Is There a Role for Heparin in the Management of Complications of Subarachnoid Hemorrhage?

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Proven effective therapy to prevent ischemic deficits and other complications after subarachnoid hemorrhage is lacking despite extensive research efforts. A literature review documented both clinical and experimental evidence suggesting that heparin may be effective in preventing ischemic deficits after subarachnoid hemorrhage by reversing vasospasm, improving blood flow through narrowed vessels, and preventing the development of a proliferative angiopathy. Additional evidence suggests that heparinization of the cerebrospinal fluid following subarachnoid hemorrhage may prevent the development of hydrocephalus. In the only clinical trial using heparin after subarachnoid hemorrhage, the incidence of rebleeding in the heparinized patients was no higher than in the control group. We conclude that the existing preliminary data concerning a role for heparin in the management of the complications of subarachnoid hemorrhage is promising, but further controlled studies are needed prior to clinical application. (Stroke 1987;18:1169-1172)

The morbidity and mortality associated with subarachnoid hemorrhage (SAH) is staggering. About 50% of patients recover from the initial effects of SAH; the other 50% either die or remain severely incapacitated. Of those who initially recover, approximately 40% subsequently deteriorate. The most important causes of deterioration are cerebral ischemia related to vasospasm, which occurs in about 30—40% of patients, rebleeding in 8—12%, and the development of hydrocephalus in 10—40% (although <10% require cerebrospinal fluid [CSF] diversion). Other factors include cerebral ischemia secondary to the development of a proliferative angiopathy, electrolyte disturbances, cardiac arrhythmias and ischemia, and infections. Despite intensive specialized care, approximately 50% of those patients with delayed deterioration die or are left with significant neurologic disability.

Rebleeding can be prevented by early surgery, but effective therapy to prevent cerebral ischemia related to vasospasm and the development of hydrocephalus has yet to be established. This paper reviews the potential role for heparin in the prevention of these major complications of SAH.

Evidence That Heparin May Be Effective in Treating Vasospasm

In a clinical trial, Kapp et al compared 112 consecutive patients with aneurysmal SAH who received systemic heparin in conjunction with carotid ligation with the results of carotid ligation alone reported in the Cooperative Study. The incidence of ischemic complications in the patients receiving heparin was 6% compared with 23% in the Cooperative Study group, with mortality reduced from 16% to 10%.

Experimental studies have focused on the role of heparin in reducing vasospasm in noncerebral arteries. LeVeen et al reported that heparin reduced the incidence and severity of diffuse and focal vasospasm following angioplasty of the iliac and femoral arteries of rabbits. Haver and Namm showed that thrombin-induced vasospasm of isolated rabbit aortas and dog coronary arteries was inhibited by heparin. To our knowledge there are no experimental studies showing similar effects of heparin on cerebral vasospasm, although White and Robertson have reported that antithrombin III (heparin cofactor) relaxed isolated canine basilar arteries that were precontracted with plasmin, thrombin, serotonin, and uridine triphosphate.

Mechanism of Cerebral Vasospasm and Why Heparin May Work

Many mechanisms have been proposed to account for vasospasm after SAH, including mechanical, neurogenic, and chemical factors as well as the development of pathologic changes in the media and intima of cerebral vessels. However, each of these mechanisms alone inadequately accounts for one or more of the characteristic phenomena associated with vasospasm, which include 1) the delay in onset (typically 3—17 days following hemorrhage), 2) the relation of vasospasm to the volume of blood around the vessels in the subarachnoid space, and 3) the fact that it is potentially reversible.

Heparin may play a role in the management of vasospasm based on the growing evidence that the products
of erythrocytes, hemostasis, and fibrinolysis may be important in vasospasm, specifically hemoglobin derivatives, thrombin, fibrin and its degradation products, and plasmin.

Plasmin has been shown to produce a sustained contraction of isolated canine basilar arteries for at least 2 hours. Fibrin clot formed in SAH stimulates the release of plasminogen activator by the brain, cerebral vessels, choroid plexus, and meninges. Plasmin, whose function is fibrinolytic, is formed from plasminogen by plasminogen activator — a process maximal about 1 week after injury, consistent with the time frame of delayed vasospasm. If plasmin is a vasospastic substance, one might expect that the antifibrinolytic agent e-aminocaproic acid, which inhibits conversion of plasminogen to plasmin, would decrease the incidence of vasospasm, yet the contrary has been reported. White and Robertson postulated that this may be because antifibrinolytic therapy prolongs the duration of fibrin clot and ultimately may enhance the release of plasmin, and e-aminocaproic acid has been reported to inhibit plasmin inhibitors.

Thrombin also produces marked contraction of canine basilar arteries, but the effect is short-lived (<1 hour) and significant tachyphylaxis develops. It is unlikely, therefore, that thrombin is directly responsible for delayed cerebrovasospasm. However, thrombin may influence vasospasm by its effects on platelet aggregation and the subsequent release of vasoactive substances. Thrombin induces platelet aggregation directly, as well as indirectly, by damaging endothelium. Antithrombin III, as noted earlier, has been shown to relax basilar arteries precontracted with plasmin and thrombin. Antithrombin III is the principal physiologic inhibitor of thrombin and other serine proteases including plasmin and trypsin.

Heparin may be useful in the treatment of cerebral vasospasm by 1) relaxing vessels previously contracted by plasmin and thrombin (heparin accelerates the formation of complexes involving antithrombin III and the serine proteases thrombin and plasmin; this acceleration results in an enhancement of the inhibitory potency of antithrombin III) and 2) improving blood flow through narrowed arteries by preventing thrombus formation and sludging in areas of low flow.

Other Potential Uses of Heparin in Management of Complications of Subarachnoid Hemorrhage

Two other relatively common complications of SAH are hydrocephalus and the development of a proliferative cerebral angiopathy. The development of hydrocephalus is thought to be due to fibrin deposition along passages used for CSF absorption, which explains the high incidence of hydrocephalus in those patients with SAH treated with the antifibrinolytic agent e-aminocaproic acid. Cognizant of this, Blasberg et al studied the effects of heparinization of the CSF of monkeys. Heparinized blood was injected intracisternally into 1 group of monkeys and nonheparinized blood into another; the absorption resistance of CSF was then studied. The monkeys given injections of nonheparinized blood maintained high CSF absorptive resistances for as long as 3 months, whereas the group that received heparinized blood had significantly lower CSF absorptive resistances that returned to the original levels within 6 weeks. This study suggests that if heparinization of the CSF could be achieved rapidly after SAH, patency of the CSF pathways could be maintained, thereby preventing hydrocephalus. Additionally, vasospasm may also be reduced by more rapid clearance of vasoactive substances from the CSF.

Heparin, a large heterogeneous group of mucopolysaccharides with a molecular weight of 12,000, ordinarily does not cross the blood–brain barrier. Nevertheless, heparinization of the CSF may be possible with systemic heparin administration after SAH since significant disruption of the blood–brain barrier has been reported to occur in that setting. Recent studies, however, have suggested that vasospasm lessens blood–brain barrier disruption after SAH, complicating the issue of CNS drug distribution following SAH.

It is tempting to believe that morphologic changes sometimes seen in the media and intima of cerebral vessels following SAH are the final common pathway of severe vasospasm. However, a strong argument against this idea is that symptomatic vasospasm is reversible both clinically and angiographically. Nevertheless, there is clinical and experimental evidence suggesting that the morphologic changes occur following SAH and play a role in cerebral ischemia.

The pathology observed has been necrosis of the media and intima of vessels, with hyperplasia and migration of smooth muscle cells and secondary intimal thickening. The mechanisms of these actions are independent of its anticoagulation effect and are related to competitive inhibition of growth factors, including platelet-derived growth factor, which binds to connective tissue at sites of endothelial injury to attract smooth muscle cells from the media into the intima.

Conclusion

There is plausible experimental evidence to suggest that heparin may be effective in the management of 3 important complications of SAH — vasospasm, hydrocephalus, and the development of a proliferative angiopathy. The obvious concern about using heparin in this setting is the risk of rebleeding. Heparin does not have fibrinolytic activity, so the risk of rebleeding once a stable fibrin clot is formed is probably not increased. However, the risk of continued bleeding...
should rebleeding occur is likely to be higher in heparinized patients. In the clinical study of Kapp et al., the incidence of rebleeding in the heparinized group was 5% (6 of 122 patients) compared with 8% (12 of 151 patients) in the nonheparinized group of patients from the Cooperative Study used as a control. However, recurrent hemorrhages were fatal in all 6 patients receiving heparin compared with 67% (8 of 12 patients) in the nonheparinized group.

We are not advocating the clinical use of systemic heparin in the management of patients with the complications of SAH at this time. However, early work does show promise, and in our opinion further research is warranted. Specific questions that need to be answered are: Does heparin augment the action of antithrombin III in preventing or reversing experimental cerebrovasospasm, and if so, at what dose (i.e., is partial heparinization sufficient)?

If properly controlled follow-up studies confirm this early promise, the likely clinical implication will be a movement toward early surgery to clip the aneurysm, during which time the CSF could be lavaged and heparinized, followed postoperatively by volume expansion and systemic heparinization. The risk of full-dose heparinization immediately after craniotomy has not been evaluated. Stern has recommended waiting at least 5 days after craniotomy before proceeding with full anticoagulation therapy. However, Barnett et al. have shown that minidose heparin may be used safely in postoperative neurosurgical patients.

Those patients for whom early surgery is undesirable may need to be managed differently because of the risk of rebleeding from an unclipped aneurysm. This could involve prophylactic infusion of non-anticoagulant heparin to prevent the proliferative angiopathy associated with SAH, with the addition of antithrombin III therapy or partial heparinization should vasospasm occur.

This approach to the management of SAH may lead to lower overall rates of rebleeding, cerebral ischemia, and hydrocephalus.

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