Combined Use of Aspirin and Heparin Inhibits In Vivo Acute Carotid Thrombosis

Zei-Shung Huang, MD; Che-Ming Teng, PhD; Ti-Kai Lee, MD; Chia-Tung Shun, MD; and Cheng-Yi Wang, MD

Background and Purpose: Carotid atherosclerotic thrombosis is an important cause of ischemic stroke in Western countries. The therapeutic efficacy of either aspirin or heparin alone in this setting is still controversial. Recently we developed a simple model, the "clamp" method, to induce acute carotid mural thrombosis in vivo in guinea pigs. In this study, we used this model to evaluate the antithrombotic effects of aspirin, heparin, and their combination.

Methods: Sixty-four male guinea pigs were divided equally into control, aspirin, heparin, and combined groups. Physiological saline, aspirin (5 mg/kg body wt), heparin (200 units/kg body wt), or a combination of aspirin and heparin, respectively, was injected via the jugular vein before the use of the clamp method. Thirty minutes after the injection of saline or drug(s), Pérán's forces was used to clamp the carotid artery at a tangent angle for 3 minutes. One hour later, the carotid artery was resected and prepared for observation under a scanning electron microscope or light microscope to evaluate the degree of mural thrombosis.

Results: The results showed that the combination of aspirin and heparin had an excellent effect in inhibiting in vivo acute carotid thrombosis (p<0.001) and was significantly better than the effect of aspirin alone (p<0.01) or heparin alone (p<0.01).

Conclusions: Our study clearly demonstrated that the combined use of aspirin and heparin produced a much better antithrombotic effect than either agent alone at sites of carotid endothelial injury when given before the injury. This combined regimen may be useful clinically in acute carotid thrombosis secondary to carotid diseases or carotid endarterectomy. (Stroke 1993;24:829–838)

Key Words • aspirin • carotid artery diseases • heparin • gerbils

Carotid atherosclerosis with severe or unstable mural plaque is an important cause of ischemic stroke in Western countries. Some authors have reported that rupture, fissuring, or ulceration of carotid plaque may trigger acute carotid thrombosis and induce acute carotid occlusion. Aspirin and heparin are well-known antithrombotic agents that have been used in the treatment of acute ischemic stroke for years. Unfortunately, the efficacy of either aspirin or heparin alone in this setting is still controversial. Recently we developed a simple animal model, the "clamp" method, which can create carotid endothelial laceration and induce acute carotid mural thrombosis in vivo in guinea pigs. In this study, we used this model to evaluate the antithrombotic effects of aspirin, heparin, and their combination. We also simultaneously compared ex vivo platelet aggregation, prothrombin time (PT), and activated partial thromboplastin time (APTT) in different study groups.

Materials and Methods

Sixty-four male guinea pigs (270–330 g) were used in this study. They were equally and randomly divided into control, aspirin, heparin, and combined groups. Physiological saline, aspirin (5 mg/kg body wt), heparin (200 units/kg body wt), or a combination of aspirin and heparin was injected via the jugular vein 30 minutes before the use of the clamp method. In the combined group, aspirin was given 5 minutes before heparin.

The procedures of the clamp method have been described in detail previously. In brief, after general anesthesia with intraperitoneal injection of pentobarbital sodium (30 mg/kg body wt), the left jugular vein of the guinea pig was isolated, and a thin polyethylene tube was inserted for injection of saline or drug(s). Thirty minutes later, the right common carotid artery was separated carefully. The carotid was then gently elevated and stretched by a small smooth forceps to a position at which the intracarotid blood flow seemed interrupted. Then, a toothed hemostatic (Pérán's) forceps was used to clamp the entire diameter of the carotid artery at a tangent angle for 3 minutes. Immediately after the release of Pérán's forceps, the carotid artery was manipulated externally along its long axis with a smooth forceps to restore blood flow at once. One hour later, the right common carotid artery was

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resected and then incised longitudinally by a microscissors. It was then prepared for observation under a scanning electron microscope \((n=10 \text{ in each group})\) or light microscope \((n=6 \text{ in each group})\) to evaluate the degree of carotid mural thrombosis. In this study, all guinea pigs were clamped by the Péan’s forceps at a particular site on that forceps. This forceps had three grids between its two handgrips, and thus three degrees of clamping force could be applied to the carotid artery. All carotid arteries were clamped to the first grid (the mildest degree). The particular site of the forceps was chosen at a location where the teeth of both arms had a very tight contact on each other when the forceps was clamped to the first grid, but had a minimal separation when the two handgrips were held together without clamping to the first grid.

The carotid specimens were prepared for observation under a scanning electron microscope as follows. Specimens were placed into 2.5% glutaraldehyde for fixation. After fixation for at least 8 hours, the specimens were dehydrated sequentially in graded ethyl alcohol. Thereafter, they were put in an acetic acid for 10 minutes, with critical point drying done using liquid carbon dioxide, and coated with gold. The specimens were then observed under a scanning electron microscope (model JXA-840, JEOL, Japan), and a photograph with \(\times 43\) magnification was taken for each specimen. Under this magnification, the entire inner carotid wall, including endotheiial folds, endothelial laceraions, and formed mural thrombus, could be seen well. Under scanning electron microscopy, the thrombi were recognized at lower magnification \((\times 43-100)\) as abnormal mural masses or materials containing fused platelet aggregates, deformed platelets, crenated erythrocytes, fibrils, and scanty leukocytes, which were identified under higher magnification \((\times 1,000-5,000)\). The degree of mural thrombosis of a carotid specimen under scanning microscope was evaluated in two ways. First, it was expressed as the total surface area \(\text{(in square millimeters)}\) of thrombi seen in that specimen, calculated by the AUTOCAD computer program with the aid of a digitizer. Second, it was graded by the extent that the edges of endothelial laceration were covered by thrombi. According to the latter system, the degree of carotid mural thrombosis was classified into three categories: 1) marked, with the edges of endothelial laceration completely or almost completely covered by thrombi; 2) moderate, with the edges of endothelial laceration partially covered by thrombi; and 3) mild, with the edges of endothelial laceration completely or almost completely free from thrombi.

The carotid specimens were prepared for observation under a light microscope as follows. Specimens were fixed in formalin for at least 8 hours. Then, they were cut longitudinally into three smaller pieces. Each three cut surfaces were prepared as thin pathological slides and stained with hematoxylin and eosin. In this preparation, the cross section of the endothelial laceration and the thrombi in or overlying the laceration could be seen. The one cut surface with the largest endothelial laceration was taken to represent the specimen. The thrombi were recognized as abnormal pink fibillary materials or masses associated with interrupted endotheiila, containing some erythrocytes and occasionally leukocytes. Fibrin fibers in the thrombi could be identified by phosphotungstic acid-hematoxylin stain. The degree of mural thrombosis was then evaluated by the following two parameters: 1) maximal width of thrombus divided by width of laceration and 2) height of thrombus \(\text{(in millimeters)}\) above the endothelial level protruding into the carotid lumen.

Ex vivo platelet aggregation, PT, and APTT were studied in 10 of 16 guinea pigs in each group. The ex vivo platelet aggregation tests were done as follows. Immediately after resection of the right common carotid artery, 9 mL of blood was drawn from the left common carotid artery directly into a 10-mL syringe containing 1 mL of 3.8% sodium citrate. It was mixed well and separated into two tubes, 5 mL in each, which were then centrifuged at room temperature at 90g for 10 minutes to obtain platelet-rich plasma \(\text{(PRP)}\). The platelet count in PRP was adjusted to \(45\times10^6/\mu\text{L}\) before performing the platelet aggregation tests. Platelet aggregation tests in PRP were induced by collagen suspension and measured by the turbidimetric method using a platelet aggregometer \(\text{(model 1020, Payton Scientific, Inc., Canada)}\) recording for 6 minutes. The degree of platelet aggregation was expressed as percentage of maximal change in light absorption within 6 minutes after adding collagen. The final concentrations of collagen used in PRP were 1, 2, 4, and 10 \(\mu\text{g/mL}\). We used collagen as the platelet activator because our previous studies had shown that the mural thrombi of our model formed on subendothelial collagen fibers and that collagen-induced platelet aggregation was more similar between humans and guinea pigs than that induced by other platelet activators. PT and APTT were measured by a computer-controlled, 10-channel coagulation analyzer \(\text{(Behring Fibrintimer 10, Behringwerke AG, Marburg, FRG)}\). All the above measurements, including the degree of mural thrombosis, were performed randomly but not in a blinded manner.

Lysine acetylsalicylic acid powder \(\text{(containing 0.5 g aspirin in a mixture of 0.9 g lysine aspirin and 0.1 g glycine)}\) was purchased from China Chemical and Pharmaceutical Co. Ltd., Taiwan, ROC. Heparin \(\text{(5,000 units/mL)}\) was obtained from Novo Industrial Co. Ltd., Denmark. Collagen \(\text{(bovine achilles tendon, type I)}\) was obtained from Sigma Chemical Co., St. Louis, Mo. The kit reagents for measuring PT and APTT were purchased from Behringwerke AG.

The results of control, aspirin, heparin, and combined groups were compared either by Student’s \(t\) test using mean±SEM or by the Mantel-Haenszel \(\chi^2\) test.

**Results**

The results of ex vivo platelet aggregation tests \(\text{(Table 1)}\) showed the following. 1) Platelet aggregations in the aspirin group were significantly less than those in the control group except for that induced by the highest concentration of collagen \(\text{(10 \mu g/mL)}\). 2) Platelet aggregations in the heparin group were, in general, less than those in the control group, but a significant difference was found only in that induced by 2 \(\mu\text{g/mL}\) of collagen. 3) Platelet aggregations in the combined group were significantly less than those in the control group. 4) Comparing the combined and the aspirin groups, platelet aggregations were, in general, less in the combined group. These results confirmed the antiplatelet effect of...
aspirin and indicated that ex vivo platelet aggregation decreased 90 minutes after bolus injection of heparin.

The results of PT and APTT measurements (Table 2) showed the following. 1) In the heparin-treated groups, PT and APTT were both significantly prolonged compared with those in the control group. 2) The prolongation of APTT was much more prominent than that of PT. 3) There was no difference in the values of PT and APTT between the aspirin and the control groups. These results indicated that the coagulation system of guinea pigs was not significantly affected by aspirin but was significantly affected by heparin, similar to the effect in humans.

Photographs of carotid specimens in the control group (Figure 1A and 1B), the aspirin group (Figure 1C), the heparin group (Figure 1D), and the combined group (Figure 1E and 1F) taken under a scanning electron microscope are shown in Figure 1. From these photographs, the total surface area of thrombi (in square millimeters) could be estimated and the extent that the edges of the endothelial laceration were covered by thrombi could be determined. Table 3 shows that the total surface area of thrombi in the aspirin, heparin, and combined groups were all significantly smaller than that in the control group (p<0.05, p<0.05, and p<0.001, respectively). The total surface area of thrombi in the combined group was the smallest among the four groups and was significantly smaller than that in the aspirin group (p<0.01) and the heparin group (p<0.05).

Table 4 shows the results of comparing carotid mural thrombosis by observing the extent that the edges of endothelial laceration were covered by thrombi under scanning electron microscopy. The degree of mural thrombosis was classified into three grades (marked, moderate, and mild), as described in “Materials and Methods.” By Mantel-Haenszel χ² test (2×2) (see Table 4), we found that mural thrombosis was most markedly suppressed in the combined group. The suppression of mural thrombosis in the aspirin and heparin groups was weak, although statistically significant, compared with the results of the control group.

Photographs of carotid specimens in the control group (Figure 2A and 2B), the aspirin group (Figure 2C), the heparin group (Figure 2D), and the combined group (Figure 2E and 2F) taken under a light microscope are shown in Figure 2. From these photographs, the width of endothelial laceration and thrombus, the ratio of maximal width of thrombus to width of laceration, and the height of thrombus protruding into the carotid lumen could be measured. Table 5 shows the results of these measurements. The ratios of maximal width of thrombus to width of laceration in the aspirin and the combined groups were significantly smaller than

### Table 1. Results of Ex Vivo Platelet Aggregation Tests Induced by Collagen in Four Study Groups

<table>
<thead>
<tr>
<th>Collagen concentration (µg/mL)</th>
<th>Maximal platelet aggregation within 6 minutes (%) (by group)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>1</td>
<td>68.7±12.5</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>2</td>
<td>92.1±1.6</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>92.2±1.4</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.05</td>
</tr>
<tr>
<td>10</td>
<td>91.8±1.2</td>
</tr>
<tr>
<td></td>
<td>p&gt;0.05</td>
</tr>
</tbody>
</table>

Degree of platelet aggregation is expressed as percentage of change in light absorption of platelet-rich plasma recorded by Payton platelet aggregometer after adding collagen. Probability values in table represent differences between indicated group and respective control group, compared by Student's t test using mean±SEM (n=10 in each group).

*p<0.05; †p<0.01.

### Table 2. Results of Prothrombin Time and Activated Partial Thromboplastin Time in Four Study Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>Control</th>
<th>Aspirin</th>
<th>Heparin</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>PT (seconds)</td>
<td>23.3±1.4*</td>
<td>21.6±1.4</td>
<td>40.5±2.9</td>
<td>39.6±1.4</td>
</tr>
<tr>
<td></td>
<td>p&gt;0.05</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>APTT (seconds)</td>
<td>21.8±1.0*</td>
<td>19.5±0.8</td>
<td>104.7±8.0†</td>
<td>115.0±3.6†</td>
</tr>
<tr>
<td></td>
<td>p&gt;0.05</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
<td>p&lt;0.001</td>
</tr>
</tbody>
</table>

*Control values of prothrombin time (PT) and activated partial thromboplastin time (APTT) in humans were 11.8±0.1 seconds (n=10) and 35.1±4.5 seconds (n=10), respectively.
†Values of APTT of several specimens in these two groups exceeded 120 seconds and were taken as 120 seconds.

Probability values in table represent differences between indicated group and respective control group, compared by Student's t test using mean±SEM (n=10 in each group).
FIGURE 1. Photographs of carotid specimens from different study groups taken by a scanning electron microscope (original magnification, ×43). Thrombi and edges of endothelial lacerations are indicated by white arrows and arrowheads, respectively. In control specimens (panels A and B), large thrombi were seen on carotid walls, presumably overlying endothelial lacerations. In aspirin-treated (panel C) and heparin-treated (panel D) specimens, thrombi were smaller than those in control specimens and covered only parts of the edges of endothelial lacerations. In specimens of the combined group (panels E and F), endothelial lacerations and their edges were nearly fully visible, with only minimal or no thrombi. Bars, 100 μm.

that in the control group \( (p<0.05 \text{ and } p<0.005) \) respectively. The ratio in the combined group was the smallest among the four study groups and was significantly smaller than that in the aspirin group \( (p<0.001) \) and the heparin group \( (p<0.01) \). The heights of thrombus protruding into the carotid lumen in the three treated groups were all significantly shorter than that in the control group, with the shortest height in the combined group.

**Discussion**

Aspirin and heparin are two well-known antithrombotic agents that have been used to treat acute ischemic stroke for years. Unfortunately, the efficacy of either
aspirin or heparin alone to treat acute ischemic stroke is still controversial.7-13 These two agents have different pharmacological actions on the thrombotic process. Aspirin, as an antiplatelet agent, inhibits platelet aggregation by suppressing platelet thromboxane A\textsubscript{2} formation.16 Heparin, as an anticoagulant agent, acts mainly by enhancing the ability of antithrombin III to neutralize thrombin.17,18 In theory, the combined use of aspirin and heparin will have a synergistic antithrombotic effect because they inhibit different pathways of the thrombotic process. However, this assumption has not yet been proved in vivo, and the few recent studies that dealt with this subject obtained no definite conclusion.19,20 Our study clearly demonstrated that the combination of aspirin and heparin, with aspirin given before heparin, had a much better effect than either agent alone in inhibiting in vivo acute carotid thrombosis. Such a trend can be seen from different evaluation methods, as shown in Tables 3, 4, and 5. In our study, we also found that the antithrombotic effect of either aspirin or heparin alone was limited, although statistically significant. This finding might partially explain the controversial results of those clinical trials using aspirin or heparin alone to treat acute ischemic stroke.

In the arterial system characterized by rapid flow and a high shear rate of blood, platelets are believed to play a more important role than coagulation factors in initiating acute thrombosis.12,21 On the other hand, coagulation factors are thought to play the major role in developing thrombosis of the venous system when blood stasis is present.19 In a severely diseased or injured artery, a special condition of having both rapid turbulent flow and focal blood stasis may exist, and coagulation factors may become as important as platelets in promoting acute thrombosis. Aspirin or heparin alone in such a circumstance may have only a limited effect in inhibiting thrombus formation. The limited effect of aspirin alone may be due to the fact that it has no direct anticoagulant action, and it cannot inhibit platelet aggregation induced by thrombin, which could be produced locally in a diseased and stenosed artery.21-23 The limited effect of heparin alone may be due to the fact that it has no direct antiplatelet action, and it has a platelet proaggregatory property, which has been reported for years.24,25 Thus, the reasons that a combina-

### Table 3. Comparison of Carotid Mural Thrombosis by Measuring Total Surface Area of Thrombi Under a Scanning Electron Microscope

<table>
<thead>
<tr>
<th>Group</th>
<th>Control (mm\textsuperscript{2})</th>
<th>Aspirin (mm\textsuperscript{2})</th>
<th>Heparin (mm\textsuperscript{2})</th>
<th>Combined (mm\textsuperscript{2})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total area of thrombi</td>
<td>1.64±0.26</td>
<td>0.91±0.16</td>
<td>0.95±0.20</td>
<td>0.38±0.10</td>
</tr>
<tr>
<td>Probability values in table represent differences between indicated group and control group, compared by Student's t test using mean±SEM (n=10 in each group).</td>
<td>p&lt;0.05</td>
<td>p&lt;0.05</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

### Table 4. Comparison of Carotid Mural Thrombosis by Evaluating Extent That Edges of Endothelial Laceration Were Covered by Thrombi Under a Scanning Electron Microscope

<table>
<thead>
<tr>
<th>Degree of thrombosis</th>
<th>Control (n=10)</th>
<th>Aspirin (n=10)</th>
<th>Heparin (n=10)</th>
<th>Combined (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marked</td>
<td>9</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Moderate</td>
<td>1</td>
<td>7</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Mild</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Comparison of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Marked</td>
<td>9</td>
<td>2</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>1</td>
<td>8</td>
<td>6</td>
<td>9</td>
</tr>
<tr>
<td>Probability values in table represent differences between indicated group and respective control group, based on Mantel-Haenszel ( \chi^2 ) test (2×2).</td>
<td>p&lt;0.005</td>
<td>p&lt;0.025</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>Other</td>
<td>10</td>
<td>9</td>
<td>9</td>
<td>3</td>
</tr>
<tr>
<td>Probability values in table represent differences between indicated group and respective control group, based on Mantel-Haenszel ( \chi^2 ) test (2×2).</td>
<td>p&gt;0.05</td>
<td>p&gt;0.05</td>
<td>p&lt;0.005</td>
<td></td>
</tr>
</tbody>
</table>

Carotid mural thrombosis was classified as marked, moderate, or mild by observing extent that edges of endothelial laceration were covered by thrombi. See "Materials and Methods" in text for details. *p<0.01.
tion of aspirin and heparin could produce a better antithrombotic effect than either agent alone may be as follows: 1) The addition of heparin to aspirin may remove abnormally formed thrombin in the diseased artery, and thus may abolish thrombin-induced platelet aggregation that is resistant to aspirin; 2) the use of aspirin before heparin may partially reverse the adverse platelet proaggregatory effect of heparin; and 3) simultaneous use of antiplatelet and anticoagulant agents may block the reinforced interaction between the activation of platelets and the activation of coagulation factors.

In Table 1, some data seem to conflict with the viewpoint that heparin has a platelet proaggregatory effect. These data showed that in the heparin-treated groups, 90 minutes after bolus injection of heparin the
ex vivo platelet aggregation became weaker, compared with those groups without heparin. Possible explanations for this finding are as follows: 1) An in vivo stimulating effect of heparin on circulating platelets immediately after its bolus injection may have exhausted the functional reserve of platelets; and 2) the preexistence of heparin in blood in vivo may abolish the formation of trace thrombin, a strong platelet aggregating factor, during blood sampling and preparing PRP from whole blood for ex vivo aggregation tests.21

In our experiments, a factor that might interfere with the degree of carotid thrombosis but could not be strictly controlled by the experimenter was the size of endothelial laceration created by the clamp method. For this reason, we used the ratio of maximal width of thrombus to width of laceration as an index to compare the degree of thrombosis in four study groups. In Table 5, several data were interesting and worth further discussion. The width of endothelial laceration in the combined group (0.19±0.03 mm, n=6) was significantly smaller than that in the control group (0.42±0.06 mm, n=6, p<0.005), but the standard errors were both small. These data indicated that the intragroup difference in the width of laceration was small within either the control or the combined group, but the intergroup difference was large between the control and the combined groups. To understand the reason for this unexpected finding, we later again observed all specimens of all groups under light microscopy. A possible explanation was that the endothelial laceration in the control group was wider because the bilateral edges of laceration had been pushed outward by the large thrombus formed in the laceration. Therefore, the shape of laceration in the control group often looked like a shallow dish in cross section (Figure 2A and 2B). In contrast, the shape of endothelial laceration in the combined group often looked more like a deep bowl (Figure 2E and 2F), probably because there was no or only minimal thrombus in the laceration, and the two edges of laceration would come closer when the carotid segment shortened immediately after being resected away from the neck.

In view of the excellent antithrombotic effect of combining aspirin and heparin in the study, we propose that this combined regimen may be valuable in the clinical field. Clinically it is usually not possible to treat an acute thrombotic event before its onset, as has been done in our study, with the probable exception of carotid endarterectomy. Our model incidentally mimics carotid endarterectomy in producing endothelial denudation, intimal injury,32,33 and possibly the consequent thrombotic process.33 Therefore, the results of our study may be able to be adequately applied to this clinical condition. Early occlusion of the carotid artery after endarterectomy is a major cause of immediate surgical failure34,35 and is often due to acute thrombus formation on the endarterectomized surface.35,36 Ischemic stroke after carotid endarterectomy is another problem, with its highest incidence in the perioperative period.37–39 Its major mechanism is thromboembolic in nature.40,41 Since the efficacy of either aspirin or heparin alone in these situations is still controversial,40,41–43 combined use of aspirin and heparin may be a useful alternative. The risk of hemorrhagic infarction may, of course, increase when aspirin and heparin are both used and should be carefully monitored. In the study, we were unable to assess the risk of hemorrhagic infarction because our model did not produce any observable

### Table 5. Comparison of Carotid Mural Thrombosis by Ratio of Width of Thrombus to Width of Laceration and by Height of Thrombus Protruding Into Carotid Lumen Measured Under a Light Microscope

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Aspirin</th>
<th>Heparin</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>Width of endothelial laceration (mm)</td>
<td>0.42±0.06</td>
<td>0.32±0.03</td>
<td>0.31±0.05</td>
<td>0.19±0.03</td>
</tr>
<tr>
<td></td>
<td>p&gt;0.05</td>
<td>p&gt;0.05</td>
<td>p&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>Maximal width of thrombus (mm)</td>
<td>0.83±0.09</td>
<td>0.30±0.04</td>
<td>0.41±0.09</td>
<td>0.05±0.02</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p&gt;0.005</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Ratio of maximal width of thrombus to width of laceration</td>
<td>2.32±0.55</td>
<td>0.93±0.06</td>
<td>1.33±0.29</td>
<td>0.21±0.1</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.05</td>
<td>p&gt;0.05</td>
<td>p&lt;0.005</td>
<td></td>
</tr>
<tr>
<td>Height of thrombus protruding into carotid lumen (mm)</td>
<td>0.35±0.07</td>
<td>0.06±0.02</td>
<td>0.09±0.03</td>
<td>0.01±0.01</td>
</tr>
<tr>
<td></td>
<td>p&lt;0.001</td>
<td>p&lt;0.005</td>
<td>p&lt;0.001</td>
<td></td>
</tr>
</tbody>
</table>

Probability values in table represent differences between indicated group and respective control group, compared by Student’s t test using mean±SEM (n=6 in each group).

* p<0.001; † p<0.01; ‡ p<0.05.
neurological consequence in 3 hours after carotid clamping. However, we did note that there was no remarkable bleeding from the surgical wound in guinea pigs receiving both aspirin and heparin.

In conclusion, our study clearly demonstrated that combined use of aspirin and heparin produced a much better antithrombotic effect than either agent alone at sites of carotid endothelial injury when given before the injury. This combined regimen may be useful clinically in acute carotid thrombosis secondary to carotid endarterectomy or carotid diseases. Clinical trials to evaluate its therapeutic efficacy and the possible risk of hemorrhagic infarction are needed.

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References
Combined use of aspirin and heparin inhibits in vivo acute carotid thrombosis.
Z S Huang, C M Teng, T K Lee, C T Shun and C Y Wang

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