Case Report

Intra-arterial Nimodipine Combined with Intra-arterial Milrinone for the Treatment of Cerebral Vasospasm Following Subarachnoid Hemorrhage

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Abstract

Cerebral vasospasm is a potentially devastating complication of subarachnoid hemorrhage (SAH) associated with substantial morbidity and mortality. Although various studies have separately examined the use of intra-arterial nimodipine and intra-arterial milrinone for the treatment of delayed cerebral vasospasm in SAH, information regarding the use of the modality combining the two treatments is scarce. This is the case of a 44 year old female patient who developed cerebral vasospasm due to the rupture of a left internal carotid artery at the level of anterior choroidal saccular aneurysm. Patients were treated with intra-arterial nimodipine 5 mg, followed by a total milrinone dose of 18 mg into the vasospastic territories preoperatively to facilitate catheter access for coiling with controlled infusion. The angiographic spasm recovered well and aneurysm coiling was done. The patient was stable throughout the hospital course and was discharged in stable condition. Intra-arterial nimodipine along with milrinone was found to be effective in this case with severe cerebral vasospasm preoperatively which is rarely reported in the literature.

Keywords: Aneurysm, hemorrhage, milrinone, nimodipine, vasospasm

Introduction

Cerebral vasospasm following aneurysm rupture is associated with substantial morbidity and mortality even with successful clipping or endovascular coiling of the aneurysm.[1] Around 30% of the patients who survive an episode of subarachnoid hemorrhage (SAH) develop cerebral vasospasm as a complication.[1] The vasospasm is thought to occur between days 4 and 21 post hemorrhage with the number of cases peaking at day 7. Clinically, cerebral vasospasm manifests itself as a global deterioration in the level of consciousness as well as focal neurological deficits depending on the territories involved. A number of endogenous substances in the blood have been identified to cause vasospasm of which oxyhemoglobin has very strong spasmogenic properties and are abundant in the resulting blood clots after hemorrhage.[2] Currently, nimodipine 60 mg Q4H per oral is being used for the prophylaxis against cerebral vasospasm.[3] Studies have shown that intra-arterial administration of nimodipine at a dose of 5 mg resolves vasospasm when infused into the vascular territories through a microcatheter.[4,5] It was also observed in studies that the phosphodiesterase inhibitor milrinone 10–18 mg infused intraarterially into the vasospastic territory shows good radiological improvement.[3,5-7] Both these medications are extremely useful even in refractory cases. Although studies on intra-arterial administration of nimodipine and milrinone are done separately, very few literature exists on a treatment modality combining both nimodipine and milrinone administered intraarterially for the treatment of cerebral vasospasm following aneurysm rupture. Here, we report a case where we used intra-arterial nimodipine and milrinone preoperatively in a controlled manner for catheter access to the aneurysm for coiling.

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Case Report

A 44-year-old female patient with known case of surgical hypothyroidism presented to the emergency department with 1-week history of severe headache and multiple episodes of vomiting. There was no history of loss of consciousness, seizures, or limb weakness. Clinically, no neurological deficits observed and the Glasgow coma scale was E4V5M6.

Computed tomography (CT) scan showed SAH Modified Fishers grade 3. Multiple detector computerized tomography brain angiogram showed the left anterior choroidal artery saccular aneurysm. The patient was stabilized in the intensive care unit and put on peroral nimodipine 60 mg Q4H, along with antiedema measures. The patient was neurologically and hemodynamically stable, but transcranial Doppler (TCD) velocities in the left middle cerebral artery were not recordable. She was taken up for endovascular coiling under general anesthesia. Intraoperatively, the left anterior choroidal artery showed severe vasospasm [Figure 1]. The patient was treated with intra-arterial nimodipine 5 mg in 20 mL normal saline at the rate of 0.5 mg/min. However, there was no significant improvement of vasospasm. [Figure 2]

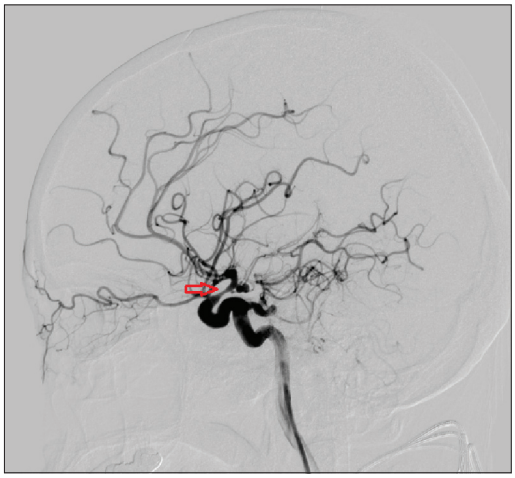

Figure 1: Anterior choroidal artery showing severe vasospasm

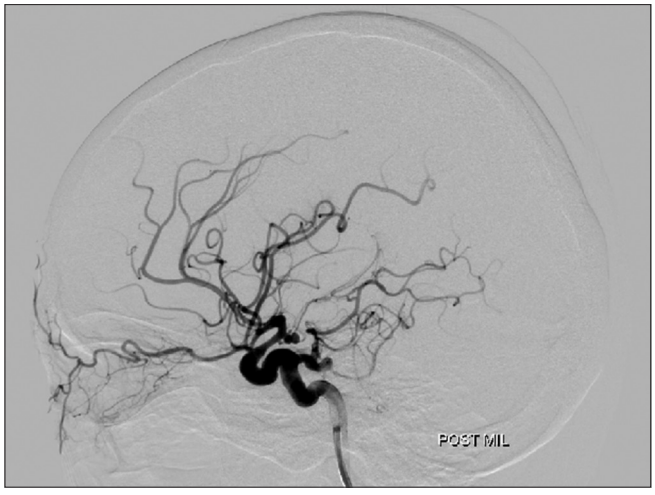

Figure 3: Increase in the flow and caliber further with milrinone

There was difficulty in access with microcatheter as more spasm was seen during navigation in to the spastic segment. Intra-arterial milrinone administration of 6 mg, per vasospastic territories to a total dose of 18 mg at the rate of 0.25 mg/min was given as a desperate measure with controlled blood pressure to reduce the chance of a rupture of the aneurysm. Vasospasm recovered well [Figure 3] and aneurysm coiling could be done.[Figure 4] Postoperatively, she was monitored with TCD which showed velocities within acceptable limits (Lindegaard's ratio of 2.5 cm on the right side and 2.3 cm left side) and was maintained on IV nimodipine with triple H therapy. Postoperative CT scan showed no evidence of ischemia and SAH was resolving well. She was neurologically stable throughout the hospital course and discharged in stable condition.

Discussion

Severe vasospasm is a phenomenon of multifactorial origin, and only limited treatment strategies exist for treating cerebral vasospasm each having its own complications and downsides. The conventional

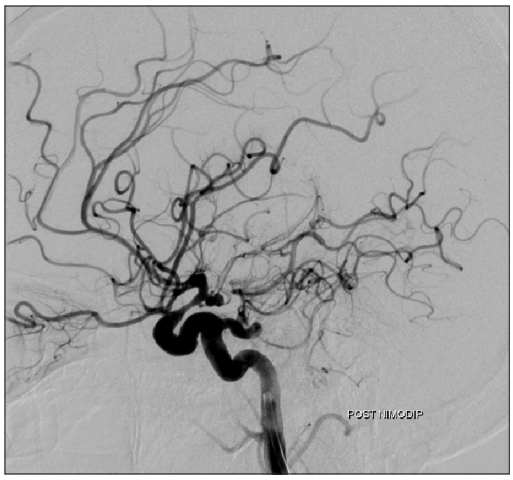

Figure 2: Post nimodipine injection: Slight improvement in the caliber of the vessel

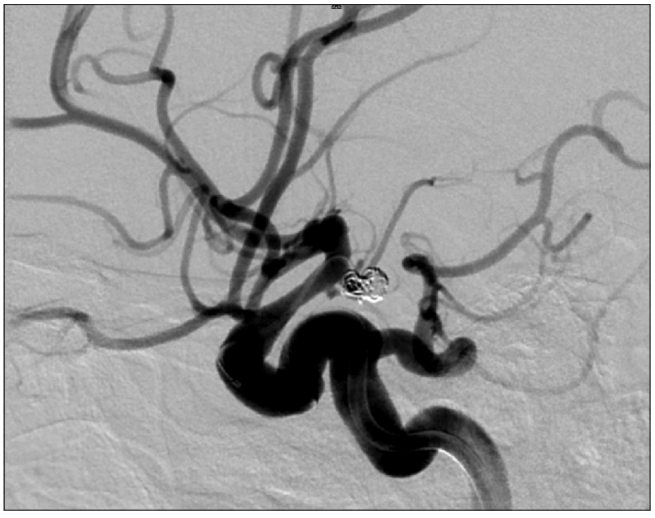

Figure 4: After treating vasospasm, aneurysm coiling was done

triple H therapy (hypertension, hypervolemia, and hemodilution) involves increasing the fluid volume using normal saline or colloids. Although the therapy is time tested, it is associated with serious complications such as hyponatremia, pulmonary edema, indwelling catheter-related complications, cerebral hemorrhage, cerebral edema, and renal medullary washout.[8] Two conventional endovascular techniques include the pharmacological option of intravenous papaverine infusion or the nonpharmacological option of balloon angioplasty. Intra-arterial papaverine administration includes various risks such as a sudden increase in intracranial pressure, brainstem depression, transient neurological deficits, and precipitation of crystal emboli during infusion, seizures, thrombocytopenia, and even paradoxical exacerbation of the vasospasm itself in some patients.[9] Balloon angioplasty also has its own disadvantages including dangers of perforation, dissection, and thromboembolic events, especially when traversing sharp angles as in the case of anterior cerebral artery. Furthermore, with balloon angioplasty, it is rather difficult to access the distal arteries compared to the proximal arteries. Nimodipine, a calcium channel blocker, has shown good effect in alleviating cerebral vasospasm.[1] Smooth muscle contraction necessary for vasoconstriction requires the influx of calcium into the cells. Calcium enters the cytosol through the calcium channels on the surface of the smooth muscle cell and due to the release of calcium from the sarcoplasmic reticulum. The resulting increase in calcium concentration in the cytosol causes calcium-calmodulin complex formation which, in turn, activates myosin light chain kinase by phosphorylating the enzyme. Myosin light chain kinase uses ATP to phosphorylate the head of the myosin molecule facilitating the interaction of myosin filament with actin filament. The resultant interaction causes the smooth muscle cell to contract resulting in vasoconstriction. Nimodipine blocks the calcium channel on the surface of the membrane preventing calcium influx into the cell. The resulting reduction in cytosolic calcium causes vasodilation. The cerebral blood vessels have been observed to be highly sensitive to nimodipine compared to all other calcium channel blockers. Currently, nimodipine 60 mg tablet administered 4th hourly is used for the prophylaxis against cerebral vasospasm.[3] However, the oral administration was found to be inadequate in refractory cases.

In patients with refractory cerebral vasospasm, the combination of nimodipine and milrinone infusion administered intraarterially in sequence into the vasospastic territories shows good response.[6,7] The addition of milrinone provides a synergistic action to nimodipine induced vasodilation through the inhibition of phosphodiesterase 3 enzyme.[10] The inhibition of phosphodiesterase 3 prevents the degradation of cyclic guanosine monophosphate (cGMP). cGMP elevation in turn causes dephosphorylation of the myosin light chain kinase through cGMP-dependent protein kinases. This results in the disruption of the interaction between actin filaments and myosin filaments causing vasodilation. The combination of intra-arterial nimodipine and milrinone is safer compared to other treatment modalities used to treat cerebral vasospasm.[5,6] It is a minimally invasive procedure and can be administered along with the endovascular coiling of the aneurysm.

Conclusion

In this case, we observed that the combined use of intra-arterial nimodipine and milrinone has a significant effect on vasospasm. It has the advantage of being minimally invasive and feasible treatment modality for symptomatic cerebral vasospasm. This has been described before by Duman *et al*. and Anand *et al*. in postoperative vasospasm, but here, we used this modality for preoperative vessel access with controlled infusion as a rescue method which is rarely described before. Since the intervention was done early in severe vasospasm demonstrated in the angiography and Doppler studies, we could come out with no neurological deficits in this case. More studies are required for the protocol-based intra-arterial treatment of vasospasm and the safety of the preoperative usage of this modality.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the legal guardian has given his consent for images and other clinical information to be reported in the journal. The guardian understands that names and initials will not be published and due efforts will be made to conceal identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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