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Clinical Study

Transient pupillary dilation following local papaverine application in intracranial aneurysm surgery

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ABSTRACT

Isolated cases of transient pupillary changes after local intracisternal papaverine administration during aneurysm surgery have been reported. This study aimed to determine the prevalence and factors associated with this phenomenon. We assessed a total of 103 consecutive patients who underwent craniotomy for cerebral aneurysm clipping for the presence of postoperative pupillary dilation (mydriasis) after intracisternal papaverine administration. Univariate and multivariate logistic regression were conducted to evaluate the association of mydriasis with patient age, sex, duration of surgery, and aneurysm location. We observed either ipsilateral or bilateral pupillary dilation in the immediate postoperative period in nine out of 103 patients (8.7%). This phenomenon was not associated with patient age or sex. There was a trend towards positive correlation with aneurysms located at the anterior communicating artery (odds ratio 3.76, $p = 0.10$), and a negative correlation with the duration of surgery (odds ratio 0.57, $p = 0.08$). All pupillary dilation resolved within several hours, and the onset and resolution were consistent with the half-life of papaverine. To our knowledge, this represents the largest study of posteropative pupillary changes due to papaverine. The current findings are consistent with the small number of prior case reports of transient pupillary changes after papaverine administration and appear to reflect the local anesthetic action of papaverine on the oculomotor nerve.

1. Introduction

Despite the increasing use of endovascular approaches for the treatment of intracranial aneurysms, operative aneurysm clipping remains a safe and durable option for many patients [1]. During intracranial aneurysm surgery, topical papaverine, a well-known vasodilator, can be applied directly to intracranial arteries to prevent or alleviate vasospasm triggered by subarachnoid blood or operative manipulation. Fewer than 10 cases of pupillary changes after intracisternal papaverine administration have been reported in the literature. Such pupillary changes can be misinterpreted as a sign of neurological deterioration and subsequently initiate a chain of diagnostic tests that delay postoperative extubation [3–5]. Prior case reports speculate on the mechanism of papaverine-induced pupillary dilation, either via smooth muscle dilation or local anesthetic effect.

However, to our knowledge, there have been no large studies of this drug-induced pupillary phenomenon in the literature. We therefore performed the first large series analysis to determine the frequency and possible contributing factors of postoperative papaverine-induced pupillary dilation in a consecutive series of 103 operative aneurysm patients.

2. Methods

We reviewed the records of 113 consecutive patients who underwent intracranial aneurysm clipping in which local papaverine was applied between 2007 and 2011 at the Brigham and Woman's Hospital. The study was approved by the Institutional Review Board. A total of 10 patients did not meet study criteria and were excluded from the study due to the following reasons: three patients had preoperative fixed and dilated pupils, one patient had missing data on postoperative pupil dilation, one patient had a distal mycotic aneurysm, and five patients had basilar tip aneurysms. Basilar tip aneurysms were excluded from

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the study because the orbitozygomatic approach may have resulted in an oculomotor palsy from the dissection itself. After applying these exclusion criteria, 103 patients were included in our analysis.

All aneurysm surgeries were performed by a single surgeon (R.D.). In the majority of our cases, intraoperative indocyanine green (ICG) angiography was performed immediately after clip placement to assess branch patency and aneurysmal occlusion in real-time [2]. The ICG procedure consisted of an ICG bolus (12.5 mg of ICG in 5 cc of sterile water) given intravenously and was completed in all patients within 5 minutes. Afterwards, papaverine was applied locally to the arteries in the basal cisterns prior to closure (10 cc, 30 mg/cc). In our cohort of patients, intraoperative ICG was used in 63 patients and traditional intraoperative cerebral angiogram was performed in 30 patients. Nine patients had both procedures performed intraoperatively. Pupil sizes was measured and recorded prior to surgery and on the first postoperative examination. Pupillary dilation was defined as greater than 1 cm change from preoperative measurement or greater than 4 cm at postoperative evaluation.

Information about patient age, sex, use of intraoperative angiogram and ICG dye, duration of surgery, aneurysm location, and pre- and postoperative pupil sizes were collected from the medical records. The location of the aneurysm was grouped into the following categories: proximal anterior cerebral artery (A1), distal anterior cerebral artery, anterior choroidal artery, anterior communicating artery (ACoA), basilar trunk, supraclinoid segment of the internal carotid artery (ICA), ICA bifurcation, middle cerebral artery, posterior communicating artery, posterior inferior cerebellar artery, and vertebral artery. Statistical analysis was performed using R (version 3.0.2). Univariate and multivariate logistic regressions were used to analyze the association of postoperative unilateral or bilateral pupillary dilation with the following variables: age, sex, duration of surgery, and ACoA aneurysm location. Individual analysis was performed on aneurysms located at ACoA as this location required the most dissection compared to other aneurysm locations evaluated.

3. Results

3.1. Patient demographics

A total of 103 consecutive patients were analyzed to assess the prevalence of postoperative pupillary dilation after the intraoperative administration of papaverine. Patient demographics are shown in Table 1. Patients ranged from 17 to 90 years old (mean 56 ± standard deviation [SD] 14), and 74.8% of the patients were females. One hundred two patients presented with classic signs of subarachnoid hemorrhage, including headache, emesis, confusion, and unresponsiveness. Only one patient was asymptomatic, with an incidental aneurysm discovered on imaging.

The mean duration of surgery was 7.2 ± SD 2 hours, and the mean duration of postoperative pupil dilation was 3.4 ± SD 3.5 hours. Intraoperative angiogram was performed in 30 patients (29.1%), while intraoperative ICG was performed in 63 (61%). Both procedures were performed in nine patients (8.7%). The duration of surgery increased when an intraoperative angiogram was performed (7.96 *versus* 6.84 hours, $p = 0.01$).

3.2. Prevalence and factors associated with postoperative pupillary dilation

We observed either unilateral (n = 7) or bilateral (n = 2) pupillary dilation unresponsive to light in the immediate postoperative period in nine out of 103 patients in our study (8.7%). Pupillary dilation was present in five patients with AcoA aneurysms, two patients with middle cerebral artery aneurysms, and two patients with posterior communicating artery aneurysms. One of the patients who had postoperative pupillary dilation had an intraoperative angiogram (Table 1).

Univariate and multivariate logistic regression models were then performed to evaluate the association of pupillary dilation with patient and aneurysm characteristics, including age, sex, duration of surgery, and ACoA aneurysm location (Table 2). Both univariate and multivariate analyses showed that there was no association between pupillary dilation and age or sex. There was a trend towards a decreased rate of postoperative pupillary dilation with longer duration of surgery in the multivariate analysis (odds ratio 0.57 [95% confidence interval 0.29–1.01], $p = 0.08$). There was also a trend towards an increased rate of postoperative pupillary dilation for anterior communicating artery aneurysms in the multivariate analysis (odds ratio 3.76 [95% confidence interval 0.78–19.77], $p = 0.10$).

4. Discussion

A small number of patients with pupillary changes after papaverine injection during aneurysm surgeries have been reported in

Table 1
Demographics of 103 patients who underwent craniotomy for cerebral aneurysm clipping with intraoperative, intracisternal papaverine administration

	All patients	No pupillary dilation	Unilateral or bilateral pupillary dilation
Patients, n	103	94	9
Age (mean ± SD)	56 ± 14	55 ± 14	60.1 ± 18
Female (%)	77 (74.8%)	71 (75.5%)	6 (66.7%)
Location of aneurysm			
A1	1	1	0
Distal ACA	4	4	0
AChA	2	2	0
ACoA	32	27	5
Basilar trunk	1	1	0
Supraclinoid ICA	6	6	0
ICA bifurcation	3	3	0
MCA	20	18	2
PCoA	25	23	2
PICA	7	7	0
VA	2	2	0
Surgical duration, hours (mean ± SD)	7.2 ± 2.1	7.2 ± 2.1	6.3 ± 1.2
Duration of postoperative dilated pupils, hours (mean ± SD)	-	-	3.4 ± 3.5
Intraoperative angiogram (%)	30 (29.1%)	29 (30.9%)	1 (11.1%)

A1 = A1 segment of anterior cerebral artery, ACA = anterior cerebral artery, AChA = anterior choroidal artery, ACoA = anterior communicating artery, ICA = internal carotid artery, MCA = middle cerebral artery, PCoA = posterior communicating artery, PICA = posterior inferior cerebellar artery, SD = standard deviation, VA = vertebral artery.