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Rationale, design and baseline characteristics of the PRO-TECT II study: PROpofol CardioproTECTion for Type II diabetics ☆
A randomized, controlled trial of high-dose propofol versus isoflurane preconditioning in patients undergoing on-pump coronary artery bypass graft surgery

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ABSTRACT

Diabetes mellitus is a leading cause of death globally and results in significant morbidity and mortality following surgery. After cardiac surgery, diabetic patients are especially at risk for low cardiac output syndrome, which can quadruple the risk for postoperative death. Attempts to prevent low cardiac output syndrome have focused on increasing myocardial tolerance to ischemia (preconditioning), which involves the myocardial mitochondrial ATP-regulated K_{ATP} channel, G-protein initiation, nitric oxide synthase, and protein kinase C. Unfortunately, the signal transduction pathways required for preconditioning are corrupted in diabetes.

Effective antioxidant intervention during ischemia–reperfusion appears important for preserving myocardial function; thus, alleviating oxidant-mediated post-ischemic injury by increasing antioxidant defenses (cardioprotection) is an alternative to preconditioning. Our previous work suggests that propofol (2,6-diisopropylphenol), an intravenous anesthetic with antioxidant potential, may confer cardioprotection. In this paper, we describe the rationale and methodology of the Pro-TECT II Study, a Phase II randomized controlled trial designed to explore the relationships of biomarkers of oxidative or nitrosative stress in diabetes, to determine the effect of propofol cardioprotection to counteract these effects in patients undergoing elective primary coronary bypass graft surgery with cardiopulmonary bypass, and to provide feasibility and sample size data needed to conduct Phase III trials.

1. Introduction and background

Diabetes mellitus affects over 171 million people worldwide and this prevalence is expected to double by 2030 [1]. Globally, diabetes is the fifth leading cause of death: one person dies every six minutes from diabetic complications, the majority of which are related to cardiovascular disease. Following cardiac surgery, individuals with diabetes suffer higher rates of perioperative morbidity, mortality, and recurrence of angina and a lower rate of survival long-term compared to patients without diabetes [2–5].

In particular, diabetic patients are at elevated risk for low cardiac output syndrome [6,7], defined as persistent hypotension (systolic blood pressure <90 mmHg) and/or low cardiac output

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(cardiac index <2.2 L/min/m^2) despite hemodynamic optimization. Prolonged use of high doses of inotropes or vasopressors and/or intra-aortic balloon counterpulsation are required. The causes of low cardiac output syndrome may include the injury that follows ischemia–reperfusion of the heart and inadequate revascularization. The diabetic heart is more sensitive to this form of injury due to defective antioxidant defenses [8,9], increased oxidative stress, and impaired endogenous myocardial protective pathways [10,11]. If inadequately treated, low cardiac output syndrome can quadruple the overall mortality rate for coronary artery bypass graft (CABG) surgery [5].

Major efforts have focused on increasing the myocardial tolerance to ischemia (preconditioning) via physical (intervals of ischemia) or pharmacological (volatile anesthetics) means [12–16]. The myocardial mitochondrial ATP-regulated K_{ATP} channel (mitoK_{ATP}) is essential for protection by preconditioning. Unfortunately in diabetes, signal transduction pathways required for ischemic or anesthetic preconditioning are corrupted [10,11] and sulfonylurea oral hypoglycemic agents, can block K_{ATP} channel opening [17]. Preconditioning is insufficient to prevent injury in the context of prolonged ischemic intervals (greater than 25 to 35 min). Such circumstances require a different therapeutic approach.

Elevated oxidant stress may occur during myocardial ischemia–reperfusion, influencing release and action of tumor necrosis factor-α (TNF-α), which inhibits cardioprotective endothelial NOS (eNOS), enhances endothelin-1 (ET-1) formation, and promotes the conversion of nitric oxide to cardiotoxic peroxynitrite. These factors cause cardiac dysfunction. Effective antioxidant intervention during ischemia–reperfusion appears important for preserving myocardial function. Thus, rather than increasing the myocardial tolerance to ischemia, we have focused on alleviating oxidant-mediated post-ischemic injury by increasing antioxidant defenses (cardioprotection).

Our previous work suggests that propofol (2,6-diisopropylphenol), an intravenous anesthetic with antioxidant potential, may confer cardioprotection [18–21]. Although conventional low doses of propofol have not been clinically effective in reducing postoperative cardiac injury or improving cardiac function, *in vitro* dose-finding and physiological studies from our laboratory suggest that high doses of propofol can reach a therapeutic concentration (≥10 to 25 mmol/L) needed for cardioprotection [20,22,23].

This paper describes the design of the PROpofol CardioproTECTtion for Type II Diabetics (PRO-TECT II) Study, a Phase II randomized controlled trial (RCT) designed to explore the relationships of biomarkers of oxidative or nitrosative stress in diabetes, determine the effect of high dose propofol cardioprotection to counteract these effects in patients undergoing elective primary coronary bypass graft surgery with cardiopulmonary bypass, and provide feasibility and sample size data needed to conduct Phase III RCTs.

2. Materials and methods

2.1. Study design

The PRO-TECT II Study is a Phase II RCT comparing high-dose propofol cardioprotection versus isoflurane preconditioning in diabetic and nondiabetic patients at risk of an adverse perioperative cardiac event who are undergoing CABG surgery requiring extracorporeal circulation. Participants, health care providers, investigators, data collectors, and laboratory staff are blinded to whether patients receive propofol or isoflurane.

2.2. Study population

Adult patients undergoing cardiac surgery at the Vancouver General Hospital are eligible if they are 18–80 years of age, are undergoing primary CABG surgery requiring cardiopulmonary bypass (CPB), require revascularization of three or more coronary arteries with an anticipated aortic cross-clamp time of at least 60 min, and have a preoperative systolic blood pressure above 90 mmHg in the absence of inotropic or mechanical support. Patients are ineligible if they have Type I diabetes mellitus (defined as an established history and diagnosis of diabetes mellitus requiring insulin therapy from the time of diagnosis), co-existing valvular heart disease (moderate to severe aortic stenosis or mitral regurgitation), an acute or evolving myocardial infarction, or a history of hypersensitivity to propofol or any of its formulation components; or are taking nonsteroidal anti-inflammatory drugs, vitamin C, or vitamin E within five days of surgery.

2.3. Randomization

Subjects are randomly allocated to either the propofol group or the isoflurane group after written informed consent. The allocation process uses a computer-generated random number table, with random permuted blocks of four or six, stratified by diabetic status and left ventricular ejection fraction as diabetes mellitus and decreased left ventricular function may affect the incidence rate of low cardiac output syndrome. For diabetic status, the two strata are no diabetes mellitus, defined as no history or diagnosis of diabetes mellitus, and Type II diabetes mellitus, defined as an established history and diagnosis of adult-onset diabetes mellitus treated with oral hypoglycemic agents (regardless of insulin use). For left ventricular ejection fraction, the two strata are normal, defined as a preoperative ejection fraction of at least 45% on angiography, and low, defined as a preoperative ejection fraction of less than 45% on angiography. The randomization scheme is unavailable to individuals involved in the recruitment, data collection, or management of the subjects.

2.4. Study protocol

Standardized anesthetic techniques are used at the Vancouver General Hospital. Intra-arterial blood pressure monitoring, central venous and pulmonary artery catheterization, and transesophageal echocardiography are used in addition to routine monitors. Subjects will undergo intravenous (IV) anesthetic induction with fentanyl 10–15 μg/kg, midazolam 0.15–0.25 mg/kg, and sodium thiopental 1–2 mg/kg followed by muscle relaxation using rocuronium 1–1.5 mg/kg to facilitate tracheal intubation. Prior to CPB, anesthesia will be maintained with isoflurane 0.5 to 1.5% (end tidal). Subjects will receive phenylephrine (1–2 μg/kg), increased anesthetic depth, fentanyl (1 to 2 μg/kg), or vasodilator therapy (e.g., nitroglycerin 0.125 to 0.25 μg/kg/min) to maintain their systolic and mean arterial blood pressures between 85 to 140 mmHg and 50