Case Report

Haemodynamic changes after intracisternal papaverine instillation during intracranial aneurysmal surgery

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Cerebral vasospasm remains a significant cause of mortality and morbidity after aneurysmal subarachnoid haemorrhage. Use of either intra-arterial or intracisternal papaverine as an alternative treatment of refractory cerebral vasospasm has been associated with various complications including haemodynamic instabilities. However, our search in literature did not reveal association of bradycardia and hypotension with the use of papaverine by either of these routes. Here, we describe a case of anterior communicating artery aneurysm followed by third ventriculostomy. Instillation of papaverine at the surgical site caused significant haemodynamic changes possibly because of stimulation of hypothalamus in the third ventricle or vagal nuclei in the fourth ventricle, or even both. We recommend cautious use of intracisternal papaverine in such scenario especially when third ventriculostomy has been performed as an adjunct surgical procedure.

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Vasospasm remains a significant cause of morbidity and mortality after subarachnoid haemorrhage (SAH).1 Prophylaxis with nimodipine2 and treatment with hypertension, hypervolaemia and haemodilution (triple-H) therapy3 have improved the outcome in such patients, but not completely eliminated the effects of vasospasm. Nevertheless, a subgroup of patients remains refractory to all the mentioned interventions. Balloon angioplasty4 and intra-arterial papaverine5 have been described as the alternative treatment modalities in patients refractory to conventional methods. However, these modalities are not free from complications.6 Application of intracisternal vasodilators such as papaverine has become a common practice after craniotomy for aneurysmal SAH7–10 but the complications associated with such procedure have hardly been described in the literature. Here we report an episode of severe haemodynamic disturbance after topical application of papaverine in a patient who underwent aneurysmal clipping.

Case report

A 50-yr-old male patient weighing 62 kg was admitted in our hospital 4 months ago with complaints of sudden severe headache followed by giddiness and vertigo. He had a history of oesophageal carcinoma and had received a complete course of chemotherapy 10 months ago. His medical history was unremarkable. The computed tomographic (CT) scan of brain showed SAH with hyperdensity in basal cisterns and hydrocephalus. The patient was diagnosed as a case of SAH Grade-II (Hunt & Hess). Intravenous digital substraction angiography (DSA) confirmed the presence of anterior communicating artery aneurysm with mild vasospasm of bilateral middle cerebral arteries (MCA), though it was clinically not apparent. The patient was planned for an elective surgical clipping of the aneurysm. Oral nimodipine 60 mg 6 hourly was started to prevent further cerebral vasospasm. On the day of surgery, the patient was premedicated with diazepam 10 mg, orally, 2 h before induction of anaesthesia. Routine monitors were connected. The heart rate and non-invasive blood pressure (BP) of the patient were 83 beats min−1 and 130/86 mm Hg, respectively, and the ECG showed normal tracings in lead II and V. After an i.v. access was secured, anaesthesia was induced with thiopentone 300 mg and fentanyl 125 μg. Tracheal intubation was facilitated with rocuronium 60 mg and xylocaine 90 mg. Anaesthesia was maintained with...
isoflurane in a mixture of O₂ and N₂O in addition to intermittent doses of rocuronium and fentanyl. Monitoring parameters included were ECG, pulse oximetry (SpO₂), end-tidal capnography (ETCO₂), arterial BP, central venous pressure (CVP), nasopharyngeal temperature and urine output. At the time of skin incision mannitol infusion was started. The surgical procedure consisted of right pterional craniotomy and clipping of the aneurysm. As the dissection was satisfactory, a permanent clip was applied directly without any need for a feeder artery being clipped temporarily. This was followed by third ventriculostomy for associated hydrocephalus, by fenestration of the lamina terminalis (anterior ventriculocisternostomy). The patient was haemodynamically stable throughout the procedure. The surgical haemostasis was completed. Before the closure of the dura, 2 ml of 3% papaverine diluted to 20 ml with 0.9% NaCl (temp. 35–37°C) was instilled topically, at the surgically exposed areas including presellar cistern, to prevent vasospasm. After 5–7 s, a sudden decrease of heart rate (HR) from 78 to 31 beats min⁻¹ and a reduction in BP from 110/70 to 45/29 mm Hg followed. This episode lasted for about 2–3 min and was managed with i.v. atropine 0.6 mg. The remaining part of the procedure was completed uneventfully. At the end of surgery the residual neuromuscular block was antagonized with neostigmine and glycopyrrolate, and the trachea was extubated. The patient had a smooth postoperative course. The patient was discharged from the hospital on the seventh postoperative day and was doing well at 1 month follow-up period.

Discussion

Symptomatic vasospasm after aneurysmal SAH may be refractory to conventional therapy. Balloon angioplasty has been used successfully in such cases to dilate the proximal part of cerebral arteries. Superselective arterial papaverine is delivered to a more distal portion of vasospastic arteries. However, both these procedures require neuroradiological intervention and are associated with complications. Papaverine, a potent vasodilator, acts by direct smooth muscle relaxation of arteries and arterioles. It causes arteriolar dilatation in systemic, coronary and cerebral circulations. A number of complications associated with intra-arterial papaverine have been described. Prominent among them are mydriasis, confusion, reversible brainstem depression, increased intracranial pressure (ICP), hypotension, tachycardia and thrombocytopenia. The possible mechanisms for such complications are hypothesized to be either primary toxic and neurodepressive effects of the drug itself or secondary ischaemic effects associated with precipitate formation.

In order to prevent refractory vasospasm, the routine use of intracisternal papaverine before closure of dura after aneurysmal clipping has been described. Incidents such as pupillary changes (mydriasis), facial nerve palsy and feature suggestive of malignant hyperthermia are reported after the use of papaverine in this route, unlike haemodynamic changes in our case. Though hypotension and tachycardia have been reported before, ours is probably the first case report of bradycardia and hypotension with the use of intracisternal papaverine instillation.

Third ventriculostomy is one of the acceptable treatment modality for associated hydrocephalus in patients with aneurysmal SAH undergoing craniotomy and clipping. Some advocate this procedure for anticipated postoperative cerebrospinal fluid (CSF) flow disturbances. In our case third ventriculostomy was done after clamping of the aneurysm, and because of fenestration of the lamina terminalis both third ventricle and the fourth ventricle remained communicable to the surgical site. We believe that the papaverine solution instilled into the surgical site could have possibly trickled into the third ventricle causing chemical irritation of hypothalamus and midbrain, which form the boundaries of the third ventricle. We also hypothesize that some amount of papaverine may have entered into the fourth ventricle stimulating the vagal nucleus in its floor. The possibility of the drug migrating into and irritating the brainstem cannot be ruled out.

Patients with arterial vasospasm are more prone to haemodynamic instability during aneurysm anaesthesia. However, in our patient, hypotension and bradycardia followed immediately after instillation of papaverine solution. This temporal association suggests the possible role of papaverine in the causation of haemodynamic disturbances, though the exact cause is still unclear. Incidences of haemodynamic changes have been reported after instillation of hot or cold saline instillation on brain tissue. In this case the above cause can be ruled out as we used papaverine diluted with normal saline, warmed to a temperature of approximately 35–37°C. As the injection of papaverine did not contain any solvent with potential neurotoxic effect, we believe the drug itself to be responsible for these complications.

Sawada and colleagues proposed the optimal dose and concentration of intra-arterial papaverine to be 20 ml of 0.4% (w/v), which has to be given over a period of 10 min for one arterial segment. Various literature mentioned empirical dosages. Nevertheless, no consensus has been reached for the safe dose of cisternal papaverine. In our institute, we routinely use intracisternal papaverine (2 ml of papaverine 3% diluted to 20 ml with normal saline) in patients with preoperative evidence of vasospasm, undergoing the anterior circulation aneurysm surgeries. Earlier, in three patients we observed mild hypotension, 5–10 s after intracisternal papaverine instillation, which did not require any intervention. We also used this agent in seven patients, before third ventriculostomy was performed. None suffered severe haemodynamic instability, as in the present case. Hence, we attribute the complications in this case to papaverine that was instilled after third ventriculostomy. The haemodynamic changes followed immediately after this. Though these changes improved with the
use of atropine, it could have had fatal consequences. We feel papaverine instillation should be done before third ventriculostomy. One should avoid using intracisternal papaverine especially if third ventriculostomy has already been performed, else one might consider using a smaller dose or a smaller volume of the papaverine instillate.

To conclude, we report a case of a 50-yr-old man undergoing craniotomy and clipping of anterior communicating artery aneurysm. The associated hydrocephalus was treated surgically by third ventriculostomy. Instillation of papaverine topically to prevent postoperative vasospasm caused severe bradycardia and hypotension possibly because of stimulation of hypothalamus or the vagal nucleus. In such scenario, cautious use of intracisternal papaverine to prevent SAH-induced vasospasm in patients undergoing third ventriculostomy as an adjunct procedure to clipping of aneurysm cannot be overemphasized.

References
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