

# The effect of irrigation of intracisternal papaverine on cerebral blood flow in subarachnoid hemorrhage

Masih Sabouri, Paiman Rahmani, Majid Rezvani, Hossein Nikbakht, Ahmadreza Rafiee, Mostaffa Torkashvand, Noorollah Eshraghi, Nahalossadat Nourian, Mehran Moradi

Department of Neurosurgery, Al-Zahra Hospital, Isfahan University Of Medical Science, Isfahan, Iran

## Abstract

**Background:** Despite different treatments, cerebral vasospasm is still the most important cause of death in patients after subarachnoid hemorrhage. This study was conducted to explore the effect of intracisternal washing with papaverine on cerebral blood flow.

**Materials and Methods:** This study was performed on 40 patients and totally 120 arteries in 2010. Then, variations in cerebral blood flow before and after washing with papaverine were measured and analyzed.

**Results:** Twenty (20) patients with aneurysm of the anterior communicating artery (ACOM) and 20 patients with aneurysm of the middle cerebral artery (MCA) were assessed. Mean blood flow before aneurysm and before washing in ACOM and MCA was  $70.68 \pm 14.8$  cm/s and  $65.66 \pm 9.3$  cm/s, respectively, which reached  $23.25 \pm 5.17$  cm/s and  $34.1 \pm 4.7$  cm/s, respectively after washing ( $P$  value = 0.016 and 0.024). Mean blood flow after aneurysm and before washing in ACOM and MCA was  $95.12 \pm 13.9$  cm/s and  $67.44 \pm 15.16$  cm/s, respectively, which reached  $35.69 \pm 6.2$  cm/s and  $38.01 \pm 8.28$  cm/s, respectively after washing ( $P$  value = 0.001 and 0.01).

**Conclusion:** Washing with papaverine significantly reduces cerebral blood flow and relieves vasospasm.

**Key Words:** Intracisternal washing, papaverine, subarachnoid hemorrhage, vasospasm

### Address for correspondence:

Dr. Paiman Rahmani, Department of Neurosurgery, Al-Zahra Hospital, Isfahan University Of Medical Science, Isfahan, Iran.

E-mail: dr.prahmani@gmail.com

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## INTRODUCTION

The incidence of subarachnoid hemorrhage (SAH) is estimated to be 6 to 8 people in 100,000 people. One fourth of these patients die within the first 24 h. Mortality rate has been estimated 45% during the first

30 days.<sup>[1]</sup> Cerebral vasospasm and delayed cerebral ischemia are still among the major causes of mortality and morbidity in patients after SAH.<sup>[1-4]</sup> Angiographic vasospasm is detected in 30 to 70% of patients during the first 5 to 14 days after hemorrhage.<sup>[5,6]</sup> Among these patients, 50% with detected vasospasm in angiography suffer from delayed cerebral ischemia, of whom 15 to 20% suffer from stroke or die.<sup>[7,8]</sup> The pathogenesis of vasospasm involves endogenous spasmogens including oxyhemoglobin and endothelin. These are believed to inhibit nitric oxide (NO) synthetase and subsequently reduce the level of endogenous vasodilators, thereby producing vasospasm.<sup>[9,10]</sup> Prophylaxis with nimodipine, hypertension, hypervolemia, and hemodilution (triple-H) have been improved the outcome of the

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patients, however, they could not completely remove the effects of vasospasm.<sup>[11-13]</sup> The use of intravascular papaverine as an alternative treatment for reversible vasospasm is associated with various side effects including hemodynamic instability like bradycardia and hypotension. Some recent studies have pointed that washing aneurysmal arteries and subarachnoid space with papaverine may not have many complications and hemodynamic disorders besides preventing aneurysmal vasospasm.<sup>[4]</sup> Because of the lack of prospective studies, the present study was conducted with a suitable sample size to examine the effect of washing subarachnoid space on the amount of cerebral blood flow.

## MATERIALS AND METHODS

This study was a clinical trial carried out in Isfahan's Alzahra Hospital in 2010.

The inclusion criterion of the study was as follow:

The patients with cerebral aneurysm

The exclusion criteria of the study were as follows:

The patients whose cerebral aneurysm was not confirmed during the operation.

The patients who could not undergo the treatment due to anesthetic issues.

The patients who did not consent to participate in the study.

Sample size: 20 people were enrolled in the study according to compare mean between 2 groups.

Method of sampling: The participants were selected through simple random sampling.

At first, the method and objective of the study were explained to the patients, then, a written consent was taken from the patients in case of their agreement to participate in the study. During the operation and before aneurysmal arteries clamping, 40 mg of papaverine, which was mixed with 20 cc of saline at 35-37°C was infused to the aneurysmal arteries in subarachnoid space of the patients. Prior to washing with papaverine, blood flow velocity was measured by help of arterial ultrasound (DWL2000 Doppler Ultrasound machine) and a (2 mm, 16 MHz) probe was applied with measurement scale of cm/s. The blood flow velocity was also measured 20 min after washing with papaverine using the arterial ultrasound.

Before administration of drug and 20 min after that, blood pressure and pulse of the patients were assessed and the results were recorded.

The statistical paired-test and SPSS18 software were

used to compare the blood flow velocity before and after washing.

## RESULTS

Mean age ( $\pm$  SD) of the studied patients was  $48.02 \pm 9.56$  years. Among the patients, 14 (35%) people were men and the rest were women. In anterior communicating group (ACOM), 6 (30%) patients were men and in middle cerebral artery (MCA), 8 (40%) patients were men ( $P$  value = 0.5). Moreover, mean age of the patients in ACOM group and MCA group was  $45.50 \pm 2.62$  years and  $50.55 \pm 1.56$  years, respectively ( $P$  value = 0.1), thus, the two groups were identical in terms of age and sex.

In all cases, blood flow velocity was significantly reduced after washing with papaverine. The comparison of blood flow velocity before and after papaverine infusion is shown in Table 1 for two groups.

There was no significant difference in the reduction of blood flow velocity before and after washing with papaverine in two arteries of ACOM and MCA [Table 2].

**Table 1: Comparison of blood flow velocity before and after papaverine infusion**

	Artery before aneurysm and before washing	Artery before aneurysm and after washing	
ACOM	70.68 $\pm$ 14.8	23.25 $\pm$ 5.17	0.016
MCA	65.66 $\pm$ 9.3	34.1 $\pm$ 4.7	0.024
	The first artery after aneurysm and before washing	The first artery after aneurysm and after washing	
ACOM	95.12 $\pm$ 13.9	35.69 $\pm$ 6.2	0.001
MCA	67.44 $\pm$ 15.16	38.01 $\pm$ 8.28	0.01
	The first artery after aneurysm and before washing	The first artery after aneurysm and after washing	
ACOM	67.44 $\pm$ 15.16	49.82 $\pm$ 8.28	0.01
MCA	52.45 $\pm$ 7.28	45.52 $\pm$ 8.18	0.005

ACOM: Anterior communicating; MCA: Middle cerebral artery

**Table 2: Comparison of blood flow velocity reduction in the studied branches for the two arteries of ACOM and MCA**

	Before washing	After washing	
Artery before aneurysm	47.43 $\pm$ 17.84	31.56 $\pm$ 12.88	0.4
The first artery after aneurysm	59.43 $\pm$ 15.24	8.25 $\pm$ 4.81	0.4
The second artery after aneurysm	17.61 $\pm$ 10.93	6.91 $\pm$ 2.14	0.3

**Table 3: Comparison of the side effects arising from papaverine for the two groups**

	ACOM (%)	MCA (%)	
Bradycardia	1 (5)	2 (10)	0.5
Hypotension	2 (10)	3 (15)	0.1

ACOM: Anterior communicating; MCA: Middle cerebral artery

Among the 40 studied patients, 3 (7.5%) of them suffered from bradycardia and 5 (12.5%) of them suffered from hypotension after papaverine infusion. There was no significant difference between the side effects and the aneurysmal artery [Table 3].

## DISCUSSIONS

Cerebral vasospasm is defined as cerebrovascular angiographic attenuation, which can be symptomatic and asymptomatic.<sup>[1]</sup> There are different drugs to treat cerebral perfusion pressure which are administered orally or intra-arterially. While orally administered, these drugs often do not reach their therapeutic concentration or they need a longer time to act. By intracisternal administration of these drugs, less time is needed to reach the appropriate therapeutic concentration. Papaverine is an alkaloid, which causes vasodilatory induction of cerebral and cardiac vessels through direct effect on the cells of smooth muscles. Mechanism of papaverine effect is the inhibition of cyclic adenosine monophosphate and cyclic guanosine 3 and 5 monophosphate intra-arterially<sup>[3]</sup> which increase NO and consequently cause the vasodilatory induction.<sup>[1]</sup> The effect of intra-arterial application of this drug has been sufficiently evaluated, although fewer prospective and controlled trial studies with adequate sample size have been conducted on the effect of intracisternal use of this drug on the vascular tone. Furthermore, intra-arterial injection of papaverine requires neuroradiological intervention and may involve complications.<sup>[14]</sup>

In this study, papaverine was found to reduce the blood flow velocity significantly in the studied vessels. In a study by Segawa *et al.*, 15 patients with ruptured aneurysm were assessed during operation by washing vessels. Intraoperative serial angiography of 7 patients showed a dilatation in anterior and middle cerebral arteries 30 min after injection of initial dose which lasted 60 min. Neurological symptoms were recovered in 7 patients, however, 6 patients did not show any responses, and the 2 other patients encountered a hematoma.<sup>[15]</sup> A study published by Kosty (2005) mentioned the vasospasm problem during surgical operations of aneurysms in subarachnoid hemorrhage. The above study explained that despite many studies in this regard, still the actual cause of this phenomenon has not been identified. These researchers pointed to the old therapies for the problem (calcium blockers) and also considered new therapy of papaverine intravascular injection as an effective treatment. They hoped that papaverine intracisternal injection may be effective too, however, it requires further

research.<sup>[16]</sup> In this respect, the present study proved the effect of washing the intracisternal space with papaverine in vasodilatation of vessels with a suitable sample size and examining 120 arteries of 40 patients. Nevertheless, this study did not examine the patients post-operatively and the prevalence of vasospasm in patients and comparing them to the control group. Therefore, this study cannot suggest anything about prophylactic effect of this method for preventing vasospasm, which requires a further study with an adequate sample size and a control group.

The complications of intra-arterial injection of papaverine include mydriasis, confusion, convulsion, reversible depression of brainstem, increase in ICP, hypotension, bradycardia, and thrombocytopenia,<sup>[14]</sup> and the complications of intracisternal injection of papaverine include mydriasis, seventh nerve palsy, and malignant hyperthermia.<sup>[16]</sup>

In the study, 7.5% of the patients suffered from temporary bradycardia and 12.5% of them suffered from hypotension, of whom the latter's blood pressure reached a stable condition only by liquid therapy.

## CONCLUSION

It was found that washing intracisternal space with papaverine reduced blood flow velocity in the studied arteries significantly and did not cause serious complication to the patients.

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