The Safety of Preoperative Vardenafil in Patients Undergoing Coronary Artery Bypass Graft Surgery

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Abstract: Phosphodiesterase 5 inhibitors are cardioprotective against myocardial reperfusion ischemic injury in animal models but are contraindicated in patients with coronary disease who take nitrates because of a risk for hypotension. We investigated the safety of vardenafil in patients undergoing coronary artery bypass grafting (CABG) surgery. A single dose of vardenafil was given to 10 patients before CABG surgery. The postoperative course of these 10 patients was compared with the postoperative course of 47 patients who did not receive vardenafil before CABG surgery. There were no perioperative deaths and no episodes of hypotension in the group receiving vardenafil. The clinical and operative characteristics of the 2 study groups were similar. There were no significant differences in postoperative serum troponin levels (9.1 ± 8.3 vs 12.5 ± 9.3 ng/mL; $P = 0.29$, respectively), duration of postoperative intubation (21.4 ± 10.1 vs 27.4 ± 15.2 hours; $P = 0.14$, respectively), or length of hospital stay (11.1 ± 13.2 vs 10.0 ± 4.7 days; $P = 0.8$, respectively) between the group receiving vardenafil and the control group. This pilot study of 10 patients suggests that vardenafil use is safe in patients before CABG surgery. A larger study is needed to explore the myocardial protective effect of the drug.

Key Words: phosphodiesterase 5 inhibitors, vardenafil, ischemia reperfusion, myocardial protection, coronary bypass surgery

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INTRODUCTION

In United States, 785,000 persons have a coronary event every year with an additional 195,000 persons having first time silent myocardial infarctions.[1] In 2008, more than 300,000 coronary artery bypass graft (CABG) surgery procedures were done in the United States according to numbers from the Healthcare Cost and Utilization Project's Nationwide Inpatient Sample.[2] CABG surgery carries a small risk of ischemia/reperfusion injury, heart failure, poor reperfusion, and no-reflow.[3] Evidence of ischemia reperfusion injury can be seen in up to 25% of patients who died within 30 days after undergoing CABG surgery.[4] Unfortunately, myocardial reperfusion injury works against the intended benefit of reperfusion of the myocardium and in experimentally induced infarct, it may be responsible for half of the myocardial infarct size.[5] Post-CABG elevation of cardiac biomarkers within 24 hours of the surgery are related to survival outcomes up to 1 year.[6] It is essential to achieve reperfusion to ischemic myocardium with a goal to decrease the extent of ischemic injury and also to avoid reperfusion injury through restoration of antegrade coronary circulation and improving the viability of myocardium. There are animal studies that have demonstrated cardiac protection from myocardial perfusion injury using various pharmacological agents acting through different mechanisms with a goal to reduce morbidity and mortality.[7] The cardioprotective effect of phosphodiesterase 5 inhibitors in ischemic reperfusion injury has shown significant promise and given an opportunity to translate the observed myocardial protective benefits against myocardial perfusion injury in animal models into clinical practice.[8–12] We investigated the safety and the effects of single dose of vardenafil, an phosphodiesterase 5 inhibitor, before CABG surgery.

METHODS

Two studies are reported in this manuscript. One study was a pilot phase II study (single-arm open label) and included 10 patients who received 1 single dose of 10 mg of vardenafil before CABG surgery. The goal of this study was to investigate the safety of vardenafil in this setting and the main end points were mortality and hypotension (clinicaltrials.gov/NCT01260285). The study was approved by the local institutional research board (after the Food and Drug Administration had stipulated that a New Drug Application [NDA] was not necessary), and all patients gave their written informed consent. The second study was a retrospective study that included 47 patients who underwent CABG surgery in the same period of time who did not receive vardenafil before surgery. Their postoperative outcomes were compared with the outcomes of the 10 patients who received vardenafil. The institutional review board approved the second study under a waiver for consent protocol. The computerized patient record system of the Veterans Health Administrations was used to collect data. The enrollment of patients was as per the set inclusion and

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exclusion criteria without any gender, age, race, or ethnicity biases.

All patients between 18 and 85 undergoing elective CABG surgery with or without valve repair/replacement were included. The exclusion criteria for those receiving vardenafil were emergent CABG surgery, acute myocardial infarction within 7 days of surgery, left ventricular ejection function less than 35%, serum creatinine greater than or equal to 2 mg/dL, prior cerebrovascular accident, severe chronic obstructive airway disease, nitrate use within past 24 hours, before CABG surgery, pregnancy, or allergy to vardenafil. Electronic medical records were reviewed for data regarding age, gender, ethnicity, height, body weight, body mass index, blood pressure, smoking status, medical history, diagnostic studies, medications, and perioperative data after CABG surgery. Use of perioperative medications like beta-blockers, HMG Co A reductase inhibitors, inotropic medication, and antiarrythmic medications were given at the discretion of the primary physician. Postoperative duration of endotracheal intubation for ventilator support, incidence of reintubation, incidence of reoperation, and length of hospital stay were documented. Patients were followed for any morbidity or mortality. GraphPad InStat 3 and GraphPad Prism 5 (both San Diego, CA) and JMP (Cary, NC) software were used for statistical analysis. Two-sided tests were used throughout. A P value of <0.05 was considered statistically significant.

RESULTS

A total of 57 patients who underwent CABG surgery from December 2010 to January 2012 were included in the study. Of these patients, 10 received a single dose of vardenafil before surgery and the remaining 47 patients who did not receive vardenafil were followed as a control group. The group of patients receiving the vardenafil tolerated the drug well. There were no perioperative deaths and no episodes of perioperative hypotension. The preoperative left ventricular function did not change significantly after surgery (52.1% ± 8.3% vs 53.0% ± 7.5%; $P = 0.8$, respectively) in this group.

The clinical characteristics of the 2 groups were similar (Table 1). The mean age of the patients was 65.6 ± 9.2 years. The preoperative left ventricular function between the 2 groups was similar (52.1% ± 8.3% vs 52.3% ± 9.8% in the vardenafil versus control group, respectively). The operative parameters were also similar between the 2 groups (Table 1). In the vardenafil group, 2 patients (20.0%) underwent combined CABG surgery and valve-replacement surgery versus 7 patients (14.9%) in the control group. The intraoperative pulmonary artery systolic pressure was numerically higher in the vardenafil group compared with the control group (35.6 ± 7.9 vs 30.5 ± 8.4 mmHg, $P = 0.08$), but the difference was not quite statistically significant.

The postoperative course of the 2 patients' groups was similar (Table 2; Figure 1). In the vardenafil group, 4 patients (40.0%) required postoperative intravenous inotropic support versus 27 patients (57.4%) in the control group, a difference that was not statistically significant ($P = 0.48$). There was no significant difference in the postoperative left ventricular ejection fraction between the vardenafil group and the control group (53% ± 7% vs 50% ± 11%, $P = 0.49$). All patients except for 1 patient in the control group had postsurgery

TABLE 1. Clinical Characteristics of the Patients

Variable	All Patients, N = 57	Vardenafil, N = 10	No Vardenafil, N = 47	P
Male, n (%)	57 (100.0)	10 (100.0)	47 (100.0)	
Age (yrs)	65.6 ± 9.2	61.1 ± 7.8	66.6 ± 9.3	0.08
LVEF (%)*	52.3 ± 9.5	52.1 ± 8.3	52.3 ± 9.8	0.94
Medications, n (%)				
Aspirin	54 (94.7)	10 (100.0)	44 (93.6)	1.00
Beta-blockers	46 (80.7)	10 (100.0)	36 (76.6)	0.18
ACE inhibitors/ ARBs	43 (75.4)	7 (70.0)	36 (76.6)	0.69
Statins	49 (86.0)	8 (80.0)	41 (87.2)	0.61
Warfarin	5 (8.8)	1 (10.0)	4 (8.5)	1.00
Plavix	6 (10.5)	2 (20.0)	4 (8.5)	0.28
Insulin	11 (19.3)	1 (10.0)	10 (21.3)	0.66
Nitrates	24 (42.1)	0 (0.0)	24 (51.1)	0.00
Comorbidities, n (%)				
CHF	6 (10.5)	0 (0.0)	6 (12.8)	0.57
[Old] MI	13 (22.8)	3 (30.0)	10 (21.3)	0.67
Diabetes	30 (52.6)	4 (40.0)	26 (55.3)	0.49
PVD	9 (15.8)	2 (20.0)	7 (14.9)	0.65
Hypertension	50 (87.7)	7 (70.0)	43 (91.5)	0.09
Afib	5 (8.8)	2 (20.0)	3 (6.4)	0.20
CKD	16 (28.1)	1 (10.0)	15 (31.9)	0.25
Hyperlipidemia	48 (84.2)	10 (100.0)	38 (80.9)	0.33
Depression	16 (28.1)	3 (30.0)	13 (27.7)	1.00
Smoking, n (%)	7 (12.3)	2 (20.0)	5 (10.6)	0.59
Creatinine (mg/dL)	1.38 ± 0.82	1.16 ± 0.26	1.42 ± 0.89	0.37
Hemoglobin (g/dL)	13.3 ± 1.7	14.2 ± 1.4	13.1 ± 1.7	0.06
PAS (mm Hg)*	34.3 ± 7.0	36.7 ± 10.4	34.0 ± 6.7	0.54
Type of operation, n (%)				
CABG surgery	48 (84)	8 (80.0)	40 (85.0)	0.86
CABG surgery/ AVR	6 (10.5)	1 (10.0)	5 (10.6)	1.00
CABG surgery/ MVR	3 (5.2)	1 (10.0)	2 (4.3)	0.44
Pump time (min)	110.8 ± 36.6	105.3 ± 36.8	111.9 ± 36.8	0.61
Cross-clamp time (min)	83.5 ± 30.7	81.4 ± 29.7	84.0 ± 31.2	0.80
PAS intraop	31.4 ± 8.5	35.6 ± 7.9	30.5 ± 8.4	0.08
Inotropes postoperative	31 (54.4)	4 (40.0)	27 (57.4)	0.48
IV nitrglycerine postoperative	9 (15.8)	1 (10.0)	8 (17.0)	1.00
IV sodium nitroprusside postoperative	8 (14.0)	2 (20.0)	6 (12.8)	0.61

*In the control group, 21 patients had PAS estimated by echo and in the vardenafil group, 3 patients had PAS estimated by echo preoperatively.

ACE, angiotensin-converting enzyme; Afib, atrial fibrillation; ARB, angiotensin receptor blocker; AVR, aortic valve replacement; CHF, congestive heart failure; CKD, chronic kidney disease; LVEF, left ventricular ejection pressure; MI, myocardial infarction; MVR, mitral valve repair; PAS, pulmonary artery systolic pressure; PVD, peripheral vascular disease.

TABLE 2. Postoperative Outcomes

Variable	All Patients, N = 57	Vardenafil, N = 10	No Vardenafil, N = 47	*P*
Hemoglobin (g/dL)	10.0 ± 1.5	10.6 ± 1.3	9.9 ± 1.5	0.15
Creatinine (mg/dL)	1.40 ± 1.19	1.13 ± 0.28	1.45 ± 1.30	0.43
CPK* (IU/L)	905.0 ± 735.3	560.3 ± 283.8	981.6 ± 783.6	0.10
TnI* (ng/mL)	11.9 ± 9.1	9.1 ± 8.3	12.5 ± 9.3	0.28
LVEF† (%)	51.1 ± 10.3	53.0 ± 7.5	50.3 ± 11.4	0.49
Length of intubation (h)	26.4 ± 14.6	21.4 ± 10.1	27.4 ± 15.2	0.14
Length of SICU stay (d)	6.2 ± 3.6	6.4 ± 6.0	6.1 ± 3.0	0.83
Length of hospital stay (d)	10.2 ± 6.8	11.1 ± 13.2	10.0 ± 4.7	0.8
Reinitiation of inotropes	0 (0.0)	0 (0.0)	0 (0.0)	
Reintubation	3 (5.3)	1 (10.0)	2 (4.3)	0.44
Reoperation for sternal wound infection	3 (5.3)	1 (10.0)	2 (4.3)	0.44
Reoperation for any other reason	0 (0.0)	0 (0.0)	0 (0.0)	
Postoperative new atrial fibrillation	14 (24.6)	1 (10.0)	13 (27.7)	0.42
Postoperative new CVA	0 (0.0)	0 (0.0)	0 (0.0)	
Postoperative new infection‡	23 (40.4)	2 (20.0)	21 (44.7)	0.17
Tracheostomy	0 (0.0)	0 (0.0)	0 (0.0)	
Postoperative death	0 (0.0)	0 (0.0)	0 (0.0)	

*Peak level (upper limit of normal: CPK, 308 IU/L; TnI, 0.49 mg/mL.

†In the control group, only 23 patients had postsurgery 2-dimensional echo to evaluate the LVEF.

‡Includes sternal wound infection, pneumonia, and urinary tract infection.

CPK, creatine kinase; CVA, cerebrovascular accident; LVEF, left ventricular ejection fraction; SICU, surgical intensive care unit; TnI, troponin I.

troponin levels checked. The peak troponin levels were numerically lower in the vardenafil group, but the difference was not statistically significant (9.1 ± 8.3 vs 12.5 ± 9.3 ng/mL; $P = 0.28$). Troponin levels peaked within 24 hours of surgery in 9 (90%) patient in the vardenafil group and in 44 (94%) patients in the control group ($P = 0.55$), whereas the creatine kinase levels peaked within 24 hours of surgery in 6 (60%) patients in the vardenafil group and in 26 (55%) patients in the control group ($P = 1$). The median duration of intubation was not significantly shorter in the vardenafil group (21.4 ± 10.1 vs 27.4 ± 15.2 hours; $P = 0.14$). The length of hospital stay was not significantly different between the vardenafil group and the control group (11.1 ± 13.2 vs 10.0 ± 4.7 days; $P = 0.8$).

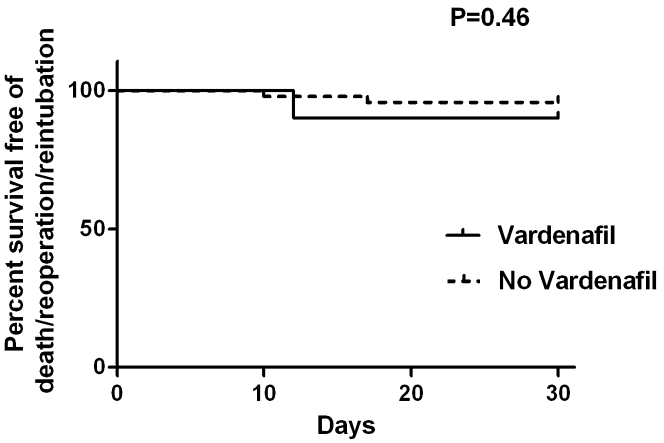

FIGURE 1. Kaplan–Meier survival curves showing freedom from death/reoperation/reintubation in patients who received vardenafil before CABG surgery and patients who did not.

DISCUSSION

In this study, we show that a single dose of vardenafil before CABG surgery is safe and is not associated with hypotension necessitating increasing the dose or restarting of inotropes. Many experimental studies suggest that it is possible to prevent reperfusion myocardial injury by use of pharmacological agents,[7] but the clinical proof has been elusive, despite several clinical trials using free radicals scavengers, antioxidants, calcium channel blockers, neutrophil inhibitors, nitric oxide, adenosine-related agents, renin–angiotensin inhibitors, endothelin receptor antagonists, Na^+/H^+ exchange inhibitors, and antiapoptotic agents.

Phosphodiesterase 5 inhibitors prolong the action of cyclic guanosine monophosphate (cGMP) through inhibition of hydrolytic breakdown of cGMP, which is a second messenger for nitric oxide. In animal models, phosphodiesterase 5 inhibitors have been found to be cardioprotective against reperfusion myocardial injury.[8,9] Phosphodiesterase 5 inhibitors can result in systemic hypotension, lower pulmonary pressures, and increased coronary blood flow without changes in inotropy or cardiac index in the animal model.[10] Intracoronary infusion of phosphodiesterase 5 inhibitor in mouse before reperfusion reduced the myocardial infarct size.[11] Sustained cardiac protection against myocardial ischemic injury can be provided by long-acting phosphodiesterase 5 inhibitors when used as a preconditioning agent and may be superior to protection provided by other agents.[12] In human studies, impaired cardioprotection by factors like age and diabetes mellitus may influence outcomes. However, it is generally accepted that protection from ischemia and myocardial reperfusion injury will decrease morbidity and potential mortality.

In our study, vardenafil was well tolerated when administered immediately before CABG surgery. Because of its' (weak) hypotensive effect and the potential synergistic

effect with nitrates, the phosphodiesterase inhibitors are contraindicated in patients who take nitrates and the intake of nitrates was an exclusion criterion in our study. However, we observed no episode of hypotension in the patients taking vardenafil and some patients even tolerated infusions of nitroglycerin and sodium nitroprusside without problems. This potential for hypotension may have been the reason why the phosphodiesterase inhibitors were not tried in CABG patients, although there have been reports about phosphodiesterase inhibitors that were tolerated well by children with pulmonary hypertension and congenital heart disease undergoing cardiac surgery.[13,14] On the other hand, Vassalos et al[15] reported a decrease in ventricular function of children receiving sildenafil on the day before cardiac surgery. We did not observe changes in left ventricular function in our group of adults receiving vardenafil before CABG surgery, but we also did not observe a decrease in intraoperative pulmonary systolic pressure, in line with the observations of Vassalos et al. Moreover, whether children without coronary disease can be compared with adults with severe coronary disease necessitating CABG surgery is doubtful. The concern regarding phosphodiesterase inhibitors and coronary disease may not be an issue in the controlled environment of the intensive care unit. Although peak troponins were somewhat lower and the duration of intubation were somewhat shorter in the group-receiving vardenafil, we could not show any statistically significant benefit in the outcomes of these patients compared with regular patients. This is the first study to evaluate phosphodiesterase 5 inhibitors in adult patients with coronary disease undergoing cardiac surgery. Moreover, after our preliminary data showed no untoward effects from vardenafil, a larger trial to evaluate efficacy in terms of reducing the peak enzyme levels and/or improving the left ventricular ejection fraction is the next step to determine whether vardenafil could become a useful drug in patients undergoing CABG surgery.

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