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In Vivo Effects of Nonionic and Ionic Contrast Media on Beta-Thromboglobulin and Fibrinopeptide Levels

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Nonionic contrast media are suggested to cause increased thromboembolism (in vivo), platelet aggregation and procoagulant effect (in vitro) as compared with ionic contrast media. To study these effects in vivo, 30 consecutive patients undergoing routine angiography were prospectively randomized to three groups of 10 patients each. Group A received diatrizoate (ionic, high osmolality), Group B ioxaglate (ionic, low osmolality) and Group C iohexol (nonionic, low osmolality). In vivo platelet alpha-granule release and fibrin-1 formation were measured by radioimmunoassay of beta-thromboglobulin and fibrinopeptide A in peripheral venous samples. Levels were estimated at three stages during the procedure: before and after left ventriculography and after coronary angiography. No differences were noted (p = NS) when the ratios of beta-thromboglobulin and fibrinopeptide A were compared among the three groups. These data suggest that the newer nonionic contrast media do not demonstrate enhanced systemic platelet activation or fibrin formation as compared with standard ionic contrast media. However, larger randomized clinical studies are necessary to conclusively establish the suggested thromboembolic potential of nonionic contrast media.

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The introduction of nonionic contrast media for angiography has been a significant advance (1,2). However, the hemodynamic advantages of nonionic contrast media over conventional ionic, high osmolality contrast media during routine angiography have been tempered by the high cost and reports of prothrombotic effects of these agents. Nonionic contrast media are suggested to cause increased thromboembolism during cardiac catheterization (3,4). In vitro studies (5–8) also suggest that they are associated with increased platelet aggregation, loss of anticoagulant effect and increased clot formation; however, their in vivo effects have not been well studied. Therefore, we conducted a prospective randomized study during cardiac catheterization to compare the effects on platelet activation and fibrin formation of a conventional contrast medium with those of newer nonionic contrast media. Markers of platelet activation (beta-thromboglobulin) and fibrin formation (fibrinopeptide A) were measured by radioimmunoassay before and after routine cardiac catheterization. Beta-thromboglobulin is a specific marker for platelet alpha-granule release (9,10). Fibrinopeptide A is a 16 amino acid peptide that is cleaved from fibrinogen by thrombin and reflects fibrin-1 formation (11,12).

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Methods

Study patients. The study group consisted of 30 consecutive patients undergoing routine diagnostic left heart angiography (coronary angiography and left ventriculography). The group included 14 men and 16 women with a mean age of 58 years (range 42 to 78). Patients previously receiving heparin, warfarin or aspirin therapy and patients with known thromboembolic disorders, a prosthetic valve, a permanent pacemaker, valvular disease, cardiomyopathy, previous myocardial infarction, unstable angina or renal failure were excluded from the study. The patients' medical regimen was unaltered during the study. Of the 65 patients surveyed, 35 were excluded from the study because of the presence of recent myocardial infarction in 11 and unstable angina in 6, the use of anticoagulant or antiplatelet agents in 12 and other reasons in 6.

The 30 patients were randomized to three groups of 10 patients each: Group A received diatrizoate meglumine and diatrizoate sodium 370 (ionic, high osmolality), Group B received ioxaglate 320 (ionic, low osmolality) and Group C received iohexol 300 (nonionic, low osmolality) during cardiac catheterization. The operators were aware of the contrast medium used during the procedure. Informed consent was obtained from all patients for participation in the study according to a protocol approved by the Committee on Human Investigation at our institution.

Cardiac catheterization. Left heart catheterization was performed by standard Judkins technique with use of 7F USCI nycore (polyurethane overjacket and nylon inner core) catheters. Both the femoral artery and vein were cannulated with 8F Teflon sheaths (USCI) by standard Seldinger tech-

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nique and 7F pigtail catheters were inserted over a wire system. Before entry of the pigtail catheter into the left ventricle, heparin (3,000 U) was delivered into the venous system. Left ventriculography, performed with use of 45 ml of contrast medium, was followed by right coronary angiography in two orthogonal views and left coronary angiography in at least four projections. The total time required for angiography after insertion of sheaths to the last left coronary angiogram was noted (mean 20 min, range 14 to 31). The total volume of contrast medium used for the group averaged 85 ml (range 65 to 105).

Blood processing and radioimmunoassay. Peripheral venous blood samples were collected with a 21 gauge scalp vein needle from an antecubital vein; a separate venipuncture was used for each sample. Only samples obtained from venipunctures followed by smooth flow of blood were utilized. Blood samples were rejected if a hematoma developed, blood flow stopped on withdrawal or the plasma after centrifuging showed hemolysis. Venous blood (9 ml) was withdrawn into a 10 ml polypropylene syringe and immediately transferred to a tube containing 1 ml of the following anticoagulant solution: 0.10 *M* sodium chloride, 0.05 *M* HEPES buffer (pH 7.4), 1,400 U/ml heparin, 10 m*M* adenosine, 20 m*M* theophylline and 1,000 U/ml aprotinin (Frasylol) (FBA Pharmaceuticals, Inc.). Blood samples were immediately placed on melting ice and within 1 h were centrifuged at 3,000 *g* and 4°C for 20 min. The supernatant plasma was transferred to polypropylene tubes with a siliconized pipette and centrifuged at 49,000 *g* for 15 min at 4°C. The resulting platelet-poor plasma was stored frozen at −80°C. Fibrinopeptide A and beta-thromboglobulin levels were measured by radioimmunoassay as described previously (10,12). Three sets of data were estimated for both beta-thromboglobulin and fibrinopeptide A for each patient. These were collected after insertion of the femoral sheaths and after heparinization, immediately after left ventriculography and later after the last coronary angiogram.

Statistical analysis. Plasma levels of fibrinopeptide A and beta-thromboglobulin were analyzed after logarithmic transformation and reported as geometric mean values and standard errors of the geometric mean. The ratio of levels before and after left ventriculography and before left ventriculography and after coronary angiography were compared among the three groups by analysis of variance. A p value < 0.05 was considered significant.

Results

Fibrinopeptide and beta-thromboglobulin levels. There were no statistically significant differences among the three groups when the ratio of fibrinopeptide levels was compared either before and after left ventriculography (Fig. 1) or before left ventriculography and after coronary angiography (Fig. 2). Similarly, there were no statistically significant differences among the three groups when the ratio of beta-thromboglobulin levels was compared for the same periods (Fig. 3 and 4).

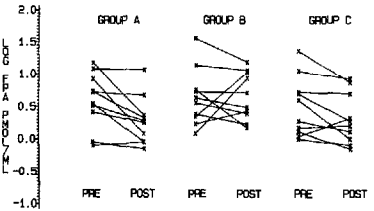
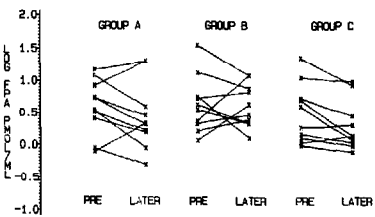


Figure 1. Comparison of levels of fibrinopeptide A (FPA) (pmol/ml) before (PRE) and after (POST) left ventriculography among the three groups (10 patients in each group). No statistically significant differences were found when the ratio of levels for the three groups was compared.

Discussion

Conventional ionic radiocontrast media infusions are associated with a variety of adverse reactions as outlined in a recent review (13). The newer nonionic, low osmolality contrast media have been recognized in clinical studies (1,2) as less chemotoxic, as causing less hemodynamic impairment and as more biocompatible in vitro than ionic contrast media. However, it was recently suggested that the use of nonionic contrast media may be associated with an increased incidence of thromboembolic complications. Robertson (3) suggested that there is enhanced blood clot formation in angiographic syringes containing nonionic than in those containing ionic contrast medium. Grollman et al. (4) reported thromboembolic complications occurring during di-

Figure 2. Comparison of levels of fibrinopeptide A (FPA) (pmol/ml) before left ventriculography (PRE) and after coronary angiography (LATER) among the three groups (10 patients in each group). No statistically significant differences were found when the ratio of levels for the three groups was compared.



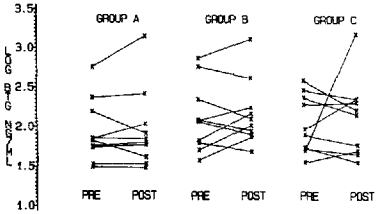
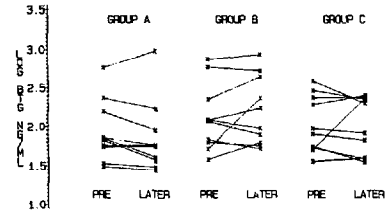


Figure 3. Comparison of levels of beta-thromboglobulin (BTG) (ng/ml) before (PRE) and after (POST) left ventriculography among the three groups (10 patients in each group). No statistically significant differences were found when the ratio of levels for the three groups was compared.

agnostic coronary arteriography in three patients despite prior heparinization.

Reported thrombotic effects of nonionic contrast media. Although in vitro evidence suggests that ionic contrast media tend to have a greater anticoagulant effect than do nonionic media, there are few supportive data in vivo (5–7). Contrast media have several effects on the hemostatic system, with the putative mechanism being binding of individual enzymes and inhibition of fibrin polymerization (6). Contrast media inhibit platelet aggregation in vitro and in vivo (6), may damage the endothelium at the injection site because of high osmolality and may activate coagulation, fibrinolytic and kallikrein systems. Dawson et al. (5) in in vitro studies reported that all contrast media inhibit platelet aggregation and fibrin formation but cause no direct activation of fibrinolysis. Stormoken et al. (6) in an in vitro and in vivo study during cerebral angiography observed a negligible influence of contrast medium on systemic hemostatic variables, but catheter-derived samples indicated the need for premedication with aspirin or heparin. Kopko et al. (7) observed thrombin generation in a contrast agent-whole blood mixture in in vitro experiments and noted that iohexol may permit thrombin generation to occur in vivo. Our study showed no systemic difference in beta-thromboglobulin or fibrinopeptide levels, suggesting no difference in platelet activation or fibrin formation in vivo, not unlike the study of Stormoken et al. (6). To allow for variations in artifactual activation of these levels during catheterization, the ratio of levels rather than the absolute levels was compared among the three study groups. In addition, the volume of contrast medium utilized and the time between estimation of levels were not different for the three groups and the catheterization protocol was kept rigorously similar for all patients. No clinical thromboembolic event occurred during our studies.

Figure 4. Comparison of levels of beta-thromboglobulin (BTG) (ng/ml) before left ventriculography (PRE) and after coronary angiography (LATER) among the three groups (10 patients in each group). No statistically significant differences were found when the ratio of levels for the three groups was compared.



Limitations of study. The lack of statistically significant differences in vivo, as in the study of Stormoken et al. (6), suggests that the concentrations in vivo may be too small to reflect differences in vitro. The use before angiography of heparin, which is an effective inhibitor of thrombin and other enzyme precursors in the coagulation system, may variably alter levels of release of these enzymes. Although this study did not show enhanced systemic platelet activation and fibrin formation among the various contrast media, other sites of measurements, downstream of the coronary artery or in the coronary sinus, may show differences. This would test the mechanism of thrombus formation by interplay of nonionic contrast medium and endothelium. In addition, estimations of thrombin and thrombin-antithrombin complex may demonstrate inhibition of fibrin polymerization rather than of fibrinopeptide A.

Clinical implications. Although this study shows no systemic differences in platelet activation and fibrin formation between ionic and nonionic contrast media, care must be taken when nonionic contrast media are used during cardiac or cerebral angiography. Continuous flushing with saline solution to prevent mixing of blood and contrast medium, premedication with heparin and use of plastic syringes remain important recommendations for the safe use of nonionic contrast media. Larger randomized clinical trials are required to conclusively determine the suggested thromboembolic potential of nonionic contrast media.

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