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Case Report: Open Access

Severe Bradycardia after Topical Use of Papaverine during a Pons Cavernoma Surgery

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Abstract

Papaverine is a potent smooth muscle relaxant and has vasodilator properties. Topical use of papaverine is widely accepted in neurosurgery to prevent cerebral vasospasm. Growing evidence supports that papaverine may have a neural toxicity effect. We present a case of a 15 years-old patient that was operated on hemorrhagic cavernoma in the floor of the fourth ventricle. A transvermian approach was performed and neurophysiological monitoring was set up. During surgery, the motor evoked potentials diminished and papaverine solution was topically applied in soaked cotton pledgets. No other surgical manipulation or action by the anesthesiologist was made. The patsient suddenly developed a severe bradycardia that was successfully managed with IV atropine. Surgery ended uneventfully. Different side effects associated with intracisternal use of papaverine have been reported in intracranial surgery, including cranial nerves dysfunction and even fatal cardiac arrest. The case we present is a good example of an adverse effect of topical use of papaverine, even when carefully applied, and adds evidence to the probable papaverine neural toxicity.

Keywords

Papaverine, Topical papaverine, Bradycardia, Neural toxicity, Intracisternal papaverine

Introduction

Papaverine hydrochloride is an opium-derived alkaloid of the benzylisoquinoline group. It is a potent smooth muscle relaxant and it is widely used to treat or prevent cerebral vasospasm due to its vasodilator properties. Vasospasm can be caused by subarachnoid hemorrhage or by direct intraoperative arterial manipulation [1-3]. Papaverine can be administrated in several forms including intra-arterial, intravenous, oral, and topical. Different side effects associated with intracisternal use of papaverine have been reported in intracranial surgery. The exact mechanism of action when applied intracisternally is not well known and growing evidence suggests that papaverine may present a direct neural toxicity effect.

Case Report (Material and Methods / Results)

A 15-year-old boy was referred to our department presenting with headache, diplopia, and right hemiparesis. Clinical examination revealed left 6th^{o}cranial nerve paresis, slight left facial paresis, and right hemiparesis. An MR showed a lesion consistent with a hemorrhagic cavernous hemangioma on the left side of the pons. The lesion enlarged the pons, and was in contact with the floor of the fourth ventricle. The patient underwent a transvermian approach. Intraoperative neurophysiological monitoring was set up. 7th^{o}, 9th^{o}, 11th^{o} and 12th^{o} cranial nerves were monitored. Brain stem auditory evoked potentials, motor and somatosensory evoked potentials for long tracts, and intraoperative mapping of the motor nuclei of fourth ventricle floor was also set up. Anesthesia was induced with injection of midazolam 0.03 mg/kg, fentany l3 µg/kg and propofol 2 mg/kg body weight. Traqueal intubation was facilitated with cisatracurium 0.15 mg/kg body weight. To monitor the depth of anesthesia bispectral index (BIS XP, Aspect Medical Systems Inc., Newton MA) was used. Invasive monitoring consisted of venous pressure (CVP; right subclavian artery) and arterial blood pressure (BP; right radial). Anesthetic maintenance was performed with an oxygen 50% air, remifentanil infusion of 0.1 to 0.25 ug / kg / min infusion of propofol to 6 mg / kg / h to maintain BIS 40-60 without neuromuscular blockade not to interfere with neurophysiological monitoring. The lesion was approached rostrally to the facial nerve fibers on the left side. By the end of the resection, the corticobulbar motor evoked potentials for both facial nerves diminished and finally were abolished. The lesion was almost totally removed except for a minimal caudal portion that had to be left because corticospinal motor evoked potentials diminished. As we do at supratentorial level when motor evoked potentials diminish during surgery next to functional areas, papaverine solution was topically applied in soaked cotton pledgets at tumor limits and adjacent neural tissues. The patient, who had been hemodynamically stable throughout the surgery, suddenly developed a severe bradycardia (heart rate decreased from 75 to 29 beats per minute) immediately after papaverine application. There was also sudden hypotension (blood pressure decreased from around 110 / 75 to 60 / 35 mmHg). This incidence lasted for about 3 minutes and was managed with i.v. atropine (2 mg) obtaining immediate normalization of heart rate. Later, the patient showed a hypertension tendency that was successfully managed with hypotensor drugs. The motor evoked potentials were recovered but it was not possible to achieve total lesion removal without affecting them. Resection stopped and closure was performed uneventfully after careful hemostasis. The patient recovered from surgery and presented with diplopia due to left 6th^{o} cranial nerve palsy, bilateral facial palsy, and moderate right hemiparesis. He presented no postoperative complication and

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was sent to a rehabilitation center. The hystopathological analysis confirmed cavernous hemangioma.

Discussion

Papaverine hydrochloride is a potent smooth muscle relaxant and it is widely used to treat or prevent cerebral vasospasm due to its vasodilator properties. Papaverine can be administrated in several forms including intraarterial, intravenous, oral, and topical. Topical use of papaverine to treat vasospasm during neurosurgical procedures was first described in 1958 [1], and has widely been used in neurosurgery since then. It has also been used to treat spastic vessels in urologic procedures [4].

Papaverine is highly lipid soluble and acts directly on smooth muscle producing diffuse dilatation of arteries and arterioles. The pharmacodynamics is thought to be mediated by elevated levels of intracellular cyclic adenosine monophosphate (cAMP) or cyclic guanosine 3',5'-monophosphate (cGMP) [5]. It blocks the calcium flux of smooth muscle when given orally or parenterally, however the exact mechanism of action when applied intracisternally is not well known [6]. Eisenman et al. [1] proposed that papaverine may act as a local anesthesic and influence the excitability of nerve fibers. Chadwick et al. [7] mentioned the neuropathic effect of papaverine which is probably associated to its acid pH (pH values about 3). Sindou [8] suggested that acute acidose effect on vessels and neural tissue is the main agent of vasodilatation and neural toxicity.

Different side effects associated with intracranial topical use of papaverine have been reported, including unilateral or bilateral pupil dilatation, facial nerve palsy, auditory dysfunction, features suggestive of malignant hyperthermia, brain stem dysfunction, hemodynamic changes, and even fatal cardiac arrest [3,9-11].

The dosage of intraarterial papavine has been mentioned in various studies, but no consensus has been reached for the safe dose of topical papaverine when given intracisternally. Rath et al. reported their use of intracisternal papaverine as 2 ml of 3% papaverine diluted to 20 ml with normal saline in patients with preoperative evidence of vasospasm [9]. Sindou reported it as 1 ml in 10 ml of Ringer's solution [8]. We use it as Rath et al. described.

The use of intracisternal papaverine is widely accepted to treat or prevent vasospasm in aneurysmal surgery. It is also used to prevent vasospasm after vestibular schwannoma surgery [11]. As mentioned before, we also use it when motor evoked potentials diminish during surgery next to functional areas in an attempt to recover the potentials. But we use it in soaked cotton pledgets applied next to functional areas, not intracisternally (where there is no control of papaverine spread).

Some authors reported adverse effects concerning hemodynamic functions after intracisternal use of papaverine, and they hypothesized that the drug might have spread through the ventricular system reaching the fourth ventricle and stimulating the vagal nucleus in its floor [9,10,12]. Similar vagal stimulation, though applied differently, could have been responsible of the severe bradycardia in the case we present.

Conclusions

Topical use of papaverine has proven beneficial effects to prevent ischemia related to vasospasm in different types of neurosurgical procedures. But it may have a neuropathic effect that is not completely understood. We suggest that topical application of papaverine should be done carefully, diluted in saline (2 ml of 3% papaverine diluted to 20 ml with normal saline solution) or Ringer's solution (1 ml in 10 ml of Ringer's solution). It should be applied by mean of soaked cotton pledgets to avoid uncontrolled intracisternal spread of it. We also suggest not applying papaverine directly on fourth ventricle structures.

Patient Consent

The patient and his next of kin have consented to the submission of the case report for submission to the journal.

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