



CASE SERIES AND LITERATURE REVIEW

Intracisternal Papaverine-Induced Oculomotor Palsy during Anterior Circulation Aneurysm Surgery: A Report of Five Cases and Literature Review

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Abstract

Introduction: Papaverine is a vasodilator commonly used to reduce the incidence of vasospasm following aneurysm clipping. In this paper, we review the literature on oculomotor nerve palsy (ONP) caused by intracisternal papaverine and report five exemplary cases.

Methods: An online PubMed database search was conducted using the following search algorithm: ("papaverine"[All Fields] OR "papaverine"[MeSH Terms] OR "papaverine"[All Fields]) AND ("intracisternal"[All Fields]). Only articles that attributed oculomotor nerve palsy solely to intracisternal Papaverine were further analysed.

Results: A total of 14 papers (34 cases) were included in this review, accounting for the five cases reported by the authors (Table 1). All aneurysms were located at the anterior circulation. In none of the cases was oculomotor nerve manipulation reported. The most common reported dosing of intracisternal papaverine was 2 ml of papaverine 3% diluted in 10 ml or 20 normal saline, used in 23.5% (n = 8) of cases. Ipsilateral mydriasis was documented in 64.7% (n = 22) of the cases, while bilateral mydriasis occurred in 23.5% (n = 8) of patients and 8.8% (n = 3) of cases had contralateral mydriasis. The resolution time ranged from 0.5 hours to 23 days.

Conclusion: Papaverine is a vasodilator that can be used during microsurgical aneurysm clipping to reduce the incidence of vasospasm. It is a generally safe drug but may cause transient ONP, a differential that should be entertained in post aneurysm clipping third nerve palsy.

Keywords

Papaverine, Intracisternal, Aneurysm surgery, Oculomotor nerve palsy

Abbreviations

AcoA: Anterior Communicating Artery; SAH: Subarachnoid Hemorrhage; IVH: Intraventricular Hemorrhage; ICH: Intracerebral Hemorrhage; MCA: Middle Cerebral Artery; ICA: Internal Carotid Artery; AntChA: Anterior Choroidal Artery; ACA: Anterior Cerebral Artery; PcomA: Posterior Communicating Artery; CT: Computed Tomography

Introduction

Anterior communicating artery (AcoA) aneurysms are the most common intracranial aneurysms accounting for about 35% of all intracranial aneurysms [1]. Vasospasm is a known major complication of aneurysmal rupture and it can be triggered by intraoperative vessel manipulation or the presence of blood in the subarachnoid space following aneurysm rupture [2-4].

Papaverine is a known smooth muscle relaxant and a potent vasodilator [5]. Topical papaverine installation is commonly used to prevent vasospasm following surgical clipping of intracranial aneurysms [5]. Intracisternal papaverine is generally safe [6]. Rarely, complications may arise such as hemodynamic changes and cranial

Table 1: Papaverine-induced ONP: Literature review.

Author/Year	Cases Number	Age/Sex	Clinical Presentation	Radiological Findings	Aneurysm Location	Surgical Approach	Papaverine Dose	Mydriasis	Resolution Time	Other Post-op Complications (Resolution Time)
Zygourakis, et al., [2]	9	---	---	---	5 ACoA 2 MCA 2 PCoA		(10 cc, 30 mg/cc)	7 Unilateral 2 Bilateral	2 to 9 h	
McLoughlin 1, et al., [7]	1	36 M	Acute Severe Headache and Vomiting and Somnolent	SAH	R MCA R ICA bifu	R Pterional	30 mg	Ipsilateral	6 d	Basal Ganglia Infarct Secondary to Cerebral Vasospasm (post-op Day 5)
Praeger, et al., [8]	1	55 F	---	---	R MCA Ant.Ch.A LACA L pericallosal		Undiluted Papaverine (120 mg/10 mL)			
Pritz, et al., [12]	3	29	---	---	R ICA bifu	Pterional	3 ml (2%)	Ipsilateral	2 h	None
		73	---	---	R MCA bifu L ICA bifu				3 h	
		55 F	---	---	ACoA				4 h	
Chittiboina, et al., [13]	3	Mean age 48	---	---	MCA	Frontotemporal	3-5 cc of a 3% Solution	Ipsilateral	3-24 h Range	
					MCA					
					ACoA					

Pritz, et al., [14]	1	55 M	---	---	---	R MCA Bifu and M2 Aneurysm	R Pterional	(((20 cc of 1.5%))) (300 mg/10 mL) Diluted in Half with Lactated Ringer's Solution	Contralateral (L-left)	80 Minutes	
Sheshadri, et al., [18]	3	43 F	History of Seizure and Two Episodes of Vomiting a Week Prior, Followed by Intermittent Headache since then	---	L MCA bifu			10 cc of 0.6% Papaverine	Contralateral and Not Reacting to Light	1 h	
		67 M	Severe Headache for 3 Days		R MCA bifu			Undiluted Papaverine (2 cc of 3%)	Bilateral and Non-Reactive to Light	Ipsilateral 0.5 h 1 h both	E1M5VT with Left Hemiparesis
		33 M	History of Headache and Vomiting of 4 Days Duration.		L MCA bifu			10 cc of 0.6%	Bilateral and Non-Reactive to Light	0.5 h Ispi 4 h both	
Bala, et al., [20]	1	50 F	Severe Headache, Nausea and Vomiting and Tonic Clonic Type of Seizures	SAH	ACoA	R Pterional		60 mg in 10 mL saline (((10 cc of 0.6%)))	Bilateral Dilated and Nonreactive Pupils	R 3 h and L 4 h	
Lang, et al., [21]	1	61 F	---	---	R MCA bifu	Pterional		240 mg in 20 mL Saline	Ipsilateral with Pupillary Areflexia	1.5 h	Prolonged Facial Nerve Palsy (2 mo)

Zhou W, et al. [27]	4	M(2) F (2) 38-65	Sudden Severe Headache	SAH	PCoA (2) ACoA (1) MCA (1)	Trans-Pterional	(3%, 60 mg)	Ipsilateral (3) Contralateral (1)	2-5 h									
Zhou X, et al. [28]	1	55 F	Sudden Onset of Severe Headache.	SAH with Left Occipital Horn IVH	Acom ACoA L MCA R MCA	Left Modified Orbitozygomatic	3 % IPPV Solution (60 mg/2 ml) (((2 ml. (3%))))	Bilateral	23 d									Vasospasm (Day 7) Stroke (Day 20)
Ausma, et al., [29]	1	---	---	---	PCoA	---	---	Bilateral with Pupillary Areflexia	4 d									Loss of Consciousness
Our Cases (Hoz, et al.)	5	46 M	Severe Headache, Vomiting	SAH and ICH	L ACoA	Pterional	3% in 20 mL Saline	Ipsilateral	4 h									None
		43 M	Headache, Seizures, DLOC	SAH and ICH	R ACoA	Pterional	3% in 20 mL Saline	Ipsilateral	4 h									None
		41 F	Headache, Vomiting	SAH	R ACoA	Pterional	3% in 20 mL Saline	Ipsilateral	12 h									None
		35 F	Headache, Vomiting, DLOC	SAH	R ACoA	Pterional	3% in 20 mL Saline	Ipsilateral	12 h									None
		39 F	DLOC	SAH	L ACoA	Pterional	3% in 10 mL Saline	Bilateral and Non-Reactive	10 h									Transient Hypotension (2 d)

nerve palsies, most commonly the oculomotor nerve [4,7-12].

In this paper, the authors report a case series of five patients with transient complete oculomotor nerve palsy (ONP) after intracisternal papaverine installation during the surgical clipping of a ruptured AcoA aneurysm and review the related literature.

Case Scenario

In this paper, we report five cases of patients with ruptured ACoA aneurysms that had oculomotor nerve palsy following intracisternal Papaverine administration during aneurysm clipping (Table 2). All cases shared the following features: (1) No cisternostomy or lamina terminalis fenestration was undertaken, (2) No oculomotor nerve manipulation, (3) The dosage was 2 mL of papaverine 3% diluted in 20 mL saline, (4) Transient post-operative ONP, (5) Urgent post-operative CT excluded other potential causes, (6) Good outcomes.

Methods

An online PubMed database search was conducted using the following search algorithm: ("papaverine"[All Fields] OR "papaverine"[MeSH Terms] OR "papaverine"[All Fields]) AND ("intracisternal"[All Fields]), yielding 31 articles. The abstract screening was then done and only articles that reported papaverine-related ONP post aneurysm surgical clipping were included for further analysis. Only journal articles published in English were included. No restrictions were made on the timing of the publications. Only articles that attributed ONP solely to intracisternal Papaverine were included. Additionally, manual searching of the reference section of each included paper was done for further relevant citations. Next, information was extracted from each paper in relation to the following parameters: patient demographics (age and gender), clinical presentation, radiological findings, aneurysm location, surgical parameters, including surgical approach, oculomotor nerve manipulation, papaverine dosing, and post-operative outcome including the presence of mydriasis and other papaverine-related complications with their resolution time, and outcome at discharge.

Results

A total of 14 papers (34 cases) were included in this review, accounting for the five cases reported by the authors (Table 1). The age range was 29-73 years with a mean of 49 years. The most common presentation was headache reported in 41.1% (n = 14). Radiological findings showed that 35.2% (n = 12) of the cases presented with subarachnoid hemorrhage (SAH) including one case that co-presented with intraventricular hemorrhage (IVH) and two cases with intracerebral hemorrhage (ICH). All aneurysms were located at the anterior circulation, including the posterior communicating artery (PCoA).

Table 2: Hoz case series of oculomotor nerve involvement after intracisternal papaverine administration during anterior communicating artery aneurysm clipping surgery.

Case	Age (Years)	Gender	Presentation	Radiological Findings	Direction of the Aneurysm	Cisternostomy and Lamina Terminalis Fenestration	Papaverine Dose	Post-Operative Complications	Time to Resolution	Outcome at Discharge
Case 1	46	Male	Headache, Vomiting		Superiorly	No	2 mL of Papaverine 3% diluted in 20 mL Saline	Ipsilateral Mydriasis	4 hours	Good
Case 2	43	Male	Headache, Seizures, Decreased LOC	SAH and ICH	Anteriorly	No	2 mL of Papaverine 3% diluted in 20 mL Saline	Ipsilateral Mydriasis	4 hours	Good
Case 3	41	Female	Headache, Vomiting	SAH	Superiorly	No	2 mL of Papaverine 3% diluted in 20 mL Saline	Ipsilateral Mydriasis	12 hours	Good
Case 4	35	Female	Headache, Vomiting, Decreased LOC	SAH	Anteriorly	No	2 mL of Papaverine 3% diluted in 10 mL Saline	Ipsilateral Mydriasis	12 hours	Good
Case 5	39	Female	Decreased LOC	SAH	Anteriorly	No	2 mL of Papaverine 3% diluted in 10 mL Saline	Dilation in the Bilateral Pupils with Transient Hypotension	10 hours 2 days for Blood Pressure Normalization	Good

LOC: Level of Consciousness; SAH: Subarachnoid Hemorrhage; ICH: Intracerebral Hemorrhage; ml: Milliliter

AcoA aneurysms represented 47.1% (n = 16) of the cases. One particular case had multiple aneurysms of the AcoA, and the right and left middle cerebral artery (MCA). MCA aneurysms were present in 47% (n = 16) of the cases. PCoA aneurysms were 14.7% (n = 5) of cases. ICA bifurcation aneurysm was 8.8 % (n = 3), ACA aneurysm was 5.9% (n = 2), anterior choroidal artery aneurysms 2.9% (n = 1).

Microsurgical clipping was achieved through the pterional approach in 16 cases (47%), the frontopolar approach in three cases (8%), and the orbitozygomatic approach in one case (2.9%). In none of the cases was oculomotor nerve manipulation reported. The most common reported dosing of intracisternal papaverine was 2 ml of papaverine 3% diluted in 10 ml or 20 normal saline, used in 23.5% (n = 8) of cases. Ipsilateral mydriasis was documented in 64.7% (n = 22) of the cases, while bilateral mydriasis occurred in 23.5% (n = 8) of patients and 8.8% (n = 3) of cases had contralateral mydriasis after intracisternal papaverine administration. The resolution time ranged from 0.5 hours and 23 days, but 2-4 hours was reported in 50% (n = 17) of cases. Besides mydriasis, other complications were prolonged facial nerve palsy in one patient (2.9%) that resolved after 2 months and transient hypotension that resolved in 2 days in another one (2.9%). All the cases had good outcomes at discharge.

Discussion

Papaverine hydrochloride belongs to the benzyloisoquinoline group of alkaloids. Papaverine exerts a vasodilating effect on blood vessels, by directly inhibiting calcium channels and phosphodiesterase enzyme in smooth muscles [13-15]. It is a common practice to install papaverine onto the cisterns during surgical clipping of intracranial aneurysms to reduce the risk of vasospasm [10,16,17].

The intracisternal route of Papaverine is generally safe but may be associated with rare complications such as cranial nerve palsies, blindness secondary to choroidal infarction [18], and a set of hemodynamic derangements, including malignant hyperthermia and metabolic acidosis [10], bradycardia and hypotension [11,19], tachycardia and hypertension [20], intracranial pressure changes [21], transient brain stem depression [22,23] and even cardiac asystole [24].

Post-operative ONP may result from several causes such as intra-operative manipulation, inadvertent injury, post-operative cerebral hematoma, edema, intracranial hypertension, cerebral herniation, and rarely intracisternal Papaverine administration [25,26]. Thus, the diagnosis of papaverine-induced ONP could only be made after the exclusion of the aforementioned, more common causes. It has been hypothesized that cranial nerve paresis related to papaverine installation are due to papaverine direct irritation and toxicity to

the already sensitive cranial nerves from the SAH -in case of aneurysmal rupture.

Also, to help establish the etiology, the mechanism of Papaverine-induced ONP should be recalled. Papaverine blocks only the superficial dorsal fibers and hence will not produce ptosis while complete damage (both superficial and deep fibers) to the oculomotor nerve is usually accompanied by ptosis as the deep fibers control the muscles [26]. As the oculomotor nerve exits the brain stem, it passes between the posterior cerebral artery and the superior cerebellar artery, parallel to the posterior communicating artery to enter the cavernous sinus [27]. The parasympathetic fibers of the oculomotor nerve that controls the sphincter pupillae muscle is located in the dorsal-medial superficial layer of the oculomotor nerve, which is exposed to the carotid pool where it is mostly being subjected to papaverine [28].

Our literature review showed that intracisternal papaverine installation can cause either ipsilateral [2,7,10,13,19,26], contralateral [11,23,26] or bilateral ONP [2,12,23,28,29]. The most commonly reported form of ONP was the ipsilateral oculomotor paresis in the form of mydriasis with non-reacting pupils in 64.7% (n = 22) of cases. Temporary facial nerve palsy is the only cranial nerve paresis other than the oculomotor nerve that has been attributed to intracisternal papaverine administration [13].

Papaverine-induced ONP was transient in all reported cases, with variable resolution time. The majority resolved within the first 24 hours. However, in three cases, the resolution time extended beyond 24 hours reaching up to 23 days in one case [17]. In these sets of cases, the delayed resolution could be attributed to a set of peri-operative circumstances, including the aneurysm location and multiplicity of the incidence of post-operative complications, including stroke and coma, and the imaging findings at presentation (Table 2).

Based on our review, there exists no recommended safe and effective regimen of intracisternal papaverine in intracranial aneurysm surgery. At our institution, 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) is the regimen used.

From this review, the correlation between aneurysm location, multiplicity, or rupture status with the incidence of post-operative ONP could not reach statistical significance. However, given the small size of our sample, definitive conclusions could not be drawn at this point. Larger multi-center randomized trials are needed to highlight the peri-operative factors linked with Papaverine-induced ONP and provide evidence on possible methods of prevention, including optimum Papaverine dosing.

Conclusion

Papaverine is a vasodilator that can be used during

microsurgical aneurysm clipping to reduce the incidence of vasospasm. It is a generally safe drug but may cause transient oculomotor nerve palsy, a differential that should be entertained in post aneurysm clipping third nerve palsy.

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Conflict of Interest

None.

Patient Consent

Patient's consent not required as patients identity is not disclosed or compromised.

Author's Contribution

All authors have contributed equally in manuscript drafting, reviewing, data search and acquisition.

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