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Oral Hypoglycemics: Increased Postoperative Mortality in Coronary Risk Patients

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Key Words
Diabetes mellitus · Coronary artery disease · Hypoglycemic agents · Insulin · Mortality

Abstract
Background: Diabetes mellitus (DM), particularly if insulin-dependent, is a predictor of increased perioperative risk, whereas stringent metabolic control with insulin is beneficial in the critically ill. ***Methods:*** The impact of oral hypoglycemics (OH) vs. insulin on outcome was determined as a secondary retrospective analysis of a cohort study in patients with coronary artery disease (CAD) and DM undergoing major non-cardiac surgery. Primary end-point was 2-year all-cause mortality; secondary endpoints were perioperative myocardial ischemia and 2-year cardiac mortality. ***Results:*** Of 173 patients, DM was diagnosed in 42 (24%) based on pre-existing treatment with OH (15%) or insulin (9%). During follow-up, 40/173 (23%) patients died. All-cause mortality was similar in the non-diabetic (20%) and insulin groups (19%) but significantly higher in the OH group (42%; p = 0.025). Cardiac mortality tended to be higher in the OH group compared with the insulin and non-diabetic groups (27 vs. 19% and 11%, respectively; p = 0.066). Multivariate analysis revealed renal failure (odds ratio [OR] = 4.9, 95% confidence interval [CI] = 1.8–13.0), treatment with OH (OR = 3.3, 95% CI = 1.2–9.0), peripheral vascular surgery (OR = 2.7, 95% CI = 1.2–6.0), and prior diuretic therapy (OR = 2.6, 95% CI = 1.1–5.7) being independently associated with 2-year all-cause death. No difference existed in postoperative ischemia among the different groups. ***Conclusions:*** Long-term mortality after major non-cardiac surgery is elevated in patients with CAD and diabetes mellitus only if they are treated with OH, but not if they are treated with insulin. Further evaluation of the impact of perioperative anti-diabetic treatment on morbidity and mortality in CAD is warranted.

Introduction

Type 2 diabetes mellitus (DM) is a significant health problem worldwide, affecting 4–6% of the population [1, 2]. While DM is an important risk factor for the development of coronary artery disease (CAD) [3], the outcome of CAD is poorer in patients with DM than in those without DM [4, 5].

While tight perioperative metabolic control improves postoperative outcome [6, 7], the influence of the type of preoperative hypoglycemic therapy on outcome in pa-

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tients with DM and known or suspected CAD undergoing non-cardiac surgery is not known. Insulin treatment is an independent predictor of cardiac risk after major non-cardiac surgery [8]. Consequently, current guidelines for perioperative cardiovascular evaluation describe DM as a predictor of risk for cardiac complications particularly if insulin-treated [9]. Nevertheless, the effects of oral hypoglycemics (OH) on perioperative outcome have not been sufficiently evaluated. This is surprising as there are conflicting results concerning cardiovascular mortality in non-surgical patients with and without documented CAD treated with OH [4, 10–14]. In contrast, insulin treatment combined with a strict blood glucose control reduces mortality in critically ill patients [7] and in patients with acute myocardial infarction [15–17]. However, mortality from myocardial infarction was not decreased when glucose levels failed to be lowered by intense insulin therapy [18]. The aim of this analysis was to determine the impact of DM and its treatment strategy (OH vs. insulin) on long-term outcome in patients with documented or highly suspected CAD undergoing major non-cardiac surgery.

Materials and Methods

Subjects and Definitions

This is a secondary analysis of a prospective observational cohort study of preoperative risk stratification in patients with or at risk for CAD [19, 20]. The local institutional review board approved the study protocol, and each of the patients gave informed written consent. In brief, patients were eligible if they had known or suspected CAD, and were scheduled for major non-cardiac surgery defined as abdominal aortic surgery, peripheral vascular surgery of the lower limb, laparotomy, major orthopedic surgery, thoracotomy, and major surgery of the neck. CAD was considered as documented if patients had myocardial ischemia in dobutamine stress echocardiography or dipyridamole thallium imaging, significant stenoses in a previous coronary angiography, a prior myocardial infarction, or prior myocardial revascularization; CAD was considered as suspected if patients had typical angina or if vascular surgery was planned and ≥2 of the following criteria were present: age >70 years, hypertension, DM, prior stroke, impaired exercise tolerance, or a pathologic resting ECG. DM was diagnosed if patients were treated with insulin or OH at admission; some of the patients may have been diabetic based on their blood glucose levels, but were analyzed as non-diabetics due to lacking drug treatment. Renal failure was defined as a calculated creatinine clearance of <30 ml/min.

Methods

Continuous ECG recording (Marquette Series 8500, Marquette Electronics, Milwaukee, Wisc., USA) was started before induction of anesthesia and continued for 48 h, and ST segment depressions of ≥2 mm ≥1 min were considered as significant. Cardiac troponin I was measured on the first and second day after surgery using a commercially available kit (AxSYM®, Abbott, Abbott Park, Ill., USA) with the normal upper limit of 2 μg/l specified by the manufacturer. Glucose levels were assessed preoperatively in all patients in a fasting state, but postoperatively only in diabetic patients using enzymatic methods (Roche Diagnostics, Basel, Switzerland). Interventions for establishing perioperative metabolic control were not pre-specified and left to the discretion of the physicians in charge.

Endpoints and Follow-Up

The primary endpoint was all-cause mortality after 2 years; secondary endpoints were cardiac mortality after 2 years, and evidence of perioperative myocardial ischemia (cardiac troponin I >2 μg/l and ST segment depressions ≥2 mm ≥1 min in the first 2 days after surgery). Semistructured follow-up interviews were performed by telephone at 6, 12, and 24 months after surgery. Cause of death was obtained from the Swiss Mortality Registry (Federal Statistical Office, Bern, Switzerland).

Statistical Analysis

Statistical analysis was performed using Stat View® software version 5.0.1 (SAS Institute Inc., Cary, N.C., USA). Continuous data were analyzed using the Mann-Whitney U and Kruskal-Wallis tests, and categorical data using Fisher's exact and χ^2 tests, where appropriate. All continuous data were expressed as median values with their range. Multivariate analysis using logistic regression was done considering baseline variables with an initial $p < 0.05$. Single variables were removed in a stepwise method until the model met a 0.05 significance level in all variables. Survival was compared using Kaplan-Meier survival curves and log-rank test. P values were two-sided and considered to indicate statistical significance if <0.05.

Results

DM was diagnosed in 42 (24%) patients from whom 26 (15%) were chronically treated with OH (OH group) and 16 (9%) with insulin only (insulin group). In the OH group, 17 patients received sulfonylureas, 2 metformin, and 1 repaglinide as only OH drug. Six patients received a combination of sulfonylureas and metformin. Three patients treated with OH and insulin were analyzed as part of the OH group. Baseline characteristics are shown in table 1. Levels of HbA_{1c} tended to be higher in patients treated with insulin, but were similar in patients with DM treated with OH and non-diabetic patients. Patients without DM had lower preoperative blood glucose levels than patients with DM, but glucose levels differed neither before nor after surgery in the two DM groups. No difference existed in postoperative ischemia among the different groups (table 2). All-cause mortality tended to be higher in diabetic than in non-diabetic patients (33 vs. 20%, p = 0.059), and was similar in insulin-treated (19%)

Table 1. Baseline characteristics

	All (n = 173)	No DM (n = 131)	OH (n = 26)	Insulin (n = 16)	p*
Age, years	73 (47–89)	73 (47–89)	75 (52–84)	72 (50–77)	0.29
Female	33	31	31	56	0.11
Body mass index, kg/m^2	25 (14–38)	25 (14–37)	26 (21–33)	28 (19–38)	0.24
Creatinine clearance, ml/min	70 (5–176)	67 (5–176)	73 (16–144)	77 (9–133)	0.71
Renal failure	15	16	8	19	0.50
Hypertension	69	66	65	81	0.17
Current smoking	25	39	19	13	0.29
Hypercholesterolemia (n = 167)	57	60	58	50	0.86
Angina pectoris	31	33	24	31	0.62
Shortness of breath	60	61	50	62	0.56
History of myocardial infarction	51	55	50	19	0.02
Prior revascularization	29	34	31	6	0.03
History of congestive heart failure	13	11	23	19	0.19
Ongoing malignant disease	25	27	19	13	0.33
Drug therapy					
Acetylic salicylic acid	59	61	50	56	0.56
Coumadin	19	15	35	25	0.06
Diuretics	37	36	46	50	0.25
Inhibitors of ACE	35	32	46	44	0.29
Beta-blockers	34	38	15	31	0.08
Ca-antagonists	27	26	27	31	0.90
Long-acting nitrates	20	18	23	25	0.73
Digoxin	8	8	15	0	0.19
Amiodarone	5	6	0	6	0.43
Surgery					
ASA classification					0.56
ASA II	9	11	4	0	
ASA III	81	79	84	88	
ASA IV	10	10	12	12	
Emergency surgery	2	2	4	0	0.72
Abdominal aortic surgery	34	37	35	6	0.046
Peripheral vascular surgery of the lower limb	32	24	46	69	0.0004
Laparotomy	23	27	8	13	0.06
Major orthopedic surgery	8	8	8	13	0.79
Thoracotomy	2	3	0	0	0.52
Major surgery of the neck	1	1	4	0	0.37

Values are median values with range or % of patients.

* Kruskal-Wallis test for continuous, χ^2 test for categorical variables.

ACE = Angiotensin-converting enzyme; ASA = American Society of Anesthesiologists; CrCl = creatinine clearance; DM = diabetes mellitus; OH = oral hypoglycemics.

and non-diabetic patients but significantly higher in patients with OH (42%; p = 0.025; fig. 1). Cardiac mortality was higher in diabetic than in non-diabetic patients (24 vs. 11%, p = 0.037), and tended to be higher in the OH group (27%) than in the insulin group (19%) and in non-diabetic patients (p = 0.066). In univariate analysis predictors of death were age >70 years, hypertension, renal failure, history of congestive heart failure, treatment with OH and diuretics, aortic surgery, and peripheral vascular surgery. Independent predictors of death were renal failure, peripheral vascular surgery, and treatment with OH and diuretics (table 3).

Table 2. Perioperative management, metabolic control, and ischemia

	All (n = 173)	No DM (n = 131)	OH (n = 26)	Insulin (n = 16)	p*
Perioperative hypoglycemic therapy, %					
Intraoperative insulin	–	–	14	58	0.016
Postoperative insulin	–	–	19	62	0.025
Insulin 1st day after surgery	–	–	19	92	<0.0001
Insulin 2nd day after surgery	–	–	29	92	0.0004
Insulin 3rd day after surgery	–	–	14	92	<0.0001
Insulin at discharge	–	–	15	100	<0.0001
OH 1st day after surgery	–	–	33	0	0.029
OH 2nd day after surgery	–	–	48	0	0.0049
OH 3rd day after surgery	–	–	52	0	0.0018
OH at discharge	–	–	80	0	<0.0001
Perioperative metabolic control, % and mmol/l, respectively					
HbA_{1c} (n = 15)	7.3 (5.1–10.2)	6.6 (5.9–7.9)	6.7 (5.1–8.8)	8.5 (6.4–10.2)	0.087
Glucose day before surgery	6.3 (3.6–16.5)	6.2 (3.9–14.0)	7.8 (3.6–14.6)	7.9 (6.2–16.5)	0.0002
Glucose 1st day after surgery	–	–	7.8 (5.0–12.5)	9.6 (5.4–22.8)	0.22
Glucose 2nd day after surgery	–	–	8.1 (4.6–12.3)	8.2 (4.4–20.1)	0.45
Glucose 3rd day after surgery	–	–	7.9 (4.5–12.0)	7.6 (3.9–15.8)	0.88
Postoperative ischemia (days 1 and 2), %					
Elevated cardiac troponin I	16	15	25	15	0.55
ST depressions (n = 117)	46	42	50	63	0.24

Values are median values with range or % of patients.

* Mann-Whitney U test and Kruskal-Wallis test for continuous, Fisher's test, and χ^2 test for categorical variables, where appropriate. DM = Diabetes mellitus; OH = oral hypoglycemics.

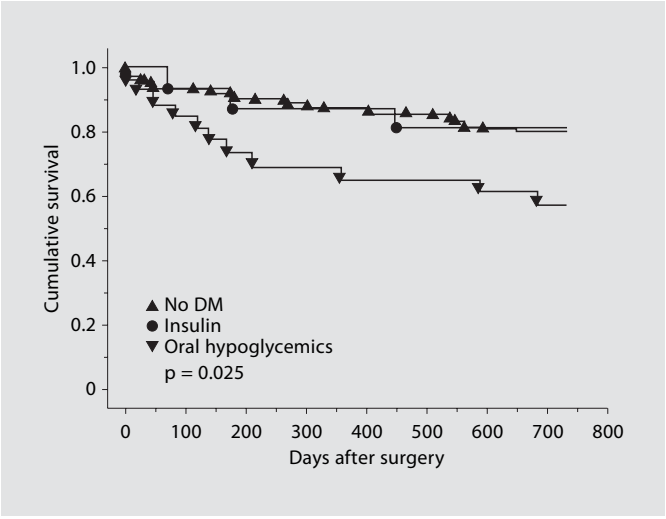

Fig. 1. Kaplan-Meier survival curves for patients without DM and for patients with DM treated with insulin and OH, respectively (p = 0.025, log-rank test).

Table 3. Multivariate predictors of 2-year all-cause mortality

	OR	95% CI	χ^2	p
Renal failure	4.9	1.8–13.0	10.2	0.0014
Oral hypoglycemic treatment	3.3	1.2–9.0	5.3	0.021
Peripheral vascular surgery	2.7	1.2–6.0	5.6	0.018
Diuretic treatment	2.6	1.1–5.7	5.2	0.022

CI = Confidence interval; OR = odds ratio.

Discussion

This study performed in diabetic patients with documented or suspected CAD undergoing major non-cardiac surgery found that treatment with OH was an independent predictor of 2-year all-cause mortality. In contrast, patients treated with insulin had the same outcome as patients without DM. This finding was unexpected as current guidelines and risk indices consider DM as a risk factor particularly if treated with insulin. Previous data show that tight metabolic control, as reflected by normoglycemia, in both diabetic and non-diabetic patients with critical diseases, was related to beneficial outcome [18, 21]. Our data do not provide an explanation for this finding, which could reflect either a beneficial effect of insulin or a detrimental effect of OH. Potential beneficial effects of insulin are better metabolic control, anti-inflammatory and anti-atherogenic effects, and beneficial effects on intracellular mechanisms in the ischemic myocardium [22, 23]. However, metabolic glucose control in the insulin group was not better than in the OH group, as could have been expected. In addition, up to 50% of the patients in the OH group received insulin during and early after surgery and, thus, were at least partially exposed to the potential beneficial effects of insulin. Thus, it is unlikely that our findings can be explained by the beneficial effects of insulin but might reflect potentially deleterious effects of OH as administered before surgery. Sulfonylureas prevent ischemic preconditioning by inhibiting cardiac KATP-channels [24]. As perioperative myocardial ischemia is common in CAD patients and associated with unfavorable outcome [20, 25], one can hypothesize that this inhibition prior to surgery might have caused the observed difference in mortality rates post surgery. However, not consistent with this hypothesis, were the similar incidences of perioperative myocardial ischemia (i.e., elevation of cardiac troponin I and ST segment depression) in all study groups. This latter finding and the lack of statistically significant differences in *cardiac* mortality among the study groups suggest that the higher all-cause mortality in OH treated patients might have been caused only partially by cardiac side effects. The multivariate analysis revealed renal failure, treatment with diuretics, and peripheral vascular surgery as additional independent predictors of 2-year all-cause mortality. Both renal failure [8] and peripheral vascular surgery [26] are known risk factors for perioperative mortality, while preoperative treatment with diuretics might be a surrogate for underlying hypertension and congestive heart failure, which were both associated with adverse outcome in the univariate analysis.

Our study has several limitations. First, it was a secondary analysis of prospectively collected data. Second, the number of patients with DM was too small to allow for final conclusions and data on the duration of DM and late diabetic complications were missing. Nevertheless, the study was large enough to clearly identify OH-treated DM as an independent predictor of all-cause mortality in our cohort, and it is unlikely that this result happened by chance. Third, the study groups were not identical regarding patient characteristics. However, the higher rate of peripheral vascular surgery and the lower rate of prior myocardial infarction with revascularization in the insulin group would have been more consistent with a higher and not a lower mortality, because mortality in peripheral vascular surgery is expected to be the highest [9, 27] and prior revascularization might provide a better postoperative survival [9, 28].

Conclusion

In conclusion, our study indicates that chronic treatment with OH but not with insulin was associated with elevated long-term mortality in diabetic CAD patients after major non-cardiac surgery. This finding might have been caused by either a beneficial effect of insulin per se, or a detrimental effect of OH during and after surgery. Due to the nature of our analysis and the limitations of our study, our data is hypothesis-generating rather than hypothesis-proving. Because of the high numbers of OH-treated patients that undergo non-cardiac surgery and the potentially high impact on outcome, our findings identify an urgent need for additional prospective trials to clarify the optimal perioperative treatment strategy in patients with DM. Meanwhile, OH-treated DM should be considered as an equivalent risk factor for adverse outcome as insulin-treated DM.

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