

Refractory Vasospasm and Arterial Ischemic Stroke in Meningoencephalitis: Novel Intrathecal Nitroprusside Treatment

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Received: 25 Oct 2021

Accepted: 17 Nov 2021

Published: 22 Nov 2021

J Short Name: ACMCR

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Citation:

Maria Jose Gonzalez, Refractory Vasospasm and Arterial Ischemic Stroke in Meningoencephalitis: Novel Intrathecal Nitroprusside Treatment. *Ann Clin Med Case Rep.* 2021; V7(16): 1-4

Keywords:

Vasospasm; Meningoencephalitis; Stroke; Intrathecal; Nitroprusside

Abbreviations:

AIS: Acute Ischemic Stroke; BME: Bacterial Meningo Encephalitis; CAV: Cerebral Arterial Vasospasm; CSF: Cerebral Spinal Fluid; EVD: Extra-Ventricular Drain; GCS: Glasgow Coma Scale; IA: Intra-Arterial; IT: Intra-Thecal; IV: Intravenous; MCA: Middle Cerebral Artery; MRA: Magnetic Resonance Angiography; MRI: Magnetic Resonance Imaging; SAH: Sub-Arachnoid Hemorrhage; TCD: Transcranial Doppler

1. Abstract

1.1. Background

Acute stroke in bacterial meningitis in children contributes to high morbidity and mortality. The incidence of stroke in pediatric meningitis is varied, with reports between 8-42%, and associated mortality as high as 25%. The majority of these are arterial ischemic strokes (80-93%). Cerebral arterial vasospasm has been proposed. We present the first case of intrathecal nitroprusside used to treat refractory vasospasm in a child with bacterial meningoencephalitis complicated by acute ischemic stroke.

1.2. Case Presentation

A 7-year-old, vaccinated male with a past medical history of autism spectrum disorder and developmental delay was admitted to PICU with GCS of 3T, and CSF findings of streptococcal meningitis. Severe transcranial doppler and MRI revealed vasospasm

in bilateral middle cerebral artery (MCA) and basilar artery, despite aggressive hemodynamic intervention, IV nimodipine, IV milrinone infusion. The patient was started on novel intra-thecal (IT) nitroprusside. After 4 doses, the patient's TCD markedly improved. A trial of discontinuing IT nitroprusside was attempted, however, was aborted due to neurological status deterioration and it was restarted. After 10 doses of IT nitroprusside, TCD values normalized and clinical improvement was observed, and the patient was eventually discharged.

1.3. Conclusion

This case highlights the use of IT vasodilator therapy in bacterial meningoencephalitis for refractory vasospasm with case-reproducibility and good outcome emphasizes the need for further studies and consensus guidelines on monitoring for vasospasm to prevent stroke in meningitis.

1.4. Background

The incidence of stroke in bacterial meningitis (BME) is 27-42%, with 80-93% being arterial ischemic stroke (AIS) and a 25% mortality rate in children [1-3]. Cerebral arterial vasospasm (CAV) is a proposed etiology for BME-associated AIS (BME-AIS), however, preventing BME-AIS has proven difficult with first line therapies [1-6].

Transcranial doppler (TCD), established in sub-arachnoid hemorrhage (SAH) for detecting AIS, has emerging evidence for utility in BME [1-3]. In a study involving 94 adults with BME, TCD detected BME-associated CAV (BME-CAV) in 41 patients, which was associated with AIS and mortality [4 -9]. Additionally, in a study involving 20 children with BME, TCD aided differentiation of hyperemia, hypoperfusion, and vasospasm [10].

Initial evidence of AIS prevention in BME-CAV suggests effective therapy may require a prolonged duration of action through permanent, repeated, or sustained contact of therapeutic agents and the arterial vessels involved. Although enteral and IV nimodipine have proven beneficial in patients with SAH, these were of no benefit in the aforementioned trial involving 94 adults [11, 12]. Furthermore, small case series using intra-arterial (IA) percutaneous transluminal angioplasty and IA nicardipine and verapamil to treat BME-CAV demonstrate promising results [13 - 15].

In search of a less invasive treatment with a more sustained effect, we present the first case of BME-CAV treated with intrathecal (IT) nitroprusside.

2. Case Report

A 7-year-old male with autism and developmental delay presented secondary to acute onset neurologic deficit with an admission Glasgow coma score (GCS) of 3T and cerebral spinal fluid suggesting streptococcal meningitis.

TCD on hospital day 2 showed vasospasm of the right middle ce-

rebral artery (R-MCA) (Table 1). MRI revealed small, multifocal lenticulostriate AIS, ventriculitis and moderate hydrocephalus with unremarkable initial MR angiography (MRA). Despite external ventricular drain (EVD) insertion and systemic antibiotics, he continued to have only trace pain response, and status epilepticus developed on day 3.

Beginning day 6, serial TCDs and MRAs revealed bilateral MCA and basilar artery vasospasm refractory to enteral nimodipine and IV milrinone. Four-vessel angiogram on day 9 confirmed severe widespread vasospasm and IA verapamil yielded no improvement.

Due to widespread severe vasospasm, evidence of AIS, and continued deterioration despite all prior treatments, IT nitroprusside 4 mg every 12 hours via EVD was started on day 10. Nitroprusside was selected due to evidence of benefit in the adult literature for treatment of CAV secondary to SAH and the availability of a preservative-free formulation. TCD findings improved markedly following the first dose with sustained suppression of vasospasm and clinical improvement over 4 doses through day 12. A discontinuation trial was conducted and aborted within 36 hours due to deterioration in neurologic status and worsening vasospasm by TCD and MRA (herein defined as case-reproducibility). Clinical status and vasospasm improved within 24 hours of reinitiating therapy. Ten total doses were given with side effects consisting of self-resolving hypertensive episodes and emesis.

Thereafter TCD values remained within normal limits and IT nitroprusside was discontinued on day 17. By day 21 the patient was extubated, milrinone infusion weaned off, and the EVD removed. At that time, he had improved encephalopathy (GCS 11) and brisk localization to stimulation. On day 23 he transferred out of the ICU followed by 4 weeks of inpatient rehabilitation. During a follow-up appointment four months after presentation, he was speaking in short phrases and walking unassisted (GCS 15) with no apparent extension of his original AISs clinically or by imaging.

Table 1: Serial Transcranial Doppler Results.

Day of hospitalization	R-MCA Velocity (cm/s)	L-MCA Velocity (cm/s)	Lindegaard ratio Right/Left	Basilar a. Velocity (cm/s)	MRA	Anti-spasmodic therapy	Exam
2	198	167	4.2/2.4		No stenosis	None	coma
6	286	165	7.9/3.3	156		-Nimodipine 1 mg/kg q6	
7	162	196	5/4.6	148	narrow caliber of the R+L MCAs	-Milrinone 0.5 mcg/kg/min -Nimodipine 1 mg/kg q6	coma
8	185	186	4.5/5.2	77		-Milrinone 0.75 mcg/kg/min	coma
9	218	168	5.7/3.7	x	narrow caliber MCAs	-IA Verapamil -Milrinone gtt 0.75 mcg/kg/min	coma
10	31	229	0.57/3.4	x	narrow caliber bilateral MCAs,	- IT Nitroprusside 4 mg x1 -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	coma

11	183	134	3.5/2	100		- IT Nitroprusside 4 mg x2 -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	coma
12	62	125	1.6/2.8	100		- IT Nitroprusside 4 mg x1 -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	Open eyes
13	154	190	3.3/3.3	107		- <i>IT Nitroprusside held</i> -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	Coma
14	200	175	4.4/4.7	89	interval increased narrowing	- IT Nitroprusside 4 mg x1 -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	Coma
15	103	138	2.5/2.8	x		- IT Nitroprusside 4 mg x2 -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	Open eyes
16	211	69	4.1/2.1	144		- IT Nitroprusside 4 mg x2 -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	Open eyes
17	213	153	3.9/2.6	x		- IT Nitroprusside 4 mg x1 -Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	Brisk localizing
20	113	140	1.66/2.86	65		-Milrinone 1 mcg/kg/min -Nimodipine 1 mg/kg q6	Brisk localizing
21	98	124	2.3/2.9	54		-Nimodipine 1 mg/kg q6	Brisk localizing

Lindegaard ratios were interpreted as indicating vasospasm if equal to or greater than 3.

a= artery; Day = day in reference to admission to intensive care unit; IT= intrathecal; L-MCA left middle cerebral artery; MRA=magnetic resonance angiography; R-MCA right middle cerebral artery; x= not visualized or not reported.

(IT nitroprusside was prepared as follows: 1 mL of nitroprusside 25 mg/mL in 11.5 mL of preservative-free 0.9% NaCl to make a final concentration of 2 mg/mL).

3. Discussion

To our knowledge, this is the first report of IT vasodilator for treatment of BME-CAV. The authors were initially concerned the lack of improvement with IV and IA vasodilators indicated a fixed anatomical narrowing of vessels from arteritis versus true vasospasm. Despite this, the risk-benefit ratio favored treatment as the imaging was more consistent with vasospasm (smooth regular narrowing of arterial walls). Confirming this hypothesis, arterial velocities and clinical exam improved quickly after IT nitroprusside initiation, worsened after treatment discontinuation, and again quickly improved with re-initiation.

Ultimately, the etiology of AIS in BME is unknown. Causative factors include anatomical obstructions from thrombi, vasculitis, and vasospasm that cause increased blood flow velocities but have different appearance on imaging [1-4].

The pathophysiology of BME-CAV is poorly understood and may be caused by decreased nitric oxide secondary to bacterial consumption [5, 6]. The authors hypothesize nitroprusside, a nitric oxide donor, was effective for this child's refractory vasospasm due to increased contact time between the drug and major cerebral arteries secondary to the IT route of administration.

Treatment duration of action is important in vasospasm from any

cause as IA-based interventions often require serial administration to maintain effectiveness and carry known complications of stroke, hemorrhage, permanent morbidity, and mortality. In comparison, IT vasodilators are not known to cause stroke, hemorrhage, permanent disability, or mortality, and may have equivalent or longer duration of action in BME, suggested to be between 24 to 48 hours by this case.

Although IT nitroprusside is established for vasospasm secondary to SAH in adults, the timing of therapy initiation, dose, and delivery modality (continuous vs intermittent) is variable [7-9]. We began IT nitroprusside after failure of maximal therapy with enteral nimodipine, IV milrinone infusion, and IA verapamil. As this was a novel approach in meningitis, a conservative dose frequency of every 12 hours was used. This compares to published SAH protocols in which frequencies of every 5 minutes or continuous IT infusions are reported.⁷⁻⁹ Further studies are needed to establish safety, efficacy, and optimal regimen.

TCD in this patient was a valuable, non-invasive tool for monitoring vasospasm and guiding therapy. TCD in BME has shown utility in predicting poor outcomes which may be related to vasospasm amenable to intervention.¹⁰⁻¹¹ More studies on the utility of TCD in pediatric BME are needed, which may prevent morbidity and mortality in children.

4. Conclusion

This sentinel case report of IT antispasmodic therapy in BME for refractory vasospasm with case-reproducibility and good outcome highlights the need for further studies. Escalation of anti-spasmodic therapy in BME to IT nitroprusside may be considered in those with refractory vasospasm or with contraindications, or lack of access, to IA treatment when indicated.

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