Contrast Media Selection in Interventional Cardiology

Schraeder R

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R. Schraeder

This paper reviews the main articles published in the literature comparing radio contrast agents in terms of thrombus formation during percutaneous transluminal coronary angioplasty (PTCA), general tolerability, as well as iodine concentration, viscosity and delivery rate, which are important in view of the progressive narrowing of PTCA-guiding catheters.

The review included 10 randomised, controlled trials comparing contrast media in coronary angioplasty, as well as two meta-analyses, another 3 large trials and safety data received by the FDA.

Contrast Media and Clotting: In the 10 randomised studies no significant differences were observed in the incidence of emergent bypass surgery (non-ionic vs. ionic, 1.3% vs. 1.1%), myocardial infarction (3.0% vs. 3.1%), and cardiac death (0.4% vs. 0.4%) in a total of 6249 patients. General tolerability: According to reports to the FDA the incidence of lethal complications per million examinations was 3.90 (ionic monomers), 6.39 (ioxaglate), and 2.07 (non-ionic monomers). There are some reports on delayed reactions after the use of non-ionic dimers. Iodine Delivery Rate: The iodine delivery rate is a function not only of catheter diameter and length, but also of contrast medium iodine content and viscosity (and temperature) The importance of using contrast media with a high iodine concentration (400 mg/ml) has been shown both in vitro and in vivo.

In conclusion, non-ionic contrast media do not have any “thrombogenic potential”. There is no correlation between major adverse cardiac events after PTCA and the type of contrast medium. Non-ionic contrast media reduce the risk of adverse drug reaction in patients undergoing both diagnostic cardiac catheterization and catheter-based coronary interventions. There are also significant differences between dimeric and monomeric non-ionic compounds. Non-ionic monomers have a higher iodine content/viscosity ratio than non-ionic dimers. As the iodine delivery rate depends on the iodine concentration and viscosity of the contrast medium, the contrast medium with the highest iodine content/viscosity ratio can ensure the best opacification.

**Key words:** contrast medium, ionic, non-ionic, PTCA, side effects

The interventional cardiologist can make a choice between four different types of radio contrast agents: ionic monomeric contrast media, ionic dimeric compounds, non-ionic monomeric agents, and non-ionic dimeric molecules. These “diagnostic drugs” have different physicochemical properties (for instance, osmolarity, viscosity), they cause different side effects, but they all must have an iodine content between 280 mg iodine/ml and 400 mg iodine/ml in order to guarantee sufficient opacification of the coronary arteries. Based on what criteria should the selection be made?

First of all, there has been an ongoing debate regarding the influence of ionic and non-ionic contrast media on thrombus formation during percutaneous transluminal coronary angioplasty (PTCA) and during the past decade, 10 randomised trials have been performed addressing this issue. Second, general tolerability should be a matter of concern, since patients may receive large contrast medium doses during interventional procedures. Third, the iodine concentration and delivery rate will be of greater importance in the near future, because the industry provides us with guiding catheters with a diameter of 6 or even 5 French and primary intracoronary stenting is becoming more and more important. These problems will be addressed in separate paragraphs.

**Contrast Media and Clotting**

Under in vitro conditions, contrast media have multiple effects on both the intrinsic and extrinsic pathway of blood coagulation, thrombocyte function, and vascular endothelium. All contrast agents act as anticoagulants to a variable extent. Non-ionic contrast media have a markedly lower inhibition of the intrinsic pathway [1–8]. The discussion regarding the relationship between non-ionic contrast media and thrombotic complications began when Robertson observed blood clot formation in angiographic syringes filled with a mixture of non-ionic contrast medium and blood that were left stagnant for 30 minutes [9]. Reports of thrombotic events occurring during diagnostic coronary angiography with non-ionic contrast media have fueled the debate with additional concern [10]. In an editorial published in 1990, Fareed even postulated a “thrombogenic potential” of non-ionic contrast media [11].

This has led to the concern that thrombus formation, abrupt vessel closure, and major adverse cardiac events after coronary angioplasty may occur more often with non-ionic than with ionic agents. Thus far, 10 randomised studies comparing the effects of non-ionic versus ionic contrast media have been published [12–21]. A total of 6249 patients have been included in these trials.

**Randomised Trials**

In the very first trial from Emory University, Atlanta, 913 patients undergoing 1058 separate PTCA procedures were prospectively randomised to receive either diatrizoate, an ionic monomer, or iopamidol, a non-ionic monomer [12]. The overall incidence of ventricular tachycardia or fibrillation, or both, during the procedure occurred more frequently when diatrizoate was used compared to iopamidol 2.5% vs 1.0%, (p = 0.045).

In the following seven trials, ioxaglate, an ionic dimer, was compared to the non-ionic monomers iopamidol, iohexol, and iomeron [13–19]. A total of 3115 patients were randomised in these trials. Due to historic reasons, no antplatelet agents (like abciximab) were used and coronary stenting was performed in one study only. The predefined endpoints varied considerably among the trials. According to the respective authors, ioxaglate seemed to be “better” than the non-ionic contrast medium in 5 of these 6 studies [13–18]. Only in one trial the non-ionic contrast medium, iomeprol, performed “better” [19]. Data are summarized in Table 1.
However, there were no significant differences observed in the incidence of emergent bypass surgery, myocardial infarction and cardiac death between the two types of contrast media in any of these trials. Among the 1555 patients randomised to receive ioxaglate, 17 patients underwent emergency bypass surgery, 24 patients suffered myocardial infarction, and 9 patients died. Among the 1555 patients receiving non-ionic contrast media, the respective numbers were 19 for emergency bypass surgery, 28 for myocardial infarction, and 8 for death.

In total, major adverse cardiac events (MACE) occurred in 50 patients (3.2 %) in the ionic contrast medium group and in 55 patients (3.5 %) in the non-ionic contrast medium group.

The trial comparing iomeprol vs ioxaglate included more patients than all the other trials put together (2000 vs 1936). It was a randomised, double-blind, parallel group, prospective trial in patients undergoing PTCA with the objective of comparing the incidence of abrupt vessel closure either during or after the procedure, and of major ischaemic complications during hospital stay with a non-ionic contrast medium vs an ionic contrast medium. No significant differences were found (Table 2) [19].

Recently, 2 studies were published comparing the ionic dimer ioxaglate 320 and the non-ionic dimer iodixanol 320: In the VIP-trial (Visipaque In PTCA), 1411 patients with stable (49 %) or unstable (51 %) angina were randomised [20]. There were no significant differences regarding the endpoints death, stroke, myocardial infarction, emergency bypass surgery, and repeat-PTCA (ioxaglate 3.9 %, iodixanol 4.7 %; $p = 0.45$). Two patients died in the ioxaglate group and there were no deaths in the iodixanol group. Contrast medium related adverse drug reactions were more frequent in the ioxaglate group (3.5 % vs 1.0 %; $p = 0.002$).

In the COURT-trial (COntrast media Utilization in high-Risk PTCA Trial) 815 patients with acute myocardial infarction (33 %), post-infarction ischaemia (13 %) and unstable angina (54 %) were randomised [21]. In-hospital major adverse cardiac events occurred more often in those receiving ioxaglate compared with those receiving iodixanol (9.5 % vs 5.4 %; $p = 0.027$). There were, however, 5 deaths in the iodixanol group as opposed to one death in the ioxaglate group. Moreover, in the 345 patients receiving abciximab, the composite primary clinical outcomes occurred in 18 (10.5 %) of the iodixanol cohort and in 20 (11.5 %) of the ioxaglate cohort ($p = 0.77$).

A meta-analysis of the 10 randomised studies comparing the effects of non-ionic vs ionic contrast media in patients undergoing PTCA that have been performed and published during the recent decade is shown in Table 3: a total of 6249 patients were enrolled. However, there were no significant differences observed in the incidence of emergent bypass surgery (non-ionic vs ionic, 1.3 % vs 1.1 %), myocardial infarction (3.0 % vs. 3.1 %), and cardiac death (0.4 % vs. 0.4 %) between both types of contrast media in any of these trials. The incidence of these endpoints combined (major adverse cardiac events) was 4.6 % in the ionic as opposed to 4.7 % in the non-ionic group. None of these differences between both contrast medium groups were significant.

Other Trials
In 1995, much attention was paid to a retrospective analysis of data from 1930 patients who had been enrolled in the EPIC trial [22]. After checking for c7E3Fab randomisation by logistic regression, ionic contrast agents were associated with a lower probability of Q-wave myocardial infarction ($p = 0.012$) and death ($p = 0.016$). Two years later, however, the same author (Aguirre) published a meta-analysis of the 30-day composite endpoint (death, myocardial infarction, urgent re-intervention) among 5129 patients enrolled in the EPIC, EPILOG, and CAPTURE trials receiving either nonionic or ionic contrast media. Contrary to the data from the EPIC trial only, the pooled data revealed no difference.

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**Table 1.** Randomized contrast medium trials in patients undergoing PTCA comparing ioxaglate 320 and different non-ionic monomers

<table>
<thead>
<tr>
<th>Author</th>
<th>pts.</th>
<th>NI-CM</th>
<th>Iox vs NI-CM</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esplugas 1991</td>
<td>100</td>
<td>iohexol</td>
<td>Angiographic evidence of thrombus</td>
<td>$&lt; 0.005$</td>
</tr>
<tr>
<td>Piessens 1993</td>
<td>500</td>
<td>iohexol</td>
<td>2 % vs 22 %</td>
<td></td>
</tr>
<tr>
<td>Lefevre 1994</td>
<td>64</td>
<td>iopamidol</td>
<td>Platelet deposits on guidewire surface area</td>
<td>0.044</td>
</tr>
<tr>
<td>Grines 1996</td>
<td>211</td>
<td>iohexol</td>
<td>Recurrent ischaemic event, recatheterization</td>
<td>0.02</td>
</tr>
<tr>
<td>Qureshi 1997</td>
<td>30</td>
<td>iohexol</td>
<td>New thrombus (angiography)</td>
<td>0.028</td>
</tr>
<tr>
<td>Malekianpour 1998</td>
<td>205</td>
<td>iopamidol</td>
<td>Subacute recoil after PTCA</td>
<td>0.0004</td>
</tr>
<tr>
<td>Schräder 1999</td>
<td>2000</td>
<td>iomeprol</td>
<td>Adverse drug reaction requiring treatment</td>
<td>0.002</td>
</tr>
</tbody>
</table>

**Table 2.** Clinical endpoints in the randomised, double-blind, parallel-group, prospective clinical trial comparing iomeprol to ioxaglate in 2000 patients undergoing PTCA [19]

<table>
<thead>
<tr>
<th>Clinical Endpoints</th>
<th>Iomeprol (n = 1001)</th>
<th>Ioxaglate (n = 999)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abrupt closure in laboratory (%)</td>
<td>29 (2.9)</td>
<td>30 (3.0)</td>
</tr>
<tr>
<td>Abrupt closure out of laboratory (%)</td>
<td>31 (3.1)</td>
<td>41 (4.1)</td>
</tr>
<tr>
<td>Emergency bypass surgery (%)</td>
<td>8 (0.8)</td>
<td>7 (0.7)</td>
</tr>
<tr>
<td>Myocardial infarction, CK increase (%)</td>
<td>11 (1.1)</td>
<td>11 (1.1)</td>
</tr>
<tr>
<td>Myocardial infarction, Q-wave (%)</td>
<td>7 (0.7)</td>
<td>9 (0.9)</td>
</tr>
<tr>
<td>Cardiac death (%)</td>
<td>2 (0.2)</td>
<td>2 (0.2)</td>
</tr>
<tr>
<td>Major adverse cardiac events (n)</td>
<td>28</td>
<td>29</td>
</tr>
<tr>
<td>Patients with major adverse cardiac events (%)</td>
<td>23 (2.3)</td>
<td>23 (2.3)</td>
</tr>
</tbody>
</table>

**Table 3.** Meta-analysis of 10 CM-trials

<table>
<thead>
<tr>
<th>MACE</th>
<th>Ionic CM 3230 patients</th>
<th>Non-ionic CM 3164 patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergent CABG</td>
<td>36 (1.1 %)</td>
<td>41 (1.3 %)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>99 (3.1 %)</td>
<td>94 (3.0 %)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>14 (0.4 %)</td>
<td>14 (0.4 %)</td>
</tr>
</tbody>
</table>
between both types of agents (8.5 % vs 8.4 %; p = 0.98). Abciximab significantly reduced event rates by a similar magnitude regardless of non-ionic or ionic contrast medium use [23]. This example illustrates the difficulties arising from the interpretation of non-randomized data.

Also in 1995, Morice et al. presented data from a registry. Between October 15, 1993 and July 15, 1994, 773 patients underwent PTCA. During different time periods (without the possibility of choosing the respective agent), ioxaglate was used in 386 patients and iopamidol in the remaining 387 [24]. The authors concluded that PTCA could be performed safely using either type of contrast medium. They found however that the activated clotting time obtained with the same dosage of heparin was significantly higher with non-ionic contrast and that there was a significantly higher rate of acute or subacute occlusions in the ionic contrast medium group (5.0 % vs 2.1 %, p = 0.03). Two years later, data from apparently the same cohort of patients were published by Lefèvre et al. [25]. They reported an acute closure rate of 2.1 % vs 4.9 % in the ioxaglate and the iopamidol group respectively (p = 0.03). Moreover, stents were less frequently used in the ionic group (21.5 % vs 28.5 %, p = 0.03). It is difficult to understand why data from the same cohort of patients generated contradictory results.

Data from the GUSTO IIb trial showed that patients receiving ioxaglate were less likely than patients receiving various non-ionic agents to reach the triple composite end point of death, reinfarction, or refractory ischaemia, both in the hospital (4.4 % vs 11 %, p = 0.02) and at 30 days (5.5 % vs 11 %, p = 0.04). However, the differences were no longer statistically significant after adjustment for imbalances in baseline characteristics [26].

Most recently, a study with an unique design was published by Scheller et al. [27]. A total of 3990 consecutive patients were enrolled over an inclusion period of 4.5 years. In all patients, diagnostic coronary angiography was performed using various non-ionic contrast media (5 monomers and 1 dimer). For the interventional procedure, the patients received either the same non-ionic contrast medium or ioxaglate, depending on the daily availability in the allocated cathlab room. Both acute and subacute stent occlusion occurred more frequently in the non-ionic (ie 5 monomers, 1 dimer) group (acute: 1.5 % vs 0.3 %, p = 0.001; subacute: 2.4 % vs 0.7 %, p = 0.001). Within 12 months, the incidence of the combined clinical endpoint (CABG, target vessel revascularization, overall mortality) was significantly reduced in the ionic (ie non-ionic/ionic) group (22.9 % vs 16.3 %, p = 0.001). Neither Scheller nor Legrand in his related editorial [28] addressed the theoretical and pharmacological issues arising from the fact that the comparison was between mixtures of contrast media, ie, a mixture of various non-ionic contrast media and a mixture of non-ions and ioxaglate. Due to the unique design with sequential contrast medium use it seems to be difficult to attribute the clinical differences observed to a specific contrast medium.

General Tolerability

Since the study of Katayama was published in 1990, it is well known that the incidence of adverse drug reactions is higher in patients receiving ionic contrast medium compared to patients receiving non-ionic compounds [29]. Lasser published FDA-data on contrast media reactions in 1997 [30]. The number of total/severe reactions per million

### Table 4. Physicochemical properties of different radio contrast media

<table>
<thead>
<tr>
<th>Contrast medium</th>
<th>Type</th>
<th>Structure</th>
<th>Iodine content (mg/ml)</th>
<th>Osmolality (mosmol/kg)</th>
<th>Viscosity 37 °C (mPaxs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ioxaglate</td>
<td>Ionic</td>
<td>Dimer</td>
<td>320</td>
<td>600</td>
<td>7.5</td>
</tr>
<tr>
<td>Iopamidol</td>
<td>Non-ionic</td>
<td>Monomer</td>
<td>370</td>
<td>796</td>
<td>9.4</td>
</tr>
<tr>
<td>Iohexol</td>
<td>Non-ionic</td>
<td>Monomer</td>
<td>350</td>
<td>820</td>
<td>10.5</td>
</tr>
<tr>
<td>Iomeron</td>
<td>Non-ionic</td>
<td>Monomer</td>
<td>350</td>
<td>610</td>
<td>7.5</td>
</tr>
<tr>
<td>Iodixanol</td>
<td>Non-ionic</td>
<td>Dimer</td>
<td>320</td>
<td>319</td>
<td>11.4</td>
</tr>
</tbody>
</table>

examinations was 193.77/37.44 with ionic monomers, 142.52/33.61 with ioxaglate, and 44.44/10.52 with non-ionic monomers. The respective numbers of lethal complications were 3.90 (ionic monomers), 6.39 (ioxaglate), and 2.07 (non-ionic monomers). Ioxaglate, although a low-osmolarity contrast medium, has the same rate of side effects as other ionic contrast media.

Ionic monomers are no longer in use for intravascular application in many countries (eg Germany). No large-scale data on the safety of non-ionic d-mers are available at this time.

Among the 10 randomised trials comparing ionic and non-ionic contrast media in patients undergoing PTCA, contrast-medium related adverse events (allergy-type) have been reported only in 5 studies [13, 17–20]. In these 5 trials, 4327 (69.2 % of the total cohort) were enrolled. The definition of contrast medium related adverse events, however, was not strictly the same in all these trials. The incidence of allergy-type drug reactions was 2.6 % (56/2172 patients) in the ioxaglate cohort as compared to 1.0 % (21/2135 patients) in the non-ionic cohort (p < 0.01).

Adverse drug reactions were observed in 10/355 patients (2.8 %) receiving iohexol [13, 17], in 4/102 patients (3.9 %) receiving iopamidol [18], in 0/1001 patients receiving Iomeron [19], and in 7/697 patients (1.0 %) receiving iodixanol [20].

Recently, Sutton et al. reported the incidence of early and late reactions after use of different contrast media in patients undergoing cardiac catheterisation [31]. Early reactions occurred in 22.2 % of those receiving ioxaglate, 7.6 % of those receiving iodixanol, and 8.8 % of those receiving iopamidol (p < 0.0001). Late skin reactions occurred in 12.2 % of those receiving iodixanol, 4.3 % of those receiving ioxaglate, and 4.2 % of those receiving iopamidol (p < 0.0001). The authors concluded that there are significant differences between contrast agents used in diagnostic cardiac catheterisation. These should be taken into account when selecting an agent and when obtaining informed patient consent.

**Iodine Concentration and Delivery Rate**

The iodine delivery rate is a function of catheter diameter and length on the one hand and contrast medium iodine content and viscosity (and temperature) on the other hand. Currently, for diagnostic catheterization 5 and 4 French catheters are used and the size of PTCA-guiding catheters has come down to 6 or even 5 French. Most investigators prefer manual contrast medium injection. Under these circumstances the physicochemical properties of the contrast media become crucial for opacification of the coronary arteries. For instance, primary coronary stenting in an obese patient using a 5 French coronary guiding catheter requires an optimal iodine delivery rate. This scenario might illustrate the “ultimate challenge” for the diagnostic quality of iodinated contrast medium. The physicochemical properties of low-osmolar contrast media are listed in Table 4.
It has been demonstrated under in vitro conditions that the iodine delivery rate is a decisive factor in the opacification of arterial vessels. Both viscosity and iodine content are important in that regard [32]. Contrast media with the lowest viscosity at a given iodine concentration will provide the highest iodine delivery rate and the best diagnostic quality, especially under critical circumstances and poor visibility. The influence of the iodine concentration may be more important than that of viscosity itself. Himi et al. have demonstrated the superiority of a iodine concentration of 400 mg/ml (osmolality, 720 mosmol/kg; viscosity, 12.6 mPa.s) compared to 350 mg/l by means of intravital comparison in 20 patients undergoing diagnostic cardiac catheterization. Densitometric measurements on the left coronary artery revealed that the radiographic density of iomeprol 400 was 13 % higher, and better than that of iopromol 350 [33]. It is conceivable that, for instance, dissections can be detected more easily even in obese individuals because of better opacification of the target lesion with an iodine concentration of 400 mg/ml.

Conclusions

Although non-ionic contrast media have weaker anticoagulant properties than ionic contrast agents in vitro, they do not have any “thrombogenic potential”. There is no correlation between major adverse cardiac events after PTCA and the type of contrast medium.

Non-ionic contrast media reduce the risk of adverse drug reactions in patients undergoing both diagnostic cardiac catheterization and catheter based coronary interventions. There are significant differences between dimeric and monomeric compounds and also between different non-ionic monomers.

Non-ionic monomers have a higher iodine content/viscosity ratio than non-ionic dimers. As the iodine delivery rate depends on the iodine concentration and viscosity of the contrast medium, the contrast medium with the highest iodine content/viscosity ratio can assure the best opacification in case of poor visibility.

References


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