CLINICAL STUDY

Exploration of Bivalirudin Use during Percutaneous Coronary Intervention for High Bleeding Risk Patients with Chronic Total Occlusion

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Summary

The safety and efficacy of bivalirudin during percutaneous coronary intervention (PCI) in high bleeding risk patients with chronic total occlusion lesions (CTO) has not been studied till date. The use of bivalirudin may increase the thrombotic events during CTO-PCI.

Between May 2013 and April 2014, a total of 117 high bleeding risk patients with CTOs underwent PCI. Bivalirudin was used in 89 cases with different strategies, including standard usage, combination of heparin, and additional bolus of bivalirudin on the basis of standard usage. The clinical characteristics, procedural details and antithrombotic strategies were assessed, and the bleeding and ischemic events were evaluated. The first 7 of 9 patients with standard application of bivalirudin exhibited acute thrombogenesis in the procedure. Heparin was then added in decreasing amounts in the next 8 patients wherein no thrombosis occurred; however, 2 patients had bleeding complications. The subsequent 72 patients were randomly assigned to the heparin bolus or additional bivalirudin bolus groups before the percutaneous transluminal coronary angioplasty (PTCA) was performed. The baseline clinical characteristics and procedure information were identical in both the groups. There were no ischemic and bleeding events in both the groups during the 6-month follow-up.

Monotherapy with bivalirudin in CTO-PCI should be treated with caution, as the potential risk of thrombogenesis may be due to the long procedure time, the frequent change of equipment and temporary blood flow convection. Combination of heparin or an additional bolus of bivalirudin before PTCA was observed to be likely to decrease the incidence of thrombogenesis.

Key words: Antithrombotic strategy, Thrombotic events, Bleeding events

Bivalirudin, a direct thrombin inhibitor, is a synthetic polypeptide derived from the native anticoagulant hirudin. Its features serve for its utilization during percutaneous coronary intervention (PCI), including a short half-life and less need for monitoring. It has been evaluated in elective procedures and across the spectrum of acute coronary syndrome (ACS) in multiple randomized trials and has been shown to be associated with a decreased incidence of bleeding events as compared to treatment with unfractionated heparin (UFH).7

Coronary chronic total occlusion (CTO) has been encountered in 15%-30% of patients who have undergone diagnostic coronary angiography, and successful CTO-PCI has been associated with an improvement in angina, left ventricular function, and survival.2,4 However, there is still a greater bleeding risk associated with CTO-PCI due to the higher incidence of coronary perforation and dissection, the longer procedure time and more antithrombotic therapy.6 It has not been proven as to whether the use of bivalirudin during the CTO-PCI could lower the bleeding risk. We therefore investigated the safety and efficacy of bivalirudin for CTO-PCI in patients with a high bleeding risk.

Methods

Study population: From March 2013 through April 2014, a total of 316 patients with CTO lesions underwent PCI therapy. CRUSADE bleeding risk score was calculated for all patients, and 117 patients were at high risk or very high risk (Score > 41).7 Bivalirudin was used in 89 patients during the procedure following the patients’ con-
Study design: Bivalirudin (Salubris Pharmaceuticals Co) was given as a bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/hour during the PCI procedure until completion of the PCI. Post-procedure, the infusion was reduced to 0.25 mg/kg per hour for 4 hours, as per the protocol. The standard doses of UFH recommended by the current guidelines were 100 IU/kg without glycoprotein IIb/IIIa inhibitors (GPI) or 60 IU/kg with a GPI. The use and type of GPI were left to the physician’s preference, and all the patients received both aspirin and clopidogrel according to the ESC recommended dosing guidelines. The choice of arterial access was left to the operator’s discretion. The study was approved by the ethics committee at Zhongshan Hospital, and all patients provided their written informed consent before the procedure.

Study endpoints: The end point of the study was the combined incidence of death from any cause, myocardial infarction, urgent target-vessel revascularization (coronary bypass surgery or PCI) due to myocardial ischemia within 6 months after the procedure, and bleeding events according to the Bleeding Academic Research Consortium criteria.8) In addition, we evaluated the frequency of perioperative myocardial infarction (PMI), defined as an elevation in serum myocardial troponin T to at least five times the upper limit of the normal range.9

Statistical analysis: Continuous variables are reported as medians and interquartile ranges. Categorical variables are reported as frequencies and percentages. The \( \chi^2 \) test was used to perform the primary analysis comparing the event proportions, and Fisher’s exact test was used in the case of sparse data.

Results

Patients and exploration of the bivalirudin use in the procedure: With no experience in the use of the CTO-PCI procedure, we tried the standard usage of bivalirudin initially and found that the former 7 of 9 patients had exhibited acute thrombogenesis. We speculated that the occurrence seemed to be related to the short half-life of bivalirudin and the long procedure time for the CTO-PCI. Therefore, in the subsequent 8 patients, we added a decrement dose of heparin (15 IU/kg) per hour, wherein none of the eight patients exhibited ischemic events; however, one patient had gastrointestinal bleeding and the other one had refractory hematuresis.

We reconsidered the cause of the 7 acute thrombogenesis cases and found that 3 of them happened after the PTCA and the other 4 cases occurred after the stent implantation. This could be related to severe coronary dissections and the slower bloodstream due to the convection of antegrade and retrograde blood flow after the application of PTCA. We assumed that the bivalirudin concentration at the occlusion lesion was under the standard level of anticoagulant and that the thrombogenesis took place as a result.

We then randomly administered extra heparin dose or additional bolus of bivalirudin based on the standard usage of bivalirudin in the remaining 72 patients in a 1:1 ratio when the guide wire location was confirmed, and thereby resolved to do the PTCA. During the in-hospital period and 6-month follow-up, no ischemic and bleeding events occurred in both the groups (Figure).
terolemia in 31%, 64.4% and 59.8% of the patients, respectively. Additionally, previous MI, TIA/CVA, and PVD had a prevalence of 57.5%, 36.8%, and 18.4% respectively. Approximately 75.8% of the enrolled patients presented with unstable angina, and the remaining patients had stable disease and were referred for an elective intervention.

**PCI Procedure-related data:** Procedure-related data are shown in Table II. Most of the target occlusion vessels were LAD (36.8%) or RCA (43.7%), and the mean occlusion lesion length was 50 mm. The retrograde wire technique was used in 38 patients, and a total of 10 patients were given tirofiban. The average procedure time and contrast volume were 179 minutes and 275 mL, respectively, which were higher than those in common PCIs. During the PCI procedure, activated clotting time (ACT) measurement was performed regularly every 30 minutes, with a range of 319 to 625 seconds (mean ACT 412 seconds). Coronary perforation occurred in 4 patients, including the placement of a man-made covered stent, with no cardiac tamponade occurring. Type C-F dissection was seen in 36.8% of the patients, according to the NHLBI criteria. Of the 7 patients with acute thrombosis, 5 patients had thrombus in the target vessel, while the other 2 were found in other vessels. Thrombus aspiration was performed in 3 patients using Thrombuster II aspiration catheter.

**In-hospital and 6-month clinical follow-up:** In-hospital and 6-month clinical follow-up assessments were completed and were made available for all patients, and the results are presented in Table III. Approximately 13.8% of the patients were diagnosed with PMI according to the new criteria. There were no cases of definite cardiac death and MI. One patient died from cerebral hemorrhage (in which group bivalirudin and a decreasing dose of heparin per hour were used). There were 2 cases of TVR: 1 case of TLR (in-stent restenosis) and 1 of non-TLR (a borderline lesion aggravated in the target vessel). Additionally, there were 2 bleeding events in the hospital (one case of gastrointestinal bleeding and the other with refractory hematuria) and 1 bleeding event after discharge (fatal cerebral hemorrhage).

**Discussion**

For decades, UFH has been widely used in catheterization laboratories for anticoagulation therapy during PCI. Due to its lower bleeding risk, the direct thrombin inhibitor, bivalirudin, has emerged as an alternative to UFH for PCI procedures.

As is well known, major bleeding has been associated with increased major adverse cardiac events, a longer in-hospital stay and higher mortality in the setting of PCI, as well as in the transcatheter aortic valve implantation. This is despite the use of the radial approach which has significantly reduced such complications. In addition, great attention has been paid to the lower rates of bleeding complications with the use of bivalirudin. In patients treated with PCI, bivalirudin reduced bleeding-associated complications. A wide array of patient populations have been included in clinical trials evaluating the use of bivalirudin, including elective PCI, NSTEMI, and most recently, STEMI and non-primary PCI. The results of related clinical trials suggest that bivalirudin provides similar ischemic protection and a decreased risk of bleeding when compared with established regimens.
AMI trials, a non-significant increased risk of acute 
basis was seen in the EUROMAX and HEAT-PPCI trials, 
similar but statistically significant increase in-stent throm-
protein (GP) 2b/3a inhibitors (GPI). More recently, a 
as compared to those with heparin, with or without gly-
mation of bivalirudin. But the BRIGHT trial and its follow-
ing researches have showed the potency of post-procedural full 
dose infusion at attenuating the risk of acute thrombosis 
in primary PCI. Uncertainty and debate therefore con-
e especially in female patients. In line with this evidence, 
guideline-writing authorities have assigned bivalirudin a 
high rating among anticoagulant agents available for 
PPI. Nevertheless, the interpretation of such a clinical out-
come endpoint can be challenging because the application 
of anticoagulation between the two treatment arms would 
be expected to have completely opposing effects on the 
incidence of thrombotic and bleeding complications. 
However, a small increase in-stent thrombosis has been 
identified in large clinical trials using bivalirudin for ACS 
in recent years. In the ACUITY and the HORIZONS-
AMI trials, a non-significant increased risk of acute 
stent thrombosis was noted in patients taking bivalirudin as 
compared to those with heparin, with or without gly-
coprotein (GP) 2b/3a inhibitors (GPI). More recently, a 
similar but statistically significant increase in-stent throm-
basis was seen in the EUROMAX and HEAT-PPCI trials. 
The reasons for the increase in-stent thrombosis are 
not clear and may be related to the different periproce-
dural antithrombotic strategies and the pharmacodynamics 
of bivalirudin. But the BRIGHT trial and its following re-
searches have showed the potency of post-procedural full 
dose infusion at attenuating the risk of acute thrombosis 
in primary PCI. Uncertainty and debate therefore con-

Table II. Procedure Related Data

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total (89)</th>
<th>Bivalirudin plus heparin bolus group (36)</th>
<th>Standard usage plus additional bivalirudin bolus group (36)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Access, radial n %</td>
<td>65 (74.7%)</td>
<td>28 (77.8%)</td>
<td>30 (83.3%)</td>
<td>0.195</td>
</tr>
<tr>
<td>Target occlusion vessel</td>
<td></td>
<td></td>
<td></td>
<td>0.061</td>
</tr>
<tr>
<td>LAD</td>
<td>32 (36.8%)</td>
<td>13 (36.1%)</td>
<td>15 (33.3%)</td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>17 (19.5%)</td>
<td>7 (33.3%)</td>
<td>5 (16.7%)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>38 (43.3%)</td>
<td>16 (41.7%)</td>
<td>15 (50.0%)</td>
<td></td>
</tr>
<tr>
<td>Occlusion lesion length (mm)</td>
<td>50.87 ± 24.95</td>
<td>45.50 ± 13.35</td>
<td>43.40 ± 19.16</td>
<td>0.087</td>
</tr>
<tr>
<td>Retrograde</td>
<td>38 (43.3%)</td>
<td>16 (44.4%)</td>
<td>14 (47.2%)</td>
<td>0.429</td>
</tr>
<tr>
<td>ACT Index (Highest)</td>
<td>625.13 ± 79.37</td>
<td>626.68 ± 71.53</td>
<td>625.8 ± 35.2</td>
<td>0.096</td>
</tr>
<tr>
<td>ACT Index (Lowest)</td>
<td>319.10 ± 34.44</td>
<td>319.33 ± 39.89</td>
<td>312.60 ± 20.96</td>
<td>0.055</td>
</tr>
<tr>
<td>(Average)</td>
<td>412.38 ± 31.90</td>
<td>419.17 ± 29.67</td>
<td>415.50 ± 19.17</td>
<td>0.11</td>
</tr>
<tr>
<td>Combined use of GPI IIb/IIIa</td>
<td>10 (11.5%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Contrast volume (mL)</td>
<td>275.26 ± 158.37</td>
<td>213.33 ± 72.78</td>
<td>300.00 ± 49.39</td>
<td>0.072</td>
</tr>
<tr>
<td>Procedure time (minutes)</td>
<td>179.49 ± 104.90</td>
<td>126.67 ± 45.99</td>
<td>156.00 ± 65.18</td>
<td>0.285</td>
</tr>
<tr>
<td>Coronary perforation</td>
<td>4 (4.60%)</td>
<td>1 (2.78%)</td>
<td>2 (5.56%)</td>
<td>0.545</td>
</tr>
<tr>
<td>Dissection after PTCA (NHLBI C-F Type)</td>
<td>32 (36.8%)</td>
<td>11 (30.6%)</td>
<td>13 (36.1%)</td>
<td>0.515</td>
</tr>
<tr>
<td>Acute thrombosis</td>
<td>7 (8.05%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Location of thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target vessel</td>
<td>5 (71.4%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Other vessel</td>
<td>2 (28.6%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Treatment for the thrombosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simply Aspiration</td>
<td>3 (42.9%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>PTCA</td>
<td>4 (57.1%)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Outcome of intervention</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PCI</td>
<td>36 (92.3%)</td>
<td>100%</td>
<td>11 (91.7%)</td>
<td>0.121</td>
</tr>
<tr>
<td>PTCA</td>
<td>3 (7.7%)</td>
<td>0</td>
<td>1 (8.33%)</td>
<td>0.109</td>
</tr>
<tr>
<td>Stents</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of stents per patient</td>
<td>1.97 ± 0.96</td>
<td>2.17 ± 0.83</td>
<td>2.00 ± 0.82</td>
<td>0.944</td>
</tr>
<tr>
<td>Stent length (mean, mm)</td>
<td>61.56 ± 30.56</td>
<td>62.67 ± 25.47</td>
<td>64.00 ± 26.05</td>
<td>0.755</td>
</tr>
<tr>
<td>Stent diameter (mean, mm)</td>
<td>2.75 ± 0.69</td>
<td>2.81 ± 0.19</td>
<td>3.00 ± 0.26</td>
<td>0.927</td>
</tr>
</tbody>
</table>

LAD indicates left anterior descending branch; LCx, left circumflex artery; RCA, right coronary artery; ACT, activation clotting time; GPI, glycoprotein inhibitors; PTCA, percutaneous transluminal coronary angioplasty; and PCI, percutaneous coronary intervention.

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indications suggest. Some of the patients using bivalirudin alone had acute thrombogenesis during the procedure. The reason for this finding was unclear.

As for the CTO case, the long procedure time and frequent change of equipment, such as the wire, microcatheter and balloon, are the differences from common lesions’ PCI procedure. Importantly, in our cases, we found that acute thrombogenesis most often occurred after PTCA. When antegrade blood flow recovered initially, the perfusion pressure was lower than the retrograde collateral flow because of the severe residual stenosis, and blood flow slowed due to the convection of antegrade and retrograde flow. As a result, the level of bivalirudin activity at the occlusion decreased, allowing gradual activation of hestostasis. As a stoichiometric inhibitor of thrombin, the anticoagulant effect of bivalirudin might be overwhelmed when coagulation is activated by the formation of a dissection, or exposure of the blood to the balloon or stent. Additionally, the bilateral angiography and the contralateral catheter, which usually play a guiding role in the procedure, have less fluidity than the operating catheter most of the time and tend to activate coagulation. Combined with the short duration of bivalirudin treatment and the multiple factors above, acute thrombogenesis was easier to generate. Based on the potential risk factors, we gave one extra heparin dose or an additional bolus of bivalirudin or heparin tentatively after the wire went through the occlusion and planned to do the PTCA, with the purpose of preventing the activation of coagulation reaction. A series of patients were observed according to the protocol and no acute thrombogenesis occurred. Additionally, in the follow-up period, both in-hospital and 6 months later, no bleeding or ischemic events occurred.

Heparin or heparin plus GPI anticoagulation is measured by the ACT. This measure has been shown to be related to ischemic and bleeding complications and is regularly monitored during PCI to guide adequate heparin administration (ACT Target ranges: 200-250 seconds in patients receiving GPI, 250-300 seconds without GPI). Limitations of ACT monitoring of bivalirudin therapy have been demonstrated previously, with the correlation between bivalirudin plasma concentration and activity being not accurately reflected by the ACT value.\textsuperscript{40-42} Product labeling suggests consideration of an additional 0.3 mg/kg bolus dose if needed, based on the ACT assessment. However, there is no guidance regarding what value of ACT warrants an additional bolus, and the utility of ACT monitoring in bivalirudin therapy remains uncertain in the setting of PCI. During our PCI procedure, ACT measurement was regularly performed and the mean ACT was 412 seconds; however, the acute thrombosis still occurred. Therefore, adjusting the use of bivalirudin during PCI according to the ACT value may be inadequate.

The strategy of bivalirudin use in CTO-PCI needs to be studied with more rigorous clinical trials, and continued research should be designed to identify the role of ACT in PCI with bivalirudin. However, our findings should also serve as an impetus for continued investigation of specific strategies to minimize thrombotic complications during PCI without substantially increasing the risk of bleeding.

**Conclusion**

The use of bivalirudin monotherapy as an antithrombotic agent in the setting of PCI has been studied in pa-
patients presenting with the entire spectrum of ACS as well as for elective PCI. Caution should be taken in patients with CTO lesions because of increasing acute thrombosis. Combining it with additional bolus bivalirudin or extra heparin before the PTCA will decrease the risk of thrombogenesis in our study.

**Study limitations:** This study evaluated the outcomes of combination of bivalirudin and heparin and a repeat bolus of bivalirudin on the basis of standard usage, wherein we obtained a preliminary result. The data was collected from a single center and the number of patients we analyzed was small. There was also a lack of one separate group of patients who used heparin only as a control. Also, the procedure time of most patients was longer than usual for the more complex PCI procedure and the former patients’ treatment strategy was at the discretion of the treating interventional cardiologist; therefore, results may not necessarily be extrapolated to apply in all the populations. Furthermore, research in a larger study population is needed.

**Disclosures**

**Conflicts of interest:** There were no conflicts of interest pertained to this submission.

**Acknowledgment**

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Heart Journal.

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