The use of mannitol as a neuroprotective factor in cases of hyper-perfusion syndrome after carotid revascularization: a proposed clinical protocol

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INTRODUCTION

Hyper-perfusion syndrome (HPS) is an early post-operative complication in patients treated for high grade carotid stenosis managed with either of carotid revascularization modalities.[1] The development of new neurological symptoms, 6 to 12 hours after the procedure, should set the suspicion of HPS, which may be presented in 1% of patients undergoing endarterectomy (CEA).[1] Post-operative high blood pressure, headache, atypical migraine and focal seizures may be associated with (HPS) and aggressive hypertension control is proposed in these cases[1].

Scarce data exist in the current literature concerning the role of mannitol immediately after carotid revascularization, carotid artery stenting or endarterectomy, in patients presenting hyper-perfusion syndrome.[2] In the acute phase of cerebral ischemia, due to embolus or hyper-perfusion, "neuroprotective" measures as well as the management of cerebral edema have been poorly evaluated and analyzed.[3] In any case, a multidisciplinary team work is mandatory in these complicated cases.[3]

Based on the current literature and our center's experience, an empirical protocol concerning the use of mannitol in patients treated for high grade carotid stenosis, or those presenting neurological deterioration immediately after carotid revascularization, has been developed and presented.

PROTOCOL

Patient selection

As the role of mannitol is not clarified in the current literature, all patients may not profit from an aggressive management or such a strategy may be harmful in cases with post-operative hypotension. Patients that seem to benefit from mannitol neuroprotection may be separated in 4 subgroups:

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1) Symptomatic patients with high grade carotid stenosis >80%

2) Asymptomatic high grade carotid stenosis, >90%, or near occlusion lesions

3) Patients combining high grade, symptomatic or asymptomatic carotid stenosis >80% with contralateral high grade carotid stenosis, >90%, or near occlusion lesions or occluded internal carotid artery

4) Patients with confusion or neurological deterioration after the accomplishment of the procedure

Use of mannitol

In cases targeting to the prevention of HPS, 75ml of intravenous (iv) mannitol are administrated within 30 minutes, intra-operatively about 10 minutes before declamping in cases of CEA or as far as the internal carotid artery (ICA) is catheterized, in carotid stenting (CAS). In patients presenting with neurologic deterioration after extubation, and the HPS is suspected, the primary dose of mannitol (75ml) is administrated immediately. By protocol, in our department, all patients receive 120mg dexamethasone iv after carotid clamping or after the catheterization of internal carotid artery in cases of carotid artery stenting. All patients are evaluated with cerebral oximetry intra-operatively. After the initial administration, the patient receives 3 additional dosages of 50ml mannitol with a 6-hour interval and 30-minute duration during the initial 24 post-operative hours, irrespectively of his/her neurological status.

Intra-operative blood pressure control

The intra-operative anesthetic blood pressure management initiates with the identification of the "normal" for the patient blood pressure target, which is estimated according to patient's baseline values. Invasive blood pressure monitoring is considered mandatory; since allows the anesthesiologist to act in a timely manner to unanticipated blood pressure swings and titrate effectively the vasopressors.[4] Anesthesiologists prefer phenylephrine, ephedrine or norepinephrine to achieve optimal values. During intra-operative monitoring, the hemodynamic goal is the blood pressure not to fluctuate more than 10-20% of the baseline values. Especially, during carotid clamping in CEA, the target mean arterial pressure (MAP) is approximately 20% above baseline; to optimize collateral cerebral blood flow to the brain.[5, 6] Nevertheless, this is a general guidance, and the data from the chosen neuro-mon-

itoring method should help with the appropriate adjustments. Thus, the best hemodynamic management relies on an individualized approach according to patient characteristics and needs.

Post-operative monitoring and medical management

The underlying carotid pathology as well as the use of mannitol, order the need for close monitoring of vital signs in the ward. Blood pressure target is between 110-140mmHg. Calcium channel inhibitors are used as a first line treatment for addressing hypertension (eg. Nifedipine 10mg). Persistent hypertension is confronted with angiotensin receptor blockers (eg Ramipril 5mg) or intra-venous glycerin trinitrate, initially with 5ml/h and adjusting according to blood pressure measurements.

As mannitol may provoke important dehydration, an input-output equilibration is mandatory. All patients are hydrating receiving 80ml per hour normal saline and urine output is re-evaluated per hour, while hydration is adjusted to patient's needs accordingly. In asymptomatic or totally recovered patients, liquid consumption initiates 6 or 12 hours after the accomplishment of the procedure or the full stabilization of the patient accordingly.

In terms of antithrombotic agents, all CEA patients continue their pre-operative antiplatelet therapy (aspirin 100mg or clopidogrel 75mg once daily). All CAS cases receive double antiplatelet therapy pre-operatively and for the first 30-days post-operatively.

Patients with neurologic symptoms after intervention

In such cases, an imminent duplex ultrasound evaluates the patency of the internal carotid artery while persistent symptomatology sets the need for urgent computed tomography angiography of the brain and neck. If there is no sign of technical failure of the revascularization or intra-cranial occlusion, the patient is closely monitored for vital signs, urine output and per hour neurological clinical evaluation for the next 24 hours at least. If the patient shows neurological improvement with attenuation of symptoms, monitoring becomes less intensive until she/he, is fully stabilized. In any case, patients with symptoms undergo cerebral CT within the 48 post-operative hours. In such cases iv mannitol, if not started before, administered in the recovery room at a dose of 75-100ml depending in patient's body mass index and continued thereafter in doses of 50ml in 30min infusions every 6 hours, up to 48 hours in total, depending on patient's neurologic condition. In some cases of HPS the neurological symptoms may begin a few hours after the intervention in an otherwise well-recovered patient, having fluctuating course, which is much affected from the systolic blood pressure (BP) of the patient. The patient is usually neurologically stable in the BP range of 110-150 mmHg, while deteriorates when BP is above or below these values, obviously for different hemodynamic reasons.

DISCUSSION

HPS is a rare complication after carotid revascularization, estimated around 1% for CEA and CAS patients, equally distributed.[1, 7] However, it is a devastating complication, difficult to distinguish from new onset cerebral event (stroke or transient ischemic attack (TIA), while its presence maybe also underdiagnosed and thus, misreported in the literature. Furthermore, symptomatic patients may be at higher risk to evolve HPS.[7] This fact may be explained by the edema around the location of the previous ischemic lesion which may mimic neurological deficits associated with the underlying infarct. Current guidelines discuss extensively HPS. However, no recommendations are included concerning patients' evaluation and management, except that aggressive blood pressure control seems to affect the incidence of HPS and hemorrhagic stroke after revascularization and that it may be associated with less morbidity comparing with new ischemic events.[1, 8]

The main mechanism associated to HPS and the evolution of cerebral edema is vasogenic while cytotoxicity plays an additional role compared to ischemic lesions where cellular apoptosis and cytotoxicity predominate over vascular mechanisms. In cases of acute ischemic events, mannitol is not generally administrated and may be associated with adverse events and higher mortality.[9-11] In cases of vasogenic edema, protein and water communicate between the vascular and interstitial compartment due to hydrostatic forces.[12] During cerebral injury, inflammation and ischemia contribute to endothelial injury and increase the permeability of blood-brain border via an increased expression of mediating factors.[12] Current experience with the use of mannitol in case of cerebral edema arises mainly from neurological sources. Anti-edema therapy may significantly decrease the mortality in a wide spectrum of cerebral conditions.[12] Especially, osmotherapy, which has been extensively evaluated in previous decades, is the cornerstone of pharmacologic therapy and includes mannitol and hypertonic saline.[13] Mannitol uses a double path mechanism; the rapid reduction of intra-cerebral pressure due to the dehydration of white matter and the alterations associated with the cerebral blood volume.[14, 15] Nevertheless, only null data exists in the vascular surgery literature.[2] However, mannitol has been used in cases of HPS after carotid revascularization with encouraging results.[2]

As this grey zone has not been clarified for the moment, newer and controversial data arise from the experimental world. Carotid bodies seem to be activated by acute saline overload rather than mannitol.[16] Such an acute phenomenon affects and increases sympathetic activity and probably affects cerebral hemodynamics and microcirculation.[16] At the same time, an osmolality elevation triggers a complex neurohumoral response which includes sympathoexcitation and hypertension. Hypertonic saline and mannitol seem to participate in this mechanism.[17] In rat models, mannitol seems to reduce brain ischemia-reperfusion injury while the combination of mannitol and dexamethasone is even more effective.[18] According to our experience, this combination seems to protect or even reverse HPS evoked by carotid revascularization. The evolution of medicine and biology may explain unknown mechanisms of the cerebral function, circulation and autoregulation in the future. Novel factors may be added to the man-

agement of brain edema associated to ischemic/reperfusion damage.[19, 20]

Based on the above mention knowledge, as well as our personal long experience with carotid interventions, we propose a quite simple protocol of mannitol administration during and after such intervention, as an effort to reduce or even minimize HPS. Patients with high-grade carotid stenosis, asymptomatic but mainly symptomatic, as well as those with significant contralateral disease, may benefit the most from such a protective protocol. In any case, it has to be understood that any evidence or even particular data are not reported in the literature so far.

CONCLUSION

Mannitol may be a helpful supplementary measure in patients at high risk for HPS. We hereby propose an intra and post-operative protocol, as an effort to reduce HPS in selected patients that undergo carotid revascularization. Of course intra-operative monitoring and strict post-operative surveillance are mandatory for an uneventful hospitalization. Dedicated studies are needed in this field to extract firm conclusions.

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