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ORIGINAL ARTICLE

Cardioprotective effect of pretreatment with β-glucan in coronary artery bypass grafting

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Abstract
Background. β-glucan pretreatment has been shown to attenuate inflammatory response and to protect against ischemia-reperfusion injury in animal studies. The aims of the present study were to examine the safety of pretreatment with β-1,3/1,6-glucan in patients scheduled for coronary artery bypass grafting (CABG), and to investigate whether β-1,3/1,6-glucan pretreatment could suppress inflammatory response and protect against ischemia-reperfusion injury following CABG. *Methods.* Twenty one patients scheduled for CABG were assigned to oral β-1,3/1,6-glucan 700 mg (Group 1) or 1 400 mg (Group 2) five consecutive days before surgery and were compared with a control group (Group 3). Blood samples were drawn preoperatively and on the first, third and fifth postoperative day for analysis of acute-phase reactants, hematology, cytokines and myocardial enzymes. *Results.* The study drug was well tolerated. Creatine kinase isoenzyme MB was significantly lower in Group 2 compared with controls on the first postoperative day ($p = 0.028$). Mean change in cardiac troponin T was lower in Group 2 compared with controls ($p = 0.028$). *Conclusions.* β-1,3/1,6-glucan pretreatment is safe in patients undergoing CABG and may protect against ischemia reperfusion injury following CABG.

Key words: *Coronary artery bypass grafting, ischemia reperfusion, cardiopulmonary bypass, myocardial protection*

β-glucans are polymers of β-1,3-D-glucose with or without β-1,6-D-glucose side chains extracted from the cell walls of *Saccharomyces cerevisiae* that are known for their ability to stimulate the innate immune responses. Pretreatment with β-glucan has previously been shown to protect against infections in animal studies (1,2) and in clinical trials (3). In murine experimental peritonitis, pretreatment with intraperitoneal β-glucan injections attenuated the endotoxin induced production of proinflammatory cytokines such as tumor necrosis factor-α and interleukin-1β (4). A rodent model of ligation and reperfusion of the left anterior descending coronary artery has shown that β-glucan pretreatment reduced myocardial infarction size by 47% and 50% after reperfusion for four and 24 hours respectively (5).

Cardiac surgery performed with cardiopulmonary bypass (CPB) provokes a systemic inflammatory response which is triggered by exposure of blood to the foreign surfaces of the extracorporeal circuit as well as the surgical trauma. The initiation of CPB is proceeded by aortic cross clamping and cardiac arrest which renders the heart globally ischemic and entails myocardial ischemia-reperfusion injury. Myocardial ischemia-reperfusion injury promotes a local inflammatory response with release of cytokines and adhesion molecules which in turn is responsible for activation of the endothelium and adhesion of leukocytes (6,7). Although the systemic inflammation and the ischemia-reperfusion injury accompanied by cardiac surgery with CPB may be hard to separate, they affect cardiac performance and contribute to the transient depression of myocardial contractility which is commonly seen postoperatively. In patients with preoperative impaired cardiac function this may lead to "low cardiac output syndrome" with the need for inotropic or mechanical

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cardiac support. "Low cardiac output syndrome" affects 9% of patients undergoing coronary artery bypass grafting (CABG) and is associated with increased mortality (8). This calls for novel strategies to protect the heart during cardiac surgery with CPB in addition to the protection afforded by hypothermic cardioplegia.

The aims of the present pilot clinical trial were to examine the safety of pretreatment with oral β-1,3/1,6-glucan in patients scheduled for CABG and to investigate whether β-1,3/1,6-glucan could attenuate inflammatory response and protect the heart against ischemia-reperfusion injury following CABG.

Methods

Enrolment of patients

From August 2004 to March 2005, 48 patients scheduled for CABG at the University Hospital of North Norway were prospectively enrolled in the study (Figure 1). Informed written consent was obtained from all patients. The study was approved by the local ethical committee (27.01.04) and the Norwegian Medicines Agency (17.06.04). Inclusion criteria included age >20 years scheduled for CABG with CPB. Because one of the main aspects with this study was to investigate whether pretreatment with β-glucan attenvates inflammatory response after CABG, patients were excluded if they had preoperative clinical or laboratory signs of ongoing inflammation (C-reactive protein >20 mg/l). Patients who were reoperated within the first five postoperative days were also excluded because these patients were subjected to a second major inflammatory stimulus. Other exclusion criteria were the following: treatment with chemotherapy within four weeks before surgery; renal failure requiring hemodialysis or peritoneal dialysis; fertile women. Fourteen of the total 48 patients were scheduled for elective surgery, while 34 patients presented with an acute coronary syndrome and underwent urgent surgery during the hospital stay. Twenty six patients were assigned to oral treatment of either 350 mg (Group 1) or 700 mg (Group 2) microparticulate β-1,3/1,6-glucan twice a day, five consecutive days prior to surgery. The treatment groups were consecutively compared to a control group of 22 patients matched for age, sex and urgent versus elective surgery (Group 3). Patients receiving β-glucan were asked to report possible side effects during and after treatment and underwent a routine clinical examination each day, including measurement of blood pressure, heart rate and temperature by the responsible surgeon. Preoperative clinical status was assessed by New York Heart Association Classification (NYHA class). Five patients from the treatment groups and two patients from the control group were excluded. Of these seven patients, three were excluded because of elevated C-reactive protein prior to surgery and four because of reoperation within the next five days. The per-protocol population thus included 41 patients, i.e. 11 patients in Group 1, ten patients in Group 2 and 20 patients in Group 3.

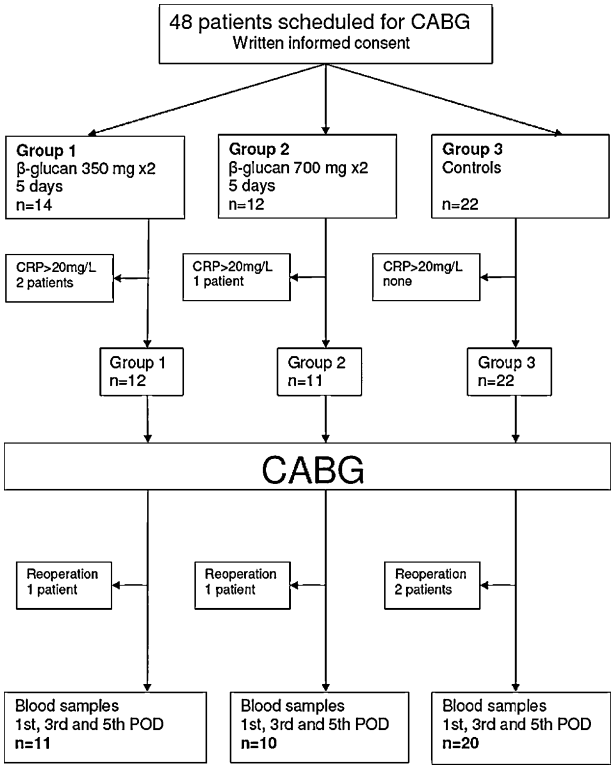

Figure 1. Study outline.

Anesthesia, cardiopulmonary bypass and surgery

Anesthesia was induced with fentanyl 5–10 μg/Kg, midazolam 30 μg/kg and thiopentone sodium until sleep. Muscle relaxation was achieved with pancuronium (0.1 mg/kg). Patients were ventilated with a mixture of isoflurane, oxygen and air. Anesthesia was maintained with propofol infusion and repeated doses of fentanyl 2 μg/kg. Heparin 3 mg/kg was given to achieve activated clotting time above 480 s before initiation of cardiopulmonary bypass. Heparin coated Bioline circuits (Jostra, Hirrlingen, Germany) primed with 1 800 ml Ringers Acetate and a Quadrox Bioline oxygenator with an extra softbag reservoir (Jostra, Hirrlingen, Germany) were used. After aortic cross clamping cardiac arrest was induced by a 750 ml (range 600–1 000 ml) bolus of cold, 4°C antegrade St. Thomas Hospital solution repeated with additional doses of 200 ml every 20th minute. CABG was performed with mild

hypothermia (34°C) and all patients received at least one internal mammary artery graft on the left anterior descending coronary artery.

Laboratory data

Standard blood samples were drawn before treatment with β-1,3/1,6-glucan, preoperatively and on the first, third and fifth postoperative day for quantification of acute-phase reactants (C-reactive protein, D-dimer and fibrinogen), myocardial enzymes (creatine kinase isoenzyme MB and cardiac troponin T) and hematological parameters (hemoglobin, hematocrit and white blood cell count).

Cytokine analyses

Blood samples for cytokine analysis were drawn before treatment with β-1,3/1,6-glucan, preoperatively and on the first, third and fifth postoperative day. The following multiplex cytokine kits (Bio-plex, Bio-Rad Laboratories Inc., Hercules, CA) were combined in one assay and analyzed according to the manufacturer's instructions: interleukin-1β, interleukin-6, interleukin-8, interleukin-10, interleukin-12 (p70) and tumor necrosis factor-α. The samples were read in a Bio-Plex array reader (Bio-Rad Laboratories Inc) and concentrations given as pg/ml.

β-glucan

Microparticulate β-1,3/1,6-glucan (Immutol) was provided by Biotec Pharmacon ASA (Tromsø, Norway).

Statistical analysis

Statistical analysis was performed using SPSS statistical software (SPSS 12.0.1, SPSS Inc., Chicago, IL, USA). To analyze differences in preoperative and intraoperative data between the groups, one way analysis of variance (ANOVA) was performed for numerical data and Fischer's exact tests for categorical data. Laboratory test results were compared between the groups with analysis of variance with repeated measures design (RANOVA) and with Student's t-test. P-values <0.05 were considered statistically significant.

Results

Preoperative and intraoperative data

Preoperative data are shown in Table I. Mean age was 66.5 years in Group 1 and 62.5 and 64.6 years in Group 2 and 3 respectively. The mean ejection fraction was lower in Group 1, but the difference was not statistically significant. One patient in Group 2 had a chronic renal failure. There were three and two patients with chronic obstructive pulmonary disease (COPD) in Group 1 and 2 respectively and no patients with COPD in the control group ($p=0.042$). All patients in Group 1 were in NYHA class III, whereas the patients in Group 2 and 3 were in either NYHA class II, III or IV. Intraoperative data are shown in Table II. There were no significant differences in extracorporeal circulation time, bleeding volume, the number of distal anastomoses and the mean of the lowest temperature between the groups. Aortic clamp time, respirator time, cardioplegic volume and the number of cardioplegic deliveries were similar in all

Table I. Preoperative data.

	Group 1 β-glucan 350 mg ×2 (n=11)	Group 2 β-glucan 700 mg ×2 (n=10)	Group 3 Control (n=20)	*p*
Age (mean±SD)	66.5±7.4	62.5±8.4	64.6±9.3	0.57
(range)	53–77	51–73	47–81	
Gender (n)				1.00
Male	8	7	15	
Female	3	3	5	
Procedure (n)				1.00
Urgent	8	7	14	
Elective	3	3	6	
EF (mean±SD)	54.6±10.7	63.9±11.0	61.9±10.7	0.11
Atrial fibrillation (n)	1	0	2	0.79
Renal failure (n)	0	1	0	0.24
COPD (n)	3	2	0	0.042
Diabetes Mellitus (n)	3	4	3	0.29
NYHA functional class (mean±SD)	3.0±0	3.3±0.68	3.3±0.64	0.40

Abbreviations: COPD-chronic obstructive pulmonary disease, EF-ejection fraction, NYHA-New York Heart Association, SD-standard deviation.

Table II. Intraoperative data.

	Group 1 β-glucan 350 mg ×2 (n = 11)	Group 2 β-glucan 700 mg ×2 (n = 10)	Group 3 Control (n = 20)	*p*
EC time (min)	64.5 ± 10.5	71.9 ± 16.8	71.9 ± 16.4	0.39
Aortic clamp time (min)	37.9 ± 7.0	41.0 ± 12.0	41.5 ± 12.4	0.68
Respirator time (min)	216 ± 142	249 ± 169	230 ± 151	0.88
Bleeding (ml)	650 ± 209	765 ± 307	777 ± 305	0.47
Retransfusion (ml)	380 ± 216	361 ± 236	577 ± 208	0.016
Distal anastomoses (n)	3.6 ± 0.5	3.9 ± 0.7	3.5 ± 0.7	0.29
Cardioplegic volume (ml)	1 005 ± 157	1 015 ± 108	1 038 ± 210	0.87
Number of cardioplegic deliveries (n)	2.1 ± 0.7	2.3 ± 0.7	2.1 ± 0.7	0.73
Lowest temperature (°C)	33.9 ± 0.7	33.3 ± 0.7	33.4 ± 1.1	0.28

Data presented as mean ± standard deviation. EC-Extracorporeal circulation.

groups. The volume of blood that was retransfused postoperatively was significantly different between the groups (p = 0.016).

β-glucan tolerance

The study drug was well tolerated and no side effects were reported. There were no differences in acute-phase reactants, myocardial enzymes, hematological parameters or cytokines before pretreatment with β-glucan and preoperatively (data not shown).

Acute-phase reactants, myocardial enzymes and hematology

C-reactive protein and white blood cell count rose from baseline measures and peaked on the third postoperative day (Table III), while returning towards preoperative levels on the fifth postoperative day. No differences between the groups were observed. There were also no differences between the groups with regard to levels of D-dimer, fibrinogen, hemoglobin, hematocrit and serum creatinine (data not shown). Creatine kinase isoenzyme MB and cardiac troponin T values are shown in Figure 2. Creatine kinase isoenzyme MB values were significantly lower in Group 2 compared with controls on the first postoperative day (p = 0.028). Mean change in cardiac troponin T between baseline and fifth postoperative day levels was lower in Group 2 compared with controls (p = 0.028).

Cytokines

Levels of tumor necrosis factor-α, interleukin-1β and interleukine-12 were below detection limit for the employed assays (< 7.8 pg/ml) in all patient samples from the study. Interleukin-10 was below detection limit in more than half of the patient samples and could not be interpreted. Interleukin-6 and interleukin-8 levels peaked on the first postoperative day, and returned towards preoperative values on the fifth postoperative day (Table III). Mean interleukin-8 was significantly higher in Group 1 compared with controls on the fifth postoperative day (p = 0.029).

Table III.

	Baseline	1st POD	3rd POD	5th POD	*p*
CRP, mg/l					
Group 1	6.3 ± 3.8	68.8 ± 18.8	223.8 ± 51.0	125.5 ± 56.1	0.37
Group 2	7.8 ± 5.9	67.8 ± 31.1	202.0 ± 64.7	94.3 ± 31.3	
Group 3	6.0 ± 2.2	62.8 ± 22.9	201.1 ± 67.4	93.3 ± 51.0	
WBC, $\times 10^9$/l					
Group 1	6.2 ± 1.0	10.1 ± 2.2	9.6 ± 2.9	7.2 ± 1.7	0.81
Group 2	6.6 ± 1.4	8.3 ± 2.1	10.0 ± 2.0	7.8 ± 1.7	
Group 3	6.5 ± 1.4	9.5 ± 1.9	10.0 ± 2.3	8.1 ± 2.5	
IL-6, pg/ml					
Group 1	4.6 ± 11.8	95.3 ± 71.9	38.8 ± 20.4	18.5 ± 15.0	0.87
Group 2	1.7 ± 5.3	72.4 ± 50.6	42.0 ± 25.8	20.4 ± 12.4	
Group 3	2.0 ± 5.0	89.6 ± 57.0	44.8 ± 39.3	13.7 ± 12.8	
IL-8, pg/ml					
Group 1	7.3 ± 6.6	27.0 ± 16.6	15.3 ± 3.7	19.1 ± 6.7	0.22
Group 2	11.3 ± 7.0	23.7 ± 15.3	19.6 ± 9.6	17.3 ± 5.5	
Group 3	6.5 ± 5.5	20.5 ± 8.1	16.0 ± 6.0	14.2 ± 4.6[a]	

IL-6-interleukin-6, IL-8-interleukin-8, POD-postoperative day, WBC-white blood cell count. [a]p = 0.029 versus Group 1 (Student's t-test).

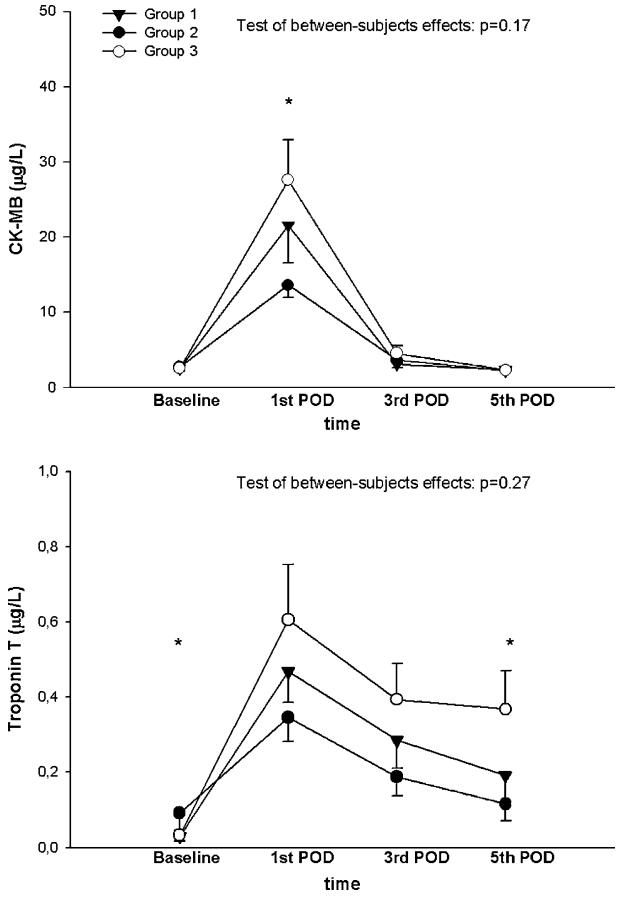

Figure 2. Mean creatine kinase isoenzyme MB and cardiac troponin T values in patients undergoing CABG pre-treated with low dose β-glucan (Group 1), high dose β-glucan (Group 2) and in untreated controls (Group 3). Error bars denote standard error of the mean. Top: * $p = 0.028$, Group 2 versus Group 3 on the first postoperative day (Student's t-test). Bottom: Mean change in cardiac troponin T between baseline and fifth postoperative day levels was lower in Group 2 compared to controls ($p = 0.028$, Student's t-test). (CK-MB: creatine kinase isoenzyme MB; POD: postoperative day; Troponin T: cardiac troponin T.)

No other differences were observed between the groups.

Postoperative outcome

Postoperative complications are shown in Table IV. The number of patients with atrial fibrillation in the postoperative period was similar in all groups. None of the patients suffered from a stroke, perioperative myocardial infarction, renal failure, respiratory failure or the need for an intra-aortic balloon pump in the postoperative period (data not shown). One patient in Group 1 and two of the controls required an inotropic agent on the first postoperative day. One patient in the control group died on the 21st postoperative day of a myocardial infarction.

Discussion

Pretreatment with intravenous β-glucan has previously been shown to reduce the number of postoperative infections and deaths in a multicenter, prospective, randomized trial of 1 100 patients undergoing high-risk gastrointestinal procedures (3). The trial was however stopped because of adverse effects more frequently occurring in patients receiving β-glucan than placebo. No such adverse effects were reported in the present pilot clinical trial, which is in accordance with other trials where oral β-glucan has been administered (9). The microparticulate β-1,3/1,6-glucan used in the present study has however not been shown to enter the systemic circulation, but most likely exerts its major effect in the gastrointestinal tract where macrophages of the gut-associated lymphoid tissue and intestinal epithelial cells are stimulated through a putative pathway involving Toll-like receptors and the β-glucan-receptor, Dectin-1 (10).

The findings of lower leakage of myocardial enzymes postoperatively in Group 2 compared with controls suggest a possible protective effect against myocardial ischemia during CABG in the patients who received the highest dose of β-1,3/1,6-glucan, approximately 20 mg/kg a day, five consecutive days prior to surgery. Furthermore, the curves indicate that β-glucan protects the heart in a dose-dependent manner. We consider this finding interesting as anti-infectious responses to β-glucan pretreatment also has been reported in a dose-dependent manner in experimental animal models (2), paraclinical studies (11) and in clinical trials (11).

There were no differences in the level of acute-phase reactants (C-reactive protein, D-dimer and fibrinogen) or hematological parameters (hemoglobin, hematocrit and white blood cell count) between the groups. Oral β-1,3/1,6-glucan pretreatment also failed to show any differences in cytokines between

Table IV. Postoperative outcome.

	Group 1 β-glucan 350 mg × 2 (n = 11)	Group 2 β-glucan 700 mg × 2 (n = 10)	Group 3 Control (n = 20)	*p*
Atrial fibrillation[a] (n)	5	3	7	0.77
Inotropic agents[b] (n)	1	0	2	0.79
Death within 30 days (n)	0	0	1	1.00

[a]Atrial fibrillation in the postoperative period requiring sotalol or amiodarone at hospital discharge. [b]Inotropic medication required to maintain systolic blood pressure above 90 mm Hg for at least 30 minutes in the intensive care unit.

the groups, except for interleukin-8, which in fact was lower in controls than in patients pre-treated with low dose β-glucan on the fifth postoperative day $p = 0.029$). Hence, we were not able to demonstrate any effect of oral pretreatment with β-1,3/1,6-glucan on attenuation of inflammatory response in the present study. A possible explanation for this finding could be that the anti-inflammatory effects of pre-treatment with β-glucan were obliterated by the powerful inflammatory stimulus accompanied by CABG.

A cardioprotective effect of pretreatment with intraperitoneal injections of β-glucan in rodent hearts subjected to ischemia reperfusion injury has recently been described by Li et al. (5). The protection from ischemia reperfusion injury was found to be mediated through altered cell signalling in the damaged myocardium; inhibiting Toll-like receptor 4 mediated activation of the nuclear factor kappa B (NFk-B) pathway, while stimulating the phosphoinositide 3-kinase/protein kinase B pathway. NFk-B is shown to be activated by ischemia and reperfusion in rodent hearts (12) as well as in human hearts subjected to cardioplegia and reperfusion during open heart surgery (6), and could serve as a therapeutic target in ischemia-reperfusion injury. This assumption is encouraged by the fact that a number of different pharmacological approaches that reduce the activation of NFk-B including β-glucan pretreatment, have been shown to reduce myocardial infarction size (5,13–16). If oral β-glucan pretreatment inhibits cell signalling through NFk-B in damaged myocardium in man, it could be a possible explanation for the lower leakage of myocardial enzymes from patients pre-treated with high dose β-glucan as observed in the present study. This is however to be determined by future research.

The p-values referring to the differences in post-operative levels of creatine kinase isoenzyme MB and cardiac troponin T between the high dose β-glucan group and controls were obtained from Student's t-tests and Levene's test which corrects for the inhomogeneity of variance. As shown in Figure 3 RANOVA failed to show any significant differences in creatinine kinase isoenzyme MB and cardiac troponin T between the three groups, indicating an overall poor statistical power for these differences. Although the groups were matched for age, sex and urgent versus elective surgery, there were differences between the groups regarding the number of patients with COPD and the volume of blood that was retransfused postoperatively. RANOVA was performed to examine whether the presence of COPD and retransfusion volume could explain some of the observed differences in myocardial enzymes between the groups, but revealed no change in mean estimated creatine kinase isoenzyme MB or cardiac troponin T when such adjustments were undertaken.

Although the present study reveals differences in the postoperative leakage of myocardial enzymes between the controls and the high dose β-glucan group, the clinical impact of this observation remains uncertain. There were no differences in clinical outcome which could have been explained by ischemia-reperfusion injury, like perioperative myocardial infarction, the need for inotropic agents/intra aortic balloon pump or atrial fibrillation in the postoperative period. We emphasize that this is a small study in which differences in clinical outcome would be highly unlikely to occur between the groups. Nevertheless, these data support our finding that pretreatment with β-glucan is well tolerated in patients undergoing CABG. Furthermore, our study includes low risk patients with normal left ventricular ejection faction, short aortic clamp time and extra corporeal circulation time who underwent a standard CABG procedure. Clearly, further research is required to establish whether pretreatment with β-glucan could serve as a novel pharmacologic strategy to enhance cardiac protection during cardiac surgery with CPB. We suggest that improvement in clinical outcome after CABG for patients pre-treated with β-glucan could be demonstrated in a larger study involving procedures with longer aortic clamp time.

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