Ticlopidine in the Prevention of Thrombus Formation after Percutaneous Transluminal Coronary Angioplasty (PTCA)

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Abstract

We studied the additive effect of ticlopidine to aspirin compared with aspirin in the prevention of thrombus formation after PTCA in two groups of 21 patients who underwent PTCA at Her Majesty's Cardiac Centre, Siriraj Hospital from January to April 1993. Patients in both groups were comparable in baseline patient data and characteristics of angiographic lesions. There was no difference in angiographic outcome including the presence of intracoronary thrombus between the two groups. We concluded that ticlopidine had no additive effect to aspirin in the prevention of thrombus formation after PTCA.

In the last decade PTCA has shown an increasing success rate, probably due to an improvement in both operator experience and improved technique. However, two major problems still remain; i.e. early occlusion due to a thrombotic process occurring at the site of angioplasty and late occlusion caused by a process of restenosis.

Early occlusion is a consequence of deep arterial injury resulting from a fracture of atherosclerotic plaque. This exposes subintimal structures; such as collagen, von Willebrand factor, smooth muscle cell or release-tissue thromboplastin, which activates coagulation pathways and platelets.

Postulated mechanisms of acute reocclusion after PTCA include coronary spasm; acute thrombus formation, extension of intimal dissection; and expanding subintimal hematoma[1-4]. Due to the complex mechanism (coagulation and platelets activation) leading to thrombus formation, immediate use of anticoagulant; such as heparin, is a routine for angioplasty and other catheter-base revascularization. It reduces the incidence of acute occlusion[5-9]. This therapeutic approach is based on the assumption that heparin given intravenously inhibits thrombin activation and ultimately limits platelets deposition[10,11].

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Experimental and clinical studies indicate that platelets play a pivotal role in the acute vascular closure that occurs immediately after angioplasty. Antiplatelets such as aspirin, dipyridamole and ticlopidine clearly demonstrate the beneficial effects of antiplatelet activity. This pharmacologic approach is expected to reduce acute complications[12,13] following PTCA. However, a combination of these drugs may or may not add any advantage. So, we designed a study to determine the effect of ticlopidine in addition to aspirin in prevention of thrombus formation after PTCA.

PATIENTS AND METHOD

We studied 21 patients who underwent PTCA from January to April 1993 at Her Majesty's Cardiac Centre, Siriraj Hospital and received ticlopidine 500 mg/day as well as ASA 300 mg/day for at least 2 weeks prior to PTCA.

By using a computer program, we matched these patients for severity of stenosis, lesion characteristics; angioplasty sites, sex, balloon size and age with another 21 patients who received only ASA but no ticlopidine.

All cine films were reviewed by one cardiologist for the presence of thrombus formation without the knowledge of treatment of the patients.

The thrombus was defined as a coarse or granular appearance of vessel intima or a well defined intraluminal defect surrounded by contrast media without evidence of obstruction[14].

The categorical data were expressed as percentage and were compared by using Chi-square test. Quantitative data were expressed as mean ± S.D. and were compared by Student's *t*-test. The p-value less than 0.05 was statistically significant.

RESULTS

There were 42 patients ; 21 in the ticlopidine group (group 1) and another 21 control group (group 2). There was no difference in the ratio between males and females. Mean age of the patients was 58 ± 9 years in group 1 and 59 ± 7 years in group 2. Other characteristics were not different between the two groups (Table 1).

PTCAs were done most commonly in LAD and its branches (71% in group 1 and 57% in group 2). There were several indications for PTCA in the study groups. The major indication was stable angina pectoris (57% in group 1, 43% in group 2). Other indications were unstable angina; angina post MI; acute MI.

The majority of the lesions were type A and type B, TIMI grade 3 flow (67% in group 1 and 76% in group 2) (Table 2 and 3).

Following PTCA, coronary dissection was found in 19 per cent and 23 per cent in group 1 and 2 respectively. The presence of intracoronary thrombus was found 38 per cent in the ticlopidine group and 33 per cent in the other group. There was no statistical significance between the two groups.

Table 1. Patients characteristics of the treatment groups.

	Ticlopidine + ASA	ASA	p-value
Number of patients	21	21	
Age	58.09 ± 9	59.14 ± 7	0.67
Sex M : F	11:10	12:9	1.00
Risk factors			
Cigarette smoking (pack-year)	11.3 ± 19.5	9.6 ± 14.8	0.74
Diabetes mellitus	7 (33%)	9 (43%)	0.53
Hypertension	15 (71%)	10 (48%)	0.17
Hyperlipidemia	7 (33%)	13 (62%)	0.06
Obesity	8 (38%)	9 (43%)	0.75
Indication for PTCA			
Chronic stable angina	12 (57%)	9 (43%)	
Unstable angina	3 (14%)	7 (33%)	
Angina post MI	6 (29%)	3 (13%)	
AMI	-	1 (5%)	
Other	-	1 (5%)	

Abbreviation: AMI = acute myocardial infarction, MI = myocardial infarction

Table 2. Angiographic characteristics of the treatment group before PTCA.

	Ticlopidine + ASA	ASA	p-value
CAD site:			
LAD + DG branches	15 (71%)	12 (57%)	
LCx + OM branches	1 (5%)	2 (10%)	0.61
RCA	5 (24%)	7 (33%)	
Type of lesion:			
type A	8 (38%)	8 (38%)	
type B	12 (57%)	11 (52%)	0.83
type C	1 (5%)	2 (10%)	
TIMI flow:			
grade 0	3 (14%)	3 (14%)	
grade 1	3 (14%)	2 (10%)	0.72
grade 2	1 (5%)	-	
grade 3	14 (67%)	16 (76%)	
Initial stenosis (%)	83.7 ± 12.3	86.9 ± 9.2	0.33
Presence of intracoronary thrombus	1 (5%)	4 (19%)	0.34

Abbreviation : CAD = coronary artery disease, LAD = left anterior descending, DG = diagonal, LCx = left circumflex artery, OM = obtuse marginal, RCA = right coronary artery

Table 3. Angiographic features of the treatment group post PTCA.

Angiographic features	Ticlopidine + ASA	ASA	p-value
TIMI flow :			
grade 0	1 (5%)	2 (10%)	0.48
grade 3	20 (95%)	19 (90%)	
Residual stenosis (%)	24.7 ± 19.5	20.0 ± 21.8	0.47
Presence of intracoronary thrombus	8 (38%)	7 (33%)	0.75
Coronary dissection	4 (19%)	5 (24%)	1.00

DISCUSSION

It has been accepted that the antiplatelets action of ASA reduces the incidence of ischemic complication following interventional procedure. In general, all patients received ASA 300 mg before, on the day of, and each day following the intervention. Because aspirin has been shown to reduce the acute ischemic complication of PTCA so effectively, managing the patient with an aspirin allergy poses a clinical challenge. Unfortunately, other antiplatelet agents drugs; such as dextran have not been demonstrated to be beneficial in preventing acute PTCA complication[15]. Ticlopidine appears to offer effective antiplatelet treatment for aspirin allergic patients undergoing PTCA[6].

Ticlopidine is a thienopyridine that inhibits platelet function in experimental models and in humans. Its inhibitory effects on platelet aggregation in humans appear 24 - 48 hours after administration of 500 mg/day. The mechanism by which ticlopidine inhibits platelet aggregation is completely different from the mechanism of aspirin because it does not have any effect on cyclo-oxygenase. Recent studies indicate that ticlopidine inhibits ADP- mediated platelet aggregation and antagonized the interaction of fibrinogen with its platelet receptor, the membrane glycoprotein II_b - III_a[16]. Hence, it may have additive effect to aspirin.

The best clinical evidence supporting the use of ticlopidine as an antiplatelet agent is in the prevention of stroke. As for it use in coronary artery disease, an Italian study has shown ticlopidine to be effective in reducing vascular death and nonfatal MI in patients with unstable angina[17]. A recent published study from University of Minnesota

showed ticlopidine HCl (250 mg per day) to be as effective as aspirin combined with dipyridamole in preventing the acute ischemic complication of PTCA[11].

The primary intention of this study was to test the hypothesis that ticlopidine had an additive effect to aspirin in prevention of thrombus formation after PTCA. However, there was no difference of thrombus formation post PTCA between the two groups (38% in group 1, 33% in group 2). So, ticlopidine may have no additive effect to ASA in prevention of thrombus formation after PTCA. This may be due to the small number patients in our study. Thus, a larger scale prospective study is required to confirm the result. The incidence of thrombus post PTCA in our study was higher than previous reports (38% and 33%)[3,6]. This result may be due to the small population and inadequate heparinization[9]. We subsequently checked the ACT level as recommended[11] and the incidence of thrombus was expected to be lower.

In summary, we could not demonstrate any additive effect of ticlopidine to aspirin in prevention of thrombus formation following PTCA.

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ผลของทิโคลปิดีน ในการป้องกันการเกิดลิ่มเลือดภายหลังการขยายหลอดเลือดโคโรนารีย์ด้วยลูกโป่ง

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ระหว่างเดือนมกราคม ถึงเมษายน 2536 ได้ทำการศึกษาผลของยา ticlopidine ต่อการป้องกันการเกิดลิ่มเลือดในผู้ป่วยโรคหลอดเลือดหัวใจที่มารับการรักษาด้วยการขยายหลอดเลือดโคโรนารีย์ด้วยลูกโป่ง (PTCA) ที่ศูนย์โรคหัวใจสมเด็จพระบรมราชินีนาถ คณะแพทยศาสตร์ศิริราชพยาบาล พบว่าผู้ป่วย 21 รายที่ได้รับ ticlopidine ร่วมกับ aspirin ก่อนการขยายหลอดเลือด มีอัตราการเกิดลิ่มเลือดภายหลัง PTCA ไม่แตกต่างจากกลุ่มที่ได้รับ aspirin เพียงอย่างเดียว (38%, 33%) ตามลำดับ

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