European Journal of Radiology 82 (2013) 1633–1637

Contents lists available at ScienceDirect

European Journal of Radiology

journal homepage: www.elsevier.com/locate/ejrad

Endovascular treatment of aneurisms: Pre, intra and post operative management

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ARTICLE INFO

Article history:
Received 29 November 2012
Received in revised form 5 February 2013
Accepted 7 February 2013

Keywords:
Cerebral aneurisms
Endovascular treatment
Complications
Anticoagulation
Antiplatelet therapy
Thrombo-embolism

ABSTRACT

The most frequent risk in endovascular aneurysm treatment is thromboembolic complications. Thus adjuvant pharmaceuticals are largely focused on preventing and treating these latter. Additionally symptomatic treatment of subarachnoid hemorrhage (SAH) and treatments to avoid vasospasm will enter into play in cases of ruptured aneurisms.

Consensus exists in the literature neither for the necessity of heparin or antiplatelets nor for the doses to be administered. The principles and rationale of the use of these medications are reviewed with a discussion of protocols according with clinical situations and technical choices.

1. Introduction

There is no identifiable consensus across teams or in the literature concerning the pharmacological accompaniment of endovascular aneurysm treatment. We will limit the present discussion to a review of the principles and rationale of the use of these medications; any discussion of protocols is strictly illustrative with no recommendatory intent.

Several methods are available in endovascular aneurysm treatment to exclude the affected vascular section from the circulation. Risks vary according to the treatment option and the conditions within which the surgery is performed. Associated treatments must thus be tailored on a case-by-case basis.

Among the most frequent risks of endovascular repair are intra and postoperative hemorrhagic rupture, a rare event, and thromboembolic complications, which are much more frequent. Thus adjuvant pharmaceuticals are largely focused on preventing and treating these latter. Additionally symptomatic treatment of subarachnoid hemorrhage (SAH) and treatments to avoid vasospasm will enter into play in cases of ruptured aneurisms.

2. Thromboembolic complications

The most frequent risk in endovascular aneurysm treatment is thromboembolic complications. Their analysis in the literature varies according to how they are considered: only symptomatic complications, intraoperative occlusions, probable ischemic abnormalities on systematic postoperative MRIs, etc. Thromboembolic complications have become less frequent and the management of their consequences has improved. Nonetheless, they remain the main risk in endovascular approaches.

The frequency of intraoperative thromboembolic complications in multicenter series can vary, ranging for example from 7% in the ATENA study (considering only non-ruptured aneurisms) [1] to 12.5% in the CLARITY study [2]; morbidity and mortality was 3.8% in this latter.

The influence of employed techniques varies across assessments. Sluzewski et al. [3,4] found that remodeling resulted in larger risks but this tendency was not detected in Altay et al.'s meta analysis [5] and Pierot et al's recent review of the literature [6]. The use of stents increased the risk of stroke per operative and in the first 48 h by 10% [7–10].

The size of the aneurysm and its neck are risk factors, with thromboembolic events being more frequent in large and giant

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http://dx.doi.org/10.1016/j.ejrad.2013.02.012

aneurysms. In the Clarity study [2], risks were 28% for aneurysms over 10 mm vs. 10.7% for those under 10 mm.

Finally, an increased frequency of thromboembolic events is associated with SAH [2,5].

The intra and postoperative use of anticoagulants and antiplatelets has been proposed to reduce the frequency and gravity of thromboembolic complications.

3. Interest and use of heparin

Consensus exists in the literature neither for the necessity of heparin nor for the quantities to be administered. Heparin is recommended during interventions due to the use of multiple intravascular tools in procedures that can last several hours.

In published multicenter studies, the use of anticoagulants was generally left to the judgment of the investigators and thus not reported. Major monocenter studies [11–13] have reported 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 s. This tactic is a compromise between thromboembolic and hemorrhagic risks, noting that thromboembolic risks in these procedures are lesser than those found in stenting or extracranial angioplasty.

Protocols found in the literature or proposed by institutions vary and often comprise a standardized loading dose and no specified controls.

The World Federation of Interventional and Therapeutic Neuroradiology (WFITN) surveyed its members in 2006 and published the results and its recommendations on its website. Most responding teams reported the use of intraoperative heparin but only 69% in a continuous infusion. The WFITN recommends a 5000 U bolus, then 1000 U/h continuously, with (monitored) ACT at about 200 s.

There are a number of recommendations for heparin use outside the field of interventional neuroradiology that may be adaptable to the endovascular treatment of aneurisms [14].

Heparin use must be monitored. Blood heparin concentrations are not accessible during our interventions. The normally employed monitoring method is ACT, with guideline values >200 s, most commonly between 250 and 300 s. 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. Doses from 70 to 80 U/kg are proposed in heparin use protocols in intensive care or cardiology to obtain efficacious anticoagulation. This is then maintained via infusion, with doses adjusted as needed according to regular (at least hourly) ACT monitoring. A practical dose adaptation table is frequently used to manage heparin in thrombosis treatment and can be adapted for use in aneurisms [15]. After a bolus injection of 70 U/kg, we used to continue with 18 U/kg/h and adjust according to ACT level and this kind of nomogram.

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. Administration of protamine sulfate dose for dose in the last hour will rapidly terminate heparinization.

At the end of aneurism treatment, heparin administration is normally stopped but not antagonized. Some teams continue heparin infusion for 24–48 h. Follow-up with low molecular weight heparin (LMWH) has been advised by certain teams, but this seems to be falling out of favor. The WFITN does not recommend pursuing anticoagulation postoperatively.

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.

However, LMWH is relevant for the prevention of deep vein thrombosis (DVT). DVT risks are elevated after a SAH (18% in the Ray et al. study) and vary according to the severity of bleeding and the duration of hospitalization [16]. This rate justifies the use of LMWH at preventative doses, especially as these latter present little morbidity risk [17].

4. Antiplatelets

To treat an aneurism, a foreign body is placed within a vascular space characterized by high-velocity blood flow and the possibility of associated intimal insults. These conditions activate platelet aggregation mechanisms and thus justify the use of antiplatelets to prevent and treat intra and post-procedure thromboembolic complications.

The interest of the preventative use of antiplatelets has been evoked often, but has not yet been subjected to randomized or large, multicenter studies to assess specific protocols. In a study involving 3 antiplatelet protocols: no treatment, only post-procedure treatment, pre and post-procedure treatment, Yamada et al. [18] reported rates of symptomatic thromboembolic complications of respectively 16%, 2.3% and 1.9%. They also reported a reduced rate of angiographically visible clots during the procedure in patients who received pre-procedure antiplatelets compared to those who didn't (1.6% and 4.5% respectively).

Antiplatelets employable in practice are acetylsalicylic acid (aspirin), clopidogrel, and more rarely flurbiprofen, as well as the newer antiplatelets prasugrel and ticagrelor.

4.1. The role of platelets in thrombus formation

The activation of platelets induces the formation and liberation of various factors including ADP and thromboxane A_2, and furthermore stimulates the formation of thrombin. This reaction spreads from platelet to platelet and a linking process begins involving fibrinogen and surface glycoprotein receptors, resulting in platelet aggregation.

Antiplatelet drugs are designed to inhibit the production and release of these different factors: acetylsalicylic acid is the main thromboxane inhibitor; clopidogrel and the newer drugs prasugrel and ticagrelor inhibit ADP receptors; and Abciximab, tirofiban and eptifibatide are glycoprotein IIb/IIIa inhibitors. Other molecules are being studied.

4.2. Aspirin

Aspirin acts by inhibiting prostaglandin H synthase, a precursor of thromboxane A_2, thus provoking a prolonged inhibition of the COX-1 pathway. Aspirin's antiplatelet activity will appear approximately 40–60 min after the administration of a dose of 75–100 mg. The effect is irreversible. Normal platelet activity will return 7 days after the final dose. Resistance to acetylsalicylic acid in as much as 50% of cases has been suggested, but the data behind this number lacks homogeneity, and comprises in particular poor compliance to treatment; truly insufficient response to aspirin is much less frequent. However, when it does occur, the risk of thromboembolic complications is greatly augmented and increasing aspirin dosage only increases the risk of aspirin-related complications with no clinical benefits. Aspirin and clopidogrel have synergistic effects and thus their association generally results in efficacious antiplatelet activity [19].

4.3. Clopidogrel

Following a loading dose of 300 mg, the antiplatelet effect of clopidogrel is observable after 2 h and remains stable for 48 h. As