



# Hypotension and Bradycardia Following Papaverine Installation During Intracranial Aneurysm Surgery: A Report of Three Cases

## *Hipotensão e bradicardia devido à papaverina intracisternal quando instilada durante a cirurgia de aneurisma: Um relato de três casos*

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### Abstract

#### Keywords

- ▶ intracisternal papaverine
- ▶ lamina terminalis
- ▶ aneurysm surgery
- ▶ hypotension

### Resumo

#### Palavras-chave

- ▶ papaverina intracisternal
- ▶ lâmina terminal
- ▶ cirurgia de aneurisma
- ▶ hipotensão

**Introduction** One of the major complications of intracranial aneurysm surgery is vasospasm. Papaverine is an effective vasodilator that can be instilled directly onto the vessels in the operative field with the aim of preventing intraoperative and postoperative vasospasm. Several case reports of hemodynamic instability in general and of hypotension, in particular, were reported after the use of topical papaverine during aneurysm clipping surgery.

**Case description** Herein, we report three cases of transient profound hypotension and relative bradycardia after intracisternal papaverine usage during ruptured anterior communicating artery aneurysm clipping surgery.

**Conclusion** Caution should be taken while using papaverine intracisternally during anterior circulation aneurysm clipping, since it may cause several serious complications, including profound hemodynamic instability, particularly when instilling on a fenestrated lamina terminalis.

**Introdução** Uma das principais complicações da cirurgia de aneurisma intracraniano é o vasoespasm. A papaverina é um vasodilatador eficaz que pode ser instilado diretamente nos vasos do campo operatório com o objetivo de prevenir o vasoespasm intra e pós-operatório. Vários relatos de casos de instabilidade hemodinâmica em geral e de hipotensão, em particular, foram relatados após o uso de papaverina tópica durante cirurgia de clipagem de aneurisma.

**Descrição de caso** Aqui, relatamos três casos de hipotensão profunda transitória e bradicardia relativa após o uso de papaverina intracisternal durante a cirurgia de clipagem de aneurisma da artéria comunicante anterior rompida.

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**Conclusão** Deve-se ter cuidado ao usar papaverina intracisternamente durante a clipagem do aneurisma da circulação anterior, uma vez que pode causar várias complicações graves, incluindo profunda instabilidade hemodinâmica, particularmente ao instilar em uma lâmina terminal fenestrada.

## Introduction

Vasospasm is one of the major complications of intracranial aneurysm surgery. Papaverine is an effective vasodilator that can be instilled directly on the vessels in the operative field with the aim of preventing both intraoperative and postoperative vasospasm.<sup>1</sup> However, intracisternal papaverine has several reported side effects, including its effects on blood pressure and heart rate. Hemodynamic instability in general and hypotension, in particular, were reported after the use of topical papaverine in aneurysm clipping surgery.<sup>2-4</sup> In the present case report, we report three cases of transient profound hypotension and relative bradycardia after intracisternal papaverine usage during ruptured anterior communicating artery aneurysm clipping surgery. All cases were operated on by the same surgeon and were conducted under cortical somatosensory evoked potentials (SSEPs) and EEG monitoring intraoperatively.

### Case One

A 50-year-old female with no history of hypertension presented to the emergency department with a sudden-onset, severe headache with repeated vomiting of 5-hour duration, after attending a party with friends. The patient was diagnosed with subarachnoid hemorrhage (SAH) secondary to a ruptured anterior communicating artery aneurysm, Hunt and Hess (H&H) grade 1 and World Federation of Neurosurgical Societies (WFNS) grade 1. The CT scan also showed ventricular dilatation and small intraventricular hemorrhage. She underwent surgical clipping of the aneurysm on the next morning. She was anesthetized using total intravenous anesthetics (injection fentanyl and propofol infusions). Opening of the Sylvian fissure followed by preparation of the ipsilateral (dominant) A1 for possible temporary clipping was performed, followed by dissection of the aneurysm neck and permanent clip application. There was no intraoperative rupture, and temporary clipping was not used. Both the lamina terminalis and the Lilliequist membrane were fenestrated to prevent postoperative hydrocephalus, which is part of our routine technique for aneurysm cases with IVH. Then, 4 ccs of 3% papaverine were instilled intracisternally over the dissected vessels to prevent vasospasm. Twenty minutes after papaverine instillation, the anesthetist reported a decrease in blood pressure (BP) from 115/70 to 85/50 along with a decrease in pulse rate (PR) from 121 to 65. All possible surgical and anesthetic causes were excluded, and 1 L of normal saline was given rapidly, but the vitals were resistant to fluid resuscitation. The brain was relaxed and closure was done. After extubation, the patient was admitted to the neurology intensive care unit (ICU) and she was conscious,

obeying commands, and without neurological deficits but the BP and PR were at 85/55 and 68, respectively. The patient was kept under close observation with no added treatment until the vitals normalized 8 hours after the incident. The patient was discharged from hospital after 5 days and she was doing well on subsequent follow-up visits.

### Case Two

A 62-year-old female with no history of hypertension presented to the emergency department with severe headache and neck pain along with drowsiness and repeated vomiting over the past 24 hours. A brain computed tomography (CT) scan revealed SAH involving the basal supratentorial cisterns, gyrus rectus hemorrhage, and IVH in the right lateral ventricle and in the third ventricle. A CT angiography showed an 11-mm aneurysm located in the anterior communicating artery. Hunt and Hiss grade 2, WFNS grade 2. Surgical clipping was conducted on the same day. Anesthesia was conducted using the routine protocol. A right pterional craniotomy was done followed by clipping of the aneurysm. Temporary clipping was not used and both the lamina terminalis and the Lilliequist membrane were fenestrated. To minimize the possibility of postoperative vasospasm, 4 ccs of 3% papaverine were instilled intracisternally. A few minutes after papaverine instillation, the patient presented with sudden hypotension and bradycardia (BP: from 125/75 to 80/45; and PR: from 110 to 52). All possible surgical and anesthetic causes were excluded and boluses of IV fluids were used, but the vitals were resistant. Inotropes were then employed to control the BP. The rest of the surgery went uneventful. An urgent postoperative brain CT showed no hematoma or hydrocephalus. Postoperatively, the patient was alert, neurologically intact, but she was kept on inotropes boluses in the ICU. Four days after the incident, the vitals were back to normal levels; the patient continued to improve and started to walk normally without any deficit. The patient was discharged home 6 days later and she resumed her normal daily activities.

### Case Three

A 39-year-old man presented to the emergency department with an altered level of consciousness, neck stiffness, recurrent bouts of vomiting of 2-day duration. A CT scan of the brain revealed a ruptured anterior communicating artery aneurysm with early hydrocephalus. The SAH was Hunt and Hiss grade 2 and WFNS grade 1. The patient underwent an urgent aneurysm clipping surgery. Anesthesia was conducted using the routine protocol. Right pterional craniotomy was pursued, and the anterior communicating artery

aneurysm was clipped through the trans-Sylvian approach. There was no intraoperative rupture and temporary clipping was not used. Both the lamina terminalis and the Lilliequist membrane were fenestrated to release the cerebrospinal fluid from the ventricles and to prevent postoperative hydrocephalus. The surgical field was irrigated by 4 cc of 3% papaverine solution. A few minutes after papaverine instillation, both the BP and PR suddenly dropped; the BP decreased from 130/80 to 80/50 mm Hg, and the PR dropped from 110 to 70 BPM. The possible surgical and anesthetic causes were urgently excluded; however, the patient remained hypotensive with relative bradycardia. Resuscitation with IV saline failed to improve the BP and the PR. We performed the closure rapidly and the patient was sent for an urgent CT scan of the brain and then to the neurology ICU. The brain CT was negative for any hematoma or new findings. The patient remained hypotensive in the ICU, but he was extubated and fully conscious without any neurological deficits. He was kept on IV saline boluses with normal arterial blood gases. Two days postoperatively, the vitals started to improve and then normalized over the next hours. The patient was discharged 9 days later and was stable both neurologically and vitally. The patient achieved a full recovery on subsequent follow-up visits.

## Discussion

The use of intracisternal papaverine during anterior communicating artery aneurysm surgery can result in transient hypotension with relative bradycardia, and this effect is amplified if papaverine is instilled after the fenestration of the lamina terminalis.

It is a common practice to use papaverine intracisternally during surgical clipping of intracranial aneurysm with the aim of preventing the possible vasospasm and its disastrous consequences<sup>5,6</sup>

Papaverine is a benzyloisoquinoline alkaloid that acts as a potent vasodilator.<sup>7</sup> It inhibits smooth muscle phosphodiesterases (cyclic adenosine monophosphate and cyclic guanosine monophosphate) and inhibits calcium channels, hence causing relaxation of smooth muscle and vasodilation.<sup>8</sup>

Several complications related to intracisternal papaverine instillation have been reported in the literature, including cranial nerve palsies,<sup>9-12</sup> malignant hyperthermia with metabolic acidosis,<sup>13</sup> bradycardia with hypotension,<sup>4,14</sup> tachycardia with hypertension,<sup>15</sup> thrombocytopenia,<sup>16</sup> intracranial pressure changes,<sup>17</sup> transient brainstem depression,<sup>18</sup> and even cardiac arrest.<sup>19</sup>

Although the precise mechanism by which papaverine exerts its circulatory effects is not understood, some reports have suggested that the local vasodilatory effect of papaverine on the hypothalamus or on the brainstem could possibly explain some of these circulatory changes.<sup>4,14,15</sup> Sinha et al. stated that the involvement of the hypothalamus can have several effects on the circulatory system, ranging from hypertension with tachycardia to hypotension with bradycardia<sup>20</sup>; the authors justified this explanation in

reference to the fact that the preoptic area of the hypothalamus is responsible for the reduction in the BP and in the PR, while the posterior and lateral hypothalamic areas have the opposite function. The role of the pontine and medullary reticular formation was also suggested by some reports as a possible mechanism for the hemodynamic changes after intracisternal papaverine application.<sup>14</sup> Papaverine can reach the hypothalamus and the brainstem via the basal cisterns and may affect these structures by direct contact; however, this would result in fewer effects, as it would not be in direct contact with the critical internal structures. Based on our experience, papaverine can reach the third ventricle more easily when it is instilled after the fenestration of the lamina terminalis. Thus, a higher dose of less-diluted papaverine can reach the hypothalamus and the brain stem through the fenestrated lamina terminalis and cause a profound effect on the vital centers in the ventricular walls; based on this observation, we changed our intraoperative practice. Therefore, we recommend that papaverine should be instilled on the dissected vessels 10 minutes prior to the opening of the lamina terminalis and to use more diluted papaverine intraoperatively to avoid these complications. Currently, 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 between 10 and 20 ml of warm 0.9% normal saline or Ringer lactate at room temperature (35–37°C) is the dosing used. The surgical field can then be irrigated and, if required, the lamina terminalis can be fenestrated 10 minutes later, although alternative regimens have been suggested by some reports.<sup>14,15</sup>

## Conclusion

Caution should be taken while using papaverine intracisternally during anterior circulation aneurysm clipping, since it may cause some serious complications including profound hemodynamic instability, particularly when instilled on a fenestrated lamina terminalis.

### Contributions of the Authors

Hoz S. S.: Case identification, manuscript drafting, literature review

Al-Sharshahi Z. F.: Manuscript review, revision of the original draft

Almurayati M. E.: Revision of the original draft

Ghanim T. M.: Revision of the original draft

Kareem Z. M.: Revision of the original draft

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