Clopidogrel did not inhibit platelet function early after coronary bypass surgery: A prospective randomized trial

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Objective: Although the beneficial effect of aspirin prescription after coronary surgery has been established, the efficacy of clopidogrel has never been compared with that of aspirin in the critical early postoperative period. We therefore conducted a prospective, double-blind, randomized controlled trial to compare the efficacies of these antiplatelet regimens.

Methods: Patients undergoing elective primary coronary artery bypass surgery were invited to participate. After the operation, patients were randomized to receive 100 mg aspirin, 325 mg aspirin, or 75 mg clopidogrel tablets daily for 5 days. Our primary outcome measure was platelet aggregation on day 5, expressed as percentage of baseline. Assessment of platelet aggregation was undertaken with the technique of Born.

Results: From September 2002 to July 2003, a total of 54 patients were randomized into the study. There were 2 self-withdrawals and 2 protocol violations, leaving 50 patients for analysis, 34 in the aspirin group and 16 in the clopidogrel arm. Compared with baseline, the mean percentage aggregations with collagen on day 5 were 56% for aspirin and 99% for clopidogrel. The mean difference between the two arms was 42% (95% confidence interval 27%-56%) in favor of aspirin. At the same time point, the effective concentration to inhibit 50% aggregation in the samples from patients randomly assigned to receive clopidogrel were not raised for our entire panel of agonists (changes of -0.04 μg/L for collagen, -0.01 μmol/L for epinephrine, and -0.02 μmol/L for adenosine diphosphate).

Conclusion: Clopidogrel, unlike aspirin, did not inhibit platelet aggregation in the first 5 postoperative days and therefore should not be used as a sole antiplatelet agent early after coronary surgery.

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Antiplatelet therapy after coronary bypass is simple to administer, cost-effective, and critical. Although the beneficial effects of aspirin in the prevention of graft occlusion has been well established, controversies have emerged regarding the optimal aspirin dose[1] and indeed the ideal antiplatelet agent. It has been reported that low-dose aspirin (100 mg) does not effectively inhibit platelet function after coronary surgery,[2] and a subanalysis from the CAPRIE study (Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events) reported striking reductions in the risk of recurrent ischemic events for patients receiving clopidogrel

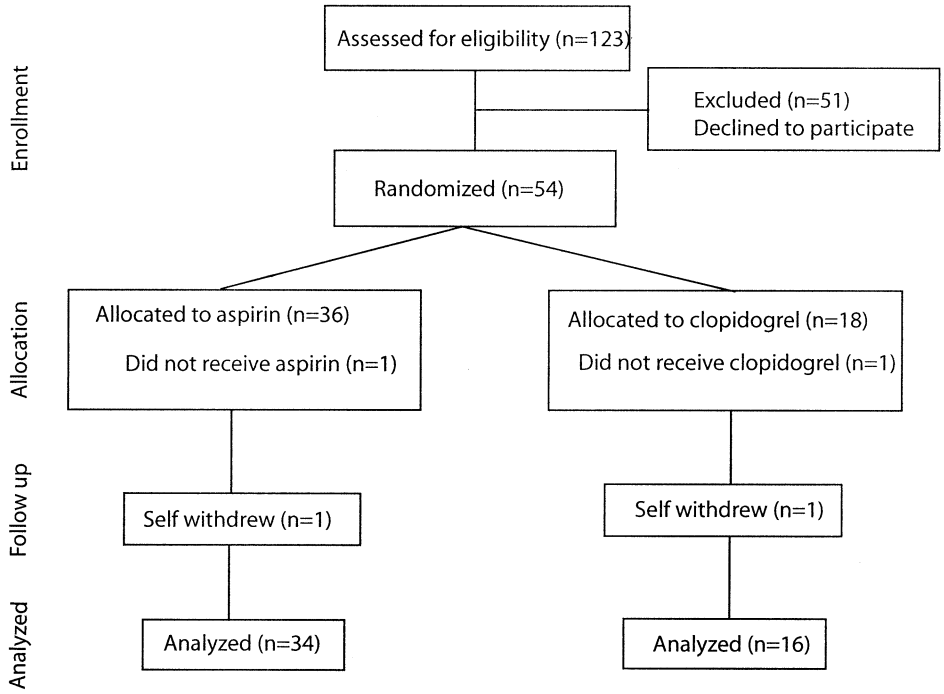

Figure 1. Trial flow diagram.

with previous history of cardiac surgery.[3] This controversy led us to investigate the effects of low- and medium-dose aspirin and clopidogrel (as an alternative antiplatelet agent) on inhibition of platelet function after coronary artery bypass surgery.

Methods

We report here the results of an analysis based on interim data from a local research ethics committee–approved prospective, randomized trial currently in progress at our institution. We planned to recruit 108 patients (36 in each of the three arms), with an interim analysis planned after 54 patients (18 in each arm). We aimed to be able to detect a difference of 30% in postoperative platelet aggregation at day 5 (expressed as a percentage of preoperative values) between any two arms. If this difference was found to be statistically significant (at 2% level), the inferior arm would be stopped. At the analysis stage there would be at least 90% power to detect a difference of at least 1.5 SDs.

All patients undergoing elective primary coronary artery bypass surgery were invited to participate, and we excluded patients if they did not discontinue antiplatelet therapy a week before surgery, had contraindications to aspirin or clopidogrel, were receiving other medications that interact with aspirin or clopidogrel, underwent surgery without cardiopulmonary bypass, received platelet transfusion during the operation or within the first 24 hours, or could not be extubated in the first 24 hours.

No restrictions were placed on operative technique, and cardiopulmonary bypass was driven by a roller pump with a membrane oxygenator with an arterial (but no leukocyte) filter, as standard at our institution. Temperature on bypass ranged between 30°C to 37°C. Tranexamic acid (but not aprotinin) was administered routinely.

On the first postoperative morning, patients were randomly assigned to receive one of the following identically encapsulated treatments: 100 mg aspirin, 325 mg aspirin, or 75 mg clopidogrel daily for 5 days. Randomization was undertaken by the pharmacy into treatment allocation blocks of 6.

Our primary outcome measure was percentage aggregation on day 5 (2 hours after drug administration) expressed as percentage of baseline, with 1.1 μg/L collagen as an agonist. Assessment of platelet aggregation was undertaken according to the technique of Born.[4] Secondary outcome measures were effective concentrations of Horm collagen, adenosine diphosphate (ADP), and epinephrine on day 5 required to produce 50% aggregation (EC_{50}) relative to baseline.

For this analysis, patients were grouped according to treatment allocation of aspirin or clopidogrel. Categoric data are presented as frequency (percentage), and continuous data are given as mean $\pm$ SD or median with interquartile range. Comparisons of categoric data between the two groups were made with the Fisher exact test or Pearson χ^2 test. Continuous data were compared with the Student t test or the Mann-Whitney test as appropriate.

Results

From September 2002 to July 2003, a total of 123 patients were invited to participate, 72 of whom consented to participate in the study. After enrollment, 54 patients were randomly allocated into study groups. Four patients were withdrawn, 2 as self-withdrawals and 2 because of protocol

TABLE 1. Patient characteristics

	Aspirin	Clopidogrel	*P* value
Sample size	36	18	
Age (y, mean ± SD)	65 ± 8	64 ± 8	.67
Mean height, m (SD)	1.7 ± 0.1	1.7 ± 0.1	.28
Mean weight, kg (SD)	86 ± 15	82 ± 11	.35
Male sex (No.)	35 (97%)	17 (94%)	.61
Diabetes (No.)	6 (17%)	5 (28%)	.34
Hypercholesterolemia (No.)	33 (92%)	16 (89%)	.74
Hypertension (No.)	19 (53%)	8 (44%)	.56
Current smoker (No.)	2 (6%)	3 (17%)	.18
No. of grafts (median, IQR)	4 (3–4)	3 (3–4)	.44
Bypass (min, median, IQR)	72 (63–85)	64 (55–78)	.14
Cholesterol lowering therapy (No.)			
None	4 (11%)	1 (6%)	
Atorvastatin	12 (33%)	8 (44%)	
Simvastatin	10 (28%)	3 (17%)	.70
Pravastatin	9 (25%)	6 (33%)	
Fluvastatin	1 (3%)	0 (0%)	

IQR, Interquartile range.

violations (did not receive study medication per protocol), leaving 50 patients for analysis. In total, 34 remained in the aspirin arms and 16 in the clopidogrel arm (Figure 1).

The patients were well matched for baseline characteristics, in particular for the use of atorvastatin (Table 1). For patients randomly assigned to receive clopidogrel, the mean ± SD aggregation with 1.1 μg/L collagen as an agonist on day 5 was 99% ± 15% relative to baseline. At the same time, the EC_{50} concentrations were not raised versus baseline for the entire panel of agonists (−0.04 μg/L for collagen, −0.01 μmol/L for epinephrine, and −0.02 μmol/L for ADP).

For aspirin, the mean aggregation with 1.1 μg/L collagen as an agonist was 56% ± 15% relative to baseline on day 5. The mean difference in aggregation between the two groups at this time point was 42% (95% confidence interval 27%-56%) in favor of aspirin. Further results in both treatment arms are presented in Table 2.

Discussion

There is no stimuli as potent as cardiopulmonary bypass for provoking an inflammatory response. The magnitude of the surgery and exposure to the extracorporeal circuit result in such marked platelet activation that normal pharmacologic response to antiplatelet agents cannot be assumed under these conditions. In healthy volunteers, inhibition of platelet aggregation by clopidogrel occurs 1 hour after dosing, with a mean percentage inhibition of 48.1% by day 5 with 5 μmol/L ADP.[5] However, we found no evidence of inhibition of platelet aggregation by clopidogrel with either ADP, collagen, or epinephrine by day 5 after coronary surgery.

With respect to a recent suggestion regarding the interaction between atorvastatin and clopidogrel[6], we report that the absence of platelet inhibition was observed uniformly in all patients in the clopidogrel arm regardless of whether they were receiving atorvastatin, simvastatin, or pravastatin.

Unfortunately, our study was on the comparative efficacies of three antiplatelet regimens in the early postoperative period and was not focused on why clopidogrel would be ineffective, which was an unexpected finding on interim analysis. Although we assume that the inflammatory response generated from cardiopulmonary bypass is important, it is impossible to discern whether our findings could be explained by inadequate clopidogrel dosage under adverse conditions, high platelet turnover, platelet receptor dysregulation, or the effects of trauma independent of cardiopulmonary bypass. The most likely explanation is an interaction of factors, and clearly other studies are required to provide further insight to the weight of each individual contribution or to offer alternative explanation.

Clinical Implications

What does matter is the timing of antiplatelet administration that is critical within the first week after surgery for the effects of improved graft patency and survival.[7] An early trial revealed that the frequency of new graft occlusions was not improved by aspirin after the first 9 days.[8] More precisely, we assume that the effects of an antiplatelet drug need to be evident within this time (if it is the antiplatelet action that is important in the preservation of graft patency). If 75 mg clopidogrel were to be used as the sole antiplatelet agent, this would be akin to giving patients a placebo in the first week, as previous work suggested that the antiplatelet effects of clopidogrel commences between the ninth and 28th postoperative days.[9]

Although the risk of recurrent ischemic events may be reduced by clopidogrel administration in patients with previous cardiac surgery, it is important to note that clopidogrel was not started immediately after surgery in the CAPRIE study, and patients could have received aspirin right up to entry into the trial. The results of our trial cannot be extrapolated beyond the early postoperative period, and we do not suggest that clopidogrel is ineffective in the long term. However, neither can the beneficial results of clopidogrel (as reported by CAPRIE) be safely extrapolated to the early postoperative phase. We have demonstrated the inefficacy of clopidogrel in this critical time frame. In view of the interim data, the clopidogrel arm has been withdrawn from our trial as we continue to evaluate the efficacy of low- versus medium-dose aspirin.

Conclusion

Because of its inability to inhibit platelet aggregation, clopidogrel at a dose of 75 mg or less should not be used as the sole antiplatelet agent early after coronary artery bypass surgery.

TABLE 2. Change in aggregation

	Aspirin	Clopidogrel	*P* value
Percentage aggregation (day 5 as percentage of baseline)			
Collagen 1.1 μg/L (mean ± SD)	57 ± 26	99 ± 15	<.001
ADP μmol/L (mean ± SD)	115 ± 83	111 ± 55	.87
Epinephrine 0.5 μmol/L (median, IQR)	53 (31 to 78)	99 (85 to 116)	.027
Difference in EC_{50} (day 5 minus baseline)			
Collagen (μg/L, median, IQR)	0.92 (0.71 to 1.4)	−0.04 (−0.10 to 0.050)	<.001
ADP (μmol/L, median, IQR)	0.17 (−0.17 to 0.46)	−0.019 (−0.46 to 0.12)	.23
Epinephrine (μmol/L, median, IQR)	1.3 (0.25 to 3.9)	−0.013 (−0.29 to 0.088)	.001

IQR, Interquartile range; *EC_{50},* effective concentration of agonist to induce 50% aggregation.

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