.

Monitoring of patients

Hemodynamic monitoring included the heart rate, mean arterial blood pressure, a continuous electrocardiograph with automatic ST-segment analysis (leads II and V), central venous pressure, urine output, blood levels of magnesium, sugar, and potassium. Furthermore, the required pharmacological and mechanical support was collected.

The values were serially collected at the following timepoints: T0: Baseline reading (before starting the administration of study medication); T1: Reading 15 min after induction; T2: Reading before CPB; T3: Reading 30 min after CPB; T4: Reading at ICU admission; T5: Reading 6^{th} h after ICU admission; T6: reading 12^{th} h after ICU admission; T7: Reading 24^{th} h after ICU admission.

Statistical analysis

Data were statistically described in terms of mean ± standard deviation, or frequencies (number of cases) and percentages when appropriate. Comparison of numerical variables between the study groups was done using the Student t-test for independent samples. Repeated measure ANOVA was used to see the effect of magnesium on the blood sugar levels at different follow-up intervals. For comparing categorical data, Chi-square test was performed. Exact test was used instead when the expected frequency is <5. P < 0.05 was considered statistically significant. All statistical calculations were done using computer program SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

Table 1 shows no significant differences regarding the demographic data, comorbidities, preoperative medications, New York Heart Association class, Euroscore, and the American Society of Anesthesiologists physical status score (P > 0.05).

Table 2 shows the changes in the blood levels of magnesium, potassium, and sugar in addition to the insulin requirement. There was no difference in the preoperative blood levels of magnesium, potassium, and sugar between the two groups (P > 0.05). After magnesium sulfate infusion, the blood magnesium level increased significantly in Group M than Group C and the difference between the two groups was statistically significant (P < 0.05). After

Table 1: Preoperative data of patients (Data are presented as mean±SD, Number, %)

Variable	Group M (*n*=61)	Group C (*n*=61)	*P*
Age (year)	55.70±12.62	56.15±13.25	0.848
Weight (Kg)	87.82±13.55	86.57±12.95	0.603
Gender			
Male:Female	37:24	40:21	0.707
Diabetes mellitus			
Total number	61	61	1.000
Oral hypoglycemic	32	37	0.465
Insulin	12	9	0.632
Oral hypoglycemic and insulin	17	15	0.837
Hypertension	47	52	0.485
Ischemic heart diseases	33	29	0.587
Valvular diseases	13	18	0.405
Ischemic heart diseases and Valvular diseases	15	14	0.727
Atrial fibrillation	25	29	0.584
Ejection fraction (%)	48.90±7.35	50.56±6.70	0.194
Diuretics	38	33	0.081
Angiotensin-converting-enzyme inhibitors	23	19	0.567
Beta-blockers	45	49	0.518
Calcium channels-blockers	30	27	0.716
Aspirin	48	42	0.405
Statins	23	20	0.704
Stroke	-	-	-
Carotid stenosis			
<50%	21	16	0.431
Unilateral	7	4	0.529
Bilateral	15	12	0.663
Smoking			
Current smokers	17	20	0.694
Ex-smokers	24	28	0.583
NYHA			
II	18	25	0.255
III	28	25	0.715
IV	15	11	0.507
ASA			
III: IV	45:16	49:12	0.518
Euroscore (%)	9.15±3.50	8.43±3.10	0.231
Hematocrit (%)	38.74±2.25	39.15±2.36	0.328
Hemoglobin A1c (%)	5.72±1.10	5.62±1.08	0.613
Body surface area (m²)	1.75±0.26	1.71±0.22	0.360

NYHA: New York Heart Association; ASA: American Society of Anesthesiologists Physical Status Score; CABG: Coronary artery bypasses grafting Group M: Magnesium sulphate group; Group C: Control group

induction, the blood sugar level increased in the patients of the two groups, but the increase was significantly lower in Group M than Group C ($P < 0.05$). Therefore, the number of patients who required insulin to manage the elevated blood sugar level was lower in Group M than Group C, and also the dose of insulin was lower in Group M than Group C ($P < 0.05$). There were minimal changes in the blood level of potassium in Group M and a significant decrease in the potassium level in the Group C and the difference between the two groups was significant ($P < 0.05$).

Table 3 shows the changes in the heart rate, mean arterial blood pressure, and central venous pressure of patients during the procedure and through the first 24 h in the ICU. There was no significant difference in the preoperative heart rate, mean arterial blood pressure, and central venous pressure. After drug infusion (T1), the heart rate decreased in Group M and increased in patients of Group C and the difference between the two groups was statistically significant ($P < 0.05$). There were minimal changes in the mean arterial blood pressure in patients of the Group M and an increase in the mean arterial blood pressure in patients

Table 2: Blood magnesium, potassium, and sugar levels, insulin requirement (Data are presented as mean±SD, Number)

Variable	Group M (*n*=61)	Group C (*n*=61)	*P*
Blood magnesium levels (mmol/L)			
T0	1.15±0.14	1.16±0.17	0.691
T1	2.13±0.27	1.25±0.20	0.001*
T2	2.27±0.29	1.23±0.22	0.001*
T3	2.35±0.30	1.26±0.25	0.001*
T4	2.40±0.38	1.25±0.27	0.001*
T5	2.45±0.41	1.22±0.15	0.001*
T6	2.43±0.37	1.27±0.21	0.001*
T7	2.48±0.43	1.24±0.28	0.001*
Blood sugar levels (mmol/L)			
T0	7.25±1.30	7.13±1.23	0.601
T1	8.17±1.19	8.38±1.26	0.345
T2	8.69±1.43	9.35±1.48	0.013*
T3	8.91±1.46	9.60±1.50	0.011*
T4	8.86±1.48	9.67±1.52	0.003*
T5	8.98±1.52	9.70±1.56	0.011*
T6	9.10±1.68	10.01±1.79	0.004*
T7	8.55±1.60	10.26±2.14	0.001*
Blood potassium levels (mEq/L)			
T0	4.48±0.33	4.53±0.34	0.411
T1	4.23±0.30	4.30±0.32	0.215
T2	4.25±0.32	4.12±0.31	0.024
T3	4.10±0.27	3.87±0.30	0.001*
T4	4.12±0.30	3.95±0.32	0.003*
T5	4.17±0.32	3.86±0.29	0.001*
T6	4.04±0.28	3.91±0.27	0.010*
T7	4,15±0.30	3.75±0.25	0.001*
Insulin requirement			
Number	23	48	0.006*
Dose (unit/hr)	3.12±1.03	5.25±2.15	0.001*

**P*<0.05 significant comparison between the two groups Group M: Magnesium sulphate group; Group C: Control group T0: Baseline reading; T1: 15 minutes after induction; T2: before cardiopulmonary bypass; T3:30 minutes after cardiopulmonary bypass; T4: on ICU admission; T5: 6th hour after ICU admission; T6: 12th hour after ICU admission; T7: 24th hour after ICU admission

Table 3: Heart rate, mean arterial blood pressure and central venous pressure of patients (Data are presented as mean±SD)

Variable	Group M (*n*=61)	Group C (*n*=61)	*P*
Heart rate (bpm)			
T0	76.42±12.57	75.38±11.95	0.640
T1	73.64±11.15	77.80±11.00	0.040*
T2	72.45±10.20	78.17±10.12	0.002*
T3	71.57±9.40	79.30±11.50	0.001*
T4	72.48±9.60	79.60±10.36	0.001*
T5	72.37±10.04	78.10±11.00	0.003*
T6	73.20±10.10	77.55±12.69	0.038*
T7	72.44±10.90	78.06±12.26	0.012*
Mean arterial blood pressure (mmHg)			
T0	106.20±15.10	104.70±14.97	0.582
T1	104.30±14.18	109.90±15.70	0.040*
T2	103.17±14.46	110.38±15.08	0.013*
T3	104.66±15.90	112.00±16.20	0.012*
T4	102.94±15.25	111.20±16.10	0.004*
T5	105.40±14.00	114.11±16.50	0.002*
T6	106.22±15.70	113.90±17.40	0.011*
T7	104.50±13.96	115.00±16.80	0.010*
Central venous pressure (mmHg)			
T0	9.78±1.61	10.03±1.37	0.357
T1	11.56±1.35	11.80±1.48	0.351
T2	12.20±1.43	12.68±1.60	0.083
T3	12.88±1.44	13.15±1.48	0.309
T4	13.18±1.70	13.72±1.61	0.074
T5	13.47±1.34	13.73±1.44	0.304
T6	13.15±1.25	12.80±1.52	0.167
T7	12.40±1.24	12.67±1.33	0.248

**P*<0.05 significant comparison between the two groups.Group M: Magnesium sulphate group; Group C: Control group T0: Baseline reading; T1: 15 minutes after induction; T2: before cardiopulmonary bypass; T3:30 minutes after cardiopulmonary bypass; T4: on ICU admission; T5: 6th hour after ICU admission; T6: 12th hour after ICU admission; T7: 24th hour after ICU admission.

of Group C and the difference between the two groups was statistically significant ($P < 0.05$). There was no change in the central venous pressure of patients between the two groups ($P > 0.05$).

Table 4 shows the intraoperative data and outcomes of patients of the two groups. There was no difference in the CPB time, cross-clamping time, blood loss, transfused perioperative fluids, transfused packed-red blood cells, hematocrit value, pacing, and IABP between the two groups ($P > 0.05$). The volume of fluid removed by hemofiltration was lower in Group M than Group C ($P = 0.016$). The weaning from CPB was easier in patients of the Group M than the Group C. Patients of Group M needed smaller doses of pharmacological support (dopamine, epinephrine, norepinephrine, and nitroglycerine) than the Group C ($P < 0.05$). The incidence of postoperative arrhythmias (atrial fibrillation and ventricular extrasystole) was lower in the Group M than the Group C ($P = 0.044$ and $P = 0.032$, respectively). The amount of intraoperative urine output was higher in Group M than Group C ($P = 0.001$). The ICU and hospital length of stay were shorter in the patients of Group M than Group C ($P = 0.029$ and $P = 0.040$, respectively). There was no neurological or pulmonary complication in the patients of the two groups. There was no significant difference regarding the incidence of mortality between the two groups ($P = 0.647$).

Table 4: Intraoperative data and outcome of patients (Data are presented as mean±SD, Number, %)

Variable	Group M (*n*=61)	Group C (*n*=61)	*P*
CABG	33	29	0.587
Valvular surgery	13	18	0.405
CABG and Valvular surgery	15	14	0.727
CPB time (minute)	112.46±22.87	108.30±24.28	0.332
Cross clamping time (minute)	90.75±20.46	88.37±17.10	0.487
Dopamine (μg/kg/min)	6.64±1.28	7.15±1.36	0.035*
Epinephrine (μg/kg/min)	0.04±0.02	0.05±0.03	0.032*
Norepinephrine (μg/kg/min)	0.05±0.02	0.06±0.03	0.030*
Nitroglycerine (μg/kg/min)	0.55±0.43	0.75±0.54	0.025*
Intra-aortic balloon pump	4	7	0.529
Pacing	15	11	0.507
Transfused P-RBC			
Number of patients	55	52	0.582
Number of units	2.57±0.60	2.43±0.51	0.167
Hematocrit (%)	35.96±2.55	36.57±2.46	0.181
Blood loss (ml)			
Intraoperative (ml)	1550.30±243.78	1497.41±226.20	0.216
Postoperative (ml/24 hr)	552.10±134.20	536.65±126.30	0.513
Intraoperative fluids			
Crystalloids (ml)			
Ringer	1560.89±327.14	1495.70±318.35	0.266
Saline 0.9%	1450.30±290.20	1470.10±310.60	0.716
Hesteril 6%	525.20±112.36	550.50±119.10	0.229
Postoperative fluids 24 hour			
Crystalloids (ml)			
Ringer	2240.38±520.15	2184.75±480.95	0.540
Saline 0.9%	2160.30±450.10	2210.40±415.48	0.524
Hesteril 6%	750.17±230.50	810.30±260.40	0.179
Intraoperative urine output (ml)	2108.60±275.40	1780.30±220.45	0.001*
Hemofiltration [Fluid removal (L)]	870.64±157.20	945.30±179.66	0.016
Atrial fibrillation	12	23	0.044*
Ventricular extrasystole	6	16	0.032*
Neurological	-	-	-
pulmonary complications	-	45	-
ICU length of stay (days)	4.65±1.53	5.27±1.58	0.029*
Hospital length of stay (days)	10.00±2.30	10.96±2.80	0.040*
Mortality	2	3	0.647

*$P<0.05$ significant comparison between the two groups.CPB: Cardiopulmonary bypass; P-RBC: Packed- red blood cells; ICU: Intensive care unit.Group M: Magnesium sulphate group; Group C: Control group T0: Baseline reading; T1: 15 minutes after induction; T2: before cardiopulmonary bypass; T3:30 minutes after cardiopulmonary bypass; T4: on ICU admission; T5: 6th hour after ICU admission; T6: 12th hour after ICU admission; T7: 24th hour after ICU admission.

Discussion

The present study showed that the perioperative magnesium infusion led to a better control of blood sugar level in patients with diabetes who underwent cardiac surgery and it decreases the requirement for insulin to manage the elevated blood sugar. Therefore, the controlled blood sugar and decreased insulin requirement minimized the change in potassium level and the incidence of arrhythmia. Furthermore, it decreased the requirement for pharmacological support for the blood pressure during and after weaning from the CPB.

The decreased blood sugar level in Group M may be as a result of increased insulin sensitivity or the increased insulin production after magnesium sulfate administration, but the insulin level was not measured during the study and other studies support this opinion.[12-14] Rosolová *et al*.[14] reported that the blood insulin level increases with the elevated blood level of magnesium and also the study showed that the hypomagnesemia was associated with insulin resistance and glucose intolerance.

Magnesium decreases the blood sugar levels through many mechanisms; (1) by improving the insulin response and action as a result of the increased affinity of insulin to its receptors;[4-6] (2) it affects the insulin secretion from the pancreas;[15] (3) It potentiates the insulin-mediated-glucose-uptake;[16-19] (4) it has a role in the regulation of glycogenolysis and glucose output in the liver;[20] (5) it decreases the release of catabolic hormones such as catecholamines, thyroid hormone, and cortisol, that increase glycogenolysis and gluconeogenesis;[21] (6) magnesium may directly affect the glucose transporter protein activity and help to regulate glucose translocation into the cell.[4]

Many studies showed that magnesium supplementation increased the insulin sensitivity and decreased the blood sugar level,[8,22-27] but these studies were not done in cardiac surgery.

Kieboom *et al*.[28] showed that magnesium-regulating genes modify the diabetes risk through serum magnesium levels and the role of magnesium in the development of diabetes is mediated through insulin resistance.

One study showed that low serum magnesium levels in children and adolescents with Type-1 diabetes mellitus are associated with an increased risk of poor glycemic control as measured by blood level of hemoglobin A1c,[29] and another study showed that a significant relationship between the increase in serum and cellular magnesium and the insulin sensitivity.[30]

A study done by Galli-Tsinopoulou *et al*.[29] showed that a higher magnesium intake reduces the risk of impaired glucose and insulin metabolism and progression from prediabetes to diabetes.

Magnesium sulfate increased the urine output as a result of inhibition of the catecholamines and vasopressin release, therefore producing renal vasodilatation and increasing the renal blood flow and urine output,[31-33] and this may increase the urinary excretion of glucose.

Against the present findings, another study showed that magnesium replacement has no effect on the insulin resistance.[34]

The present study showed the level of potassium was maintained in Group M while decreased in Group C and this may be related to the decreased blood sugar, insulin infusion, and catecholamines infusion which decrease the intracellular shift of potassium and maintaining the level of potassium in Group M. While the increased blood sugar,[35] insulin infusion[36] and catecholamines infusion[37] increase the intracellular shift of potassium and decreasing the level of potassium in Group C.

There are limitations to the present study. First, the blood insulin level was not measured as the kits were not available in the main laboratory during the study; second, small study populations of the present study; and third, limited researchers talking about the same topics as the present study to discuss these findings in details.

Conclusion

The magnesium sulfate produced a better-controlled effect on the blood sugar level. It decreased the requirement of insulin infusion and minimized the changes in the blood level of potassium.

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Conflicts of interest

There are no conflicts of interest.

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