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Editorials

Ionic or non-ionic contrast media during coronary intervention: does it make a difference?

See page 385 for the article to which this Editorial refers

Blood clot formation has been observed in an angiographic syringe containing non-ionic contrast media[1]. Interaction of these agents, resulting in blood coagulation, has been extensively evaluated in vitro and in vivo. The first reported in vitro data indicated that low osmolar non-ionic contrast media confers less of an anticoagulant effect than ionic contrast media. The latter interacts with the haemostatic system at various levels, mostly inhibiting fibrin monomer polymerization, binding and inactivating protein of the coagulation cascade, but also hindering the ability of thrombin to activate platelets. All these properties are less evident with non-ionic agents. On the other hand, both agents alter fibrin assembly making thrombi more difficult to lyse when they occur[2–8]. These experimental observations were corroborated by several clinical studies showing less thrombus formation, fewer acute vessel closures and a significant reduction in deposits of platelets and thrombi on the guide wire during angioplasty procedures with the use of ionic contrast media[9–12].

The potential clinical benefit of the ionic agent ioxaglate has been challenged by three recent publications, however. Two trials comparing low osmolar non-ionic and ionic contrast media failed to demonstrate any differences in major ischaemic complications[13,14], while a third study showed a significant reduction in adverse clinical outcomes during PTCA for acute coronary syndromes with the use of the non-ionic isosmolar dimer iodixanol[15].

Conversely, in this issue, Scheller *et al.*[16] show that patients receiving stent placement experienced fewer acute and subacute stent occlusion when imaged by ionic contrast media (ioxaglate). In addition, these patients experienced a lower 1 year cardiac event rate, and notably fewer repeat revascularization procedures.

Why are these results so different ? A glance at the characteristics of the populations studied in the four large scale trials and at the treatment applied may provide some answers. In the COURT trial[15] all patients suffered acute coronary syndromes. The proportion of patients with unstable angina was about 33% in Scheller's study[16], 50% in the VIP trial[14] and less than 20% in Schrader's study[13]. The use of stents was around 30% in the Schrader and COURT studies, 60% in VIP and 100% in Scheller's trial. Various anticoagulant and antiplatelet regimens were used (high dose heparin in Schrader's investigation, use of glycoprotein IIb/IIIa inhibitors in 42% of COURT patients). In addition, the dose of contrast agent administrated varied markedly from one trial to the other and, although the ionic contrast agent was the same (ioxaglate), there was heterogeneity between studies regarding the non-ionic contrast agent used: non-ionic dimer iodixanol in COURT and VIP, non-ionic monomer iopremol in Schrader's study and six different non-ionic agents in Scheller's trial. The thrombogenic potential of contrast agents was also evaluated with different primary end-points: the incidence of clinically evident abrupt coronary closure in Schrader's and Scheller's studies, or in-hospital major adverse cardiac events in the VIP and COURT trials, coronary vessel closure being a secondary end-point in these two later multicentre studies.

The paper by Scheller suggested that use of non-ionic contrast media may adversely affect stent patency. This observation somewhat confirms the previous reports, which revealed more platelet deposits or thrombus formation on wires used during interventional procedures[9–10]. However, discrepancies exist when looking at the incidence of vessel closure in the last four largest trials. Vessel closure occurred in 7·1% or 6·0% (P=ns)[13] and in 1·0% or 3·7% (P<0·001)[16] for ionic or non-ionic contrast media in the two single centre randomized trials, with combined vessel closure and ischaemic complications as primary end-points. In the multicentre VIP and COURT studies, the respective figures were 3·4% or 2·6% (P=ns) and 2·4% or 0·7% (P<0·05). Such variability in (sub) acute thrombosis from one study to

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the other surely reflects the heterogeneity of the population, the angioplasty procedures and/or the definition of vessel closure. It may also suggest a statistical α error.

Although vessel closure may represent a surrogate of a thrombotic event related to contrast media when supported by multivariate analysis, other confounding known and unknown procedural anatomical or biological variables, which have not been assessed in these studies, may also lead to subacute vessel occlusion. Conversely, thrombotic occlusion may be unrecognized if it is silent, transient or partially occlusive. For these reasons, and from a clinical point of view, it is more relevant to assess major adverse clinical events. In this respect, it is fair to say that none of the studies comparing contrast agents demonstrate an undoubted superiority of one agent over another in the prevention of in-hospital complications, even when the higher risk patients undergoing percutaneous coronary intervention are considered. Continuous improvements in interventional cardiology aim for optimal angiographic results and prevention of thrombotic complications. This is achieved with the use of newer stents, intracoronary assessment of the anatomy or physiology and appropriate use of antiplatelet and anticoagulant agents. Thus, the clinical impact of contrast media will be even more difficult to demonstrate, particularly in patients undergoing stent implantation.

The valuable contribution by Scheller published in this issue stresses not only that ioxaglate may reduce (sub)acute stent thrombosis, but may also favourably influence late outcome. This is the first study which has demonstrated that an ionic contrast agent may influence late outcome after stenting, reducing death and late revascularization procedure by 29% (16·3 vs 22·9% $P<0·001$). If this observation is confirmed by other studies, it could have a major clinical impact surpassing, the potential benefit of this agent to reduce acute periprocedural thrombosis.

Finally, because diagnostic and therapeutic angiographic procedures are increasingly performed, we need, more than ever, an ideal contrast agent, that, should not only have antithrombotic properties, but be devoid of renal, myocardial or thyroid toxicity without a negative influence on coronary flow and with minimal allergic reactions. But this looks like the quest of the Holy Grail!

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