Veli Gökhan CİN[1]
Ahmet TEMİZHAN[2]
Hasan PEKDEMİR[1]
Mehmet TOKAÇ[2]
Okan TARTANOGLU[2]

The Effects of Ticlopidine in Acute Myocardial Infarction as an Adjunctive Treatment to Aspirin in an Intermediate Term Setting

[1]Department of Cardiology, Faculty of Medicine, Mersin University, Mersin,
[2]Department of Cardiology, Faculty of Medicine, Selçuk University, Konya - Turkey

Abstract: Antiplatelet therapy reduces the risk of subsequent ischemic events in patients suffering from acute myocardial infarction (AMI). In this respect, the multi-agent therapy to be used along with aspirin remains to be determined. In this study, ticlopidine was tried in AMI for its potential additive effects over aspirin. Ninety patients with similar clinical characteristics were involved and were followed up for 3 and 6 months. All patients were assigned to receive ticlopidine plus aspirin or aspirin alone. Major cardiac events such as death and reinfarction were primary end-points whereas the need for revascularization was the secondary end-point at 3 and 6 months. Although no variable was significantly different, it was noteworthy that the ticlopidine group showed less need for revascularization (mainly coronary bypass surgery at 3 and 6 months (15.9% vs. 30.4%, 20.5% vs. 30.4%) and reinfarction rates (4.5% vs. 10.9% and 6.8% vs. 13%). This study was one of the few to evaluate the effects of adjunctive ticlopidine treatment in AMI. Despite the lack of significant superiority over aspirin alone, the additional effects of ticlopidine could be a reduction in reinfarction rates and the need for bypass surgery at 3- and 6-months if more patients were involved. Nevertheless, comprehensive, large-scale studies are essential to disclose the net effect.

Key Words: Acute myocardial infarction, aspirin, ticlopidine

Introduction

The pathophysiology of acute coronary syndromes is common. Basically, the platelets are the mainstay of such a complicated atheromatous plaque. Thus, much effort has been directed towards the blockade of these interestingly activating blood cells. However, all agents employed intentionally can only block one of the pathways involved in thrombogenesis (1). Ticlopidine, an antiplatelet agent, mainly antagonizes ADP-induced platelet aggregation. On the other hand, it is believed to be indirectly blocking the final pathway of fibrinogenesis via glycoprotein IIb/IIIa receptors on platelets (2). The antiaggregant effects of ticlopidine and aspirin in coronary interventions have been published elsewhere (3-5). However, it is not clear to what extent it can contribute in the setting of acute myocardial infarction. Accordingly, our aim was to disclose the difference between monotherapy (aspirin) and therapy in which ticlopidine was used as an adjunct agent to aspirin in acute myocardial infarction in terms of mortality, morbidity and need for revascularization over 3- and 6-month periods.

Materials and Methods

The study was conducted in the Selcuk University, department of cardiology Konya, from January 1998 through June 1998. All the patients were those admitted to the coronary care unit with the diagnosis of AMI, determined by ECG, clinical presentation and enzymatic assay. Patients were randomized to receive aspirin plus ticlopidine or aspirin alone after related adjustment was made with clinical status. All patients underwent maximal treadmill stress testing (Bruce protocol; ST depression $\geq$ 1 mm was considered positive) and echocardiographic examination both at 3- and 6-month intervals.

Two groups were assigned: the aspirin group (AG) and ticlopidine group (TG). After the diagnosis was clarified, 46 patients received standard therapy (aspirin 300 mg, streptokinase 1.5 MU, beta blocker (metoprolol) 25 to 100 mg/day, heparin 5000 U bolus followed by 1000 U/h infusion for 5 to 7 days, nitroglycerin 10-20 µ/min infusion for 12 to 24 h and ramipril 1.25 to 2.5 mg in 24 h and thereafter for 6 months. Meanwhile, TG received plus ticlopidine 250 mg twice daily in 24 h and thereafter for 6 months.

Patients with Killip's class 3-4, those who presented with mechanical complications, post MI angina in 5 days (due to the onset of ticlopidine effect in 2 to 5 days), with compromised hepatic and renal functions were excluded. Patients with signs of pump failure despite ramipril and thiazid diuretics were given dobutamin and/or digoxin. Those with ongoing chest pain and unstable clinical picture due to pump failure or arrhythmias underwent coronary angiography and intervention when appropriate.

A comprehensive biochemical assessment was obtained for each patient focusing on lipid profile within 48 h. All patients underwent echocardiographic examination and treadmill stress test before discharge to stratify the current risk for future events. Holter monitoring, radionuclid studies and even electrophysiologic studies were done when indicated. Patients with low risk were given various doses of aspirin, metoprolol, ramipril, atorvastatin and isosorbide mononitrate for follow-up. Exceptionally, TG patients were called back on day 15 for complete blood count to determine the major side effect, neutropenia. Patients were followed up for a mean duration of 6 months; all attended at 3 and 6 months.

Primary end-points of the study were; recurrent angina, cardiovascular mortality, reinfarction, heart failure and stroke in 6 months. Secondary end-points were coronary angiography and revascularization. During follow-up, all clinical comprehensive laboratory assessments were repeated for each case. Results were analyzed at 3 and 6 months.

Statistics

All statistical calculations were done on SPSS for Windows 8.0. Categoric variables were expressed as counts and percentages. Comparisons of categoric variables were made by Pearson Chi-square test or Fisher's Exact Chi-square test. In identifying statistical significance, Student's t test was used for continuous variables. The Mann-Whitney U test was used for continuous variables with marked standard deviation. A p value of < 0.05 was considered significant. All variables were given as mean ± standard deviation and percentage.

Results

Ninety patients, 82 male, 8 female, mean age 54 ± 10 years in the ticlopidine group, 55 ± 9 years in the aspirin group, were enrolled. Neither group was statistically different in terms of age, gender, risk factors, infarct localization or overall therapy. Left ventricular ejection fractions as a marker of the pump function were almost identical at both echo and left ventriculography between groups (Table 1). When the enzymatic assay for the infarct area was examined no difference between the groups was observed (p > 0.05).

The extent of coronary artery disease was similar in the two groups, as well as the degree of stenosis of epicardial arteries (Table 2). The major side effect of ticlopidine was neutropenia, as expected, seen in 2 (4.5%) patients. However, there was no statistical difference between the groups with respect to the side effect profile. All other tests, concerning hepatic and renal function, were performed for each patient, and no significance was found (p > 0.05) (Table 3).

Neither the primary nor secondary end-points showed any significance, either at 3 months or 6 months, although the reinfarction rate and need for coronary bypass surgery were lower in TG (Table 4; Table 5; 15.9% vs. 30.4% at 3 months, 20.5% vs. 30.4% at 6 months for CABG, 4.5% vs. 10.9% at 3 months, 6.8% vs. 13% at 6 months for reinfarction). Additionally, echocardiographic examination and treadmill stress testing either at 3- or 6-month intervals revealed no difference between the groups with regard to left ventricular systolic functions or recurrent ischemia (p > 0.05) (Table 4).

Discussion

There are many studies evaluating the role of antithrombotic agents in acute coronary syndromes, most of which are published elsewhere (6-8), and built the basis for their routine use in each individual case. The efficacy of aspirin as a single antiaggregant agent seems to be between 35% and 40% at the most, as determined by sophisticated aggregometers (10,11). This naturally raises the issue of a more potent antiplatelet regimen without side effects, which is supposed to bring about more salutary results for the clinician and the patient. The particular question should be whether a successful combination of aspirin and ticlopidine, as in the case of stenting, would act the same way with AMI. In our study, the answer was no, although the reinfarction rate and need for CABG were lower in TG. It is the authors'

Table 1.   Patient Characteristics.

		Ticlopidine (n = 44)	Aspirin (n = 46)	p value
Age		54 ±10	55 ±9	0.330
Gender	Female	3 (7%)	5 (11%)	0.714
	Male	41 (93%)	41 (89%)	0.500
BMI (kg/m^2)		26 ± 2.8	25 ± 2.6	0.250
Smoking		30 (68%)	29 (63%)	0.608
Diabetes Mellitus		10 (23%)	6 (13%)	0.230
Hypertension		15 (34%)	10 (22%)	0.191
Heredity (<45 years)		9 (21%)	6 (13%)	0.346
Hyperlipidemia		21 (48%)	24 (52%)	0.673
Low HDL		12 (27%)	14 (30%)	0.741
Previous MI		9 (26%)	9 (20%)	0.916
İnfarct localization				
	Anterior	22 (50%)	26 (57%)	0.535
	Inferior	16 (36%)	13 (28%)	0.411
	Non-Q wave	6 (14%)	7 (15%)	0.831
Postmenopausal women		3 (7%)	4 (9%)	1.000
Therapy				
	Thrombolytic Therapy	30 (68%)	28 (61%)	0.469
	Aspirin	44 (100%)	46 (100%)	-
	Heparin	44 (100%)	46 (100%)	-
	Beta blockers	15 (34%)	20 (44%)	0.361
	ACE inhibitors	21 (48%)	30 (65%)	0.940
	Nitrates	44 (100%)	46 (100%)	-
	Ca antagonists	21 (48%)	30 (65%)	0.248
	Antiarrhythmics (lidocaine)	4 (9%)	3 (7%)	0.649
	Digitalis	9 (21%)	10 (22%)	0.881
Laboratory				
	Total Cholesterol(mg/dl)	194 ± 44	203 ± 44	0.391
	LDL Cholesterol(mg/dl)	121 ± 40	127 ± 36	0.515
	HDL Cholesterol(mg/dl)	40 ± 9	40 ± 9	0.954
	Triglycerides (mg/dl)	162 ± 74	180 ± 95	0.537
	EF (%)	51 ± 9	50 ± 9	0.50
	ESD* (cm)	3.3 ± 0.43	3.3 ± 0.42	0.58
	EDD* (cm)	4.9 ± 0.38	4.87 ± 0.44	0.21

*ESD: End Systolic Diameter, *EDD: End Diastolic Diameter

Table 2.   Extent of Coronary Artery Disease and Percent Stenosis of Involved Coronary Arteries.

	Ticlopidine (n = 44)	Aspirin (n = 46)	p value
Single Vessel Disease	12 (46.2%)	6 (33.3%)	0.692
Multi Vessel Disease	13 (50%)	11 (61.1%)	0.467
Non-Significant Stenosis	1 (3.8%)	1 (5.6%)	1.000
LAD (% ±)	17 (67 ± 33)	12 (68 ± 32)	0.810
CX (% ±)	9 (35 ± 39)	8 (47 ± 38)	0.337
RCA (% ±)	12 (47 ± 37)	10 (55 ± 37)	0.447

	Ticlopidine (n = 44)	Aspirin (n = 46)	p value
Leucocyte count (cell/mm^3)	6732 ± 1274	6881 ± 1219	0.57
Blood Urea (mg/dl)	34 ± 10	33 ± 7	0.16
Blood Creatinin (mg/dl)	1.03 ± 0.2	0.99 ± 0.2	0.30
SGOT (mg/dl)	30 ± 9	29 ± 7	0.74
SGPT (mg/dl)	25 ± 8	24 ± 9	0.49
Total cholesterol (mg/dl)	213 ± 39	215 ± 32	0.75
LDL (mg/dl)	133 ± 34	139 ± 28	0.42
HDL (mg/dl)	39 ± 8	40 ± 7	0.64
Triglycerides (mg/dl)	205 ± 854	185 ± 63	0.22

Table 3. Biochemical Assay at 6 months.

	Ticlopidine (n = 44)	Aspirin (n = 46)	p value
Treadmill stress testing (positive)			
3rd month	10 (22.7%)	11 (23.9%)	0.894
6th month	8 (18.2%)	13 (28.3%)	0.258
EF (%)			
3rd month	57.42 ± 12.9	54.29 ± 14.8	0.296
6th month	55.48 ± 18.3	55.62 ± 14.5	0.865
Recurrent Angina			
3rd month	22 (50%)	20 (43.5%)	0.535
6th month	25 (56.8%)	25 (54.3%)	0.814
Reinfarction			
3rd month	2 (4.5%)	5 (10.9%)	0.263
6th month	3 (6.8%)	6 (13.0%)	0.325
Mortality			
3rd month	0	1 (2.2%)	0.325
6th month	1 (2.3%)	3 (6.5%)	0.328
CHF			
3rd month	7 (15.9%)	5 (10.9%)	0.482
6th month	7 (15.9%)	5 (10.9%)	0.482
Stroke	0	0	

Table 4. Primary End-Points at 6 months.

		Ticlopidine (n = 44)	Aspirin (n = 46)	p value
Revascularization				
	3rd month	20 (45.5%)	21 (45.7%)	0.985
	6th month	22 (50.0%)	22 (47.8%)	0.837
Revascularization Type				
3rd month	None	24 (54.5%)	25 (54.3%)	0.985
	PTCA-Stent	13 (29.5%)	7 (15.2%)	0.102
	CABG	7 (15.9%)	14 (30.4%)	0.103
6th month	None	22 (50%)	24 (52.2%)	0.837
	PTCA-Stent	12 (27.3%)	7 (15.2%)	0.161
	Re-PTCA-Stent	1 (2.3%)	0	0.489
	CABG	9 (20.5%)	14 (30.4%)	0.278
	Emergency CABG after PTCA or Stent	0	1 (2.2%)	1.000

Table 5. Secondary End-Points at 6 months.

opinion that if a larger group of patients were involved, the difference could be significant.

Contrasting experimental and clinical data on the additional effects of ticlopidine are present in the literature (12-15). On the other hand, there are few studies on combined antiplatelet therapy in the setting of AMI testing the effects of blocking additive antiaggregant pathways other than cyclo-oxygenase inhibition (16,17). The largest trial comparing either aspirin alone vs. aspirin and ticlopidine or ticlopidine alone vs. aspirin and dipyridamol combination comes from Ishikawa et al. (16) with a secondary prevention group trial. All patients in this study received the antiplatelet agents right at the beginning, through a mean duration of 12 ± 1.8 months. The highlighted result was a reduction in MACE (major cardiac events) in the combination arm of the study with aspirin and ticlopidin. (3.1% vs. 7.3%, 40% risk reduction in one year). Another study, conducted by Balsano et al. (17) (STAI), tried to demonstrate the effect of ticlopidine in unstable angina. In this study, ticlopidine showed a 46.8% reduction in MACE compared to aspirin with a 41% reduction. However, it is not clear in this randomized but non-blind study if ticlopidine is superior to aspirin nor was the combination therapy applied during therapy. Farrell et al. (18) carried out an experimental study on 9 otherwise healthy volunteers and 325 mg aspirin was compared with 325 mg aspirin and 250 mg ticlopidine twice daily. On day 5, aggregometric results showed no beneficial additive effect over aspirin alone. Although the figure is tiny, it can give an idea of the negative basis for the combination therapy.

In TIMI-12 (19), it has been shown that the platelet reactivity persists after AMI, until the end of the first month at least. For our part, the possible salutary effect of adjunctive ticlopidine in the long term can be deduced, although this remains to be determined by cumulative data. Similar results have been obtained for aspirin in the Antiplatelet Trialists Colloboration (20) in 1 and 2 year periods, showing the established role of antiplatelet agents in secondary prevention. This is one of the initial studies trying to compare aspirin vs. aspirin and ticlopidine in the setting of AMI, adjusted for age, gender, and medication, AMI localization and secondary prevention.

The major pitfall of our study was the small number of patients involved (90) and the lack of a ticlopidine arm alone during follow-up. However, the effects of ticlopidine as a single antiplatelet in AMI were taken for granted, appearing as a proven surrogate for aspirin. Larger trials are essential in this respect to determine the net effects of the aspirin + ticlopidin combination.

Correspondence author:

Veli Gökhan CİN

Department of Cardiology,

Faculty of Medicine,

Mersin University,

33070 Mersin - TURKEY

References

1. Bang NU, Wilson DB. Normal platelet function and antiplatelet drugs. ACC Current Journal Review January/February: 13-16, 1999.

2. Fuster V, Verstraete M. Hemostasis, thrombosis, fibrinolysis, and cardiovascular disease. Heart disease a textbook of cardiovascular medicine (Ed. Braunwald E.) W.B. Saunders Comp. 5th edition, Philadelphia, 1997, pp: 1809-42.

3. Ishinger TA. Antitrombotics in Interventional Cardiology: Optimizing treatment and strategies. Am J Cardiol 82: 25-28, 1998.

4. Tcheng JE. Glycoprotein IIb/IIIa receptor inhibitors: Putting the EPIC, IMPACT II, RESTORE, and EPILOG trials into perspective. Am J Cardiol 78: 35-40, 1996.

5. Taylor RR, Gibbons FA, Cope GD, et al. Effects of low-dose aspirin on restenosis after coronary angioplasty. Am J Cardiol 68: 874-878, 1991.

6. Califf RM. A perspective on the regulation of the evaluation of new antithrombotic drugs. Am J Cardiol 82: 25-35, 1998.

7. Hennekens CH, Dyken ML, Fuster V. Aspirin as a therapeutic agent in cardiovascular disease. A statement for heathcare professionals from the American Heart Association. 1997.

8. Hennekens CH. Update on aspirin in the treatment and prevention of cardiovascular disease. Am Heart J 137: 9-13, 1999.

9. Steinhubl SR, Tan WA, Foody JM, Topol EJ. Incidence and clinical course of thrombotic thrombocytopenic purpura due to ticlopidine following coronary stenting. EPISTENT Investigators. Evaluation of platelet IIb/IIIa inhibitor for stenting. JAMA 281: 806-10, 1999.

10. Schwartz L, Baurassa MG, Lesperance J, et al. Aspirin and dipyridamole in prevention of restenosis after percutaneous transluminal coronary angioplasty. N Engl J Med 318: 1714-19, 1988.

11. The RISC Group. Risk of myocardial and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. Lancet 336: 827-30, 1990.

12. Rupprecht HJ, Darius H, Borkowski U, et al. Comparison of antiplatelet effects of aspirin, ticlopidine, or their combination after stent implantation. Circulation 97: 1046-52, 1998.

13. Pepine CJ. Aspirin and newer orally active antiplatelet agents in the treatment of the post myocardial infarction patient. JACC 32: 1226-8, 1998.

14. Balsano F, Risson P, Violi F, et al. Antiplatelet treatment with ticlopidine in unstable angina. Circulation 82: 17-26, 1990.

15. Zidar JP. Low-molecular-weight heparins in coronary stenting (the ENTICES trial). Enoxaparin and ticlopidine after elective stenting. Am J Cardiol 82: 29-32, 1998.

16. CAPRIE Steering Committee. A randomized, blinded, trial of clopidogrel versus aspirin in patients at risk of ischemic events (CAPRIE). Lancet 348: 1329-39, 1996.

17. Verstraete M, Fuster V. Thrombogenesis and antithromotic therapy. Hurst's The Heart (Eds. Alexander RW, Schlant SC and Fuster V.) McGraw-Hill, 9th edition, New York, 1998, pp: 1501-51.

18. Farrell TP, Hayes KB, Sobel BE, Schneider DJ. The lack of augmentation by aspirin of inhibition of platelet reactivity by ticlopidine. Am J Cardiol 83: 770-4, 1999.

19. Ault KA, Cannon CP, Mitchell J, et al. Platelet activation in patient after an coronary syndrome: Results from the TIMI-12 Trial. J Am Coll Cardiol 33: 634-9, 1999.

20. Antiplatelet Trialists' Collaboration, anonymous. Collaborative overview of randomised trials of antiplatelet therapy-I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ; 308: 81-106, 1994.