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Heparin Administration and Monitoring for Neuroangiography

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PURPOSE: To establish the optimal protocol of heparin administration during interventional neuroradiology. **METHODS:** We assessed 100 cases of neuroangiography, including endovascular surgery, and measured activated coagulation time before and 5 minutes after heparin administration, and before and 5 minutes after protamine neutralization. In some cases actual heparin concentration was assayed using a chromogenic substrate technique. **RESULTS:** The actual plasma heparin concentration significantly correlated with the dose of heparin administered intravenously ($r = .98$; $P < .0001$) and changes in activated coagulation time ($r = .85$; $P < .0001$). The change in activated coagulation time significantly correlated with the dose of heparin injected intravenously ($r = .54$, $P < .0001$). The ratio of change in activated coagulation time significantly correlated with time elapsed after heparin administration ($r = -.70$, $P < .0001$). **CONCLUSIONS:** The activated coagulation time is useful in monitoring administration and neutralization of heparin during neuroangiography, and a bolus injection of 60 U/kg heparin should be adequate to carry out neuroangiography for 75 minutes safely, even for endovascular surgery.

Index terms: Heparin; Cerebral angiography, technique; Interventional neuroradiology

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Recently tremendous progress has been made in endovascular surgery, which is becoming a common procedure for intracranial lesions, such as arteriovenous malformations, aneurysms, vasospasm, and embolism of major arteries. However, this procedure is not completely safe because we occasionally encounter patients who experience life-threatening cerebral embolism and hemorrhage during catheterization (1). Furthermore, we have to take into consideration that ischemic events occur in 1.3% of conventional neuroangiographic procedures without endovascular surgery (2). Although there is no definite proved benefit of heparin administration in neuroangiography, the anticoagulant effect of heparin should be useful in preventing ischemic complications during the procedure. On the other hand, it always should be considered that excessive heparin may result in spontaneous bleeding (3). It is, therefore, important to use both an adequate and safe dose of heparin. However, precise guidelines for heparin administration and neutralization during neuroangiography, including endovascular surgery, have not yet been established.

There are several methods of monitoring heparin concentration, such as activated partial thromboplastin time and chromogenic substrate assays (factor Xa and factor IIa inhibition), but these are time consuming and require centrifugation to obtain plasma. On the other hand, activated coagulation time (ACT) is widely used to monitor heparin administration during cardiopulmonary bypass (4). ACT is a rapid and convenient assay and does not require any special preparation (5).

To understand the pharmacokinetics of heparin during endovascular procedures and to establish the optimal protocol for heparin administration, we assessed neuroangiography by means of ACT.

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Materials and Methods

One hundred patients (46 men and 54 women) undergoing neuroangiography were studied. Conventional angiography alone was performed in 62 of these 100 patients, embolization in 31 patients, balloon occlusion testing in three patients, percutaneous transluminal angioplasty in two patients, and proximal occlusion with balloons in two patients.

All patients were anticoagulated with conventional heparin (Novo Nordisc A/S, Copenhagen, Denmark) followed by neutralization with protamine sulfate (Shimizu Pharmaceutical Co., Shimizu, Japan). Heparin was given as a bolus and protamine sulfate as a 5-minute injection. The doses (mean ± 1 SD) of heparin and protamine sulfate were 68 ± 14 (range: 39–109) U/kg and 26 ± 9 (range: 0–50) mg, respectively.

ACT was measured in each patient before and 5 minutes after heparin administration and before and 5 minutes after protamine administration. A Hemochron System (International Technidyne Corp, Edison, NJ) was used to determine ACT. Each time, 2 mL of blood was drawn by syringe and transferred into a Hemochron test tube, CA510, containing celite, and the tube was placed into a portable coagulation timer.

Additional blood samples for heparin concentration assay were taken from some of the patients. Chromogenic substrate (factor Xa) assay was was performed using S-2222 (Kabi, Stockholm, Sweden) to measure heparin concentration.

Linear regression analysis was performed to assess the pharmacokinetics of heparin in the patients undergoing neuroangiography (Figs 1–4). Values were expressed as mean plus SD.

Results

Clinically neither embolic nor hemorrhagic complications were observed during the procedures.

ACT values before (ACT1) and 5 minutes after heparin administration (ACT2) and before (ACT3) and 5 minutes after protamine neutralization were 131 ± 17, 237 ± 58, 195 ± 38, and 130 ± 14 seconds, respectively. The duration of the angiographic procedures was 56 ± 29 minutes.

The actual heparin concentration in plasma 5 minutes after heparin administration correlated significantly ($P < .0001$) with the dose of heparin (in units per kg) injected intravenously in 22 patients ($Y = 0.014X - 0.031$; $r = .98$) (Fig 1).

There was a significant ($P < .0001$) correlation between the increase in ACT (ACT2 or ACT3 minus ACT1) and heparin concentration in plasma in 30 blood samples from 15 patients ($Y = 88.4X - 0.6$; $r = .85$) (Fig 2).

The change in ACT 5 minutes after heparin administration (ACT2 minus ACT1) correlated significantly ($P < .0001$) with the dose of heparin injected intravenously ($Y = 1.55X - 1.88$; $r = 0.54$) (Fig 3).

The ratio of the increase in ACT before protamine neutralization (ACT3 minus ACT1) to the increase in ACT 5 minutes after heparin administration (ACT2 minus ACT1) (the ratio of ACT

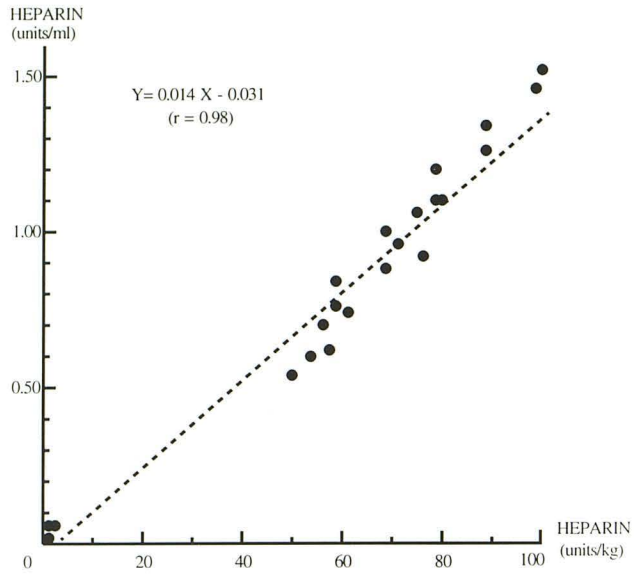

Fig. 1. Graph shows a significant ($P < .0001$) correlation ($Y = 0.014X - 0.031$; $r = .98$) between the dose of injected heparin and the heparin concentration in plasma 5 minutes after the initial dose in 22 patients. Sixty units per kg of heparin is required to obtain a 0.8-U/ml heparin concentration in plasma.

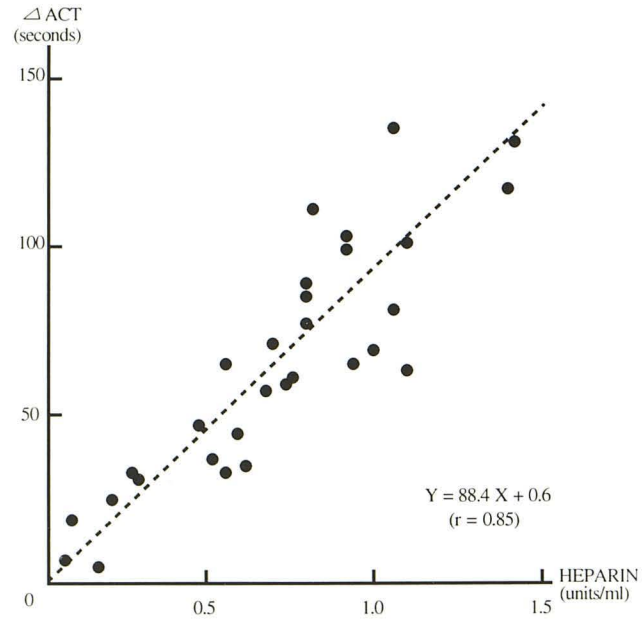

Fig. 2. Graph shows a significant ($P < .0001$) correlation ($Y = 88.4X + 0.6$; $r = .85$) between the increase in ACT and plasma heparin concentration in 30 blood samples from 15 patients.

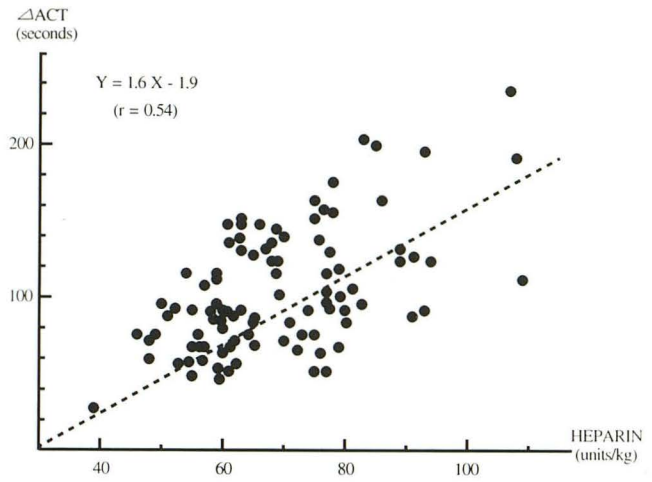

Fig. 3. Graph shows a significant ($P < .0001$) correlation (Y = 1.6X − 1.9; $r = .54$) between the increase in ACT and dose of heparin 5 minutes after injection in 100 patients.

change) correlated significantly ($P < .0001$) with time (minutes) elapsed between heparin administration and protamine neutralization (Y = −0.52X + 89.5; $r = -.70$) (Fig 4).

Discussion

The main complication associated with heparin therapy is spontaneous bleeding. Although the mechanism of heparin-induced bleeding is unclear, many reports claim that the risk of bleeding should increase with both heparin dose and response (3). Heparin inhibits blood coagulation by accelerating the inhibition of activated coagulation factors and also inhibits platelet aggregation. In excessive concentrations, its inhibitory effect on platelet function may induce bleeding (6). Throughout cardiopulmonary bypass more than 3.0 U/ml of heparin is usually required, because the bypass procedures, especially the oxygenator, generate a large amount of thrombin and consume hemostatic factors, including platelets (7). Except for cardiopulmonary bypass, the recommended therapeutic range of heparin is usually expressed as actual heparin concentration of plasma or the ratio (not actual values) of activated partial thromboplastin time, that is, 0.2 to 0.8 U/ml of heparin in plasma (full heparinization) corresponding to activated partial thromboplastin time and ACT values 1.5 to 2.5 times the baseline values (8, 9). This range is a compromise between the desire to prevent the formation of thrombi and the fear of major bleeding. At this level of heparin, thrombus formation in experimental animals can be prevented. However, at high concentrations of heparin, greater than 0.8 U/ml (corresponding to activated partial thromboplastin time and ACT prolonged more than 2.5 times the baseline values), the risk of major bleeding should increase (8, 9). It is, therefore, important for the heparin level to stay within the therapeutic range (heparin concentration in plasma: 0.2 to 0.8 U/ml) during neuroangiography because endovascular surgery is associated with the risk of cerebral hemorrhage and cerebral embolism.

Based on the correlation between actual heparin concentration and dose of injected heparin, 60 U/kg of heparin is required to obtain a 0.8-U/ml heparin concentration in plasma (Fig 1). It is, however, somewhat complicated to estimate the residual anticoagulant activity of heparin. In this study, the ratio of ACT change was used to determine the residual anticoagulant activity for the following reasons: 1) to equalize various ACT responses to heparin; and 2) to balance various heparin doses used. If ACT response to a certain heparin concentration in plasma was constant in all patients, the residual anticoagulant activity could be easily determined using the correlation between the change of actual ACT values and heparin concentration in plasma (Fig 2). Although our study revealed a significant correlation between the change in ACT and the actual heparin concentration in a small number of patients (Fig 2), the increase in ACT after administering a constant dose (units per kg) of heparin to achieve

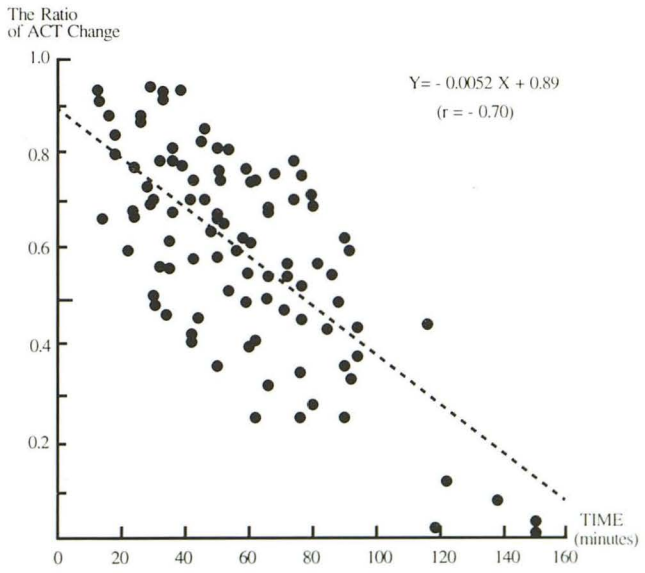

Fig. 4. Graph shows a significant ($P < .0001$) correlation (Y = −0.0052X + 0.89; $r = -.70$) between the ratio of ACT change and time elapsed after heparin administration in 100 patients. The ratio of ACT change (ie, residual anticoagulant activity) is reduced to almost half 75 minutes after heparin administration.

a constant heparin concentration in plasma (units per ml) was reported to vary according to patient conditions (Fig 3), including body weight, gender, age, and smoking history (8). Therefore, the peak values of increase in ACT shortly after heparin administration are necessary to estimate ACT response to heparin. Hence, the ratio of ACT change should become more suitable to estimate the residual anticoagulant activity of a patient than the change in actual ACT, because the change in actual ACT (ACT3 minus ACT1) cannot reflect the individual variability of ACT response to heparin concentration. The ratio of ACT change is considered 1.0 (peak value of anticoagulating activity after first heparin administration) 5 minutes after heparin administration and 0 (no anticoagulating activity) when ACT3 reaches ACT1. Therefore, the residual anticoagulant activity of heparin is easily determined by means of ACT because in individual patients there is a linear correlation between ACT values and anticoagulant activity (heparin concentration in plasma) within the therapeutic range (5, 10) (ie, 0.8 × [the ratio of ACT change] U/ml [when 60 U/kg of heparin is administered]). Moreover, the ratio of ACT change is convenient to estimate appropriate doses of protamine sulfate for heparin neutralization. It is common to administer 1 mg of protamine sulfate/100 U of heparin in order to neutralize heparin (9). The appropriate dose of protamine sulfate can be easily determined on the basis of ACT (ie [the initial heparin dose administered] × [the ratio of ACT change] × [1/100] mg).

In order to assess the guideline of heparin administration in facilities where a Hemochron system is not available, the elimination rate of heparin was assessed using the ratio of ACT change. On the basis of the correlation between the ratio of ACT change and time (Fig 4), the ratio (ie, the residual heparin anticoagulant activity) is reduced to almost half of its initial activity 75 minutes after heparin administration. The concentration of heparin in plasma is also expected to be reduced to half 75 minutes after heparin administration because of the correlation between the change in ACT (ACT2 or ACT3 minus ACT1) and actual heparin concentration in plasma (Fig 2). Therefore, we can expect the heparin concentration in plasma to become approximately 0.4 U/ml 75 minutes after a bolus injection of 60 U/kg. When half of the initial dose of heparin (30 U/kg) is administered in addition, the heparin concentration in plasma is expected to be 0.8 U/ml. Residual anticoagulant activity of heparin 30, 60, and 90 minutes after initial heparin administration is also expected to be approximately 75%, 60%, and 40% of the initial anticoagulant activity, respectively (Fig 4). On the basis of these expected anticoagulant activities, an approximate dose of protamine sulfate can be estimated to neutralize heparin using the equation above.

In conclusion, our study suggests that the heparin concentration in plasma should be approximately 0.8 U/ml 5 minutes after a bolus injection of 60 U/kg of heparin, and that 75 minutes after the initial injection, heparin activity should remain within the recommended therapeutic range (0.2–0.8 U/ml). When endovascular surgery continues for more than 75 minutes, additional injections of heparin are required to keep the actual heparin concentration in plasma from 0.4 to 0.8 U/ml (the upper part of the therapeutic range). Half of the initial dose should be adequate for another 75 minutes. However, the pharmacokinetics of heparin vary depending on the patient's condition. Hence, ACT is helpful in verifying heparin activity and estimating appropriate doses of protamine sulfate to neutralize the heparin.

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