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Intracisternal papaverine toxicity in anterior circulation aneurysm clipping surgery. A literature review

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Keywords
Intracisternal papaverine toxicity, anterior circulation aneurysm, clipping surgery

ABSTRACT

Introduction. Cerebral vasospasm is a major cause of mortality in patients with subarachnoid haemorrhage. Irrigation of intracisternal papaverine has been adopted as a strategy to reduce the incidence of aneurysm-surgery-associated vasospasm.
Aim. The aim of this literature review is to summarize the reported complications associated with intracisternal papaverine administration.
Patients and Methods. We searched the following databases: PubMed, Google Scholar, Cochrane Library, Clinical Key, Embase, Emerald, Health Business Elite, MEDLINE at OVID, EBM Reviews and Research Gate. The following keywords were used: Intracisternal papaverine, topical papaverine, direct papaverine, a vasodilator for aneurysm surgery, papaverine in aneurysm clipping, papaverine complications and papaverine side effects. The search criteria included all articles published between 1980-2019, in the English language.
Results. Our search yielded a total of 19 articles describing 43 cases. The most common reported complication was ipsilateral oculomotor nerve palsy. Other local complications included: Bilateral oculomotor nerve palsy, ipsilateral facial nerve palsy, and monocular blindness. Although less common, reports pointing to papaverine systemic toxicity did exist. Examples of such complications included: Profound hypotension, bradycardia, hypertension and tachycardia, hyperthermia and metabolic acidosis, cardiac arrest and even death.
Conclusion. Intracisternal papaverine irrigation is an effective strategy in reducing peri-operative vasospasm associated with aneurysm surgery. Although uncommon, both local and systemic side effects have been linked to papaverine use, calling for careful dosing and close monitoring to enhance its safety profile.

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INTRODUCTION

The use of intracisternal papaverine to prevent vasospasm during aneurysm surgery was first described in the fifties of the 19th century (1). Papaverine is a vasodilator that can be installed directly onto the

the vessels in the exposed cisterns during aneurysm clipping. Papaverine's main role is to prevent intraoperative and postoperative vasospasm and to alleviate its deleterious consequences (1). The application of intracisternal papaverine is considered to be a safe procedure as compared to other routes of administration such as the intra-arterial, and intravenous routes along with the slow release pellets as these routes often entail several serious direct side effects (2-4). To date, there are few reports that describe the complications associated with the installation of intracisternal papaverine.

In this article, we reviewed the available literature regarding the adverse effects related to the intracisternal papaverine use during aneurysm surgery.

Patients and methods

We conducted a literature review of all articles published on PubMed, Google Scholar, Cochrane Library, Clinical Key, Embase, Emerald, Health Business Elite, MEDLINE at OVID, EBM Reviews and Research Gate from 1980-2019. The following keywords were used: Intracisternal papaverine, topical papaverine, direct papaverine, vasodilator for aneurysm surgery, papaverine in aneurysm clipping, papaverine complications and papaverine side-effects. The reported cases were analyzed in relation to the location of the aneurysm, the association with subarachnoid hemorrhage (ruptured or unruptured aneurysm), the dose of papaverine used, the reported side effects, the resolution time of these effects and the fenestration status of the lamina terminals. The demographic data and the surgical approaches were excluded from the results as these parameters were not mentioned in the majority of the reported cases.

Results

Our search yielded 19 articles, with a total of 43 aneurysms. As for the types of articles; there were two original articles (5,6), two case reports and reviews (7, 8), one case series (9), nine case reports (10-18), and five letters to the editor (19-23). The two most common aneurysm locations that were associated with topical papaverine complications were the middle cerebral artery (MCA) and the anterior communicating artery (AcomA) with 18 and 17 cases, respectively. Other reported locations included posterior communicating artery aneurysm (6 cases), internal carotid artery bifurcation aneurysm (one case), and ophthalmic artery aneurysm (one case). There was one report where the location of the aneurysm was not specified. Notably, amongst the 43 reported papaverine toxicity cases, 42 cases were associated with ruptured aneurysms while only one case was associated with an un-ruptured aneurysm (13) while the remaining cases did not specify the status of aneurysm rupture.

This literature review showed that intracisternal papaverine can cause ipsilateral (6, 9, 11-13, 18), contralateral (6, 7, 21), and even bilateral oculomotor nerve palsy (7-10, 19). The ipsilateral oculomotor palsy in the form of mydriasis with a non-reacting pupil was the most common reported complication of intracisternal papaverine installation (18 out of 43 patients). Temporary facial nerve palsy was the only other reported cranial nerve paresis after the oculomotor nerve (13).

Hemodynamic and metabolic adverse effects were reported in a total of 15 cases. These effects included profound hypotension (5, 20, 22), bradycardia (5), both hypotension and bradycardia (14, 16, 23), and hypertension and tachycardia (17). Two of the three reported cases of intracisternal papaverine complications in the form of both hypotension and bradycardia progressed to cardiac arrest and death (16, 23); these were the only reported deaths related to cisternal papaverine. McLoughlin et. al described the unique toxicity of papaverine as hyperthermia and metabolic acidosis (12). One other rare complication was permanent monocular blindness resulting from choroidal infarction with an unknown mechanism of causation (15). (Table 1)

Out of all the reviewed reports on the complications of the intracisternal papaverine, only three reports by Rath et al. 2006 (14), Singla et al. 2009 (22), and Baltaci et al. 2010 (16) included the fenestration of the lamina terminalis within the parameters under study; the authors described serious complications related to intracisternal papaverine installation after the fenestration of the lamina terminalis; namely, profound hemodynamic changes, severe hypotension, and cardiac arrest respectively.

The resolution time of the adverse effects of papaverine was variable. The oculomotor-related complications usually resolved within the first day

with the majority of patients recovering within the first 5 hours. However, in three cases the resolution extended beyond 4-7 days and even up to 23 days in one report (8, 10, 12). As compared to cranial nerve paresis, the hemodynamic complications of intracisternal papaverine were more abrupt with the majority of reports charting a resolution time of few minutes; only two cases, that reported hypotension, recorded a resolution time of more than one hour (20, 22).

Our review revealed that papaverine hydrochloride ampule was used in all cases. The concentration used ranged between 30 and 300 mg of 3% papaverine, diluted in 10 up to 100 ml of warm 0.9% normal saline or Ringer lactate with only a few cases reporting the use of undiluted (60 mg)of papaverine. The recommended papaverine regimen, based on our review, was 2 cc of 3% papaverine (60 mg) diluted in 10-20 ml of warm 0.9% normal saline or Ringer lactate at room temperature (35-37 °C).

Table 1: Review of the reported complications of intracisternal papaverine

Adverse effects	Number of reported cases	Percent of the total reported cases with toxicity
Ipsilateral oculomotor nerve palsy	18	42%
Bilateral oculomotor nerve palsy	7	16%
Contralateral oculomotor nerve palsy	3	7%
Ipsilateral facial nerve palsy	1	2%
Monocular blindness	1	2%
Profound hypotension	7	16%
Bradycardia	3	7%
Severe hypotension and bradycardia*	3	7%
Hypertension and tachycardia	1	2%
Hyperthermia and metabolic acidosis	1	2%

*Two of the cases end with cardiac arrest and death.

Discussion

The topical papaverine installation on the dissected cisterns after aneurysm clipping and just prior to dural closure can cause rare but diverse adverse effects ranging from temporary cranial nerve paresis to cardiac arrest and even death.

The association of these complications with papaverine use was confirmed in all reports after the exclusion of all possible anesthetic and surgical causes. Furthermore, the temporal association between the application of papaverine and the development of side effects confirmed that the primary cause was the drug itself rather than other factors. Also, the type of papaverine formula used had no neurotoxic solvent in its composition (14). It is worth noting that although the distribution of the reported aneurysm locations was found to follow the classic pattern of incidence of the surgically managed intracranial aneurysms, one cannot deny the possibility of papaverine related complications may increase with both AcomA and MCA aneurysms as the surgery for such locations entails more arachnoid dissection and involve the opening of more subarachnoid cisterns than surgeries in other proximal locations. Additionally, we suggest that aneurysm rupture may be one of the factors that contribute to papaverine toxicity as subarachnoid hemorrhage may render the brain and the cranial nerves more sensitive for the direct effect of papaverine, increasing the rate of complications.

The most commonly cited theory for the reason behind papaverine-associated cranial nerve paresis is that papaverine likely exerts direct chemical toxicity, working in synchrony with the subarachnoid blood to irritate the already-sensitized cranial nerves. The hemodynamic and metabolic changes were explained in the literature by the possible effect of papaverine while in contact with vital centers in the hypothalamus and brainstem.

As for the three reports that linked papaverine toxicity to the anterior third ventriculostomy (opening of lamina terminalis), the authors of these reports hypothesized that the introduction of papaverine into the ventricular cavity through the

fenestrated lamina terminalis may have resulted in direct chemical irritation to the hypothalamus and midbrain in the walls of the third ventricle and the vagal nucleus in the walls of the fourth ventricle (14, 16, 22). These complications can occur when papaverine is installed in the cistern after the fenestration of lamina terminalis (anterior third ventriculostomy or anterior ventriculo-cisternostomy). Thus, papaverine can easily enter the third ventricle and become in direct contact with the hypothalamic nuclei in the ventricular wall. Papaverine can also reach the fourth ventricle through the aqueduct of Sylvius and exert its effect on the brainstem nuclei in the floor of the fourth ventricle. These complications would, inevitably, be more evident when papaverine is used in a non-diluted form or in a relatively high dose. Considerable variability was found in the description of the used doses (concentration and amount) of papaverine to be installed into the cisterns during aneurysm clipping surgery. Whether to dilute the papaverine or not and what is the best diluting fluid are still debatable issues and the decisions currently based on the surgeon's personal experience.

Conclusion

Intracisternal papaverine use is an effective method for the prevention of perioperative vasospasm during intracranial aneurysm clipping surgery. However, this is not a completely safe intervention and may be associated with toxicity, mainly in the form of temporary paresis to the adjacent cranial nerves or variable hemodynamic consequences. Thus, precautions regarding dosing and monitoring must be contemplated when introducing topical papaverine into the surgical field.

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