Original Studies

Comparison of Intracoronary vs. Intravenous Administration of Abciximab in Coronary Stenting

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There have been animal and human studies looking at intracoronary (IC) use of abciximab with good short-term clinical outcomes. There exists no data comparing intracoronary with intravenous (IV) administration of abciximab beyond 30 days. We compared the clinical outcomes between the IC (n = 101) and IV (n = 72) group of patients. Patients who had coronary stenting and received abciximab were included in the study. All the patients received the standard systemic bolus dose of abciximab 0.25 mg/kg either via the IC or IV route, followed by a 12-hr IV infusion at 0.125 µg/kg/min. The 6-month composite endpoint of death or myocardial infarction was slightly higher in the IV (13.9%) than in the IC group (5.9%; P = 0.04). The frequency of bleeding complications was similar in both groups. The IC bolus route of abciximab may be superior to the intravenous route. Prospective randomized trials are warranted to validate these findings.


Key words: local delivery; glycoprotein IIb/IIIa inhibitors; stenting; outcomes

INTRODUCTION

Abciximab is known to improve outcomes in percutaneous coronary intervention (PCI) [1–3]. It is administered as an intravenous (IV) bolus followed by a 12-hr infusion. Previous animal studies on intracoronary (IC) abciximab have been associated with intramural deposition of abciximab at the angioplasty site [4] and enhanced lysis of platelet-rich thrombi [5]. The use of intracoronary abciximab appears attractive as one is injecting the bolus dose directly into the culprit coronary artery and hopefully gets the maximal antiplatelet effect locally. There have been reports of intracoronary use of nonsystemic doses of abciximab in human beings in the presence of intracoronary thrombus [6,7]. A recent study [8] showed reduction in the incidence of major adverse cardiac events at 30 days in the patients who received IC bolus dose of abciximab. All of these showed good short-term outcomes. There have been no studies comparing clinical outcomes of IV with IC administration of a bolus dose of abciximab in PCI beyond 30 days. There exists no data on bleeding complications either.

We present a study that compared clinical outcomes of the two different routes, IV vs. IC, of giving bolus doses of abciximab followed by a 12-hr IV infusion. The primary objective of the study was to compare the composite endpoint of death or myocardial infarction (MI) at 6 months in both groups. The secondary objective was to analyze the incidence of immediate major bleeding and 6-month rates of rehospitalization, MI, and target vessel revascularization (TVR) in the two groups.

MATERIALS AND METHODS

Patient Selection and Procedure

Patients were drawn from a consecutively compiled PCI registry from January 2001 to June 2002. Patients who received coronary stent implantation and abciximab were included in the study. The patients who had only balloon angioplasty or did not have 6-month follow-up

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were excluded from the study. All patients received the standard systemic bolus dose of abciximab 0.25 mg/kg either via the IC or IV route, followed by a 12-hr IV infusion at 0.125 μg/kg/min. Route of administration of abciximab was based on operators’ discretion. There were three operators and there was an approximately 50% chance of receiving abciximab by either route. The intracoronary bolus administration was given via the guide catheter, which was used for PCI. The intravenous administration was given via the peripheral intravenous catheter. All patients received standard pharmacological therapy, including intraprocedural unfractionated heparin, aspirin, and clopidogrel if not contraindicated. All patients received clopidogrel poststenting. Heparin bolus dose was 70 IU/kg IV and additional doses were given to keep the activated clotting time between 200 and 250 sec.

Clinical Endpoints

Demographic and angiographic data, coronary risk factors, medication, procedure indications, and coronary intervention data were collected from the registry. The data were analyzed on outcomes including MI, death, TVR, and rehospitalization within 6 months. Composite of death or MI was calculated. Immediate major bleeding was defined as that occurred during the hospitalization using TIMI criteria [9]. Routine follow-up hemoglobin and a diligent examination to rule out significant bleeding were done on all patients. An in-hospital MI was defined as the presence of new significant Q-waves (according to the Minnesota code) in two or more contiguous electrocardiographic leads or an elevation of creatine kinase or its MB isoenzyme to at least three times the normal in two samples collected at different times [10]. Subsequent myocardial infarction was defined as the development of new Q-waves or an elevation of creatinine kinase or its MB isoenzyme to more than two times the upper limit of the normal [10]. Telephone contact was made if follow-up data were missing.

Statistical Analysis

The chi-square or Fisher’s exact test was used to compare the IC and IV groups on qualitative variables (comparison of two proportions). The Wilcoxon rank-sum test was used to compare them on quantitative variables—age and ejection fraction (comparison of two means)—due to nonnormality of these variables in either group. Logistic regression was used to compare the two groups on outcomes adjusting for significant differences on other factors between them. A 5% level of significance was used for all statistical tests. SAS version 8.2 was used for statistical computing.

RESULTS

Patient Characteristics

The two groups were compared on their baseline demographic characteristics and coronary artery disease risk factors prevalence. Furthermore, indications for PCI were similar for both groups, the majority being non-ST elevation MI (NSTEMI)/unstable angina (UA). The mean ejection fraction was similar in both groups (Table I).

Procedural Data

Stent implantation was utilized as the treatment modality in all cases. The IC group had a higher number of patients with coronary thrombus, but this was not statistically significant. The left anterior descending artery was most frequently intervened on, followed by the right coronary artery. There was a lower incidence of saphenous vein graft intervention in the IC group, but again this was not statistically significant (Table II).

Although the two-group comparisons on characteristics listed in Tables I and II were not significant at 5% level, the two groups were not identical on baseline characteristics. There were several differences that were significant at 10% and 20% levels of significance. We accounted for these differences in comparing the two groups on clinical outcomes with the use of multivariate analysis.

Clinical Outcomes

The composite of death or MI in the IV group at 6 months was 13.9% vs. 5.9% in the IC group. The difference was not significant using the chi-square test (univariate analysis, \( P = 0.08 \)). However after controlling for the effects of possible risk factors (sex, race, diabetes, ejection fraction, age, smoking, hypertension, hyperlipidemia), the difference between the two groups was significant \( (P = 0.04) \), using multiple logistic regression with stepwise selection of variables as predictors for death or MI; Table III). In the IC group, there was no periprocedural MI; two patients had MI in the first 30 days and three patients had MI between the second and the sixth month. One patient died at 5 months in the IC group. In the IV group, there were two patients who had periprocedural MI; one more had MI within first 30 days and another five had MI between the second and the sixth month. There were two deaths in the IV group: at 6 weeks and 2 months, respectively. The majority of the MIs were NSTEMI; only one in the IC group and two in the IV group were Q-wave MI. The odds of death or MI for the IV group were 3.23 times those for the IC group, which is statistically significant (95% CI = 1.1–9.9; \( P = 0.04 \)).

While major bleeding postprocedure appeared higher in the IV group with odds 3.01 times those of the IC
group (95% CI = 0.67–2.92; P = 0.15), the observed difference was not statistically significant (Table III).

Subgroup analysis was done to look for any difference in composite of death or MI between the two groups in patients with diabetes, STEMI, NSTEMI/UA, and stable angina with a positive stress test. There was no significant difference in the odds between the IV vs. the IC group on the above-mentioned variables.

**DISCUSSION**

The use of abciximab given intravenously in PCI is now well established. Recent studies [6,7] have used IC abciximab in the presence of coronary thrombus with good short-term outcomes. The dosage of abciximab in these studies was low (5–10 mg), and in the presence of coronary thrombus only. A recently published study [8] showed better 30-day cardiac outcomes in the IC group compared to the IV group. The idea of local bolus delivery of abciximab followed by systemic 12-hr infusion seems attractive, as it may provide both fast local and then systemic antiplatelet effects. Yet its outcomes beyond 30 days and hemorrhagic complications are unknown and have not been compared to the standard IV bolus route.

The results of our study suggest that the IC administration of bolus dose of abciximab may be superior to the IV bolus route. There was a marginally significant difference in the composite of death or MI at 6 months, which was the primary aim of the study (P = 0.04). The odds of having worse clinical outcomes were higher with IV bolus route. The beneficial effects of IC bolus dose of abciximab extend beyond 30 days and reduce death or MI at 6 months. The incidence of death at 6 months in the

<table>
<thead>
<tr>
<th>TABLE I. Patient Characteristics</th>
<th>Intracoronary bolus abciximab (n = 101)</th>
<th>Intravenous bolus abciximab (n = 72)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Variable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, mean (SD)</td>
<td>55.4 (9.7)</td>
<td>58.5 (10.6)</td>
<td>0.10</td>
</tr>
<tr>
<td>Male sex</td>
<td>78 (77.2%)</td>
<td>52 (72.2%)</td>
<td>0.45</td>
</tr>
<tr>
<td>African American</td>
<td>29 (28.7%)</td>
<td>12 (16.7%)</td>
<td>0.07</td>
</tr>
<tr>
<td>Smoker</td>
<td>66 (65.4%)</td>
<td>38 (53.5%)</td>
<td>0.12</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>72 (71.3%)</td>
<td>57 (79.2%)</td>
<td>0.24</td>
</tr>
<tr>
<td>Hypertension</td>
<td>83 (82.2%)</td>
<td>58 (80.6%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Diabetes</td>
<td>28 (27.7%)</td>
<td>27 (37.5%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Indication</td>
<td></td>
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<td>0.11</td>
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<tr>
<td>Stable angina</td>
<td>10 (9.9%)</td>
<td>11 (15.3%)</td>
<td></td>
</tr>
<tr>
<td>ST elevation myocardal infarction</td>
<td>23 (22.8%)</td>
<td>8 (11.1%)</td>
<td></td>
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<tr>
<td>Non-ST elevation myocardial infarction/unstable angina</td>
<td>68 (67.3%)</td>
<td>53 (73.6%)</td>
<td>0.51</td>
</tr>
<tr>
<td>Left ventricle ejection fraction, mean (SD)</td>
<td>57.3 (13.8)</td>
<td>58.9 (13.4)</td>
<td></td>
</tr>
<tr>
<td>Medications</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Aspirin</td>
<td>99 (98.0%)</td>
<td>70 (97.2%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Statins</td>
<td>79 (78.2%)</td>
<td>62 (86.1%)</td>
<td>0.20</td>
</tr>
<tr>
<td>β-blocker</td>
<td>89 (88.1%)</td>
<td>60 (83.3%)</td>
<td>0.37</td>
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<tr>
<td>Angiotensin-converting enzyme inhibitors</td>
<td>57 (56.4%)</td>
<td>42 (58.3%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>93 (92.1%)</td>
<td>70 (97.2%)</td>
<td>0.20</td>
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</table>

<table>
<thead>
<tr>
<th>TABLE II. Procedural Characteristics</th>
<th>Intracoronary bolus abciximab (n = 101)</th>
<th>Intravenous bolus abciximab (n = 72)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedural characteristics</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Left main</td>
<td>2 (2%)</td>
<td>1 (1.4%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Left anterior descending</td>
<td>44 (43.6%)</td>
<td>36 (50.0%)</td>
<td>0.40</td>
</tr>
<tr>
<td>Left circumflex</td>
<td>24 (23.8%)</td>
<td>22 (30.6%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Ramus</td>
<td>5 (5%)</td>
<td>4 (5.6%)</td>
<td>0.99</td>
</tr>
<tr>
<td>Right coronary artery</td>
<td>39 (38.6%)</td>
<td>19 (26.4%)</td>
<td>0.09</td>
</tr>
<tr>
<td>Saphenous vein graft</td>
<td>3 (3%)</td>
<td>6 (8.3%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Coronary thrombus</td>
<td>15 (14.8%)</td>
<td>6 (8.3%)</td>
<td>0.20</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>TABLE III. Clinical Outcomes</th>
<th>IC bolus abciximab (n = 101)</th>
<th>IV bolus abciximab (n = 72)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical outcomes</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Six-month outcomes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>1 (1%)</td>
<td>2 (2.8%)</td>
<td>0.57</td>
</tr>
<tr>
<td>MI</td>
<td>5 (5%)</td>
<td>8 (11.1%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Composite of death or MI</td>
<td>6 (6%)</td>
<td>10 (13.9%)</td>
<td>0.44</td>
</tr>
<tr>
<td>Target vessel revascularization</td>
<td>20 (19.8%)</td>
<td>11 (15.3%)</td>
<td></td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>27 (26.7%)</td>
<td>21 (29.2%)</td>
<td>0.72</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>4 (4%)</td>
<td>6 (8.3%)</td>
<td>0.32</td>
</tr>
</tbody>
</table>

*P < 0.05, significant difference at 5% level factor using multiple logistic regression with stepwise selection of variables as predictors for death or MI.
IC group was similar or lower than other published data [10,11] and was lower than the IV group.

An argument can be made that all the circulating platelet glycoprotein IIb/IIIa receptors need to be inhibited, so it does not matter whether abciximab is given by either route. But by giving an IC bolus followed by a 12-hr infusion, it is possible to derive both the local and the systemic benefits of abciximab. It has been shown that upon local delivery, abciximab gets deposited onto the angioplasty site [6], thereby preventing the thrombotic complications of PCI. Intracoronary thrombus may be present even when it is not seen angiographically [12], and locally administered abciximab may help in its lysis [4,6,7]. We can postulate that IC bolus helps by dissolution of the thrombus that may not be apparent on angiography. It has also been demonstrated that abciximab attenuates coronary microvascular endothelial dysfunction [13] and decrease inflammation [14] after coronary stenting, and it is possible that an IC bolus may prove to be more beneficial in this regard. Therefore, if IC bolus of abciximab followed by 12-hr IV infusion is used, this may not only inhibit the circulating platelet glycoprotein IIb/IIIa receptors but also provide local antithrombotic effects in the coronary artery.

Study Limitations

Being a retrospective study is the major limitation of this study. Even though it is the practice at our institution to give abciximab before stent implantation, the exact timing may have been difficult to estimate. The small number of patients is also a limiting factor. We did not collect data on minor bleeding as it was not apparent in all cases on medical record review and may have been misleading.

Intracoronary administration of a bolus dose of abciximab may be superior to the intravenous route. Six-month outcomes were slightly better in patients who received intracoronary bolus dose of abciximab as opposed to intravenous infusion. Future prospective randomized controlled studies are indicated to validate these findings.

REFERENCES