The Evaluation of In Vitro Effects of Dipyridamole on Coronary Artery Bypass Grafts

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ABSTRACT

Objective: The aim of this study is to evaluate the efficacy of dipyridamole in relieving the vasospasm of coronary artery bypass grafts.

Material and Methods: Twenty two patients who underwent elective coronary artery bypass grafting (CABG) were admitted to the study (Men/Women: 14/8, mean age: 62.4±8.8 years). Ten samples from left internal mammary (LIMA), radial arterial (RA) and saphenous vein (SV) grafts were collected for each. The samples were transported to the vascular laboratory in 4°C Krebs solution. Submaximal smooth muscle contraction was achieved first by 10−7M of phenylephrine solution. Dipyridamole was then added, starting from a concentration of 10−9M to a concentration of 10−3.5M in two minutes intervals and half logarithmic dose increments. The concentration-response curves were obtained of the vasodilatation response relative to the beginning.

Results: In the LIMA graft samples, the vasodilation response to dipyridamole was 43.2±1.6% and 97.6±4.1% at concentrations of 10−6M and 10−3.5M respectively. In RA graft samples, the vasodilation response to dipyridamole was 36.3±1.8% and 95.3±2.7% at concentrations of 10−6M and 10−3.5M respectively. In SV graft samples, however, the vasodilation response to dipyridamole was 43.2±1.4% and 96.6±2.2% at concentrations of 10−6M and 10−3.5M respectively.

Conclusions: The amplitude of relaxation response to dipyridamole of all graft samples were similar, without statistically significant difference among the LIMA, RA and SV grafts in the in vitro tissue bath system. These results prove that dipyridamole has a potential use as a vasodilatory drug in all graft types.

Key Words: Dipyridamole, coronary artery bypass graft, left internal mammary artery, radial artery, saphenous vein.

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Introduction

The importance of coronary artery bypass grafting (CABG) and the different types of grafts consequently has increased due to a rising incidence of cardiovascular diseases. In CABG, myocardial ischemia is relieved by the use of grafts resulting in a higher quality of life in patients. The internal mammary artery (IMA), radial artery (RA) and saphenous vein (SV) grafts are the most frequently used grafts for this purpose (1-3). The choice and preparation of the optimum graft is critical in the long term graft patency. Mechanical trauma or the pharmacological agents used during the preparation of the graft are known to have a negative impact on long term graft patency (1-3). Several studies have addressed the ways to prevent spasm of arterial or venous grafts. Vasodilators like papaverin, diltiazem and nitroglycerine are widely used for this purpose but the data on the efficacy of dipyridamole is very limited.

Dipyridamole, which was first introduced 50 years ago as a coronary vasodilator, increases interstitial adenosine concentration by blocking adenosine uptake and relieves ischemia. It is widely used in coronary and peripheral arterial disease, restenosis and stroke (4).

The aim of this study is to evaluate the efficacy of dipyridamole in relieving vasospasm of coronary artery bypass grafts under in vitro conditions.

Material and Methods

Graft Sampling

Twenty two patients (14 men and 8 women) were included in the study after the approval of the local ethics committee. The mean age was 62.4±8.8 (42-77) years. Ten samples were studied for LIMA, RA and SV grafts each. In total, 30 vessel samples were studied in an organ bath setting.

Organ Bath

The LIMA and RA grafts were collected together with the adjacent vein, fascia and adipose tissue with the aid of dissection scissors. The graft tissues were not exposed to any vasoactive drug. The SV samples were collected without being inflated to prevent barotrauma. The samples were transported to the vascular laboratory in 4°C Krebs solution, which contained (mM) NaCl 122, KCl 5, CaCl2 1.25, NaHCO3 25, NaHPO4 1.2, KH2PO4 1.0, glucose 11.5. Ten mililiters of solution found...
in the tissue bath was continously oxygenated by 95% O₂ and 5% CO₂. The grafts were dissected from the adjacent tissues and was sliced into 3mm width vascular rings under the microscope. The vascular rings were suspended into the classical tissue bath system via steel hooks. The upper end of the hook was attached to a tension transducer and the lower end was kept stable. Active tension of 1 to 4 gr, was applied to all of the samples. The vascular rings were suspended under this tension for a minimum of 60 minutes. The samples were kept alive by 37ºC oxygenated Krebs solution baths every 20 minutes. In order to measure the relaxation response, the samples were exposed to phenylephrine (Merck, Turkey) (10⁻⁷M) first for submaximal constriction. Dipyridamole (Persantin Ampule, Boehringer Ingelheim, Spain) was then added starting from a concentration of 10⁻⁹M in two minutes intervals and the dose incremented half logarithmically until a concentraion of 10⁻³M was reached. The concentration-response curves were obtained. The data were transferred to the computer with the help of the Transducer Acquisition System (COMMAT TDA-10-A, COMMAT, Turkey) and was stored as POLWIN97.

Statistical analysis
The statistical analysis of the data was performed by Graphpad Prism 4 Version Demo. The concentration-response curves were also constructed by this program. Nonlinear regression analysis (variable slope) and one way ANOVA were applied to the graphics. A value of $p<0.05$ represented the statistically significance cut-off value.

Results
The vasodilatation response to dipyridamole was studied in phenyephrine pre-treated graft samples. In the LIMA graft samples, the vasodilatation response to dipyridamole was 43.2%±1.6% at a concentration of 10⁻⁶M and reached its maximal response (97.6± 4.1) at a concentration of 10⁻³M (Figure 1).

In RA graft samples, the vasodilatation response to dipyridamole was 36.3%±1.8% at a concentration of 10⁻⁶M and was 95.3%±2.7% at a concentration of 10⁻³M (Figure 2).

In SV graft samples, however, the vasodilatation response to dipyridamole was 43.2±1.4% at a concentration of 10⁻⁶M and 96.6%±2.2% at a concentration of 10⁻³M (Figure 3).

Figure 4 demonstrates the vasodilatation response curves of all three tissue samples reveal the fact that no statistically significant difference exists among the samples, all of which respond with the same amount of vasodilatation.

Discussion
Dipyridamole, which is a well-known antiplatelet drug, has also been demonstrated to inhibit human and rabbit vascular smooth muscle cell proliferation in vitro. Dipyridamole acts through the metabolism and transport of adenosine by preventing the reuptake of adenosine by erythrocytes and other cells, increasing intravascular adenosine levels and thereby reducing the cyclic adenosine monophosphate (cAMP) intracellularly, causing vasodilatation (5-10). Due to its vasodilatory feature, it is a widely used drug in coronary and peripheral vascular diseases (11-13).
Chrillo et al. (14), investigated the augmentation of flow rates in IMA and SV grafts by dipyridamole induced stress echocardiography in patients with CABG. They found the same amount of increase with dipyridamole both in SV and IMA grafts. This in vivo experiment is in concordance with our in vitro findings.

Vroom et al. (9), used phosphodiesterase III enzyme inhibitors and demonstrated vasodilation in small arteries independent of potassium channels or nitric oxide release. However, we studied both larger sized arteries and veins, where we showed that dipyridamole has the same vasodilatory effects on both.

In conclusion, dipyridamole induced vasodilatation response studied in an in vitro tissue bath system has produced the same amount of vasodilatation in all IMA, RA and SV grafts.

Conflict of Interest
No conflict of interest was declared by the authors.

References
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