Effect of the Radiographic Contrast Material Iopamidol on Hemostasis: An Observational Study in Thirty Cardiac Patients

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ABSTRACT

Background: In vitro studies have shown that nonionic radiographic contrast material may induce the generation of thrombin in blood, whereas ionic contrast agents, such as iohexol, do not. However, knowledge of the effects of contrast material on coagulation and fibrinolytic systems in vivo is limited.

Objective: This study was designed to assess the effects of the nonionic radiographic contrast material iopamidol on hemostasis in patients undergoing coronary angiography or cardiac catheterization.

Methods: Patients aged ≥ 18 years with chest pain and/or dyspnea who underwent coronary angiography or cardiac catheterization with intra-arterial contrast material were assessed for hemostasis. Blood samples were drawn before and 3 minutes after injection of iopamidol. Complete blood count and coagulation profile (bleeding time, clotting time, clot retraction time, euglobulin lysis time [ELT], prothrombin and partial thromboplastin times, coagulation factor I [CFI] level, and platelet factor 3 [PF-3] availability) were assessed. The natural coagulation inhibitors protein C, protein S, and antithrombin III (AT-III) also were measured.

Results: Thirty patients (7 males, 23 females; mean [SD] age, 51.3 [20.2] years; range, 17–79 years) were included in this single-center study. All hematologic variables (hemoglobin, white blood cell count, and platelet count) decreased significantly ($P < 0.001$, $P < 0.001$, and $P < 0.05$, respectively) after administration of iopamidol but remained within normal limits. Mean levels of protein C, protein S, and AT-III did not change significantly after administration of iopamidol. Bleeding time was not changed significantly, and PF-3 availability was prolonged in both groups, but the changes were not statistically significant.

Conclusions: In this study population, although hemostasis remained grossly intact after injection of nonionic contrast material, the coagulation system may have been affected by the accelerated consumption of CFI and platelets.

The affected variables were platelets, clot retraction time, ELT, and natural coagulation inhibitors (protein C, protein S, and AT-III). Although the natural coagulation inhibitors remained within the normal range, the correlations were found significant. These changes in hemostasis affected the vascular phase. If the vascular compartment, especially the endothelium, remained intact, the infusion of nonionic agents in low concentrations might be safe for angiography and other procedures; however, more studies are needed. (*Curr Ther Res Clin Exp.* 2003;64:461–472) Copyright © 2003 Excerpta Medica, Inc.

Key words: iopamidol, contrast material, hemostasis, natural coagulation inhibitors.

INTRODUCTION

Iopamidol, a nonionic radiographic contrast material with low osmolality (0.796 osm/kg) and very low intrinsic chemotoxicity, is used for angiography.^{1,2} It is highly biocompatible and possesses certain advantages over conventional agents. It is excreted mainly by the kidneys. Nonionic agents permit the generation of procoagulants, which (on repeat injection) are theoretically capable of causing clotting even in unclottable mixtures.³ All of these properties impact physiologic status and may cause adverse effects. Renal toxicity and allergic reactions due to contrast materials have not yet been identified. In addition, the concept of increased risk for thrombosis with nonionic material is controversial.^{4–6} Ionic agents are reported to have antithrombotic potential, whereas nonionic agents are considered to be more thrombogenic.⁷ Cardiovascular thrombotic complications (eg, coronary embolus, transient ischemic attack, or stroke) may occur during catheterization.⁸ The effects of nonionic contrast material on thrombus formation and growth also have been found in animal models.^{9,10} In vitro studies^{9–11} have shown that nonionic contrast material may induce the generation of thrombin in blood, whereas ionic contrast agents, such as iohexol, do not. However, knowledge of the effects of contrast material on coagulation and the fibrinolytic system in vivo is limited.¹¹

This study was designed to assess the effects of the nonionic radiographic contrast material iopamidol on hemostasis in patients undergoing coronary angiography or cardiac catheterization.

PATIENTS AND METHODS

Patients aged ≥ 18 years with chest pain and/or dyspnea who were to undergo coronary angiography or cardiac catheterization were eligible for this single-center, observational study. Patients were excluded if they had had unstable angina pectoris or acute myocardial infarction and had received anticoagulant or fibrinolytic therapy. Patients who were pregnant, possibly pregnant, or breastfeeding were not eligible for the study. Patients were required to use an

effective method of birth control throughout the study. All patients were taking aspirin 100 mg/d.

Written informed consent was obtained from each patient before the study. The study was approved by the local ethics committee at the School of Medicine, Çukurova University (Adana, Turkey).

Patients were to receive 120 to 300 mL of iopamidol* injection as contrast material. A cardiologist (A.B.) performed the injections. Each vial contained iodine 370 mg/mL and iopamidol 75.5 mg/100 mL at a viscosity of 20.9 Pa · s at 20°C. Blood samples were drawn before and 3 minutes after injection of iopamidol.

Coronary angiography or left ventriculography and cardiac catheterization were performed by the Judkins method¹² using the Advantx LC Dx model 1994 angiographic system (model 1993, General Electric Co., New York, New York) (125 kV, 1000 mA, with a single-plan digital subtraction angiography C arm).

For the hemostasis profile, the following were determined: platelet count, coagulation profile (bleeding time, clotting time, clot retraction time, euglobulin lysis time [ELT], prothrombin time [PT], partial thromboplastin time [PTT], coagulation factor I [CFI] level, and platelet factor 3 [PF-3] availability), and the natural coagulation inhibitors (protein C, protein S, and antithrombin III [AT-III]). Complete blood count was obtained at the time of blood collection, with Coulter count and platelets determined using phase-contrast microscopy. Blood samples were drawn by a hematologist (İ.Ş.) into polystyrene tubes containing 0.109 mol sodium citrate at a ratio of 1:9 of blood. Plasma was separated after centrifugation for 15 minutes at 2500 rpm at room temperature and was frozen at 20°C until assayed; assays were performed within 1 month. Quantitative determination of functional protein C depended on the prolongation of activated partial thromboplastin time (aPTT) (STA-CLOT®, Diagnostica Stago, Inc., Asnieres sur Seine, France). Protein S was determined in accordance with the inhibition of activated factor V. AT-III levels were assessed by light absorption of microlatex particles covered with specific antibodies. After the initial blood draw, 400 IU of unfractionated heparin was given in physiologic saline to wash catheters. A second blood sample was taken within 3 minutes after coronary angiography or cardiac catheterization was completed. Each assay was performed in a hemostasis laboratory by a physician and a technician from the Department of Cardiology.

Statistical Analysis

The means (SD) were calculated for the study variables. The differences between the pairs of means were determined by paired Student *t* test, and correlation analyses also were performed. Statistical Package for Social Sciences version 8.0

*Trademark: Iopamiro® (nonionic monomer of iopamidol, Bracco, S.p.A., Milan, Italy).

(SPSS Inc., Chicago, Illinois) was used to calculate the data. $P \leq 0.05$ was considered statistically significant.

RESULTS

Thirty patients (7 males, 23 females; mean [SD] age, 51.3 [20.2] years; range, 17–79 years) were included in the study. Twenty-eight patients (93.3%) underwent coronary angiography and 2 (6.7%) underwent left ventriculography and right and left cardiac catheterization because of valvular heart disease. Eighteen patients (60.0%) had at least 1 critical lesion, defined as being caused by a $\geq 50\%$ reduction in the internal diameter of the coronary artery. In the 2 patients who underwent cardiac catheterization, 1 each (3.3%) had aortic regurgitation and aortic stenosis.

Hematologic, coagulation, and hemostasis profiles were assessed in all patients. The results of hematologic tests before and after iopamidol administration are shown in Table I.

All of the hematologic variables (hemoglobin level, white blood cell [WBC] count, and platelet count) decreased significantly ($P < 0.001$, $P < 0.001$, and $P < 0.05$, respectively) after iopamidol administration, but remained within the normal range. During the procedures, the patients received only a small amount of iopamidol (mean [SD] 168.86 [46.03] mL), an amount we think would be insufficient to affect the hematologic variables of hemodilution. Hemoglobin

Table I. Hematologic profile in study patients (N = 30) before and after iopamidol injection.

Component	Normal Value	Before Injection	After Injection	P
Hemoglobin, g/dL	Men: 14.00–17.50; Women: 12.00–15.00			
Women (n = 23)				
Mean (SD)		13.61 (1.90)	12.62 (2.36)	<0.001
Range		10.20–15.00	8.80–15.00	
Men (n = 7)				
Mean (SD)		14.68 (0.80)	13.61 (1.32)	<0.001
Range		13.20–15.00	12.00–15.00	
WBC count, cells $\times 10^9/L$	4.50–11.00			
Mean (SD)		6.73 (1.77)	5.79 (1.55)	<0.001
Range		3.80–10.80	3.60–10.10	
Platelet count, cells $\times 10^9/L$	150.00–450.00			
Mean (SD)		247.13 (68.52)	225.40 (71.14)	<0.05
Range		145.00–395.00	140.00–480.00	

WBC = white blood cell.

and hematocrit could have been affected by the activity of adhesion molecules together with WBCs and consumption of platelets for clot or thrombus formation during the procedures. A positive correlation was found between WBC count and CFI level ($r = 0.50$; $P < 0.04$) and between platelet count and AT-III ($r = 0.48$; $P < 0.006$).

The coagulation profiles before and after administration of iopamidol are shown in Table II. Vascular bed and platelet functions were grossly intact after iopamidol injection. However, the coagulation system was affected. Mean clotting time ($P < 0.025$), PT ($P < 0.001$), and PTT ($P < 0.001$) were significantly increased, whereas clot reaction time ($P < 0.05$), CFI ($P < 0.001$), and ELT ($P < 0.05$) were significantly decreased. Bleeding time and PF-3 availability were not significantly changed. The mean changes in coagulation variables did not show a correlation between iopamidol and clotting. Figure 1 shows the positive

Table II. Coagulation profiles of patients with coronary artery disease or valvular disorders before and after iopamidol injection (N = 30).

Parameter	Normal Value	Before Injection	After Injection	P
Bleeding time, min	1.00–8.00			
Mean (SD)		2.68 (1.12)	2.55 (1.10)	NS
Range		1.50–5.50	1.00–5.00	
Clotting time, min	1.00–8.00			
Mean (SD)		5.25 (1.87)	6.13 (1.19)	<0.025
Range		2.00–10.00	3.50–9.00	
Clot retraction time, min	≤120.00			
Mean (SD)		61.83 (22.49)	54.83 (22.49)	<0.05
Range		25.00–120.00	15.00–110.00	
Platelet factor 3 availability, sec	≤60.00			
Mean (SD)		76.59 (30.90)	65.73 (24.14)	NS
Range		39.00–120.00	32.00–120.00	
Prothrombin time, sec	11.00–14.00			
Mean (SD)		12.40 (1.00)	13.57 (1.17)	<0.001
Range		10.00–14.00	11.00–16.00	
Partial thromboplastin time, sec	20.00–45.00			
Mean (SD)		36.16 (9.20)	48.80 (17.18)	<0.001
Range		24.00–70.00	25.00–110.00	
CFI, g/L	1.50–3.50			
Mean (SD)		3.82 (0.69)	3.34 (0.58)	<0.001
Range		2.37–5.52	2.20–4.86	
ELT, min	60.00–120.00			
Mean (SD)		102.00 (23.36)	93.33 (26.11)	<0.05
Range		20.00–120.00	25.00–120.00	

CFI = coagulation factor I; ELT = euglobulin lysis time.

Figure 1. Relationships between euglobulin lysis time (ELT) and (A) coagulation factor I (CFI) level before iopamidol injection ($r = 0.45$; $P < 0.01$) and (B) bleeding time ($r = -0.54$; $P < 0.02$) after iopamidol injection.

Table III. The natural coagulation inhibitors of patients with coronary artery disease or valvular disorders before and after iopamidol injection (N = 30).*

Component	Normal Value	Before Injection	After Injection
Protein C, IU/mL	0.56–1.30		
Mean (SD)		0.80 (0.46)	0.87 (0.14)
Range (SD)		0.12–1.80	0.70–1.20
Protein S, %	65.00–140.00		
Mean (SD)		70.87 (21.77)	68.06 (13.92)
Range (SD)		29.60–112.40	45.00–96.60
Antithrombin III, %	80.00–120.00		
Mean (SD)		59.50 (12.62)	54.00 (11.51)
Range (SD)		34.00–83.00	27.00–73.00

*No significant differences were found.

correlation found between ELT and CFI ($r = 0.45$; $P < 0.01$) and the negative correlation found between ELT and bleeding time ($r = -0.54$; $P < 0.02$).

Mean levels of protein C, protein S, and AT-III, the natural coagulation inhibitors, did not change significantly after iopamidol administration (Table III).

Correlations between the hematology, coagulation, and hemostasis variables are shown in Table IV. A strong correlation was found between the protein C and protein S values before and after iopamidol administration ($r = 0.71$; $P < 0.001$) (Figure 2).

Table IV. Statistical correlations before and after iopamidol injection (N = 30).*

Parameter	<i>r</i>
ELT [†] –ELT [‡]	0.69
Clot retraction [†] –clot retraction [‡]	0.71
Protein C [‡] –protein S [‡]	0.71
Protein S [†] –protein S [‡]	0.72
Protein C [†] –protein C [‡]	0.75
Platelet [†] –platelet [‡]	0.73
Protein C [†] –protein S [†]	0.67
Protein C [†] –protein S [‡]	0.69

ELT = euglobulin lysis time.

* $P < 0.001$ for all variables.

[†]Before iopamidol administration.

[‡]After iopamidol administration.

Figure 2. Relationship between protein C and protein S levels after iopamidol injection ($r = 0.71$; $P < 0.001$).

DISCUSSION

In general, high-osmolar ionic contrast materials are more likely to be associated with severe adverse effects than nonionic contrast materials, but these effects are rarely life threatening.¹³ Ionic agents are stronger anticoagulants than nonionic agents.^{14,15} The immediate concern is the thrombogenic potential of the contrast material.¹⁶ Some data regarding the effects of contrast material on coagulation are available. Gasperetti et al¹⁴ reported new thrombus formation during coronary angioplasty in 18% and 4% of patients who received nonionic and ionic contrast material, respectively. Ionic contrast material prolongs anti-coagulation by inhibiting platelet activation.⁴ Stormorken et al¹⁷ and Dawson et al¹⁸ demonstrated that both ionic and nonionic materials prolong aPTT and thrombin time. Grabowski¹⁹ showed that iopamidol prolongs clotting time in whole blood. Nonionic contrast materials might decrease the efficacy of thrombolysis by altering clot structure and disturbing fibrin polymerization.²⁰ After injection of nonionic contrast material, the number of fibrin monomers per fiber cross-section decreased significantly from 13% to 25% depending on the sampling site.²¹ Thromboembolic events during catheterization might be associated with the use of nonionic contrast material.²² Several studies showed that no clotting occurred in a bolus of whole blood.^{23,24} In our study, mean hemoglobin concentration and WBC and platelet counts decreased significantly after iopamidol injection. This could be interpreted as hemodilution, activity of adhesion molecules together with the WBCs, and consumption of platelets for clot or thrombus formation during procedures,²² which support the findings of Belleville et al.²⁰

Also, contrast material may modify CFI and/or its binding to the platelets, thereby changing platelet aggregation.^{25,26} Platelet degranulation induced by nonionic contrast agents occurs despite the use of aspirin or heparin, and this degranulation augments the role of platelets in the activation of thrombin. Nonionic contrast material has been associated with decreased CFI concentration.¹¹ Our results confirm the finding of De Caterina and Limbruno²⁷ that non-ionic monomeric, low-osmolality media interfere much less than ionic media with the physiology of vascular and circulating blood cells and with hemostatic functions. Although heparin and some radiographic contrast agents inhibit coagulation, thrombi can still form in their presence. The chemical environment affects the ability of plasminogen to lyse thrombi.²¹ Decreases in CFI concentration parallel decreases in platelet count and ELT, which indicates the consumption of coagulation factors, particularly CFI and platelets. The aggregation of platelets may be due to endothelial damage and a tendency to cause thrombosis and to activate plasminogen. Although ELT remained within normal limits, it was shortened in our study. This finding contradicts that of Giedrojc et al¹¹ and may depend on variations in the vascular wall endothelium of the patients in the 2 studies. In the present study, patients had only cardiac complications.

Stormorken et al¹⁷ and Dawson et al¹⁸ showed that platelet function is inhibited both with nonionic and ionic material and that hyperosmolality contributed to antiplatelet activity. Also, Rasuli²⁸ theorized that when blood contacts non-ionic contrast agents in vitro, a disordered aggregation of erythrocytes may result; this reaction may be mediated by essentially the same mechanism as the aggregation that occurs when blood contacts hypertonic solutions. These aggregates are sometimes confused with clots; however, they are extremely fragile and easily disrupted by small changes in environment or by stress.^{2,19} The platelet inhibitory effect of 100 to 300 mL of contrast medium clearly observed in parallel in vitro studies^{24,28,29} is almost completely lost by absorption into the general circulation. Contrast agents in low concentrations seem to have no clinically important effect on platelet function. Kopko et al²⁹ listed the negligible effects of all nonionic material tested for <20 minutes.

Although some studies^{4,8} described the risk for thrombosis, we did not observe this effect of contrast material on platelet function. Before injection, PF-3 availability was prolonged, but decreased somewhat after iopamidol was infused, although all values remained within the normal range. This change was nonsignificant, but might indicate that platelet function was stimulated and augmented with nonionic contrast material.

In our study, although iopamidol did not grossly affect clot retraction time or PF-3 availability, which indicate platelet function, the other coagulation factors were affected, although they remained within normal limits. The significant decreases in CFI ($P < 0.001$) and ELT ($P < 0.05$) also indicate consumption of these proteins. Giedrojc et al¹¹ found a significant decrease in CFI but prolongation of ELT. The differing results for ELT may have resulted from differences

in time of blood sampling, concentration of contrast material, or status of vascular endothelium. Contrast media cause fibrin-altering activities in plasma. Fibrin formed in the presence of some agents may be significantly more resistant to fibrinolysis. Two studies^{30,31} showed similar platelet activation and prethrombotic marker presence in patients given ionic or nonionic contrast media, indicating equivalent thrombogenic risk with both media.

There appears to be no disadvantage of nonionic contrast media in terms of thrombotic complications.³² Nonionic contrast material affects vasculature, which concomitantly stimulates consumption of CFI and platelets. At damage sites, tissue plasminogen activator and plasminogen activator inhibitor also may be activated sequentially or concomitantly.³³ Although iopamidol may cause some changes in hematologic variables, these effects are balanced by the coagulation cascade and natural coagulation inhibitors. In our opinion, contrast material can be used safely in patients with ischemic heart disease.

CONCLUSIONS

In this study population, hemostasis remained grossly intact after injection of nonionic contrast material. However, the coagulation system may have been affected by the accelerated consumption of CFI and platelets. The affected variables were platelets, clot retraction time, ELT, and natural coagulation inhibitors (protein C, protein S, and AT-III). Although the natural coagulation inhibitors remained within the normal range, the correlations were found significant. These changes in hemostasis affected the vascular phase. If the vascular compartment, especially the endothelium, remained intact, the infusion of nonionic agents in low concentrations might be safe for angiography and other procedures; however, more studies are needed.

Because of the small number of patients in our study, future studies should include larger sample sizes. Coagulation or fibrinolysis might occur concurrently. To clarify the differences between the hemostasis profiles of ionic and nonionic contrast materials, hemostasis should be assessed in future studies in selected homogeneous study groups in the same situations.

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