Anti-thrombotic and Anticoagulant Treatment in Interventional Cardiology

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Abstract

Efforts to improve Percutaneous Transluminal Coronary Angioplasty (PTCA) have resulted in the usage of new antiplatelets, and antithrombotic agents. These new agents may increase bleeding complications. However, EPIC, EPILOG and CAPTURE trials showed benefits of 7E3, a GPIIb/IIIa platelets receptor blocker, in high risk PTCA patients. On the other hand, direct thrombin inhibitors, Hirudin and Hirulog, did not clearly show any benefit when compared to heparin in patients with unstable angina undergoing PTCA. Combination of oral antiplatelets, ticlopidine and aspirin, is widely utilized following stent implantation. However, its benefit over aspirin alone has not been demonstrated. This article aims to review mechanisms and benefits of these new agents in cardiovascular field.

The role of anticoagulant and antithrombotic therapy during interventional procedures has been emphasized since the introduction of percutaneous transluminal coronary balloon angioplasty (PTCA). By its mechanism, angioplasty increases vessel luminal diameter by breaking atheromatous plaque and exposing subendothelial structures such as collagen and other plaque materials to blood which results in activation of coagulation system. Platelets and thrombus play a major role in this process. It may lead to acute vessel closure and restenosis after PTCA[1-3]. Hence, platelet and thrombus have been targets of pharmacologic agents in efforts to prevent acute and subacute vessel closure as well as restenosis. The importance of these agents, anticoagulants, antithrombotics and antiplatelets, has grown as the procedures have included an increasing number of patients with acute ischemic syndromes and myocardial infarction. Patients in these situations are in higher thrombogenic state compared to patients in a chronic stable condition. Moreover, the widespread use of intracoronary stent requires aggressive antiplatelet and anticoagulant therapy.

Antiplatelet Agents

At present, aspirin remains the first-line antiplatelet therapy[4-8]. It has been shown to reduce acute thrombosis in patients undergoing coronary intervention[7,8]. Aspirin is targeted only toward the arachidonic acid pathway, one of many different pathways leading to platelet activation.

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Most platelet agonists can independently expose the GPIIb/IIIa and platelet aggregation can occur even if the arachidonic acid pathway is completely blocked with aspirin. Aspirin irreversibly inhibits cyclooxygenase enzyme which is responsible for synthesis of eicosanoids. This action prevents generation of thromboxan A_2 and results in decreased platelet aggregation[6]. It also acts to block synthesis of prostacyclin, which further inhibits platelet aggregation, although this latter effect occurs at higher aspirin doses[9-11]. Aspirin appears to have a greater effect than antiplatelet agents such as Sulfinpyrazone[12]. Addition of dipyridamole experimentally did not appear to enhance the effectiveness of aspirin[12,13]. Schwartz et al showed that aspirin and dipyridamole were not associated with a decreased restenosis rate after angioplasty (37.7% and 38.6% drug *versus* placebo), but did have a dramatic effect on thromboembolic complication (6.9% and 1.6%, p = 0.01, placebo *versus* drugs)[7].

At the present time, patients undergoing interventional procedures should be treated with aspirin unless it is contraindicated or cannot be given. Pretreatment 24 hours prior to the procedure is optimal. Because of lower absorbance, enteric-coated aspirin should be avoided if possible. A high dose of aspirin and chewable or intravenous route of administration appear to reduce platelet aggregation and thrombus formation more quickly and effectively[10,11]. Effervescent-buffered aspirin can also substantially increase absorption. However, despite aspirin therapy, patients with unstable angina or MI continue to have heightened platelet activity and enhanced propensity for platelet thrombus formation on an injured artery[14].

Nowadays, dipyridamole is rarely used in combination with aspirin in interventional cardiology. This drug inhibits phosphodiesterase, activates adexylate cyclase and increases adenosine, all of which result in decreased platelet activity. It has been shown that a combination of aspirin and dipyridamole 75 mg tid is effective in maintaining vein graft patency after coronary bypass graft surgery[4,5]. However, it is now believed that aspirin alone is as effective. The combination was also initially used following stent implantation. Its usage is now uncommon in coronary intervention.

Ticlopidine is a more potent antiplatelet agent than aspirin. If aspirin cannot be used it is an alternative. It inhibits the first and second phases of ADP-induced platelet aggregation which is the inhibition of binding of fibrinogen to the platelet GPIIb/IIIa receptor. It is 85 per cent effective at inhibiting platelet aggregation. Its effect is both dose and time dependent. Although ticlopidine exerts its maximal antiplatelet effect at 3-5 days, antiplatelet effects can be detected within hours after ingestion. It has been suggested that loading with 500 mg bid for the first 2-3 days may reduce platelet aggregation more than the conventional 250 mg dose. In a randomized trial, ticlopidine when compared to aspirin reduced the stroke rate in patients with transient ischemic attacks[15,16]. It also reduced the rate of MI and rest angina in patients with unstable angina[17]. Ticlid and aspirin act synergistically[18]. In humans, it has been shown to reduce the post-PTCA thrombus generation[19]. It is widely recommended that combination of the two drugs should be used pre and for one month post coronary intervention.

The newest generation of antiplatelet agent blockers the GPIIb/IIIa receptor, leads to a dose dependent inhibition of platelet aggregation. The EPIC[20,21] (Evaluation of 7E3 in the Prevention of Ischemic Complications, n = 2099) trial showed that the acute and 6 months ischemic endpoint in high risk PTCA patients (unstable angina, MI or high risk coronary morphology) were reduced following both primary angioplasty (n = 42) and rescue angioplasty (n = 22)[22]. Among the 489 patients with unstable or post MI angina the rate of MI was 1.8 per cent *vs* 9 per cent in 7E3 and placebo groups respectively[23]. Eventhough the early (30 days) rate of death or revascularization was not different, a significant difference was observed at 6 months in favor of 7E3 (1.8% *vs* 6.6%, p = 0.038). These beneficial effects were achieved at the risk of increased major bleeding from 7 per cent to 14 per cent[24]. The use of 7E3 plus aspirin was also shown to profoundly inhibit platelet aggregation after thrombolysis. This combination was found to be well tolerated and associated with fewer post thrombolysis ischemic events. The same study also showed that infarct related artery patency in 7E3 group was 92 per cent *vs* 56 per cent in the control group[25].

It was thought that 7E3 increased bleeding complications in the EPIC trial because of higher ACT levels in this group. Hence, the EPILOG study used medium and low dose heparin. This study demonstrated a therapeutic benefit by reduction of asymptomatic CK elevation[26] with no increased risk of bleeding. CAPTURE study in which patients with medically refractory unstable angina were randomized to 7E3 *vs* placebo also showed reduction of the combined endpoint of in-hospital ischemic complications. However, because of its high cost, most interventionists are not using 7E3 prophylactically.

Another GPIIb/IIIa antagonist, a peptide - Integrelin, was tested in 4000 PTCA patients. There was no significant difference in the death rate, MI, urgent revascularization or need for stenting observed between placebo and Integrelin groups at 30 days[27]. Currently many oral and intravenous forms IIb/IIIa antagonists are being evaluated. Results are awaited.

Antithrombin Inhibitors

Since thrombin is the most potent platelet activation, inhibition of thrombin should theoretically improve PTCA outcome. Direct thrombin inhibitors are not dependent on anti-thrombin III for their anticoagulant action like heparin. Thus, they are better inhibitors of fibrin bound thrombin and are not inhibited by platelet factor 4 or heparinase. Moreover, these agents have more predictable anticoagulation response to a given dose.

Hirudin, a peptide derived from the medicinal leech has been shown to reduce platelet deposition and restenosis in angioplasty animal models. There was no clear benefit demonstrated when compared to heparin in 1141 patients with unstable angina undergoing PTCA. Although ischemic events within the first 96 hours were higher in the heparin group compared to the two hirudin groups (11.0 *vs* 7.9 *vs* 5.6%, p = 0.03), this benefit was not sustained[28]. It did not reduce the restenosis rate. Frequency of angina and major cardiac events and minimal luminal diameter on follow-up angiography were similar in all groups at 7 months. Hirulog, a synthetic peptide, also did not reduce ischemic events when compared to heparin (11.4% *vs* 12.2%) in 4098 patients undergoing PTCA for unstable angina or post MI angina, but hirulog did lower the incidence of bleeding (3.8% *vs* 9.8%)[29].

Despite these new agents, the mainstay of anticoagulation and antithrombotic therapy during coronary intervention in general is heparin. It has a number of different effects on blood coagulation and platelet actions. Its anticoagulation action is dependent on binding of antithrombin III[30]. Heparin administration is required for all interventional procedures. A number of different regimens have been described, but in general an ACT level should be above 300 seconds and maintained at this level throughout the procedure. This level of ACT or above during the entire procedure has been shown to reduce the risk of abrupt closure in elective cases[31]. The optimal level of ACT is not clear. It has been shown in 4000 patients who underwent PTCA for unstable angina that, higher levels of anticoagulation reduced ischemic events. For each 10 second increase in ACT, abrupt closure was reduced by 1.3 per cent, even up to ACTs of 400 seconds[32]. Nairns found that there was an inverse linear relationship between abrupt closure and ACTs (p=0.018). From his study of 1290 PTCA patients, those who had abrupt closure, had significantly lower ACT levels (376 *vs* 346 sec, p = 0.009)[33]. The EPIC trial showed a higher mean ACT level of 40 seconds in the 7E3 group compared to the placebo[24]. Hence, it is possible that some of the improved outcome may have been due to potentiation of heparin activity. Care must be given not to underdose patients who are brought to the catheterization laboratory with heparin infusion. Studies have shown that despite higher initial ACTs, the procedural heparin requirement was no different for patients not on continuous heparin[34].

Few data exist regarding the optimal dose and duration of heparin infusion after PTCA. Prolonged infusion is commonly used after the procedures if the final results are suboptimal, or a significant dissection is seen at the end of the procedure. It is not known if this practice is beneficial. However, if prolonged heparin is used, it should not be abruptly stopped since a rebound hypercoagulable state may occur and increase the risk of reinfarct[35-39]. Low molecular weight heparin given subcutaneously may be an alternative. However, the superiority of low molecular weight heparin over regular heparin during angioplasty has not been demonstrated in a clinical study.

SUMMARY

In the future there will be significant changes in the specific antithrombotic and antiplatelet medication usage in cardiology. Currently available antithrombotics; heparin, hirudin, hirulog and antiplatelet; aspirin, ticlopidine, 7E3, integrelin will be used in clinical trials in different dosages and regimens to try to achieve optimal results. Newer agents will also soon be available in the market. However, reduction of thrombotic complications is at the expense of increased bleeding complications, high cost is another concern. It is possible that specific antithrombosis will take the place of heparin and IIb/IIIa receptor blockers may replace aspirin.

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การใช้ยากลุ่ม anti-thrombotic และ anticoagulant ในผู้ป่วยโรคหัวใจและหลอดเลือด

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การใช้ยากลุ่ม antiplatelets และ antithrombotic มีบทบาทมากขึ้น โดยเฉพาะในผู้ป่วยที่ได้รับการขยายหลอดเลือดหัวใจ การศึกษาเปรียบเทียบพบว่าผู้ป่วยได้รับประโยชน์จากการได้ยา antiplatelet ประเภท GPIIb/IIIa receptor blocker แต่ยากลุ่ม direct antithrombin เช่น Hirudin และ Hirulog กลับไม่เห็นความแตกต่างชัดเจนในผู้ป่วยหลังการขยายเส้นเลือด ผู้นิพนธ์ได้ทบทวนข้อมูลของยากลุ่มดังกล่าวในผู้ป่วยโรคหัวใจและหลอดเลือด

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