Local Antithrombotic Therapy Using a Novel Porous Balloon Catheter

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SUMMARY

The efficacy of local treatment of thrombosis with low-dose antithrombotic drugs (heparin: 30 U/kg, or argatroban: 0.02 mg/kg) was investigated using a novel porous balloon catheter. This novel balloon catheter can deliver drug into arterial walls without causing vascular trauma. Thrombus formation was significantly inhibited in balloon-injured and locally-treated iliac arteries compared with control balloon-injured arteries in 12 dogs. In the systemic high-dose delivery group (ten times as high as the low dose), thrombus formation in injured arteries was significantly less than that of controls in 7 dogs. Low-dose systemic delivery was not effective at inhibiting this thrombus formation. Thus, local treatment with an antithrombotic drug using this novel porous balloon catheter can prevent thrombosis without influencing systemic coagulability. (Jpn Heart J 2000; 41:87-95)

Key words: Local delivery, Thrombosis, Antithrombin, Porous balloon catheter

INTRAARTERIAL thrombosis is the major etiologic factor of acute coronary syndrome and cerebral infarction, and heparin has been shown to be effective for treating thrombotic lesions.1-6) However, hemorrhagic complications may occur following systemic infusion of any antithrombotic drug. It is desirable to treat the thrombogenic lesion itself to prevent thrombus formation. Local delivery of heparin or antithrombin has been investigated using a porous balloon catheter,7) a dispatch balloon catheter,8) a hydrogel-coated balloon catheter,9) or special experimental systems.10,11) The local delivery of thrombolytic drugs can be used...
not only for the prevention of thrombosis, but also for thrombolytic therapy. Angiography has been used for the detection of thrombus. Although angiography can demonstrate the presence of thrombus as a filling defect, this technique is not sensitive for mural thrombus detection. Angioscopy has been shown to be more sensitive for thrombus detection than angiography.

Although local delivery of antithrombotic drug has been shown to partially prevent thrombosis, the local delivery effect of currently available local delivery catheters is limited by their low efficiency. Therefore, the development of a new local delivery catheter is necessary for local delivery therapy. To evaluate thrombus formation, angioscopy has been shown to be a useful technique for serial observation of vascular stenosis with thrombus since thrombus can be clearly distinguished from the vessel wall with this technique.

We developed a new porous balloon catheter for local delivery of drug without causing mechanical vascular trauma. The present study was designed to determine whether local delivery of heparin is efficacious for the prevention of thrombus formation.

**MATERIALS AND METHODS**

Twenty-nine mongrel dogs weighing 8.2 to 14.5 kg were used. The dogs were sedated with sodium pentobarbital (30 mg / kg) intravenously and intubated, and ventilated using a Harvard respirator with air. Anesthesia was maintained with additional intravenous administration of sodium pentobarbital if necessary. The study was approved by the University of Tokyo and conformed to American Heart Association guidelines.

**Novel porous balloon catheter:** The novel porous balloon catheter used was invented by Dr. Takanobu Tomaru (University of Tokyo) and Hisayuki Mukai (DYMEC Co. Ltd, Chiba, Japan). It is composed of a dumbbell-shaped 3 mm balloon (20 mm in length) perforated with 12 small holes each 30 μm in diameter (DYMEC) (Figure 1A). Through this balloon, the drug is infused from small holes into the space between the vessel wall and the balloon surface and cannot be infused into the vessel wall directly (Figure 1B). This allows indirect drug infusion through this space into the vascular wall. This system appears to cause less vascular trauma than a conventional porous balloon catheter, which is composed of a 3 mm balloon with 20 small perforating holes 30μm in diameter.

In 4 dogs, this novel porous balloon catheter was inserted into one femoral artery (3 mm diameter) and 2 ml of saline was infused at 2 atmospheres (atm). Into the contralateral femoral artery, 2 ml of saline was infused at 2 atm using a conventional 3 mm porous balloon catheter at 2 atm. It took 70 to 104 seconds for local delivery of 2 ml of saline. After the procedure, the arteries were resected.
Prevention of experimental iliac arterial thrombosis with local delivery of antithrombotic drug using the novel porous balloon catheter: After a midline abdominal incision was made, the aorta and both iliac arteries were isolated, and a 7-French catheter sheath was introduced into each external iliac artery in a retrograde fashion from the femoral artery in 12 dogs. A segment of one common iliac artery was injured by the inflation of a PTCA balloon catheter (USCI 4 mm in diameter) at 4 atm for 3 minutes while the segment was constricted to half of its original diameter at 3 different sites by threads (one thread for each site). After balloon inflation, the threads were released and the novel porous balloon catheter and fixed with 10% formalin for histological examination.

Figure 1. A: Dumbbell-shaped balloon of the porous balloon catheter. B: Schematic representation of fluid infusion from the porous balloon catheter. At first, infused fluid occupies the lumen between the balloon surface and vascular wall, and then infiltrates into the vascular wall by positive pressure.

Figure 2. Schematic representation of experimental system. The porous balloon is inserted into the iliac artery through a distal catheter sheath for local drug delivery and angioscopy can also performed by replacing blood with saline infusion from the sheath.
was advanced to the injured segment (Figure 2). Then 2 ml of saline was infused through this catheter at 2 atm for 1 minute, and blood flow was reestablished for 1 hour. In the contralateral iliac artery, balloon arterial injury was produced in a similar manner. After balloon injury, the novel catheter was advanced to the injured segment and heparin (30 U/kg) or argatroban (0.02 mg/kg) diluted in 2 ml of saline was locally delivered through this catheter for 1 minute. Angioscopy was then performed at 60 minutes after the drug administration to evaluate the thrombotic obstruction.

Experimental iliac arterial thrombosis and systemic delivery of antithrombotic drug: Another experimental model was used to evaluate the effect of high-dose systemic administration of antithrombotic drugs. After a midline abdominal incision was made, the aorta and both iliac arteries were isolated, and a 7 French catheter sheath was introduced into each external iliac artery from the femoral artery. A segment, approximately 2 cm long, of one common iliac artery was injured as described in experiment 1. After the 1 hour-old thrombus was evaluated as a control by angioscopy, intravenous heparin (200 U/kg) infusion was initiated via a jugular vein route and then continued for 30 minutes. Twenty minutes after the drug administration was initiated, the other side of the iliac segment was injured by balloon under the same conditions of thread constrictions (3 constricted portions in a 2 cm-long segment). Angioscopy was then performed to evaluate thrombus formation at 60 minutes after the balloon injury.

The same experimental model for high-dose systemic administration was used to evaluate the effect of low-dose systemic administration of heparin (30 U/kg).

Angioscopic evaluation of the iliac artery: An Olympus PF 14 angioscope (1.4-mm outer diameter, Olympus Co., Ltd, Tokyo) was used for angioscopic visualization. Ten to 20 ml of saline was injected from the sheath to clear the blood from the field under ligation of the aorta. Angiography was performed by manual injection of 10 ml of contrast medium (Iopamirone) through the sheath and a baseline angiogram of the iliac artery was obtained. Angioscopic color images were obtained with an Olympus CCD Camera connected to a video monitor system (Sony Corporation, Tokyo). Angioscopic pictures were taken with a videoprinter (Sony). The percent luminal stenosis due to thrombus shown on an angioscopic image was calculated using planimetry. All angioscopic images were traced by two investigators independently, and discrepancies were resolved by subsequent simultaneous tracing and reading. The cross-sectional area of a normal vessel (A) at the thrombosed site was traced and measured, and the lumen occupied by thrombus (B) was also measured\(^1\) The percent area stenosis with thrombus was then calculated using the formula \(\frac{B \times 100}{A}\). The angioscopic percent area stenosis was semiquantified as follows: grade 0: 0%, grade I: > 0
and < 25%, grade 2 : 25 and < 50%, grade 3 : 50 and < 75%, grade 4 : 75 and < 100%, and grade 5 : 100%.

Hematologic Study: Arterial blood samples were collected in 3.8% sodium citrate (9 vol blood into 1 vol citrate) before the drugs were administered and at 60 minutes after administration to evaluate activated partial thromboplastin time (APTT). The APTT values were assessed using clotting methods.

Statistics: Paired t-test was used to analyze differences in the degree of luminal stenosis between groups. Analysis of variance test (ANOVA) followed by Scheffe’s F-test was used to analyze the changes in thrombotic luminal stenosis, PT, APTT, and fibrinogen levels. A p value less than 0.05 was considered significant for statistical comparison.

RESULTS

Antithrombotic effect of local delivery of antithrombotic drug using a novel porous balloon catheter: The effects of antithrombotic drugs could be angioscopically evaluated in 12 dogs. By angioscopy, balloon injuries, including intimal flaps and small dissections, were observed both in control and locally-delivered arteries. An occlusive mural thrombus had usually developed in the injured iliac artery on the control side, while a tiny mural thrombus or no thrombus had formed at the locally-delivered arteries (Figure 3). Sixty minutes after balloon inflation, the

Figure 3. Angioscopic findings of the preventive effect of local delivery of argatroban using the porous balloon catheter. Left panel: Angioscopy shows thrombus formation at the injured-iliac artery. Right panel: No thrombus formation was observed at the injured lesion with local delivery of argatroban.
angioscopic percent area stenosis with thrombus in the control arteries ranged from 50 % to 100 %. Thrombus formation was prevented in locally-treated arteries in each group (less than 25 % area stenosis with thrombus) 60 minutes after local delivery of the antithrombotic drug. Angioscopy revealed a mural thrombus or no thrombus formation at the locally-delivered segment. Table I summarizes the results.

In 4 dogs, histological examination of the arterial segments at the site of the porous balloon inflation for local saline delivery revealed minimal intimal damage and no dissection, whereas local saline delivery with a conventional porous balloon catheter produced deep vascular injury.

Effect of systemic delivery of heparin: Seven dogs were available for angioscopic evaluation of the high-dose systemic administration effects of heparin. Thrombotic stenosis was formed at the balloon-injured site on the side of the iliac artery without drug treatment (control side). After administration of heparin, angioscopy demonstrated that thrombus formation was strongly inhibited (Table II).

Low-dose systemic administration of heparin was performed in 6 dogs. Thrombotic stenosis was formed at the balloon-injured site on the one side of the iliac artery without drug treatment (control side). After administration of heparin, angioscopy revealed thrombotic stenosis in all animals (Table II).

Changes in hematologic variables: Local delivery of heparin did not affect APTT significantly (from 26 ± 5.1 to 27 ± 9.5 seconds). In the group with systemic

**Table I.** Preventive Effect of Local Delivery of Antithrombotic Drug or rt-PA on Thrombus Formation

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<th>Angioscopic stenosis with thrombus (grade)</th>
<th>Thrombus weight (mg)</th>
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<tr>
<td>1. Control</td>
<td>6</td>
<td>3.5 ± 0.55</td>
</tr>
<tr>
<td>Heparin</td>
<td>6</td>
<td>0.67 ± 0.52 **</td>
</tr>
<tr>
<td>2. Control</td>
<td>6</td>
<td>3.8 ± 0.75</td>
</tr>
<tr>
<td>Argatroban</td>
<td>6</td>
<td>0.17 ± 0.41 **</td>
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Data are expressed as mean ± SD. Angioscopic: grade 0 : 0, 1 : 25, 2 : >25, 3 : >50, <75, 4 : >75, <100, 5 : 100%. *p < 0.005, **p < 0.0005 vs each control.

**Table II.** Preventive Effect of Systemic Administration of Heparin on Thrombus Formation

<table>
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<tr>
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<th>Angioscopic stenosis with thrombus (grade)</th>
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<tr>
<td>1. Control</td>
<td>7</td>
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<tr>
<td>High dose heparin</td>
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<td>2. Control</td>
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<td>Low dose heparin</td>
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Data are expressed as mean ± SD. Angioscopic: grade 0 : 0, 1 : 25, 50, 3 : >50, <75, 4 : >75, <100, 5 : 100%. *p < 0.0005 vs each control.
high-dose delivery, the administration of heparin prolonged APTT (from 23 ± 4.9 to 116 ± 36, p < 0.0001).

**DISCUSSION**

This study demonstrates that local intravascular delivery of low-dose heparin using this novel porous balloon catheter can prevent macroscopic thrombus formation safely and effectively as evaluated by angioscopy and pathologic examinations without affecting systemic coagulability.

**Mechanism of action of antithrombotic drugs at the injured arterial lesion:**

Arterial injury triggers activation of the coagulation system and platelet activation, and thus produces subsequent arterial thrombosis. For the prevention of thrombus formation, systemic administration of high-dose antithrombotic drugs is usually required, and this may be associated with bleeding complications. Heparin has been shown to bind to thrombogenic-damaged arterial wall and to have inhibitory effects on the thrombogenicity of the damaged vascular wall. Thus, local delivery of heparin or other antithrombotic agents has the potential to inhibit thrombus formation on the damaged arterial wall not through its anticoagulant action on the circulating blood, but by its vascular binding and inactivation of the thrombogenic site.

Recently, local delivery of heparin has been investigated using various methods. Wolinsky, et al. demonstrated that with the use of a perforated balloon catheter concentrated heparin can be delivered into the wall of a normal canine artery without subsequent vascular wall damage, even at high pressure. However, direct fluid infusion at high pressure through a conventional porous balloon surface may cause vascular wall perforation, as demonstrated in our present study. We developed this novel porous balloon catheter with a dumbbell-shaped balloon, the catheter of which allows local delivery of highly concentrated drug to the vascular wall without conspicuous vascular damage. Thus, this catheter, given its efficacy and safety, is likely to be an extremely useful device for percutaneous local drug delivery therapy for the treatment of vascular diseases.

**Evaluation of experimental arterial thrombosis:** Arterial thrombosis is produced by balloon injury and luminal stenosis to simulate clinical conditions. In this study, we used angioscopy to evaluate the antithrombotic effect of the drug. Although angioscopy is a very sensitive means of detecting macroscopic thrombus, there may be limitations with respect to quantifying the amount of thrombus. However, in our study, there were differences between the groups in the percent thrombus, and the semiquantification methods are thought to have been adequate for the evaluation of the antithrombotic effect of local treatment.
Moreover, macroscopic pathological examination was performed as an amount of thrombus.

This study has demonstrated that local delivery of heparin using a novel porous balloon catheter is effective in preventing macroscopic thrombus formation. Compared with occlusive thrombus formation at the control injured vascular surface, only a tiny mural thrombus or no thrombus was formed at the locally-delivered vascular surface. The high efficacy of low-dose local anti-thrombotic drugs may be related to the high local concentration and prolonged surface interaction. Systemic infusion of high-dose heparin was also effective at preventing thrombus formation. However, administration of high-dose heparin prolonged PT and APTT significantly. This may result in bleeding complications in clinical situations.

Conclusions: The results of this study suggest that (1) low-dose local delivery of heparin using this novel porous balloon catheter can prevent macroscopic thrombus formation safely and effectively without significant changes in coagulability, (2) high-dose systemic delivery of antithrombotic drug could prevent thrombosis, although it did decrease systemic coagulability, and (3) clinical use of this novel porous balloon catheter is safe and may effectively prevent thrombotic reobstruction and restenosis after PTCA.

REFERENCES


