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EFFICACY OF TICLOPIDINE ON PLATELET AGGREGABILITY IN PATIENTS WITH A VVI PACEMAKER

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Several studies have previously reported an increased platelet aggregability in patiens with VVI pacemakers; moreover, some authors have showed that antiplatelet drugs may be effective in reducing platelet aggregation, thus suggesting an increased formation of platelet activation markers in these patients. In this respect, platelet aggregability was investigated in twenty five VVI patients and fifteen control subjects. In addition, β-thromboglobulin (β-TG) and platelet factor 4 (PF_4) plasma levels were measured to determine the degree of platelet activation before and after ticlopidine treatment.

Plasma β-TG and PF_4 levels were significantly increased in VVI patients as compared with control subjects (147.84 ± 44.15 vs 75.64 ± 31.77, P < 0.001 and 62.90 ± 71.93 vs 21.88 ± 11.10, p < 0,001; respectively). Additionally, plasma β-TG and PF_4 levels after ticlopidine treatment were significantly decreased as compared with that before ticlopidine treatment (43.69 ± 16.56 vs 147.84 ± 44.45, P < 0.001 and 15.07 ±7.17 vs 62.90 ± 71.93, P < 0.001; respectively).

Our data confirm an increased of platelet aggregability in patients with VVI pacemakers and show the efficacy of ticlopidine in reducing platelet aggregability.

Key words: *VVI pacemaker, platelet aggregability, β-thromboglobulin, platelet factor 4.*

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VVI pacemakerlı hastalarda tiklopidinin platelet agregabilitedeki etkinliği

Birkaç çalışma VVI pacemakerlı hastalarda platelet agregabilitede bir artış olduğunu daha önceden saptamış idi; üstelik bazı yazarlar, bu hastalarda platelet aktivasyon belirteçlerinin artmış oluşumunu gösteren platelet agregasyonunun azalmasında antiplatelet ilaçların etkili olabildiğini gösterdi. Bu hususta, platelet agregabilite 25 VVI pacemaker hastasında ve 15 kontrol grubunda araştırıldı. Ayrıca, β-thromboglobulin (β-TG) and platelet faktör 4 (PF_4)'ün plazma düzeyleri tiklopidin tedavisi öncesi ve sonrası plateletlerin aktivasyon derecesini saptamak için ölçüldü.

Plazma β-TG and PF_4 düzeyleri kontrol grubuyla karşılaştırıldığında VVI'lı hastalarda önemli ölçüde artmış idi. (Sırasıyla, 147. 84 ± 44.45, 75.64 ± 31.77, P<0.001 ve 62.90 ± 71.93, 21.88 ± 11.10, P < 0.001). Ayrıca ,tiklopidin tedavisi sonrası plazma β-TG ve PF_4 düzeyleri tiklopidin tedavisi öncesindeki düzeylerle karşılaştırıldığında önemli oranda azalmış idi. (Sırasıyla, 43.69±16.56, 147.84 ± 44.45, P < 0.001 ve 15.07 ± 7.17, 62.90 ± 71.93, P < 0.001).

Verilerimiz, VVI pacemakerlı hastalarda platelet agregabilitede bir artış olduğunu doğrulamakta ve platelet agregabiliteyi azaltmakta tiklopidinin etkili olduğunu göstermektedir.

Anahtar kelimeler: *VVI pacemaker, platelet agregabilite, β-thromboglobulin, platelet faktör 4.*

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Some prospective studies have suggested a greater number of thromboembolic events in patients with VVI pacemakers as compared with patients with DDD or AAI pacemakers [1,6]. Fazio et al [7] showed that long term treatment with an antiplatelet drug is effective in reducing thromboembolic events in VVI patients, thus suggesting an increased formation of platelet thrombi in these patients. Moreover, Sasaki et a [8] reported that in a group of patients with VVI pacemaker treated with anticoagulants the incidence of thromboembolic episodes was significantly lower when compared with that occurring in control subjects.

The aim of the present study was to evaluate whether short-term treatment (12 weeks) with ticlopidine reduces platelet aggregability in patients with VVI pacemakers.

PATIENTS AND METHODS

Twenty-five patients (mean age 54 ± 9 years, range from 32 to 80) with VVI pacemakers were included in the study. All patients with VVI pacemakers were treated with ticlopidine (250 mg twice daily) for a duration of 3 months. Seventeen patients were men and 8 were women. Additionally, fifteen normal volunteers (mean age 27 ± 5 years, range from 18 to 32) with no history or physical findings of cardiovascular disease were studied, five patients had systemic hypertension, 3 diabetes mellitus and 2 congestive heart failure.

Measurement of plasma levels of β-thromboglobulin (β-TG) and platelet factor 4 (PF_4) were performed to detect increased platelet activation before and after treatment.

We have used a commercial kit for the assay of B-TG and PF_4 [9]. Blood samples were collected in the tubes provided by the manufacturer of the commercial kit previously stored at 0°C. Venipuncture was performed in the shortest possible time (<2 min) to avoid platelet activation.

All values were expressed as mean ± SD. The two-tailed unpaired student t-test was used for statistical analysis. A p value of< 0.05 was taken as significant.

RESULTS

Table 1 shows plasma β-TG, PF_4 levels in VVI patients and control subjects. Plasma β-TG and PF_4 levels were significantly increased in VVI patients as compared with control subjects (P < 0.001).

Table 1. Plasma β-TG, PF_4 levels in VVI patients and control subjects

	PM N: 25	CS N: 15	P Value
β-TG	147.84 ± 44.45	75.64 ± 31.77	P < 0.001
PF_4	62.90 ± 71.93	21.88 ± 11.10	P < 0.001

β-TG = β-thromboglobulin; PF_4 = Platelet factor 4;

CS= Control subjects PM= Patients with pacemaker

Table 2 shows plasma β-TG, PF_4 levels in VVI patients before and after ticlopidine treatment. After 12 weeks of ticlopidine treatment, there was a significant reduction of plasma β-TG and PF_4 levels in patients with VVI pacemakers (P<0.001).

Table 2. Plasma β-TG, PF_4 levels in VVI patients before and after ticlopidine treatment.

	PM-BT N: 25	PM-AT N: 15	P Value
β-TG	147.84 ± 44.45	43.69 ± 16.56	P < 0.001
PF_4	62.90 ± 71.93	15.07 ± 7.17	P < 0.001

β-TG = β-thromboglobulin; PF_4 = Platelet factor 4;

PM-BT= Patients with pacemaker before treatment; PM-AT= Patients with pacemaker after treatment.

DISCUSSION

Many studies have showed that platelet inhibitors may improve prognosis in patients with cardiovascular disease, such as myocardial infarction, transient ischemic attack, and stroke [10,11]. Some reports have specifically demonstrated that patients with VVI pacemakers have an inreased incidence of thromboembolic events, thus suggesting that in these patients there is an increased formation of platelet thrombi[12, 13]. The major mechanisms that could explain the increased platelet activation are: (1) The atrioventricular asynchronism that causes numerous atrial contractions against closed atrioventricular values[6]; (2) The presence of the lead in the

right ventricle[14]; (3) The old age of the patients with pacemaker; (4) The interventricular and intraventricular asynchronism of contraction[15].

Platelet activation was evaluated by measuring plasma levels of both platelet factor 4 (PF_4) and β-thromboglobulin, which are platelet specific proteins secreted from the granules during the reaction[16,17]. PF_4 binds to the endothelial surface heparin- like molecules and hence has a short half life, whereas β-thromboglobulin is not bound by vascular endothelium.

Ticlopidine is a platelet inhibitor drug that acts by interfering with fibrinogen and the Von Willebrand factor binding to platelets. It prolongs the bleeding time and block the platelet release reaction[18, 20]. Therefore, the plasma levels of β-TG and PF_4 were measured to determine the efficacy of antiplatelet drug therapy.

The results of the study demonstrate that an increase of platelet aggregability is present in patients with VVI pacemaker and that short-term treatment (12 weeeks) with ticlopidine produces a significant reduction of platelet aggregability in VVI patients.

In a previous study, Fazio et al[7] observed a reduction of thromboembolic events in patients with a VVI pacemaker treated with ticlopidine, which supports the hypothesis of an increase of paletelet activity in these patients. Therefore, even if our data are not conclusive for the presence of a precise causal relationship between plasma β-TG, PF_4 levels and increase of thromboembolic events observed in patients with a VVI pacemaker, the present study have reported the efficacy of ticlopidine (250 mg twice daily) in reducing platelet activation in patients with VVI pacemakers.

The primary analysis of efficacy was based on a pronounced reduction of platelet activatior markers. For this reason, β-TG and PF_4 levels may be a means of monitoring the efficacy of antiplatelet drug therapy.

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