Preoperative lipid-control with simvastatin reduces the risk of postoperative thrombocytosis and thrombotic complications following CABG[1]

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Abstract

Objective: It has earlier been suggested that postoperative thrombocytosis frequently occur after coronary artery bypass grafting (CABG) and may be linked to lipid disturbances. A prospective randomized study was undertaken to evaluate if preoperative lipid-control, using HMG-CoA-reductase inhibitor (Zocor®), simvastatin, reduces the risk of postoperative thrombocytosis. **Methods**: Seventy-seven patients with symptomatic coronary artery disease and hypercholesterolemia (total cholesterol $\geq$ 6.2 mmol/l), planned for CABG where randomly assigned to; undergo CABG without preoperation lipid control (group I, $n = 37$) or undergo simvastatin-treatment (20 mg daily) to control their lipids (4 weeks) prior to CABG (group II, $n = 40$). **Results**: Patient characteristics and operation data did not differ between the groups. Serum-cholesterol, cholesterol/HDL-cholesterol, LDL-cholesterol, Apolipoprotein A1 and Plasminogen were all significantly higher in group I patients compared with group II just prior to surgery. Other laboratory parameters did not differ. **Results**: In group II, total cholesterol and cholesterol/HDL-cholesterol quota were significantly lowered by simvaststin (−2 and −29%, respectively). Post-operative thrombocytosis (platelet counts $\geq$ 400 000/μl) occurred significantly more frequently in group I 81% (30/37) compared with 3% (1/40) in group II, $P < 0.0001$. Myocardial infarction after the 7th postoperative day was more often diagnosed in group I, 14 vs. 0% in group II. Postoperative transient renal failure occurred also more frequently in group I, 24% compared with 8% in group II. Other postoperative complications and laboratory data did not differ. **Conclusions**: This study once again underlines the importance of lipid control using HMG-CoA-reductase inhibitors (e.g. Zocor®) in patients with established coronary artery disease. For the first time it is shown that lipid-control with simvastatin prior to CABG reduces the risk of postoperative thrombocytosis, thus lowers the risk for thrombotic complications. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Myocardial revascularization; Hypercholesterolemia; Thrombocytosis; Lipid lowering drugs

1. Introduction

Major surgical procedures, including cardiac surgery, are known to be followed by altered platelet behaviour. A decrease in platelet count during cardio-pulmonary bypass (CPB) is well documented [1]. This decrease is due to dilution, platelet destruction and adhesion (heparinization and platelet sequestration), which can result in thrombocytopenia and platelet dysfunction and lead to postoperative haemorrhage. Following the initial decrease in platelet counts, a pronounced increase in both platelet count and platelet adhesivity has been noticed.

In recent studies it has been demonstrated that the post-CPB increase in platelet count was overwhelming (postoperative thrombocytosis, platelet count $\geq$400 000/μl) in a large proportion (20–30%) of patients undergoing coronary artery bypass grafting (CABG) [2,3]. This postoperative thrombocytosis was associated with a significant increase in late thrombotic complications such as late vein graft occlusion and myocardial ischaemia and infarction [2,3]. Furthermore, it was found that the only common denomi-

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nator in patients who subsequently developed postoperative thrombocytosis was serum lipid disturbance, in particular presence of hypercholesterolemia [3]. Patients with hypercholesterolemia have increased cholesterol content in the platelet membrane, which may increase the platelet sensitivity to aggregation agents [4,5].

High serum cholesterol is regarded as the main cause of coronary artherosclerosis. Expert panels both in Europe and the USA have therefore recommended dietary changes and, if necessary, addition of drugs to reduce high cholesterol concentrations – specifically low-density-lipoprotein (LDL) cholesterol especially in patients with coronary heart disease. Statins, resins and nicotinic acid are effective in lowering LDL cholesterol [6].

A prospective, randomized study was undertaken to evaluate whether preoperative lipid-control, using an HMG-CoA-reductase inhibitor, simvastatin, (Zocor®, Merck Sharp and Dohme, Whitehouse Station, NJ), reduces the incidence of postoperative thrombocytosis and thus the risk for postoperative thrombotic complications or not.

2. Materials and methods

2.1. Study design

The objectives of the study were to evaluate if pre-operative lipid-control, using the HMG-CoA-reductase inhibitor simvastatin, reduces the risk of postoperative thrombocytosis and thrombotic complications. The study was undertaken between November 1997 and April 1998. The inclusion criteria were: all adult patients with coronary artery disease and hypercholesterolemia (total serum-cholesterol ≥6.2 mmol/l) and planned for myocardial revascularization with CABG were included in the study. A serum lipid profile including total serum cholesterol, HDL-cholesterol, LDL-cholesterol, Triglyceride, Apolipoprotein A1 and lipoprotein(a) was initially analyzed. The patients were randomly assigned either to proceed directly to surgery, Group I (control group), or to undergo a 4 week preoperative treatment with simvastatin, (Zocor®, MSD, Glattbrugg, Switzerland), in order to obtain lipid-control prior to surgery, group II. Simvastatin was administrated in standard doses (normally 20 mg once daily) and renewed lipid profiles were analyzed after 2 treatment weeks and just prior to surgery (4 weeks treatment).

Informed consent was obtained and the study was approved by the Ethics Committee on Human Research, 'Commission d'ethique', Geneva, Switzerland, (Ref. no. 97–19). The study was also approved and registered by Office Intercantonal de contrôle des médicaments, Berne, Switzerland, (Ref. no. 1997S02368).

Postoperative thrombocytosis is defined as platelet counts greater than 400 000/mm^3 on consecutive daily measurements. Platelet count was performed in all patients preo-

peratively and on a daily basis until hospital discharge. Mean platelet volume (MPV) and platelet distributional width (PWD), plasminogen and fibrinogen and platelet adhesivity was measured preoperatively and on the 7th postoperative day. Serum haemoglobin, haematocrit, white blood count, urea and creatinine, as well as creatine phosphokinase (CK) and CK-MB fractions were monitored on a regular basis, together with ECG throughout the postoperative period. Control angiography was not routinely performed postoperatively. Postoperative myocardial infarction is defined as appearance of new Q waves or significant loss of R-wave forces, together with peak creatine kinase-MB fractions greater than 10% of the total creatine kinase.

All preoperative clinical and catheterization data, operative data, as well as registration of postoperative complications were entered into a computer data base at the time of hospitalization. Definitions were made before the start of the study and were not changed during the study period. The left ventricular ejection fraction was calculated from the preoperative ventriculography. All other interventions and procedures were standardized and remained the same for all patients in the two groups.

2.2. Patient profile

A total of 77 patients were admitted in the study, 37 patients in group I, and 40 patients in group II. The mean age was 64.1 ± 10.8 years in group I and 62.7 ± 11.3 years in group II, ($P = 0.59$, not significant). Sex distribution, and preoperative risk factors did not differ between the groups (Table 1). Preoperative lipid profile (group I) and pre-simvastatin treatment lipid profile (group II) revealed a higher total cholesterol level as well as a higher cholesterol/HDL cholesterol quota in group II patients (Table 1). All other preoperative laboratory data did not show significant group differences.

2.3. Angiography data

The mean left ventricular ejection fraction (LVEF) was 0.51 ± 0.12 in group I and 0.49 ± 0.12 in group II, ($P = 0.55$, not significant). In 84% of the patients (65/77) triple vessel coronary artery disease was present and 22% of the patients (17/77) had left main coronary artery stenosis >70%, without group differences.

2.4. Operative and cardiopulmonary bypass techniques

Anaesthesia, CPB and surgical techniques were standardized and did not change during the study period. Two independent surgeons, who were both unaware of the patients group identity, performed all operations. Myocardial revascularization was performed during normothermic CPB (35–37°C). For myocardial protection, intermittent

Table 1

Patient profiles for the two study-groups, group I, controls and group II, preoperatively lipid-control group

	Group I (*n* = 37)		Group II (*n* = 40)		
	N	%	*N*	%	*P*-value
Age, mean ± SD	64.1 ± 10.8		62.7 ± 11.3		0.59 n.s.
Male gender	31	83.8	31	77.5	n.s.
Preoperative risk factors					
Hypertension	20	54.1	19	47.5	n.s.
Diabetes, insulin	5	13.5	5	12.5	n.s.
Diabetes, NID	4	10.8	4	10.0	n.s.
Smoker, current	18	48.7	16	40.0	n.s.
Multifocal vascular disease	8	21.6	8	27.5	n.s.
M.I. within 6 weeks	6	16.2	7	17.5	n.s.
M.I. older than 6 weeks	16	43.2	15	37.5	n.s.
Elective operation	33	89.2	34	85.0	n.s.
Redo-CABG	1	2.7	4	10.0	n.s.
CCS-angina class, mean ± SD	3.5 ± 0.5		3.6 ± 0.50		0.35 n.s.
Lipid profile	Preoperatively (group I)		Pre-simvastatin treatment (group II)		
Total cholesterol	6.6 ± 0.6		6.9 ± 0.5		0.013
HDL-cholesterol	1.4 ± 0.4		1.3 ± 0.3		0.09 n.s.
LDL-cholesterol	4.4 ± 0.9		4.3 ± 1.2		0.80 n.s.
Triglycerides	1.9 ± 1.0		1.7 ± 4.0		0.55 n.s.
Apolipoprotein A1	1.4 ± 0.3		1.2 ± 0.2		0.001
Lipoprotein(a) ≥ 210 mg/l	554 ± 230 (*n* = 28)		472 ± 330 (*n* = 14)		0.35 n.s.
Total cholesterol/HDL quota	5.0 ± 1.4		5.7 ± 1.5		0.04

NID, non-insulin dependent; M.I., myocardial infarction; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society's angina classification; n.s., statistically, no significant difference.

cold crystalloid cardioplegia (St Thomas', with addition of 100 mg allopurinol) along with topical hypothermia with iced slush was employed. All operations were performed through a median sternotomy. A cell-saving device was routinely used.

The internal thoracic artery (harvested as a pediculated graft) was used in 87% of all patients (67/77), sequential vein bypass in 74% of the patients (57/77) and coronary artery thombendarterectomy was performed in three patients (4%) without any statistically significant differences between the groups. No other arterial grafts were used in this series.

On average group I patients received 3.8 ± 1.2 distal anastomoses and group II the average was 3.2 ± 1.2 (*P* = 0.053, not significant). Ischaemia times and cardiopulmonary bypass times did not differ between the groups (60.9 ± 24.7 vs. 63.9 ± 31.9 (*P* = 0.66) and 82.2 ± 34.8 vs. 78.3 ± 31.4 (*P* = 0.61), respectively).

2.5. Statistical analysis

All statistical analyses were performed using computer software StatView v.4.5 (Abacus Concepts, Berkeley, CA). Student's *t*-test, Mann–Whitney and Fisher's exact test were employed to assess differences between groups for statistical significance, where appropriate, as well as Wilcoxin's signed rank test for within-group comparisons. A probability level of *P* < 0.05 was regarded significant. Data

was presented as mean ± standard deviation for continuous variables.

3. Results

3.1. Serum lipids prior to, and after 4 weeks simvastatin treatment

Following 4 weeks simvastatin treatment, the mean total serum cholesterol level in group II patients had decreased by 25 ± 6%, LDL-cholesterol by 32 ± 6% and serum-triglycerides by 14 ± 5%. At the same time HDL-cholesterol levels increased by 7 ± 2% and Apolipoprotein A1 levels increased by 3 ± 1%. The total cholesterol/HDL cholesterol quota decreased significantly from 6 ± 01 prior to simvastatin treatment to 4 ± 1 just prior to surgery, *P* > 0.0001. Platelet counts did not significantly change during simvastatin treatment (Table 2).

3.2. Postoperative thrombocytosis and thrombotic complications

Postoperative thrombocytosis occurred was diagnosed in 30 patients in group I (81%) but in only one patient in group II (3%), *P* < 0.0001. The postoperative thrombocytosis that occurred in this series, followed the same characteristics

Table 2

Serum lipid levels before and after 4 weeks simvastatin treatment in group II patients

	Prior to treatment with simvastatin	4 weeks treatment (= pre-operative)	*P*-value
Total cholesterol	6.9 ± 0.5	5.2 ± 0.6	<0.0001
Range (4.0–6.2 mmol/l)	6.2–7.9	3.7–6.1	
HDL-cholesterol	1.3 ± 0.3	1.4 ± 0.4	0.26 n.s.
Range (>1.10 mmol/l)	0.7–1.8	0.7–2.1	
LDL-cholesterol	4.3 ± 1.2	3.0 ± 0.9	<0.0001
Range (<3.35 mmol/l)	1.6–6.2	1.1–5.0	
Triglycerides	1.7 ± 0.7	1.5 ± 0.7	0.16 n.s.
Range (0.30–1.80 mmol/l)	0.9–4.0	0.6–3.7	
Total cholesterol/ HDL-cholesterol	5.7 ± 1.5	4.1 ± 1.1	<0.0001
Range (<5.0)	3.7–9.5	2.3–6.5	
Apolipoprotein A1	1.2 ± 0.3	1.3 ± 0.3	0.67 n.s.
Range (0.94–1.78 g/l)	0.8–1.8	0.9–1.9	
Lipoprotein(a) (<300 mg/l)			
>210 mg/l	472 ± 330 *n* = 14	544 ± 389 *n* = 13	0.06 n.s.
<210 mg/l[a]	*n* = 26	*n* = 27	

[a]Levels <210 mg/l are not quantified in our laboratory. n.s., statistically, no significant difference. Mean ± SD. Normal values in our laboratory within parenthesis.

described earlier [2], with the diagnosis established by the 7th postoperative day (Fig. 1).

The patient in group II who developed a postoperative thrombocytosis had not normalized his lipids preoperatively and presented prior to surgery with a total cholesterol/HDL-cholesterol quota of 5.5, despite an increased dose of simvastatin (40 mg/day). His peak platelet count was rather low, 448.000/μl, and he sustained no postoperative thrombotic complications.

Late myocardial infarction, caused by symptomatic vein graft occlusion, and transient renal failure was overrepresented in group I patients (Table 3).

3.3. Hospital mortality and other postoperative morbidity

There were no hospital moralities in either of the studied groups. Septicemia, mediastinitis and wound infections did not occur during the study period. Haemorrhage, neurological events and gastro-intestinal complications occurred rarely and were equally distributed between the groups.

Time required postoperatively in the intensive care unit was 2.0 ± 0.9 days in group I and 2.1 ± 0.8 days in group II ($P = 0.61$, not significant). Mean length of hospital stay was 11.5 ± 2.2 days in group I and 11.6 ± 3.2 days in group II ($P = 0.09$, not significant).

4. Discussion

Platelets contribute to thrombosis and may play an important role in atherosclerosis [7]. Postoperative thrombocytosis occur frequently (20–30%) following CABG using CPB and is associated with an increase in late thrombotic complications [2]. Postoperative thrombosis is diagnosed around the 7th postoperative day and may last for as long as 5 weeks [8]. Platelet survival time is shortened in patients with coronary artery disease [9]. The common denominator in patients that subsequently develop postoperative thrombocytosis is hyperlipidemia, especially hypercholesterolemia. Recently an association between lipoprotein(a), tissue plasminogen activator and tissue plasminogen activator inhibitor levels and the presence of arterial atherosclerotic disease has been demonstrated [10].

The plasma levels of total cholesterol and LDL cholesterol are important risk factors for coronary heart disease [11]. European and American recommendations for coronary heart disease prevention put patients with clinically manifest coronary heart disease, or other major atherosclerotic disease, as the top priority for prevention [12,13]

In coronary patients, selected prophylactic drug therapy is indicated in the form of aspirin, beta-blockers, ACE inhibitors and systemic anticoagulants which, together with lipid lowering drug therapy, have all been shown to reduce coronary mortality and improve life expectancy [14–18].

Resins, statins and nicotinic acid are effective in lowering LDL cholesterol, whereas the effect of fibrates on LDL cholesterol are only moderate. Triglycerides are moderately lowered by statins, while HDL cholesterol is slightly or moderately increased by statins [6]. Simvastatin is an inhibitor of hydroxy-methylglutaryl coenzyme A (HMG-CoA) reductase.

In the 4S [18], patients with coronary heart disease (myocardial infarction or angina) and a cholesterol between 5.5 and 8.0 mmol/l (220–320 mg/%) who took simvastatin had a significant (30%) reduction in coronary morbidity and mortality, and a greater life expectancy, compared with those on placebo. This result was reinforced by CARE trial in post myocardial infarction patients with cholesterol below 6.2 mmol/l and an average of 5.4 mmol/l. In patients on pravastatin, there was a 24% reduction in non-fatal myocardial infarction and coronary heart disease death, and this benefit was seen in coronary patients with cholesterol levels down to 4.8 mmol/l [19].

The WOSCOPS trial was a primary prevention trial, but also included some high-risk patients with angina, and similarly demonstrated that diet and pravastatin in men with cholesterol levels above 6.5 mmol/l significantly reduced by 31% the combined end-point of non-fatal myocardial infarction or death from coronary heart disease [20].
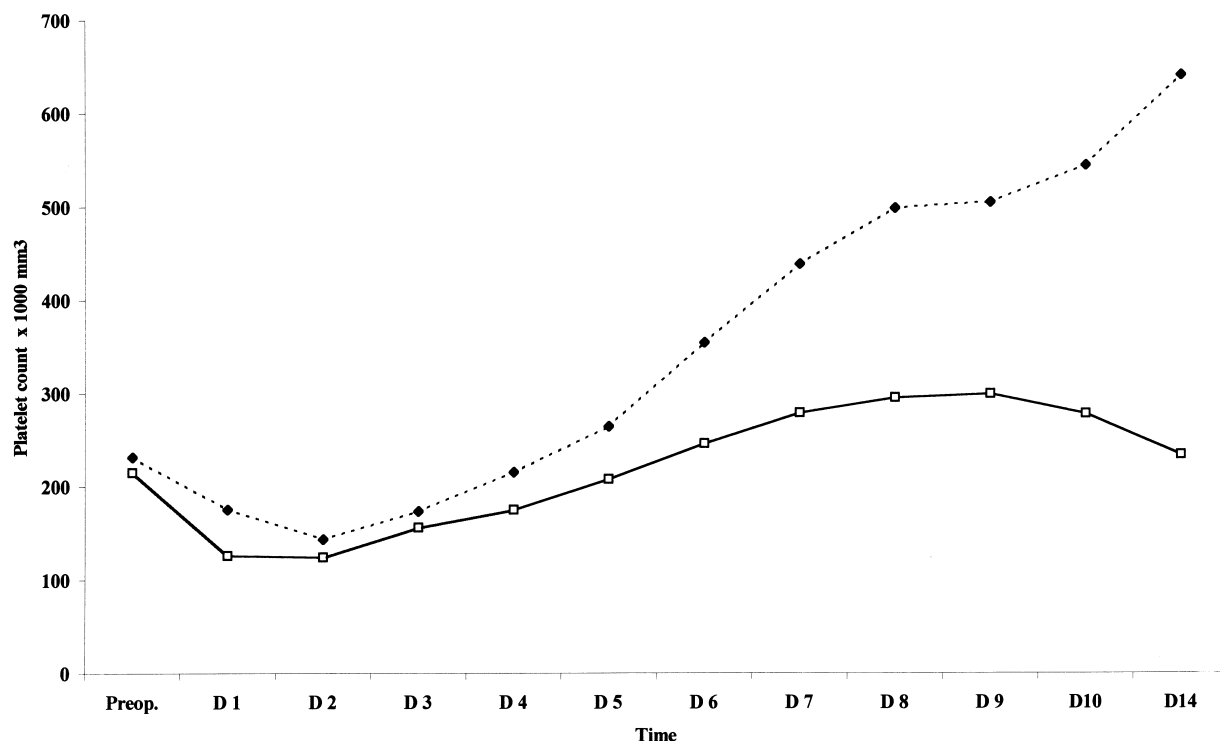
Fig. 1. Preoperative and postoperative platelet counts in the two study groups; group I (♦······♦) control group, and group II (□–□), patients receiving preoperative lipid control with simvastatin.

Despite these overwhelmingly clear data it was, in a recent study, performed in Switzerland, found that only 50% of patients with an established coronary artery disease were treated with acetyl-salicylic acid, 20% with ACE inhibitors, 17% with beta-blockers and only 10% received treatment with statins [21]. Furthermore, it has been shown that when serum cholesterol levels are lowered by drugs, platelet survival increases [22].

The impact of good preoperative lipid control on the incidence of postoperative thrombocytosis and thrombotic complications has not earlier been studied. However, an antiatherothrombotic effect of statins has been described earlier both in animal studies and in patients [23,24]. The present study has clearly demonstrated an anti-thrombotic effect of simvastatin, which is probably independent of the drug's lipid lowering effect, since the anti-thrombotic effect is appears so quickly (following only a few weeks of treatment with simvastatin). Further studies on this interesting feature are required.

The two study groups were comparable regarding preoperative patient characteristics, angiography and operative data as well as preoperative laboratory data.

The limitation of the present study is that we have chosen a total serum-cholesterol level of ≥6.2 mmol/l as the inclusion value, which is the upper normal limit in our laboratory for normal patients. This level may be the suitable one for treatment in patients without artherosclerotic manifestations, but is most likely much too high for coronary patients,

Table 3

Postoperative complications in the two study-groups, group I, controls and group II, preoperative medicamental lipid-control

	Group I ($n = 37$)		Group II ($n = 40$)		
	n	%	n	%	P-value
Thrombocytosis (Platelet count >400000/μl)	30	81	1	3	< 0.0001
Low cardiac output (Cardiac index < 2.0 l/min per m^2)	10	27	8	20	n.s.
Myocardial infarction[a]					
Within 7 days postop.	0	0	0	0	–
Beyond 7 days postop.	5	14	0	0	0.09 n.s.
Transient renal failure[b]	8	22	3	8	0.05 n.s.

[a]Appearance of new Q waves or significant loss of R-wave forces, together with peak creatine kinase-MB fractions greater than 10% of total creatine kinase.
[b]Serum urea ≥ 9 mmol/l and serum creatinine ≥ 125 μmol/l in a patient with normal preoperative values.

where a cholesterol level of ≥4.7 mmol/l has been suggested [6]. The reason for choosing the higher level, was that the patients were scheduled for coronary surgery and there was not enough time to first install a proper dietary regimen.

In the treatment group total serum cholesterol and LDL cholesterol were significantly lowered, and mean serum lipid levels before and during treatment with simvastatin corresponds well to those previously reported on by others [25].

Postoperative thrombocytosis (platelet counts ≥400 000/μl) occurred significantly more frequently in group I 81% (30/37) compared with 3% (1/40) in group II, $P < 0.0001$. Myocardial infarction beyond the 7th postoperative day was more often diagnosed in group I, 14 vs. 0% in group II, and symptomatic vein graft occlusion was diagnosed in all these patients. Postoperative transient renal failure occurred also more frequently in group I, 24% compared with 8% in group II, $P < 0.05$. Other postoperative complications and laboratory data did not differ.

This study once again underlines the importance of lipid control using HMG-CoA-reductase inhibitors (e.g. simvastatin) in patients with established coronary artery disease. For the first time it has been demonstrated that lipid-control with simvastatin prior to CABG reduces the risk of postoperative thrombocytosis, thus lowers the risk for thrombotic complications. These patients are now followed, in order to evaluate the impact also on long-term outcome.

Acknowledgements

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Appendix A. Conference discussion

Dr R. Martinez (*La Laguna, Spain*): Do you use usually antiplatelet or low-weight heparin?

Dr Christenson: According to the protocol that is used at our institu-

tion, these patients all receive anticoagulation therapy postoperatively. If postoperative thrombocytosis occur, aspirin is added to the postoperative treatment. All patients are thus treated in a similar way.

Dr F. Mohr (*Leipzig, Germany*): How do you manage that? Do you postpone the patients when they are referred to your centre for four weeks treatment prior to surgery in order to treat them, or do all the patients get a letter informing them they have to take aspirin?

Dr Christenson: No. Patients are not postponed, but we are reaching a point where we now will issue a recommendation to all the cardiologists, to ensure that patients with hypercholesterolemia receive lipid-lowering drug therapy and have normalized their lipid status prior to surgery.

Dr R. Gutti (*Hyderabad, India*): What is your recommendation to those patients who have preoperative normal lipid levels?

Dr Christenson: Patients with normal lipid levels preoperatively, are just recommended to be followed in a normal fashion.