Recent Metformin Ingestion Does Not Increase In-Hospital Morbidity or Mortality After Cardiac Surgery

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BACKGROUND: Perioperative treatment of type 2 diabetes with metformin, an oral hypoglycemic drug, is thought to increase the risk of life-threatening postoperative lactic acidosis. In contrast, metformin improves serum glucose control and has beneficial cardiovascular effects, which may decrease the risk of adverse outcomes. In this investigation we sought to determine the influence of metformin treatment on mortality and morbidity compared with treatment with other oral hypoglycemic drugs in diabetic patients undergoing cardiac surgery.

METHODS: In this retrospective investigation, 1284 diabetic patients, with recent oral hypoglycemic ingestion (presumed to be 8–24 h preoperatively), underwent cardiac surgery from 1994–2004. Propensity scores were calculated from a logistic model which included baseline characteristics and perioperative variables. Four-hundred-forty-three (85%) of the metformin-treated patients were matched on nearest propensity score using greedy matching techniques with 443 nonmetformin-treated patients. Postoperative outcomes were compared between matched metformin- and nonmetformin-treated patients.

RESULTS: In-hospital mortality, cardiac, renal, and neurologic morbidities were similar between groups. Metformin-treated patients had less postoperative prolonged tracheal intubation [OR (95% CI), 0.3 (0.1, 0.7), $P = 0.003$], infection [0.2 (0.1, 0.7), $P = 0.007$] and overall morbidities [0.4 (0.2, 0.8), $P = 0.005$].

CONCLUSIONS: These data suggest that recent metformin ingestion is not associated with increased risk of adverse outcome in cardiac surgical patients. Alternatively, metformin treatment may have beneficial effects.

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Metformin, an oral hypoglycemic drug, is widely used for treatment of type 2 diabetes mellitus. Metformin lowers blood glucose levels by sensitizing target tissues to insulin, inhibits hepatic glucose production, and increases peripheral glucose uptake (1). Metformin is similar in chemical structure to phenformin, which was removed from the United States market because of an unacceptably high incidence of life-threatening lactic acidosis. Lactic acidosis has also been associated with metformin, but at a 10–20-fold lower rate [3–8 cases per 100,000 patient-years (1,2)]. Although this complication is rare, metformin-associated lactic acidosis is associated with a mortality of approximately 50% (1).

To decrease the risk of lactic acidosis, strict prescribing guidelines for metformin therapy have been developed (3). Absolute contraindications include renal insufficiency, congestive heart failure, and metabolic acidosis. Relative contraindications include conditions associated with hypoxemia and hypovolemia, such as those that may occur in the perioperative period. Indeed, perioperative metformin-associated lactic acidosis has been reported (4,5). Moreover, diabetic patients are already at increased risk for lactic acidosis (6) and other adverse outcomes (7,8) after cardiac surgery. Current guidelines which aim to decrease the risk of perioperative lactic acidosis are controversial. Some reports recommend discontinuing metformin treatment for up to 48 h before surgery (4,5,9). Yet, others disagree (10). In addition, the incidence of lactic acidosis has been reported only during chronic administration of metformin (measured in patient-years), which makes it difficult to quantify the risk for lactic acidosis in patients undergoing a specific, high-risk event, such as cardiac surgery. Improved guidelines regarding use of metformin in the perioperative period are clearly warranted.

Despite these risks, metformin provides effective glucose control in the perioperative period, which may be jeopardized with early discontinuation. Certainly, effective treatment of hyperglycemia in the perioperative period may decrease the risk of postoperative mortality

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and morbidity (11,12). In addition, chronic therapy with metformin has favorable effects on other cardiovascular risk factors (2,13,14).

The objective of this investigation was to determine whether the frequency of adverse outcomes are higher for metformin-treated diabetic patients after major cardiac surgery compared with patients receiving other oral hypoglycemic therapy. In addition, we evaluated whether characteristics of patients currently treated with metformin conformed to strict published guidelines for metformin therapy.

METHODS

Patient Population and Data Collection

Patient data were obtained from the Cardiothoracic Anesthesia Patient Registry of the Department of Cardiothoracic Anesthesia at the Cleveland Clinic using methods which have been reported previously (15). Research use of this Registry was approved by the IRB. All data were collected daily, concurrent with patient care on preprinted forms, by experienced and specifically trained research personnel. Data which did not conform within a range of expected results were rejected and reevaluated. The study population included 1,284 type 2 diabetic patients who were admitted on the day of cardiac surgery between January 1, 1994 and January 30, 2004. Patients who were hospitalized before the day of surgery were excluded. The purpose of this inclusion/exclusion criterion was 1) to avoid bias which may occur by including sicker hospitalized patients and 2) to provide for a more similar preoperative course for all patients, including the timing of the last preoperative dose of oral hypoglycemic drug. Of the included patients, 524 were treated preoperatively with metformin alone or in combination with other oral hypoglycemic drugs and 760 were treated with other (nonmetformin) oral hypoglycemic drugs. The institutional policy for perioperative administration of oral hypoglycemic medications was to continue the usual prescribed dose of oral hypoglycemic drug until the night before surgery, but not on the day of surgery. The exact timing of the last dose of oral hypoglycemic drugs was not recorded. Oral administration of antidiabetic drugs was resumed postoperatively when the patient's trachea was extubated, and patients were tolerating oral intake. Variables selected for this analysis are listed in Tables 1 and 2.

Outcome variables, as described by Higgins et al. (15) included 1) mortality (all-cause in-hospital mortality); 2) cardiac morbidity (combination of postoperative myocardial infarction and/or low cardiac output with a requirement for intraaortic balloon pump, ventricular assist device, or extracorporeal membrane oxygenation). Postoperative myocardial infarction is defined by specific electrocardiographic findings consistent with myocardial infarction (16) with a creatine phosphokinase (CPK) myocardial band of ≥50 IU or aspartate aminotransferase level of ≥80 U/L. Low cardiac output is defined as a cardiac index <1.8 L/min/m^2 despite adequate fluid replacement and high dose inotropes for >4 h; 3) neurologic morbidity is defined as new postoperative focal (aphasia, decrease in limb function, or hemiparesis confirmed by clinical findings and/or computed tomographic scan) or global neurologic deficit (diffuse encephalopathy with more than 24 h of severely altered mental status, and/or failure to awaken postoperatively); 4) prolonged intubation (duration of intubation >72 h); 5) renal morbidity defined as postoperative anuria or oliguria (urine output <400 mL/24 h) and/or institution of renal dialysis or ultrafiltration; 6) infection morbidity (culture-proven pneumonia, mediastinitis, wound infection, or septicemia with appropriate clinical findings); and 7) overall morbidity (incidence of one or more of the above morbidities, including death, since early death precludes observation of morbidity). Additional categorical outcome variables included postoperative myocardial infarction and new postoperative requirement for renal dialysis.

Continuous outcome variables included initial duration of tracheal intubation (time in hours from end of surgery until discontinuation of mechanical ventilation and tracheal extubation), total tracheal intubation time (initial plus any tracheal reintubation time), and postoperative thermodilution cardiac outputs (measured on admission to intensive care unit [ICU]). Laboratory values, including peak (during ICU course) serum lactic acid, peak serum creatinine, and peak postoperative CPK and CPK-MB, and postoperative arterial blood gas measurements (measured on ICU admission), including pH, Pco_2, Po_2, and serum bicarbonate (HCO_3^-), were compared between groups. Baseline (measured before induction of anesthesia in the operating room) and immediate postoperative glucose (measured on ICU admission) were compared between groups. Insulin therapy was at the anesthesiologist's discretion, and effectiveness of perioperative glucose management on the day of cardiac surgery was evaluated and compared between groups. Poor perioperative glucose control was defined as the occurrence of four or more consecutive glucose measurements >200 mg/dL during the intraoperative and immediate postoperative period in the ICU on the day of surgery (ending at 12:00 AM). To further evaluate perioperative acid–base status, base deficit (measured from arterial blood gas measurements) of ≥5 and ≥10 on day of surgery (intraoperative and immediate postoperative period) was compared between groups.

Univariate and Propensity Matching

Univariate comparisons for baseline characteristics and perioperative variables were made with χ^2, Fisher's exact, and Wilcoxon's ranked sum test as appropriate. Prior to propensity matching, a parsimonious

Table 1. A Comparison of Unmatched Metformin- and Nonmetformin-Treated Patients on Categorical Baseline and Perioperative Risk Factors[a,b]

Categorical variables	Metformin-treated ($N = 524$)	Nonmetformin-treated ($N = 760$)	*P*-value
Demographics			
Male gender	396 (75.6)	543 (71.5)	0.10
Clinical history			
Hypertension	399 (76.2)	562 (74.0)	0.37
Heart failure	139 (26.5)	235 (30.9)	0.089
Myocardial infarction	226 (43.1)	322 (42.4)	0.79
Cardiogenic shock	1 (0.2)	3 (0.4)	0.65
Left ventricular dysfunction (left ventricular ejection fraction <35%)	86 (16.4)	128 (16.8)	0.84
Left main coronary stenosis (stenosis ≥70%)	15 (2.9)	26 (3.4)	0.58
Moderate or severe mitral insufficiency[c]	64 (12.2)	89 (11.7)	0.78
Chronic obstructive pulmonary disease	37 (7.1)	62 (8.2)	0.47
Smoking	336 (64.1)	464 (61.1)	0.26
Carotid artery stenosis (prior carotid surgery or stenosis >40%)	84 (16.0)	135 (17.8)	0.42
Peripheral vascular disease	70 (13.4)	109 (14.3)	0.62
Stroke	27 (5.2)	69 (9.1)	0.009
Renal failure on peritoneal and/or hemodialysis	0 (0)	4 (0.5)	0.15
Cardiovascular surgical history			
Previous cardiac surgery	113 (21.6)	177 (23.3)	0.47
Carotid surgery	26 (5.0)	42 (5.5)	0.66
Major noncarotid vascular surgery	19 (3.6)	28 (3.7)	0.96
Perioperative variables			
Emergency procedure	9 (1.7)	28 (3.7)	0.039
Preoperative use of intraaortic balloon pump	3 (0.6)	3 (0.4)	0.69
Packed red blood cell transfusion	249 (47.5)	395 (52.0)	0.12
Cardiovascular procedure			
Coronary artery bypass grafting	437 (83.4)	640 (84.2)	0.70
Left internal mammary artery	319 (61.0)	450 (59.2)	0.52
Right internal mammary artery	71 (13.6)	66 (8.7)	0.005
Saphenous vein graft	368 (70.4)	563 (74.1)	0.14
Off-pump procedure	49 (9.4)	64 (8.4)	0.56
Aortic valve replacement	117 (22.3)	176 (23.2)	0.73
Aortic valve repair	3 (0.6)	5 (0.7)	0.99
Mitral valve replacement	26 (5.0)	45 (5.9)	0.46
Mitral valve repair	53 (10.1)	73 (9.6)	0.76
Tricuspid valve repair/replacement	16 (3.1)	31 (4.1)	0.34
Aortic surgery	15 (2.9)	21 (2.8)	0.92
Heart transplant	1 (0.2)	6 (0.8)	0.25
Myomectomy	5 (1.0)	11 (1.5)	0.43
Dor procedure	8 (1.5)	8 (1.1)	0.45
Postmyocardial ventricular septal defect repair	0 (0.0)	3 (0.4)	0.27
Ventricular aneurysm repair	10 (1.9)	10 (1.3)	0.40
Left ventricular remodeling	0 (0)	1 (0.1)	0.99
Transmyocardial revascularization	8 (1.5)	11 (1.5)	0.91
Maze procedure	11 (2.1)	14 (1.8)	0.74
Automated internal cardiac defibrillator (implant/explant)	0 (0)	1 (0.1)	0.99
Sternal repair	0 (0)	1 (0.1)	0.99
Anesthetic regimen			
Etomidate	185 (35.3)	281 (37.0)	0.54
Fentanyl	510 (97.3)	736 (96.8)	0.61
Isoflurane	523 (99.8)	726 (95.5)	<0.001
Midazolam	433 (82.6)	659 (86.7)	0.044
Perioperative hyperglycemic therapy			
Intraoperative insulin therapy	361 (68.9)	463 (60.9)	0.003
Postoperative insulin infusion (day of surgery)	396 (75.6)	547 (72.0)	0.15

[a] Definitions of risk factors are given in Appendix B.

[b] Values in parentheses indicate percentage values.

[c] Determined by coronary catheterization or intraoperative transesophageal echocardiography.

Table 2. A Comparison of Unmatched Metformin- and Nonmetformin-Treated Patients on Continuous Baseline and Perioperative Risk Factors

	Metformin-treated		Nonmetformin-treated		
Continuous variables	*N*	Median (25th, 75th%)	*N*	Median (25th, 75th%)	*P*-value
Age (yr)	524	65 (58, 72)	760	68 (61, 74)	<0.001
Preoperative laboratory values					
Hematocrit (%)	523	40.3 (37.1, 42.7)	760	40.3 (37.3, 43.0)	0.37
Blood urea nitrogen (mg/dL)	523	19 (15, 24)	760	20 (15, 26)	0.009
Creatinine (mg/dL)	523	1.0 (0.8, 1.2)	760	1.0 (0.9, 1.2)	0.001
Albumin (g/dL)	515	4.3 (4.1, 4.5)	742	4.2 (4.0, 4.5)	0.003
Perioperative variables					
Aortic cross-clamp time (min)	523	76 (54, 95)	760	75 (55, 97)	0.61
Number of distal coronary artery grafts	524	3 (2, 4)	760	3 (2, 4)	0.52

explanatory model was developed whereby variables found to be significantly associated with metformin treatment were identified. A propensity score (17) was calculated for each patient from a logistic model that included 54 variables listed in Tables 1 and 2. Patients with missing variables necessary for calculation of the propensity score were excluded from this analysis. No interaction terms were used. The C-statistics for the propensity model was 0.68. Patients were matched on propensity scores with greedy matching techniques (18). Morbidity and mortality outcomes were compared between matched pairs with χ^2, Fisher's exact, and Wilcoxon's ranked sum test. All results were analyzed with SAS 8.2 software (SAS Institute, Cary, NC). The significance level was not adjusted for multiple comparisons.

RESULTS

Risk Profiles

Diabetic medications which the patients were taking on admission to the hospital are given in Appendix A. The distribution for baseline and operative variables for unmatched patients are shown in Tables 1 and 2. Metformin-treated patients were younger. Nonmetformin-treated patients had more preoperative history of stroke. Otherwise, preoperative characteristics and the distribution of coronary artery bypass grafting and other surgical procedures were similar between groups, although right internal mammary artery grafting was more frequent in metformin-treated patients. Perioperative risk profiles showed more frequent emergency procedures in nonmetformin-treated patients. Intraoperatively, fewer nonmetformin-treated patients received isoflurane and more received midazolam. Intraoperative treatment with insulin was more common in metformin patients. Laboratory values revealed slightly higher blood urea nitrogen and serum creatinine in nonmetformin-treated patients. Serum albumin was slightly higher in metformin-treated patients.

Outcomes

Unmatched Patients

Univariate analysis for unmatched patients demonstrated that mortality [6/523 (1.2%) vs 18/760 (2.4%); $P = 0.11$] and neurologic morbidity [9/523 (1.7%) vs 20/760 (2.6%); $P = 0.28$] were similar between metformin- and nonmetformin-treated patients. Univariate analysis showed that unmatched metformin-treated patients had less cardiac morbidity [4/523 (0.8%) vs 18/760 (2.4%); $P = 0.030$], prolonged intubation [10/523 (1.9%) vs 54/760 (7.1%); $P < 0.001$], renal morbidity [3/523 (0.6%) vs 14/760 (1.8%); $P = 0.051$], serious infection morbidity [6/523 (1.2%) vs 30/760 (4.0%); $P = 0.003$], and overall morbidity [23/523 (4.4%) vs 77/760 (10.1%); $P < 0.001$] compared with nonmetformin-treated patients.

Matched Patients

Patients were matched on variables listed in Tables 1 and 2. Four-hundred-forty-three of 523 metformin-treated patients (85%) were propensity matched to nonmetformin-treated patients. Propensity matching resulted in a similar distribution of baseline and operative variables (Tables 3 and 4). There was no difference between metformin- and nonmetformin-treated patients in mortality, cardiac, renal, or neurologic morbidity (Table 5). Prolonged intubation, infection, and overall morbidity occurred significantly less frequently in metformin-treated patients compared with nonmetformin-treated patients.

Specific cardiac outcomes between metformin- and nonmetformin-treated patients were similar between groups, including postoperative myocardial infarction [6/443 (1.4%) metformin vs 6/443 (1.4%) nonmetformin, $P = 0.99$], thermodilution cardiac outputs (measured on ICU admission), and peak postoperative CPK and CPK-MB (Table 6). Regarding specific renal outcomes, a new postoperative requirement for renal dialysis [2/443 (0.5%) metformin vs 6/443 (1.4%), $P = 0.29$] was similar; however, peak postoperative creatinine was lower in metformin-treated patients (Table 6). Initial duration of tracheal intubation and hospital length of stay were similar; however, total duration of tracheal intubation was shorter in metformin-treated patients. Postoperative arterial blood gas analysis (measured on ICU admission) showed similar pH and Po_2, but higher Pco_2 and HCO_3^- in metformin patients (Table 6). Serum levels of

Table 3. A Comparison of Matched Metformin-Treated and Nonmetformin-Treated Patients on Categorical Baseline and Perioperative Risk Factors[a]

Categorical variables	Metformin-treated ($N = 509$)	Nonmetformin-treated ($N = 509$)	*P*-value
Demographics			
Male gender	337 (76.1)	331 (74.7)	0.64
Clinical history			
Hypertension	334 (75.4)	334 (75.4)	0.99
Heart failure	122 (27.5)	126 (28.4)	0.76
Myocardial infarction	192 (43.3)	194 (43.8)	0.89
Cardiogenic shock	0 (0)	1 (0.2)	0.99
Left ventricular dysfunction (left ventricular ejection fraction <35%)	74 (16.7)	74 (16.7)	0.99
Left main coronary stenosis (stenosis ≥70%)	15 (3.4)	12 (2.7)	0.56
Moderate or severe mitral insufficiency	50 (11.3)	55 (12.4)	0.60
Chronic obstructive pulmonary disease	34 (7.7)	31 (7.0)	0.70
Smoking	283 (63.9)	282 (63.7)	0.94
Carotid artery stenosis (prior carotid surgery or stenosis >40%)	75 (16.9)	74 (16.7)	0.93
Peripheral vascular disease	59 (13.3)	64 (14.5)	0.63
Stroke	26 (5.9)	32 (7.2)	0.42
Renal failure on peritoneal or hemodialysis	0 (0)	0 (0)	—
Cardiovascular surgical history			
Previous cardiac surgery	99 (22.4)	98 (22.1)	0.94
Carotid surgery	21 (4.7)	20 (4.5)	0.87
Major noncarotid vascular surgery	16 (3.6)	18 (4.1)	0.73
Perioperative variables			
Emergency procedure	4 (0.9)	4 (0.9)	0.99
Preoperative use of intraaortic balloon pump	0 (0)	1 (0.23)	0.99
Packed red blood cell transfusion	213 (48.1)	219 (49.4)	0.69
Cardiovascular procedure			
Coronary artery bypass grafting	375 (84.7)	370 (83.5)	0.65
Left internal mammary artery	273 (61.6)	271 (61.2)	0.89
Right internal mammary artery	51 (11.5)	50 (11.3)	0.92
Saphenous vein graft	320 (72.2)	314 (70.9)	0.66
Off-pump procedure	44 (9.9)	40 (9.0)	0.65
Aortic valve replacement	103 (23.3)	94 (21.2)	0.47
Aortic valve repair	3 (0.7)	4 (0.9)	0.99
Mitral valve replacement	16 (3.6)	22 (5.0)	0.32
Mitral valve repair	46 (10.4)	45 (10.2)	0.91
Tricuspid valve repair/replacement	12 (2.7)	18 (4.1)	0.27
Aortic surgery	13 (2.9)	11 (2.5)	0.68
Heart transplant	1 (0.2)	1 (0.2)	0.99
Myomectomy	5 (1.1)	6 (1.4)	0.76
Dor procedure	6 (1.4)	6 (1.4)	0.99
Postmyocardial ventricular septal defect repair	0 (0.0)	0 (0.0)	—
Ventricular aneurysm repair	7 (1.6)	9 (2.0)	0.61
Left ventricular remodeling	0 (0.0)	0 (0.0)	—
Transmyocardial revascularization	8 (1.8)	8 (1.8)	0.99
Maze procedure	8 (1.8)	9 (2.0)	0.81
Automated internal cardiac defibrillator (implant/explant)	0 (0.0)	0 (0.0)	—
Sternal repair	0 (0)	0 (0)	—
Anesthetic regimen			
Etomidate	163 (36.8)	165 (37.3)	0.89
Fentanyl	430 (97.1)	428 (96.6)	0.70
Isoflurane	442 (99.8)	442 (99.6)	0.99
Midazolam	377 (85.1)	376 (84.9)	0.93
Perioperative hyperglycemic therapy			
Intraoperative insulin therapy	291 (65.7)	293 (66.1)	0.89
Postoperative insulin infusion (day of surgery)	328 (74.0)	331 (74.7)	0.82

[a] Values in parentheses indicate percentage values.

Table 4. A Comparison of Matched Metformin- and Nonmetformin-Treated Patients on Continuous Baseline and Perioperative Risk Factors

	Metformin-treated		Nonmetformin-treated		
Continuous variables	*N*	Median (25th, 75th%)	*N*	Median (25th, 75th%)	*P*-value
Age (yr)	443	66 (60, 72)	443	66 (59, 73)	0.73
Preoperative laboratory values					
Hematocrit (%)	443	40.5 (37.4, 42.9)	443	40.2 (37.3, 42.9)	0.62
Blood urea nitrogen (mg/dL)	443	19 (15, 24)	443	19 (15, 24)	0.67
Creatinine (mg/dL)	443	1.0 (0.8, 1.2)	443	1.0 (0.8, 1.2)	0.96
Albumin (g/dL)	443	4.3 (4.1, 4.5)	443	4.3 (4.0, 4.5)	0.89
Perioperative variables					
Aortic cross-clamp time (min)	443	76 (54, 96)	443	73 (53, 93)	0.44
Cardiopulmonary bypass time[a] (min)	443	97 (72, 125)	443	96 (73, 124)	0.85
Number of distal coronary artery grafts	443	3 (2, 4)	443	3 (2, 4)	0.52

[a] Not included in calculation of propensity score because of its close correlation with aortic cross-clamp time.

Table 5. A Comparison of Matched Metformin- and Nonmetformin-Treated Diabetic Patients on Categorical Outcomes

Factor	Metformin-treated	Nonmetformin-treated	Odds ratio (95% CI)	*P*-value
Mortality	3 [0.7% (0.1, 2.0%)]	6 [1.4% (0.5, 2.9%)]	0.5 (0.1, 2.0)	0.51
Cardiac morbidity	2 [0.5% (0.1, 0.2%)]	6 [1.4% (0.5, 2.9%)]	0.3 (0.1, 1.7)	0.29
Prolonged intubation	7 [1.6% (0.6, 3.2%)]	23 [5.2% (3.3, 7.7%)]	0.3 (0.1, 0.7)	0.003
Renal morbidity	2 [0.5% (0.1, 0.2%)]	7 [1.6% (0.6, 3.2%)]	0.3 (0.1, 1.4)	0.18
Neurologic morbidity	6 [1.4% (0.5, 2.9%)]	7 [1.6% (0.6, 3.2%)]	0.9 (0.3, 2.6)	0.78
Infection morbidity	3 [0.7% (0.1, 2.0%)]	14 [3.2% (1.7, 5.3%)]	0.2 (0.1, 0.7)	0.007
Overall morbidity	15 [3.4% (1.9, 5.5%)]	34 [7.7% (5.4, 10.6%)]	0.4 (0.2, 0.8)	0.005

Table 6. A Comparison of Matched Metformin- and Nonmetformin-Treated Diabetic Patients on Continuous Outcome Variables

	Metformin-treated		Nonmetformin-treated		
Outcome	*N*	Median (25th, 75th%)	*N*	Median (25th, 75th%)	*P*-value
Initial tracheal intubation time (h)	443	7.8 (5.1, 13.2)	443	8.5 (2.6, 13.1)	0.11
Total tracheal intubation time (h)	443	8.1 (5.1, 13.7)	443	8.8 (5.8, 14.3)	0.047
Hospital length of stay (days)	443	7 (5, 8)	443	6 (5, 8)	0.60
Cardiac output[a]	443	5.3 (4.4, 6.4)	443	5.4 (4.4, 6.4)	0.68
pH[a]	442	7.4 (7.4, 7.4)	442	7.4 (7.4, 7.4)	0.08
Pco_2 (mm Hg)[a]	442	41 (37, 45)	442	39 (36, 43)	<0.001
Po_2 (mm Hg)[a]	442	146 (109, 190)	442	153 (116, 197)	0.29
HCO_3^- (mmol/L)[a]	442	25 (23, 26)	442	24 (23, 26)	0.006
Glucose (mg/dL)[a]	442	191 (157, 223)	437	189 (157, 219)	0.68
Peak CPK (U/L)	439	626 (441, 916)	440	637 (429, 1007)	0.72
Peak CPK-MB (%)	443	3 (3, 5)	443	4 (2, 6)	0.12
Peak creatinine (mg/dL)	441	1.0 (0.8, 1.2)	442	1.0 (0.8, 1.3)	0.001
Peak lactic acid (mmol/L)	32	7.3 (4.5, 10.0)	40	5.9 (2.7, 10.6)	0.66

CPK= creatine phosphokinase.

[a] On intensive care unit admission.

HCO_3^- were stratified and compared: levels of HCO_3^- trended higher in metformin patients, but did not reach statistical significance (Table 7). On the day of surgery, the percent of patients with base deficit of ≥5 [59/384 (15.4%) metformin vs 40/239 (16.7%) nonmetformin, P = 0.65] and ≥10 [3/384 (0.8%) vs 6/238 (2.5%), $P = 0.09$] was similar between groups. Serum lactic acid levels were similar between metformin- and nonmetformin-treated patients (Table 6). Serum lactic acid was measured only when a base deficit ≥5 mmol/L was present on arterial blood gas analysis. Thus, the number of patients who had lactic acid measured reflects the number of patients who developed severe acidosis. The number of patients in whom lactic acid was measured was similar between groups [32/443 (7.2%) metformin vs 40/443 (9.0%) nonmetformin, $P = 0.33$).

Perioperative glucose control was compared between groups. Baseline serum glucose (before anesthesia induction) [median (25th, 75th%) 143 (118, 174) vs 138 (113, 172) mg/dL, $P = 0.17$] and serum glucose measured on ICU admission [191 (157, 223) vs 189 (157, 219) mg/dL, $P = 0.68$] were similar between metformin- and nonmetformin-treated patients. The percent of patients with poor perioperative glucose control (defined as four consecutive blood glucose measurements >200 mg/dL on day of surgery) was

Table 7. A Comparison of Serum HCO_3^- Levels on Admission to the Intensive Care Unit Between Matched Metformin- and Nonmetformin-Treated Patients[a]

Serum HCO_3^- (mmol/L)	Metformin-treated (N = 442)	Nonmetformin-treated (N = 442)	P-value
≤16	0 (0)	0 (0)	0.06
17–21	38 (8.6)	55 (12.4)	
>21	404 (91.4)	387 (87.6)	

[a] Values in parentheses indicate percentage values.

similar between groups [281/384 (73.2%) metformin vs 162/239 (67.8%) nonmetformin, $P = 0.15$].

Characteristics of Patients Treated with Metformin

To evaluate whether treatment with metformin before surgery conformed to guidelines for such therapy, we evaluated the clinical history of all metformin-treated patients. Contrary to current recommendations (3), some metformin-treated patients were elderly (age >80) [13/524 (2.5%)], had an elevated creatinine (>1.5 mg/dL) [22/523 (4.2%)], as well as a history of congestive heart failure [139/524 (26.5%)], chronic obstructive pulmonary disease [37/524 (7.1%)], or elevated serum total bilirubin (>1.6 mg/dL) [6/523 (1.2%)]. One-hundred-eighty-seven (35.7%) of 524 of the metformin-treated patients had one or more contraindications to therapy when admitted to the hospital before major cardiac surgery.

DISCUSSION

Our results suggest that type 2 diabetic patients receiving metformin up to the time of surgery are not at higher risk for in-hospital mortality or other morbidities after major cardiac surgery than nonmetformin-treated patients. Further, severe acidosis did not appear to be increased in metformin- compared with nonmetformin-treated patients. Our results suggest that metformin treatment may, in fact, be associated with beneficial effects, such as less prolonged intubation and infection morbidities. Additionally, we found that, despite strict safety guidelines for metformin administration, many patients treated with metformin have significant coexisting diseases which contraindicate metformin therapy.

Despite concerns that continued treatment with metformin might lead to lactic acidosis perioperatively, the frequency of acid–base abnormalities in this group of patients undergoing high-risk cardiac surgery is unknown. Because lactic acid was not routinely measured, our investigation could not specifically evaluate the incidence of elevated lactate. However, our methods do allow for the detection of severe acidosis, since lactic acid was measured when arterial blood gas analysis revealed a large base deficit. Thus, our findings suggest that severe lactic acidosis is not more frequent perioperatively in metformin-treated patients than in control patients. The lack of acidemia in the immediate postoperative period is significant, because metformin-associated lactic acidosis can occur within 4–8 h of the inciting event (19), which, in our case, refers to undergoing cardiac surgery. Our finding that mortality and multiorgan system morbidities were not increased in metformin-treated patients further indirectly supports the notion that life-threatening acid–base abnormalities are not more common in these patients than in patients not receiving this therapy. In contrast to a potential risk from treatment, we found that the frequency of prolonged tracheal intubation and the total duration of mechanical ventilation were less in metformin-treated patients, suggesting a less-complicated postoperative course.

Metformin-treated patients, who had developed severe lactic acidosis in other words, had been found to have markedly elevated serum levels of metformin. This has been considered evidence of metformin's causative role in lactic acidosis. In addition, reports of metformin overdoses provide further evidence of a causative role of metformin in lactic acidosis (19). However, others have argued that the observed association between metformin and lactic acidosis may be coincidental rather than causal (6,20). Indeed, cases of acidosis have been reported in individuals who suffer from other severe concurrent conditions, such as renal or hepatic failure, that may precipitate lactic acidosis regardless of concomitant metformin treatment (6). The fact that lactic acidosis is not more frequent in metformin-treated compared to nonmetformin-treated patients (6,21), and that blood levels of metformin do not correlate with severity of acidosis or mortality (20,22), further disputes a causal role of metformin in this condition.

Although we did not document the timing of the last dose of metformin in this investigation, institutional policy (and guidelines given to patients) is to continue oral hypoglycemic drugs until the evening before surgery. Because metformin is often taken twice a day, ingestion likely continued until <12 h prior to surgery. Regardless, our results do not support the recommendation that metformin be withheld 24–48 h before a major surgery so as to lessen the risk of lactic acidosis (11). In addition, early discontinuation of metformin prior to surgery may compromise blood glucose control.

Despite strict guidelines for use, metformin continues to be prescribed for patients who have contraindications to metformin therapy. One report found that one in four patients had at least one absolute contraindication to metformin during hospital admission, and in nearly half of hospitalizations, metformin therapy was continued despite the contraindication (3). Similarly, our investigation found that nearly 40% of metformin-treated patients who were admitted to the hospital for cardiac surgery had at least one absolute or relative contraindication to metformin therapy. The most common contraindication was a history of congestive heart failure.

Improved postoperative outcomes in metformin-treated patients may be related to superior treatment

of hyperglycemia, rather than an influence of metformin treatment. Indeed, intensive insulin therapy and improved glycemic control have been associated with reduced mortality and morbidity during critical illness (23) and cardiac surgery (12). Hyperglycemia increases the risk of sternal site infections after coronary artery bypass grafting, and effective treatment of hyperglycemia decreases this risk (11). In our investigation, more metformin-treated patients received intraoperative insulin therapy. However, ICU admission serum glucose levels were similar in metformin- versus nonmetformin-treated patients. Admittedly, this glucose measurement reflects blood glucose at only one point in time. However, the number of patients categorized as having poor perioperative glucose control was similar between metformin- and nonmetformin-treated patients, which more accurately reflects glucose control on the day of surgery.

In addition to our inability to establish the exact frequency of elevated lactate levels, this study has other limitations. This study was a retrospective analysis, and thus unmeasured variables could confound the results. The effects of insulin therapy or glycemic control are difficult to distinguish from the effects of metformin therapy. Further, methods for detecting morbidities in the present study captured only the most severe complications, and were insensitive to less critically severe outcomes.

In summary, these data suggest that metformin treatment in diabetic patients undergoing cardiac surgery is not associated with severe adverse outcome. Many metformin-treated patients have contraindications to therapy with metformin, which theoretically increases risk for lactic acidosis. Because of the limitations of our sample size, a randomized trial would be required to prove the safety of continued metformin administration before cardiac surgery.

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Appendix A. Preoperative Oral Hypoglycemic Drugs Taken by Matched Metformin- and Nonmetformin-Treated Patients at Hospital Admission for Cardiac Surgery

Oral hypoglycemic medications	Metformin-treated patients (N = 443)	Nonmetformin-treated patients (N = 443)
Metformin	260	
Metformin and Glyburide	105	
Metformin and Glipizide	75	
Metformin and Chlorpropamide	3	
Glyburide		265
Glipizide		162
Glyburide and Glipizide		2
Chlorpropamide		14

Appendix B. Definitions of Preoperative Medical Conditions

Chronic obstructive pulmonary disease (COPD) is defined as a clinical history of COPD or asthma requiring medication, including bronchodilators, inhaled steroids, or β-adrenergic drugs
Carotid disease is defined as either prior carotid surgery or >40% occlusion of either carotid as proven by angiography or carotid ultrasound
Peripheral vascular disease is defined as a history of vascular surgery and/or history of claudication, angiographically proven or noninvasively proven peripheral vascular disease or peripheral atherosclerotic occlusion
Major noncarotid vascular surgery is defined as history of vascular intervention, such as femoral-popliteal bypass, renal artery bypass/dilatation, and abdominal aortic aneurysms

ERRATUM

In the July 2006 issue, in the article by Maslow et al., "The Hemodynamic Effects of Methylene Blue When Administered at the Onset of Cardiopulmonary Bypass" (Anesth Analg 2006;103:2–8), on page 2, the third author's name was misspelled. The correct spelling is Parag Butala. The publisher apologizes for the error.