





# Chemical Angioplasty with Nitroglycerin for Vasospasm after Subarachnoid Hemorrhage: Case Series and Review

## *Angioplastia química com nitroglicerina para vasoespasm após hemorragia subaracnóide: Série de casos e revisão*

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### Abstract

#### Keywords

- ▶ intracranial vasospasm
- ▶ balloon angioplasty
- ▶ nitroglycerin
- ▶ aneurysmal subarachnoid hemorrhage
- ▶ cerebral hemorrhage
- ▶ vasodilator agents

**Introduction** Vasospasm is a common and potentially devastating complication in patients with subarachnoid hemorrhage, causing high morbidity and mortality. There is no effective and consistent way to prevent or treat cerebral vasospasm capable of altering the morbidity and mortality of this complication. Animal and human studies have attempted to show improvement in aneurysmal vasospasm. Some sought their prevention; others, the treatment of already installed vasospasm. Some achieved only angiographic improvement without clinical correlation, others achieved both, but with ephemeral duration or at the expense of very harmful associated effects. Endovascular techniques allow immediate and aggressive treatment of cerebral vasospasm and include methods such as mechanical and chemical angioplasty. These methods have risks and benefits.

**Objectives** To analyze the results of chemical angioplasty using nitroglycerin (GTN). In addition, to perform a comprehensive review and analysis of aneurysmal vasospasm.

**Methods** We describe our series of 77 patients treated for 8 years with angioplasty for vasospasm, either mechanical (with balloon), chemical (with GTN) or both.

**Results** Eleven patients received only balloon; 37 received only GTN; 29 received both. Forty-four patients (70.1%) evolved with delayed cerebral ischemia and 19 died

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(mortality of 24.7%). Two deaths were causally related to the rupture of the vessel by the balloon. The only predictors of poor outcome were the need for external ventricular drainage in the first hours of admission, and isolated mechanical angioplasty.

**Conclusions** Balloon angioplasty has excellent results, but it is restricted to proximal vessels and is not without complications. Chemical angioplasty using nitroglycerin has reasonable but short-lived results and further research is needed about it. It is restricted to vasospasm angioplasties only in hospitals, like ours, where better and more potent vasodilator agents are not available.

## Resumo

**Introdução** O vasoespasmó é uma complicação comum e potencialmente devastadora em pacientes com hemorragia subaracnóidea, resultando em alta morbimortalidade. Não existe uma forma eficaz e consistente de prevenir ou tratar o vasoespasmó cerebral capaz de alterar significativamente a morbidade e mortalidade desta complicação. Estudos em animais e humanos tentaram mostrar melhora no vasoespasmó aneurismático. Alguns buscaram sua prevenção; outros, o tratamento de vasoespasmó já instalado. Alguns conseguiram apenas melhora angiográfica sem correlação clínica, outros conseguiram ambos, mas com duração efêmera ou às custas de efeitos colaterais muito deletérios. As técnicas endovasculares permitem o tratamento imediato e agressivo do vasoespasmó cerebral e incluem métodos como a angioplastia mecânica e química. Estes métodos apresentam riscos e benefícios.

**Objetivos** Analisar os resultados da angioplastia química utilizando nitroglicerina (GTN). Além disso, fazer uma revisão e análise global acerca do vasoespasmó aneurismático.

**Métodos** Descrevemos nossa série de 77 pacientes tratados por 8 anos com angioplastia para vasoespasmó, seja mecânica (com balão), química (com GTN), ou ambas.

**Resultados** Onze pacientes receberam apenas balão; 37 receberam apenas GTN; 29 receberam ambos. Um total de 44 pacientes (70,1%) evoluíram com isquemia cerebral tardia e 19 faleceram (mortalidade de 24,7%). Dois óbitos foram diretamente relacionados à ruptura do vaso pelo balão. Os únicos fatores preditores de mau resultado foram a necessidade de drenagem ventricular externa nas primeiras horas de admissão e a angioplastia mecânica isolada.

**Conclusões** A angioplastia com balão tem excelentes resultados, mas é restrita a vasos proximais e não é isenta de complicações. A GTN possui resultados razoáveis, porém efêmeros, e mais pesquisas são necessárias. Fica restrita para as angioplastias por vasoespasmó apenas a hospitais, como o nosso, nos quais não há disponibilidade de agentes vasodilatadores melhores e mais potentes.

## Palavras-chave

- vasoespasmó intracraniano
- angioplastia com balão
- nitroglicerina
- hemorragia subaracnóidea aneurismática
- hemorragia cerebral
- agentes vasodilatadores

## Introduction

Cerebral vasospasm after aneurysmal subarachnoid hemorrhage (aSAH) is one of the most complex topics in medicine. It usually occurs between 4 and 21 days after subarachnoid hemorrhage (SAH) and represents a major cause of morbidity and mortality.<sup>1-5</sup> Nowadays, there is no consistent way to prevent this complication. Several studies have attempted to improve outcomes in aneurysmal vasospasm, part focused on prevention and part concentrated on treatment of already installed vasospasm. While some achieved only angiographic improvement without clinical correlation, others achieved both, but either with ephemeral duration or at the expense of

very deleterious side effects. Endovascular techniques enable immediate and aggressive treatment for cerebral vasospasm and include methods such as percutaneous transluminal angioplasty (PTA) with balloon (mechanical PTA) and intra-arterial vasodilator infusion (chemical PTA). Both methods have risks and benefits, thus we present a series of patients with vasospasm treated by PTA.

## Material and Methods

During the period from February 2013 to August 2020, a total of 802 ruptured aneurysms were treated by endovascular

procedures or microsurgical clipping at a single institution. A total of 77 consecutive patients with a diagnosis of cerebral vasospasm underwent PTA using drugs or balloon. There were no exclusion criteria for the procedure or choices for the best candidate.

The treatment was performed under general anesthesia in all cases. Diagnostic angiography was performed through the femoral artery (preferably in the right one) using low-osmolar nonionic contrast agent (Omnipaque, Nycomed, Oslo, Norway). Anticoagulation during the procedure was not employed. Initial intravenous boluses of heparin of 5,000 IU were infused when starting angiography, followed by 1,000 IU at each hour of the procedure. A 6F guide catheter (Chaperon, Microvention, Inc., Tustin, CA, USA; or Neuron, Penumbra, Inc., Alameda, CA, USA) was placed in the internal carotid or vertebral artery. Continuous flushing through catheters was maintained by infusion of 5,000 IU heparin per 1-L sodium chloride solution. Patients with symptomatic proximal stenosis (intracranial internal carotid artery [ICA], M1 segment of the middle cerebral artery [MCA] and A1 segment of the anterior cerebral artery [ACA]) were treated with balloon, while those presenting with distal stenosis were treated with drugs. Chemical PTA was performed by infusing a saline solution with 10% glyceryl trinitrate (GTN) in an average volume of 10 mL (ranging from 5 to 20 mL). Mechanical PTAs were performed employing a remodeling balloon (HyperForm 4 × 20 or 4 × 30; Medtronic, Irvine, CA, USA) over a guidewire (SilverSpeed, Avigo or X-Pedion, Medtronic, Irvine, CA, USA). The balloons were inflated under direct visualization by radioscopy and road-mapping and were kept opened for 3 seconds. All patients underwent control angiogram immediately and computed tomography (CT) scan or magnetic resonance imaging (MRI) within 24 hours after the procedure. At the end of the catheterization, intravenous heparin administration was interrupted but not antagonized. All patients were transferred to the intensive care unit (ICU), and low molecular weight heparin was maintained in prophylactic doses, without reaching anticoagulation. The outcome was evaluated immediately and at a 3-month clinical follow-up. The last consultation was held between 1 and 71 months (an average follow-up of 19.7 months).

Although it is not possible to compare the two groups, one in which the endovascular intervention was performed preferentially in large skull base arteries (carotid siphon, A1 and M1) and the other was performed by vasospasm in smaller distal arteries, we performed a multivariate search analysis searching a predictor of poor prognosis. The objective is not to seek superiority of one group over the other, as the angiographic vasospasm profile is different.

## Statistical Analysis

Results of quantitative variables were described as mean, standard deviation (SD), median, minimum and maximum. Categorical variables were described by frequencies and percentages. The Fisher exact test or the chi-squared test was used to assess the association between two categorical variables. For the analysis of factors associated with poor

neurological outcome ( $mRS \geq 3$ ), logistic regression models were adjusted. The estimated association measure was the odds ratio (OR). Factors associated with survival time were analyzed by adjusting Cox Regression models. The estimated measure of association was the hazard ratio. In all adjusted models, the Wald test was used to assess the significance of the variables. For measures of association between factors and outcomes, 95% confidence intervals (Cis) were presented. P-values  $< 0.05$  indicated statistical significance. The data were analyzed using the computer program Stata/SE v.14.1 (StataCorp, College Station, TX, USA).

## Results

Angioplasty for vasospasm was performed in 77 patients, of which 63 were female (81.8%) and 14 were males (18.2%), with a mean age of  $52.7 \pm 11.2$  years old (20 to 75 years old). Hunt & Hess and Fisher mean scores were 2.8 and 3.5, respectively.

In this sample, the 77 patients had a total of 140 aneurysms; 33 patients had multiple brain aneurysms (42.9%), of which the MCA was the most common site, in 51 patients (36.42%). The most common topography of ruptured aneurysm was also the MCA in 23 cases (29.9%), followed by the anterior communicating artery (22 cases; 28.57%) and posterior communicating artery (17 patients or 22%). Ruptured aneurysms from other locations occurred in 15 patients (19.48%). Patient characteristics are summarized in ► **Table 1**.

Forty-five patients had a history of smoking (58.4%) and 32 never smoked (41.6%). The average smoking burden known among 28 smokers was  $30.1 \pm 16.4$  pack-years. Twenty patients (26%) needed to undergo external ventricular drainage (EVD) in the first hours of hospital admission; 38 underwent microsurgical clipping of ruptured aneurysm and 39 underwent endovascular treatment (49.4 versus 50.6%, respectively), and this definitive treatment was performed in an average time of 4.64 days since the ictus (ranging from 0 to 60<sup>th</sup> ictus day).

Early treatment of the aneurysm, considered until the 3<sup>rd</sup> day of the ictus, was performed in 45 patients (58.4%). The remaining 32 patients (41.6%) had their ruptured aneurysm closed from the fourth day onwards.

The 77 patients underwent a total of 94 sessions of endovascular treatment with 117 angioplasties. One session corresponds to each time the patient was transported from the ICU to hemodynamics, with a femoral puncture and under the same general anesthesia. PTA is understood in each intervention, either with balloon or with GTN, both of which can be performed in the same session. These sessions were carried out on an average of 9.32 days, varying from the 1<sup>st</sup> to the 60<sup>th</sup> day of the ictus.

Sixty-six patients received GTN, in a total of 74 PTAs with GTN (either alone or with a balloon). Thirty-nine patients received balloon, in a total of 43 balloon PTAs (either alone or with GTN). Eleven patients received only balloon; 37 patients received only GTN; 29 patients received both GTN and balloon. There were 74 GTN chemical PTAs and 43 balloon PTAs (63.3 versus 36.7%).

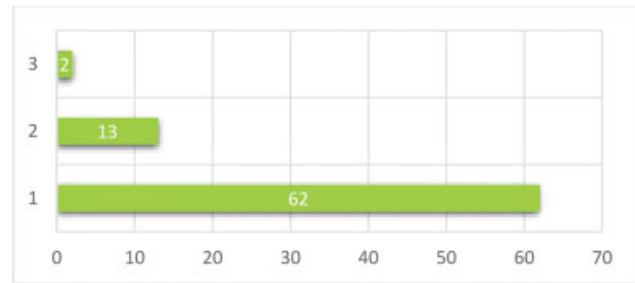
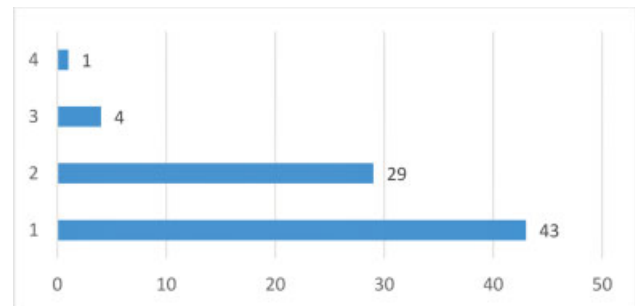
**Table 1** Epidemiological characteristics of patients

Age (years old) (mean)	52.7 ± 11.2 (20–75)	
Gender	Female	63 (81.8%)
	Male	14 (18.2%)
Year of ictus	2013	1
	2014	2
	2015	5
	2016	10
	2017	17
	2018	12
	2019	15
	2020	15
Hunt Hess (n)	1	12 (15.6%)
	2	19 (24.7%)
	3	29 (37.7%)
	4	7 (9.1%)
	5	10 (13%)
Fisher (n)	I	1 (1.3%)
	II	7 (9.1%)
	III	21 (27.3%)
	IV	48 (62.3%)
Ruptured aneurysm	MCA	23 (29.9%)
	ACom	22 (28.6%)
	PCom	17 (22.1%)
	Others	15 (19.5%)
Multiple aneurysms	Yes	33 (42.9%)
	No	44 (57.1%)
EVD	Yes	20 (26%)
	No	57 (74%)
Definitive treatment modality	Endovascular	39 (50.6%)
	Clipping	38 (49.4%)

Abbreviations: ACom, anterior communicating artery; EVD, external ventricular drainage; MCA, middle cerebral artery; PCom, posterior communicating artery.

Each patient underwent an average of 1.22 sessions: 62 patients underwent only 1 session, 13 patients underwent 2 sessions, and 2 patients underwent 3 sessions. Each patient underwent an average of 1.52 PTAs: 43 with only one PTA, 29 with 2 PTAs, 4 with 3 PTAs, and 1 patient underwent 4 PTAs. Sessions and angioplasties are summarized in ►Figures 1 and 2.

Regarding the clinical/neurological response after each session, 39 patients showed no improvement after the 1<sup>st</sup> session, 7 improved only temporarily, 17 improved partially, and 14 improved completely. After the 2<sup>nd</sup> session, 10 patients showed no improvement, 4 partially improved, and only 2 progressed with total improvement. The only 2 patients who underwent a 3<sup>rd</sup> session both improved partially. ►Figure 3 shows the clinical response.

**Fig. 1** Number of patients submitted to 1 / 2 / 3 sessions of endovascular treatment for vasospasm – Total of 92 sessions.**Fig. 2** Number of angioplasties (PTAs) for vasospasm – Total of 114 PTAs.

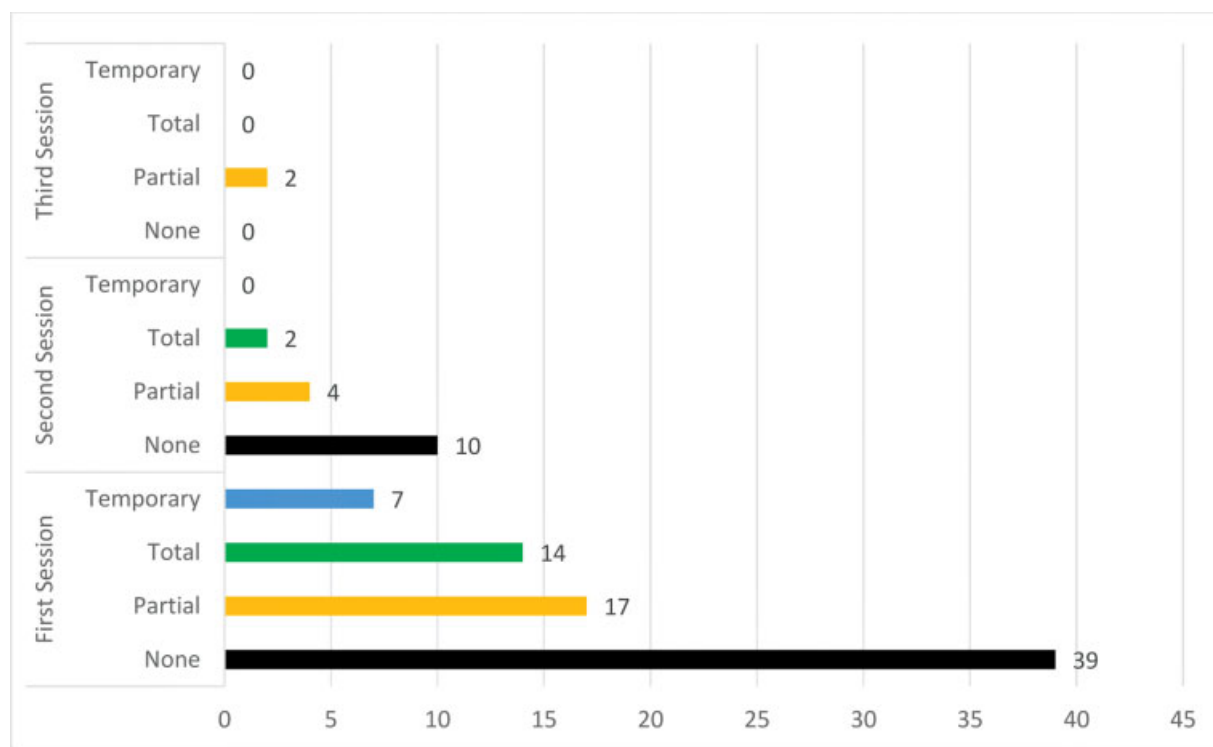
Fifty-four patients evolved with delayed cerebral ischemia (70.1%). The overall mortality was 24.7% (19 patients), with 2 cases directly related to PTA complication: on insufflation-ruptured left MCA (►Fig. 2). All 19 patients died on average 18.5 ± 17.6 days after the ictus, ranging from 5 to 82 days. The Glasgow Coma Scale (GCS) mean score on hospital discharge among the 58 survivors was 12.8 ± 2.4, ranging from 5 to 15. An average follow-up of 19.7 months (ranging from 1 to 71 months) found an average GCS of 13.4 ± 2.4 and an mRS average score of 2.08. ►Figure 4 shows late mRS.

The multivariate analysis showed no statistical difference as a predictor of poor prognosis, whether death or mRS ≥ 3, among most data. Only needing EVD in the first hours of hospitalization and not showing any clinical improvement after the first endovascular session were predictive of poor long-term neurological status. Need for EVD was also a predictor of death, as well as having received only balloon PTA (►Tables 2 and 3).

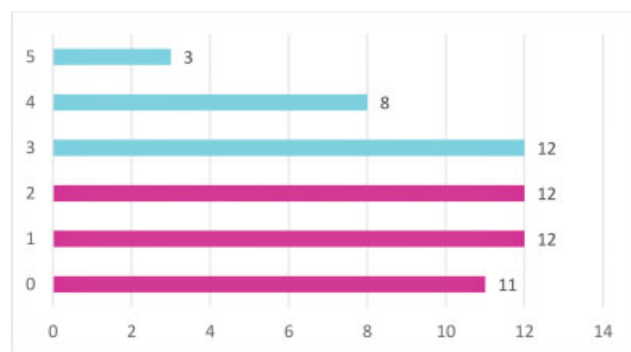
## Discussion

### 1. EPIDEMIOLOGY

Aneurysmal SAH occurs in ~ 15/100,000 individuals each year.<sup>3</sup> At angiography, about 70% of patients have arterial narrowing and ~ 30 to 40% of them will manifest neurological deficit that is symptomatic vasospasm.<sup>2</sup>



**Fig. 3** Clinical / neurological response to each session of endovascular treatment for vasospasm.



**Fig. 4** Late Modified Rankin Scale (mRS) (19.7 months, ranging from 1 to 71).

## 2. PATHOPHYSIOLOGY

Understanding the pathophysiology of vasospasm is extremely complex. A cascade of events leads to the development of vasospasm due to the thickening of all its layers.

The pathogenesis of aSAH vasospasm involves the release of endogenous spasmogens secondary to the presence of blood in the subarachnoid space of the skull base, and the action of the products of its degradation.<sup>1,6</sup> Adherence of clots also occurs in adventitia, leading to infiltration of inflammatory cells and perivascular nerve degeneration and thickening of the intima can occur due to edema, desquamation, and loss of intercellular junctions. The breakdown products of hemoglobin in the subarachnoid space trigger the contraction of the smooth muscle of the tunica media. Intimal proliferation may occur later due to the

formation of necrosis and collagen fibers, which may explain the definitive effect of balloon inflation on mechanical PTA, breaking down these collagen fibers.<sup>1,2</sup> With the increase in the intensity of vasospasm, the compensation mechanism is depleted and, in the absence of adequate collateral circulation (more often occurring in diffuse spasm), delayed cerebral ischemia will develop.<sup>6</sup>

Several theories try to describe the pathophysiology, none mutually exclusive.

- A) Immunological response (first cellular and then humoral through the passage of leukocytes through the breakdown of the blood-brain barrier). It has been observed in animal models and in humans with aSAH an increased presence in the cerebrospinal fluid of cytokines, eicosanoids, complement, immunoglobulins, CD4, CD8, T cells, and macrophages.
- B) Inflammatory response: it was also seen presence of adhesion molecules (selectins, ICAM-1, VCAM-1, integrins), endothelin-1, and acute phase reagents (interleukin 1 [IL-1], interleukin 6 [IL-6], TNF).
- C) Structural effects on the affected vessel wall: cell proliferation mediated by substances released by platelets in the subarachnoid space; p53-mediated endothelial apoptosis, leading to impairment of endothelium-dependent vasorelaxation.
- D) Blood degradation products: "spasmogenic" substances such as serotonin, prostaglandins, catecholamines, histamine, angiotensin, oxyhemoglobin, and free radicals are released through this degradation process. Free radical production has been associated with nitric oxide (NO) inactivation, which is a potent vasodilator,

**Table 2** Predictive factors for poor outcome (mRS  $\geq 3$ )

Quantitative Variables	mRS < 3	mRS $\geq 3$	p-value*	OR (IC95%)	
Age (years old)	50.3 $\pm$ 10.6 (20–75)	53.4 $\pm$ 11.3 (26–66)	0.301	1.03 (0.98–1.08)	
Definitive Treatment (Days)	5.4 $\pm$ 10.4 (0–60)	4.3 $\pm$ 2.8 (0–12)	0.634	0.98 (0.91–1.06)	
First Session of Endovascular Treatment (Days)	9.9 $\pm$ 9.0 (4–60)	8.5 $\pm$ 3.5 (2–15)	0.524	0.97 (0.87–1.07)	
Categorical Variables	Classification	n	mRS $\geq 3$ n (%)	p-value	OR (95%CI)
Gender	Female	50	18 (36)	0.453	1.78 (0.40–7.98)
	Male	8	4 (50)		
Hunt Hess	1	11	3 (27.3)		
	2	13	5 (38.5)		
	3	24	8 (33.3)		
	4	4	2 (50)		
	5	6	4 (66.7)		
Hunt Hess (grouped)	1 or 2	24	8 (33.3)	0.545	1.4 (0.47–4.16)
	3, 4 or 5	34	14 (41.2)		
Fisher	1	1	1 (100)		
	2	7	0 (0)		
	3	18	2 (11.1)		
	4	32	19 (59.4)		
Fisher (grouped)	1 or 2	8	1 (12.5)	0.143	5.07 (0.58–44.4)
	3 or 4	50	21 (42)		
Multiple Aneurysms	No	32	14 (43.8)	0.313	0.57 (0.19–1.69)
	Yes	26	8 (30.8)		
MCA	No	42	16 (38.1)	0.967	0.98 (0.30–3.20)
	Yes	16	6 (37.5)		
ACom	No	40	15 (37.5)	0.920	1.06 (0.34–3.33)
	Yes	18	7 (38.9)		
PCom	No	47	19 (40.4)	0.422	0.55 (0.13–2.35)
	Yes	11	3 (27.3)		
Other Aneurysms	No	45	16 (35.6)	0.490	1.55 (0.45–5.42)
	Yes	13	6 (46.2)		
Smoke	No	27	13 (48.2)	0.138	0.44 (0.15–1.30)
	Yes	31	9 (29)		
>20 pack-years	No	11	2 (18.2)	0.822	1.29 (0.14–11.5)
	Yes	9	2 (22.2)		
EVD	No	48	13 (27.1)	0.004	24.2 (2.79–210)
	Yes	10	9 (90)		
Treatment Modality	Endovascular	28	10 (35.7)	0.737	1.20 (0.41–3.48)
	Clipping	30	12 (40)		
Early definitive treatment ( $\leq 3$ days)	Yes	33	10 (30.3)	0.172	2.12 (0.72–6.25)
	No	25	12 (48)		
Number of Sessions	1	47	19 (40.4)		
	2	9	3 (33.3)		
	3	2	0 (0%)		

(Continued)



**Table 2** (Continued)

Quantitative Variables	mRS < 3	mRS ≥ 3	p-value*	OR (IC95%)	
Number of Sessions (grouped)	2 or 3	11	3 (27.3)	0.422	1.81 (0.42–7.71)
	1	47	19 (40.4)		
Timing of 1 <sup>st</sup> Session (days)	≤ 7	24	8 (33.3)	0.595	1.38 (0.42–4.60)
	8 to 11	22	9 (40.9)		
	≥ 12	12	5 (41.7)		
Number of PTAs	1	30	13 (43.3)	0.381	1.61 (0.55–4.72)
	2	25	9 (36)		
	3	2	0 (0)		
	4	1	0 (0)		
Number of PTAs (grouped)	2, 3 or 4	28	9 (32.1)	0.146	3.78 (0.63–22.6)
	1	30	13 (43.3)		
PTAs with GTN	0	6	4 (66.7)	0.195	2.13 (0.68–6.71)
	1	46	16 (34.8)		
	2	5	2 (40)		
	3	1	0 (0)		
PTAs with GTN (grouped)	1, 2 or 3	52	18 (34.6)	0.015	8 (1.5–42.6)
	0	6	4 (66.7)		
PTA with Balloon	0	29	11 (37.9)	0.469	2 (0.31–13.1)
	1	27	11 (40.7)		
	2	2	0 (0)		
PTA with Balloon (grouped)	0	29	11 (37.9)	0.015	8 (1.5–42.6)
	1 or 2	29	11 (37.9)		
PTA and Balloon	No	35	15 (42.9)	0.342	0.58 (0.19–1.77)
	Yes	23	7 (30.4)		
Endovascular Treatment of Vasospasm	GTN and Balloon	23	7 (30.4)	0.573	1.40 (0.44–4.47)
	GTN only	29	11 (37.9)		
	Balloon only	6	4 (66.7)		
Ischemia	No	22	6 (27.3)	0.195	2.13 (0.68–6.71)
	Yes	36	16 (44.4)		
Improvement after 1st Session	No	22	13 (59.1)	0.015	8 (1.5–42.6)
	Partial	16	4 (25)		
	Temporary	6	3 (50)		
	Total	14	2 (14.3)		
Improvement after 1st Session (grouped)	Total	14	2 (14.3)	0.015	8 (1.5–42.6)
	Partial	16	4 (25.0)		
	No or tempory	28	16 (57.1)		

Abbreviations: ACom, anterior communicating artery; CI, confidence interval; EVD, external ventricular drainage; GTN, glyceryl trinitrate; MCA, middle cerebral artery; OR, odds ratio; PCom, posterior communicating artery; PTA, percutaneous transluminal angioplasty.

\*Cox Regression Model and Wald test,  $p < 0.05$ .

and increased activity of lipid peroxidases. In turn, NO inactivation may result in increased activity of lipid protein kinase C, with subsequent release of intracellular calcium. Calcium has been shown to activate calmodulin, which in turn activates the myosin kinase light chain, leading to phosphorylation of the myosin

light chain that interacts and degrades the thin protein-associated filament to cause vascular smooth muscle contraction and luminal narrowing. Myosin light chain phosphorylation by calcium-dependent activation of the myosin kinase light chain is accepted as the key to vascular contraction.<sup>2–4</sup>

**Table 3** Predictive factors for death

Variable	Classification	n	Death n (%)	p-value*	OR (95%CI)
Gender	Female	63	13 (20.6)	0.073	2.42 (0.92–6.38)
	Male	14	6 (42.9)		
Hunt Hess	1	12	1 (8.3)		
	2	19	6 (31.6)		
	3	29	5 (17.2)		
	4	7	3 (42.9)		
	5	10	4 (40)		
Hunt Hess (grouped 1)	1 or 2	31	7 (22.6)	0.783	1.14 (0.45–2.90)
	3, 4 or 5	46	12 (26.1)		
Hunt Hess (grouped 2)	1, 2 or 3	60	12 (20.0)	0.096	2.21 (0.87–5.62)
	4 or 5	17	7 (41.2)		
Fisher	1	1	0 (0)		
	2	7	0 (0)		
	3	21	3 (14.3)		
	4	48	16 (33.3)		
Fisher (grouped)	1 ou 2	8	0 (0)		
	3 ou 4	69	19 (27.5)		
Multiple Aneurysms	No	44	12 (27.3)	0.526	0.74 (0.29–1.88)
	Yes	33	7 (21.2)		
MCA	No	54	12 (22.2)	0.512	1.37 (0.54–3.47)
	Yes	23	7 (30.4)		
ACom	No	55	15 (27.3)	0.415	0.63 (0.21–1.91)
	Yes	22	4 (18.2)		
PCom	No	60	13 (21.7)	0.239	1.79 (0.68–4.71)
	Yes	17	6 (35.3)		
Others Aneurysms	No	62	17 (27.4)	0.317	0.47 (0.11–2.05)
	Yes	15	2 (13.3)		
Smoke	No	32	5 (15.6)	0.129	2.21 (0.79–6.13)
	Yes	45	14 (31.1)		
>20 pack-years	No	12	1 (8.3)		
	Yes	16	7 (43.8)		
EVD	No	57	9 (15.8)	0.002	4.09 (1.65–10.1)
	Yes	20	10 (50)		
Treatment Modality	Endovascular	39	9 (23.1)	0.779	1.14 (0.46–2.8)
	Clipping	38	10 (26.3)		
Early definitive treatment ( $\leq 3$ days)	No	32	7 (21.9)	0.557	1.32 (0.52–3.36)
	Yes	45	12 (26.7)		
Number of Sessions	1	62	15 (24.2)		
	2	13	4 (30.8)		
	3	2	0 (0)		
Number of Sessions (grouped)	1 (ref)	62	15 (24.2)	0.881	1.09 (0.36–3.28)
	2 ou 3	15	4 (26.7)		

(Continued)



**Table 3** (Continued)

Variable	Classification	n	Death n (%)	p-value*	OR (95%CI)
Timing of 1 <sup>st</sup> Session (days)	≥ 12 (ref)	15	3 (20.0)		
	8 a 11	28	6 (21.4)	0.411	1.72 (0.47–6.25)
	≤ 7	34	10 (29.4)	0.880	1.11 (0.28–4.45)
Number of PTAs	1	43	13 (30.2)		
	2	29	4 (13.8)		
	3	4	2 (50)		
	4	1	0 (0)		
Number of PTAs (grouped)	1 (ref)	43	13 (30.2)	0.220	0.55 (0.21–1.44)
	2, 3 ou 4	34	6 (17.7)		
PTAs with GTN	0	11	5 (45.5)		
	1	59	13 (22)		
	2	6	1 (16.7)		
	3	1	0 (0)		
PTAs with GTN (grouped)	1, 2 or 3	66	14 (21.2)	0.045	2.85 (1.02–7.95)
	0	11	5 (45.5)		
PTAs with Balloon	0	37	8 (21.6)		
	1	37	10 (27)		
	2	3	1 (33.3)		
PTAs with Balloon (grouped)	0	37	8 (21.6)	0.466	1.40 (0.56–3.49)
	1 or 2	40	11 (27.5)		
Endovascular Treatment of Vasospasm	(3) GTN and Balloon	29	6 (20.7)		
	(1) GTN only	37	8 (21.6)	0.984	1.01 (0.35–2.91)
	(2) Balloon only	11	5 (45.5)	0.082	2.87 (0.87–9.43)
Ischemia	No	23	1 (4.4)		
	Yes	54	18 (33.3)		
Improvement after 1st Session	No	39	17 (43.6)		
	Partial	17	1 (5.9)		
	Temporary	7	1 (14.3)		
	Total	14	0 (0)		
Improvement after 1st Session (grouped)	No or tempory	46	18 (39.1)		
	Partial	17	1 (5.9)		
	Total	14	0 (0)		

Abbreviations: ACom, anterior communicating artery; CI, confidence interval; EVD, external ventricular drainage; GTN, glyceryl trinitrate; MCA, middle cerebral artery; OR, odds ratio; PCom, posterior communicating artery; PTA, percutaneous transluminal angioplasty.

\*Cox Regression Model and Wald test,  $p < 0.05$ .

E) Neurogenic factors: Contact of the blood from the subarachnoid space with the adventitial layer and the outer tunic of the cerebral vessels would cause a denervation of the parasympathetic and mainly sympathetic network there. This disruption of neuronal regulation mechanisms would cause vessel contraction induced by hypersensitivity of vasoconstrictor neurotransmitters, including calcitonin, substance P, and calcitonin gene related peptide (CGRP).<sup>2</sup>

In a study, Wistar albino rats received a single bolus intracisternal injection of GTN and papaverine and their vasospasm in the basilar artery was assessed by angioresonance.<sup>1</sup> The authors demonstrate an improvement in vasospasm with papaverine, but not with GTN.<sup>1</sup> They concluded that the pathogenesis of the vasospasm is more due to the action of the cGMPase enzyme rather than to the inhibition of NO synthetase by the spasmogens, and deduce that short-acting NO donors are not as effective in ameliorating vasospasm.<sup>1</sup>

Cyclic nucleotides have been thought of as second messengers in various tissues, including platelets and vascular smooth muscle cells.<sup>7</sup> Particular attention has been paid to the intracellular levels of cAMP and cGMP because both are among the important intracellular messengers that can cause relaxation in vascular smooth muscle cells by different pathways.<sup>7</sup>  $\beta$ -adrenergic stimulators and prostacyclin, for example, relax vascular smooth muscle cells by elevating cAMP.<sup>7</sup> Nitrovasodilators, the EDRF, and atriopeptins also relax the vasculature through cGMP-dependent mechanisms.<sup>7</sup> Several investigators reported that in cerebral vasospasm after SAH, cGMP levels were decreased and cAMP levels actually increased.<sup>7</sup>

Another primate study looked at the relation between vasospasm, cGMP and GTN. After laboratory-induced SAH, angiographic vasospasm was found in the basilar and middle cerebral arteries, and a drastic reduction in cGMP level as well as local cerebral blood flow (CBF). With the administration of GTN for 3 hours, the level of cGMP increased, but did not match basal, and vessel diameter increased. There were no significant changes in cAMP levels in SAH and after GTN treatment. The authors concluded that the vasodilatory effect of GTN might not be mediated by an increase in cGMP levels, suggesting an involvement of hyperpolarization of smooth muscle cells. Given the increase in regional CBF, GTN may be therapeutic for the treatment of vasospasm.<sup>7</sup>

A clinical study compared transdermal GTN (9 patients) with placebo in aSAH patients.<sup>7</sup> The medicated group had better results in transcranial Doppler velocities (Lindegard ratio) and CT perfusion (regional CBF, but not parietal cortical CBF), even though their mean blood pressure was significantly lower. Thus, GTN influences the cerebral vascular tone and once again proved effective against vasospasm.<sup>5</sup>

### 3. DIAGNOSIS

Clinical vasospasm can manifest different presentations: consciousness impairment, new focal neurological deficit (aphasia and hemiparesis), headache, and seizures.<sup>8</sup> Angiographic vasospasm can be classified as mild, moderate, or severe, according to vessel stenosis (0–33%, 34–66%, and >67% decrease in arterial diameter, respectively).<sup>8</sup> The clinical presentation of delayed cerebral ischemia (DCI) secondary to aneurysmal subarachnoid hemorrhage is heterogeneous in terms of timing of presentation, clinical manifestations, location of spasms in the vasculature, severity of vessel stenosis, and response to treatment. Severe vasospasm is associated with severe ischemia and infarction, but hypoperfusion is also reported in areas without macrovascular vasospasm on perfusion studies.<sup>8</sup> Focal neurological deficit is a more reliable sign of segmental vasospasm, especially if there is a correlation with a greater amount of blood on CT in the corresponding vascular territory.<sup>6</sup> In general, there is an increase in headache and signs of meningeal irritation, fever, arterial hypertension, and tachycardia preceding clinical vasospasm, while drowsiness, numbness, and confusion are unspecific signs.<sup>6</sup>

Daily monitoring with transcranial Doppler (TCD) during the peak period of vasospasm is very useful in assessing the

evolution of blood velocity in the MCA, the most important and assessable vessel in vasospasm. That accuses vasospasm as the cause of clinical manifestations, when their installation coincides with a progressive speed increasing.<sup>6</sup> The normal speed of blood in the MCA is <60 cm/second, and a speed >120 cm/sec indicates vasospasm, while >200 cm/sec is commonly associated with symptomatic vasospasm and cerebral ischemia.<sup>6</sup> In addition, increase in the Lindegard index (MCA/ICA) is useful to diagnose vasospasm. As other factors can increase the flow in the MCA, an initial TCD is important to have a parameter for each patient, as well as to enable evaluating the speed. An increase in flow may precede symptomatic vasospasm, and rapid increase in flow of >50 cm/sec/day is highly suggestive of an imminent installation of clinical vasospasm, permitting early treatment.<sup>6</sup>

Unfortunately, we do not have a transcranial DTC in our hospital, which is one of our greatest difficulties in the management of these patients.<sup>6</sup>

### 4. Treatment

Although various treatment modalities are available, none are really curative.<sup>1,2,9</sup> The cornerstone of the medical treatment of cerebral vasospasm was, for many years, the hemodynamic increase through the “triple H therapy”, a combination of hypervolemia, hemodilution, and induced hypertension to decrease blood viscosity and increase CBF and cerebral perfusion pressure.<sup>2</sup> However, patients randomized to hypervolemia showed greater bleeding, congestive heart failure, and infections.<sup>10</sup> Hypervolemia was also associated with a higher cost.<sup>10</sup> Therefore, the current literature suggests that hypervolemia does not improve the outcome and is associated with increased cardiopulmonary complications.<sup>2</sup> Hemodilution has also fallen out of favor as a treatment strategy for vasospasm; however, there is controversy regarding the “ideal” hemoglobin in patients with aSAH.<sup>2</sup> Although hemodilution increases CBF through better rheology, it also reduces the oxygen transport content and does not result in a net increase in cerebral oxygen supply.<sup>2</sup> A recent study showed that hypertension is still desired in these cases, since hypotension was associated independently with poor functional outcomes at the last clinical follow-up. Besides that, blood pressure variability, which incorporates the dynamic changes in blood pressure over time, has recently gained recognition as a prognostic marker of mortality in these patients.<sup>11</sup>

Most of the experimental settings have demonstrated varying levels of ability to predict accurately what occurs in human aSAH. Therefore, although animal models have been developed to test new therapies, most of the treatment effects have been shown to be less compelling when trials have been conducted in clinical settings.<sup>9</sup>

A meta-analysis with 453 studies showed that outcome from aSAH has improved in recently, partly due to improved treatments and partly due to a better understanding of the mechanisms of vasospasm.<sup>9,12</sup> Mortality declined 0.4% per year, after adjustment for age, between 1973 and 2002.<sup>12,13</sup>

The most widely used and best evidenced chemical PTA drug is nimodipine. However, its injectable form is not

licensed by the National Health Surveillance Agency in Brazil. Other alternative options include milrinone, verapamil, and nicardipine, but they are not available in the Brazilian public health system, being reserved for private patients only. Currently, the use of papaverine is discouraged due to possible neurotoxicity and risk of intracranial hypertension.<sup>14</sup> That is why GTN was left, which would not be the best option for the treatment of vasospasm, but unfortunately it is the only one available in our reality.

Systemic administration of GTN has failed to be established in some clinical settings as preventing vasospasm because of its adverse effects, particularly hypotension.<sup>3</sup> The pathophysiological mechanisms are mainly the dysfunction of the NO-producing enzyme nitric oxide synthase (NOS) and scavenging of NO due to the presence of deoxy-hemoglobin and its high affinity for NO.<sup>3,15</sup> One drawback with NONOates is that they have been shown to open the blood-brain barrier at higher doses and thus provoke brain infarction and toxicity.<sup>3,16</sup> Intrathecal sodium nitroprusside, a different class of NO donor, is the only NO donor that has been tested intrathecally in clinical studies after SAH, and has also been proven to dilate constricted vessels.<sup>3</sup>

To try to avoid lowering mean blood pressure, another clinical study performed continuous intravenous dopamine infusion concomitantly with GTN. There was an increase in intracranial pressure early on, but minimal and transient. There was no change in cerebral arteriovenous oxygen difference during GTN infusion, although cerebral perfusion pressure decreased between 75 and 94% of the control value after GTN administration. Therefore, this double infusion showed beneficial effects on the CBF of patients with aSAH.<sup>16</sup>

A similar study of intrathecal GTN infusion, but this time continuously and in rabbits, also showed that vasospasm was prevented with no toxic effects (it did not even affect arterial blood pressure).<sup>3</sup> Similar results were obtained in the group receiving nimodipine (calcium channel antagonist), and both were significantly more effective at preventing basilar artery angiographic constriction compared with the control with NACl.<sup>17</sup> The clinical status and the arterial blood pressure at day 5 did not indicate a drop in blood pressure compared with day 0. Since the vasodilatory effect is present after 5 days of continuous infusion, the authors conclude that there is no drug tolerance in this short period of treatment.<sup>3</sup>

## Nitroglycerin for Vasospasm Trend Topics:

- GTN increases CBF, lowers average blood pressure, dilates spastic cerebral arteries, and reduces the clinical occurrence of delayed ischemic neurological deficits.<sup>5</sup>
- The usual clinical dose may cause the theft phenomenon, dilating the intact arteries.<sup>18</sup>
- At a low dose, it significantly improved vasospasm without significant changes in systemic circulation.<sup>18</sup>
- High doses increase vessel size above low dose. However, infusing GTN for a longer time may increase this effect and counteracting systemic hypotension produced using an agent such as dopamine.<sup>19</sup>

- Systemic administration may induce the development of drug tolerance as well as the phenomenon of hypertensive rebound after discontinuation.<sup>4</sup>
- The main disadvantages of intrathecal use: its action time (residual effect up to 5 days), which, if used at higher doses, opens the blood-brain barrier causing toxicity and cerebral infarction.<sup>20</sup>

## Conclusions

Balloon angioplasty has good results when performed early; however, this technique is restricted to proximal vessels. Considering the ephemeral effect of nitroglycerin, more efficient drugs need to be developed to treat distal vasospasm, and mainly to prevent its development.

Despite excellent and promising results from the use of this drug in animal models of aSAH, whether intravenous or intrathecal, single bolus or continuous infusion, either to prevent or treat, such results were never faithfully reproduced in human studies. The exact timing of onset, duration, and reduction of GTN administration regarding the appearance of vasospasm may have a strong impact on the success of such a therapy. Some clinical trials with this nitric oxide donor have yielded good or reasonable results. While we recognize the limitation of our article, our extensive experience may contribute to future research, as well as to the study of other doctors who, like us, do not have other better chemical agents to perform drug angioplasty.

## Conflict of Interests

The authors have no conflict of interests to declare.

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