Nimodipine for delayed cerebral ischemia prevention

Oral administration of a calcium channel blocker, nimodipine, has been introduced in the European and American guidelines for the prevention of DCI in aSAH patients. Nimodipine was initially developed to prevent CV, however with the approved dosage the incidence of angiographic vasospasm was not decreased, probably due to insufficient levels reached at the site of CV occurrence due to the presence of the blood-brain barrier. An increase in dose is limited by the severe systemic side effect of the drug, such as unusually fast or slow heartbeats, fainting or severe dizziness, easy bruising or bleeding, and unusual weakness due to hypotension.

These side effects are often causing interruption of the treatment even at the prescribed dosage (60 mg every 4 hours). In a recent retrospective analysis conducted on 270 aSAH patients admitted at the Charité in Berlin between 2009 and 2014, was shown that only 43.6% of the aSAH patients successfully completed the whole treatment according to the guideline-recommended dosage. The rate of dose reduction and discontinuation, due to the side effects, occurred with a significantly higher frequency in patients in poor clinical condition, those who are at the highest risk of vasospasm [1)].

Prevention of DCI primarily relies on nimodipine administration and optimization of blood volume and cardiac performance. Neurological monitoring is essential for early DCI detection and intervention. Serial clinical examination combined with intermittent transcranial Doppler ultrasonography and CT angiography (with or without perfusion) is the most commonly used monitoring paradigm and usually suffices in good-grade patients. By contrast, poor grade patients (WFNS grades 4 and 5) require more advanced monitoring because stupor and coma reduce sensitivity to the effects of ischemia. Greater reliance on CT perfusion imaging, continuous electroencephalography, and invasive brain multimodality monitoring are potential strategies to improve situational awareness as it relates to detecting DCI. Pharmacologically-induced hypertension combined with volume is the established first-line therapy for DCI; a good clinical response with reversal of the presenting deficit occurs in 70 % of patients. Medically refractory DCI, defined as failure to respond adequately to these measures, should trigger a step-wise escalation of rescue therapy. Level 1 rescue therapy consists of cardiac output optimization, hemoglobin optimization, and endovascular intervention, including angioplasty and intra-arterial vasodilator infusion. In highly refractory cases, level 2 rescue therapies are also considered, none of which have been validated [2)].

The calcium channel blocker nimodipine remains the only therapeutic intervention proven to improve functional outcomes after SAH. The recent failure of the drug clazosentan to improve functional outcomes despite reducing vasoconstriction has moved the focus of research into DCI away from cerebral artery constriction towards a more multifactorial aetiology. [3)].

Nimodipine and induced hypertension using vasopressors are an integral part of standard therapy. Consequences of the opposite effect of nimodipine and vasopressors on blood pressure on patient outcome remain unclear [4)].

Aggressive therapy combining hemodynamic augmentation, transluminal balloon angioplasty, and intra-arterial infusion of vasodilator drugs is, to varying degrees, usually implemented. A panoply of drugs, with different mechanisms of action, has been studied in SAH related vasospasm. Currently, the most promising are magnesium sulfate, 3-hydroxy-3-methylglutaryl-CoA reductase inhibitors, nitric oxide donors and endothelin-1 antagonists [5].

Early goal directed fluid therapy (EGDT) is beneficial for reducing DCI and improving postoperative functional outcome in patients with poor clinical grade [6].

Current treatment guidelines to prevent delayed cerebral ischemia is limited to oral nimodipine, maintenance of euvolemia, induction of hypertension if ischemic signs occur and endovascular therapy for patients with continued ischemia after induced hypertension. Future investigations will involve agents targeting vasodilation, anticoagulation, inhibition of apoptosis pathways, free radical neutralization, suppression of cortical spreading depolarization and attenuation of inflammation [7].

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