Use of heparin in neurointervention: a review of the literature

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Abstract

Background: The use of heparin is routine in endovascular procedures as a strategy in many centers that perform neurointerventional procedures to prevent occlusion of the catheters, but the use of this drug carries risks such as heparin-induced thrombocytopenia.

Objective: The purpose of this paper is to present a review of the literature.

Material and methods: We conducted an extensive search and review of published papers about heparin and neurointerventional procedures.

Results: The evidence in the literature is weak in relation to the use of heparin and the reduction of embolic effects associated with their use in endovascular procedures.

Conclusion: The evidence on the use of heparin for the prevention of thromboembolic events in endovascular procedures are of low quality. There is insufficient evidence to conclude a potential benefit of heparin is useful in neurointerventional procedures. Prospective studies are needed to determine the effectiveness of heparin and avoid exposing patients to potential risks.

Key words: heparin, neurointervention, neuroangiography, arterial catheters.

Introduction

During neurointerventional procedures, the use of catheters is a key step in the realization of the same, many international centers have traditionally used heparin infusion in order to prevent the formation of clots inside the devices; this potential thrombus can migrate to different parts of the body and cause injury. Complications of angiography and endovascular procedures, whichhave historically been used for the diagnosis and treatment of neurovascular diseases, have rarely been described in the literature.The most frequent complication reported in the literature is bruising during these procedures. Complications derived from angiographic procedures such as anaphylaxis and death account for 0.03 % and 0.06 %, respectively.

Uses of heparin

Heparin is the anticoagulant most frequently used in hospitalized patients in many neurosurgical centers. In

industrialized nations, there are applied 80 million doses annually.

The use of heparin is directed to maintain the integrity of catheters used in endovascular therapy. Currently the use of low molecular weight heparins is to prevent venous thromboembolism. Heparin is a mucopolysaccharide acid with variable molecular weight (4.000 to 40.000Da). Since 1935, high-molecular weights-heparins have been usedto inhibit platelet activityalso. Heparin acts in vitroas antithrombininhibitor, activating the plasma, which disables the thrombin and factor Xa, then is metabolized byfast N-desulfation after administration in the body. Usually heparin and similar products cause immunologically mediated thrombocytopenia, which usually occurs between the 5th and the 10th day.

Usually the action of heparin is reversed by protamine sulfate, being the only agent that can stop heparin anticoagulation;complications of the use of protamine include systemic arterial hypotension, pulmonary arterial hypertension, bradycardia and oxygen consumption declination.

Kaufmann et al. evaluated and analyzed the complications of diagnostic angiographyin 19826 consecutive patients, in that work thrombotic events were only 9 (0.05%). Neurological complications occurred within the first 24 hours of angiography in 2.63% of patients. (1)It has been reported the presentation of intracerebral hemorrhage associated to endovascular procedures in which heparin was used. (2) The vasodilatory effects of heparin have been reported due to rapid administration, in the form of boluses.

Therapeutic uses

Venous thromboembolism: Heparin have beenextensively used for prevention of venous thromboembolism, a fixed dose of heparin of 5000 IU subcutaneously administered, every 8 hours reduce from 60 to 70% the risk of venous thrombosis and decrease in mortality of 0.2% compared with control groups which evidenced a mortality of 0.7%. (5).

Heparin has been used for many therapies along neurointervensionism evolution, such as aneurisms, (3, 4)atherothrombotic vertebrobasilar occlusion, (5) as part of the reperfusion strategies for acute ischemic stroke, (6–11) for free-floating carotid thrombus, (12) cerebral venous sinus thrombosis, (9, 13) primary stent revascularization, (14) among others.Heparin is recommended during interventions due to the use of multiple intravascular tools in procedures that can last several hours. (3) Currently, neurointerventional procedures are performed under therapeutic heparinization - even in cases of ruptured aneurysms - to prevent thromboembolic events. (15) Due to the fact that many published multicenter studies about the use of anticoagulants have left the doses to the judgment of the investigators, these had notbeen reported. However, doses reported   by major monocenter studies (16–18) have been of initial boluses ranging from 3000 to 5000 IU followed by 20-40 IU/kg/h continuously to maintain a monitored activated clotting time (ACT) between 200 and 300 seconds. (3) Protocols vary largely, and often comprise a standardized loading dose and no specified controls.

In other kind of endovascular procedures, after a baseline ACT is obtained, intravenous heparin (70 IU/kg) is

generally given to a target prolongation of approximately 2 to 3 times the baseline value. Then heparin can be given continuously or as an intermittent bolus with hourly monitoring of ACT. (19)

Only 69% of the surveyed members of The World Federation of Interventional and Therapeutic Neuroradiology (WFITN), uses heparin intraoperatively and in a continuous fashion. (3) The WFITN recommends a 5000 IU bolus, then 1000 IU/h continuously, with (monitored) ACT at about 200s. Nevertheless, there are many recommendations for heparin use outside the field of interventional neuroradiology that may be adaptable to the endovascular treatment of aneurisms. (20) The normally employed monitoring method is ACT, with guideline values > 200 s, most commonly between 250 and 300 seconds. (21)

It is recommended to test the efficacy of the heparin regularly during the intervention. Loading and continuous doses must be adapted to the patient's weight to rapidly attain and maintain ACT objectives during the intervention, which may take several hours (3).

Preoperative oral anticoagulants are usually stopped 5 days before the intervention and replaced by heparin, which has the advantage of being easily antagonized in cases of intraoperative aneurism rupture. (3) Protamine sulfate dose for dose in the last hour will rapidly terminate heparinization. Some teams continue heparin infusion for 24–48 h, but the WFITN does not recommend pursuing anticoagulation postoperatively. (3)

Any rationale for postoperative use of heparin is unclear. Indeed, no convincing clinical results have been published, and from a biological perspective it seems more pertinent to use antiplatelets. (3) On the other hand, there is insufficient evidence to support the use of either systemic or local thrombolysis in patients who have cerebral sinus venous thrombosis (CVST) according to European Federation of Neurologic Societies guidelines.

Heparin use must be monitored. The effect of the heparin lasts for at least a few hours and patients usually need to be placed on antiplatelet therapy after the procedure. (15)

In the resuscitation phase of any intracranial catastrophe, when the patient is receiving heparin, the presence of hemorrhage should elicit immediate heparin reversal (1 mg protamine for each 100 units of heparin given) and low normal mean arterial pressure. (19)

There are reports regard the use of heparin as an adjunct to neurointerventional procedures that can result in rapidly progressive intracerebral hemorrhages; (2) abciximab, aspirin, thienopyridinederivates are also reported. Careful management of coagulation is required to prevent thromboembolic complications during and after the neurointerventional procedure. (19)

When a patient may be refractory to attempts to obtain adequate anticoagulation, (19) should be considered the switching from bovine to porcine heparin or vice versa. If antithrombin III deficiency is suspected, administration of fresh frozen plasma may be necessary to allow heparin to have its desired anticoagulant effect. (19)

Thrombolytic therapy with recombinant tissue plasminogen activator (rt-PA) and secondary anticoagulation with heparin to prevent rethrombosis in acute stroke patients has been shown to be beneficial in large randomized trials, (22) but the major

complication of this therapy is secondary postischemic symptomatic intracranial hemorrhage (SICH), (23) which can be devastating. It is necessary to detect microbleeds (MBs) or hemorrhagic transformation (HT) early and accurately, and to institute rapid treatment decision-making according to neuroimaging findings to prevent development of a hemorrhage-prone state and improve neurologic recovery. (24–26)

Other complications derived from the use of heparin, is the heparin-related ICH, which is rare and data are sparse regarding appropriate treatment. One reasonable approach would be to reverse heparin with IV protamine sulfate at a dose of 1 mg to 1.5 mg per 100 units of heparin with a maximum dose of 50 mg. (27,28)

Heparin-induced thrombocytopenia (HIT) is a rare but important adverse event for heparin anticoagulation. (19)The incidence of HIT in neurological patients continues to increase with expansion of indication for neurointerventional procedures. The pathophysiology of HIT is related to a hypersensitivity reaction against complex platelet factor 4. (29) The diagnosis is mostly clinical and is often confirmed by laboratory testing. (29) Patients with HIT have a higher rate of thromboembolic complications, both arterial and venous, and with worse neurological outcomes at the time of discharge. Early diagnosis and heparin cessation are essential in the management of those patients. Both immediate and prolonged alternative anticoagulation are necessary. Understanding of the mechanism of action, indication and drug interaction of the alternative anticoagulants (direct thrombin inhibitors, fondaparinux and danaparoid) and warfarin is essential during management of these patients. (29)

Often, the thromboembolic risks in the endovascular treatment of aneurisms are lesser than those found in stenting or extracranial angioplasty (3).

Conclusion

Clearly, heparin is not an innocuous molecule; indications for its use should be clearly stated in individualized patients, assessing factors such as comorbidities, age, allergic states, time for use, and clinical evolution. However heparin may be useful only in cases where the patient has prothrombotic states. As stated previously, clinical studies had lead dosage to author's criteria, thus there is not a widely assessed dosage for heparin, especially in patients with neurovascular conditions. It is needed more unification for indication, dosage and cessation criteria. Prospective studies are needed to determine the effectiveness of heparin and avoid exposing patients to potential risks.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials or device describe in this article.

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