

PRACTICAL PEARL

# Reversible Cerebral Vasoconstriction Syndrome Responsive to Intravenous Milrinone



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## Introduction

Reversible cerebral vasoconstriction syndrome (RCVS) causes reversible multifocal constriction of cerebral arteries. It is triggered by several conditions, including vasoactive medications, postpartum, migraine, hypertension, and arterial dissection [1]. Suspension of the precipitating agent, supportive care, and oral calcium channel blockers are the mainstay of treatment for most patients [2]. However, the development of refractory vasospasm, ischemic stroke, or intracerebral hemorrhage (ICH) may require further interventions, including intravenous (IV) or intra-arterial vasodilators and balloon angioplasty [2]. Yet, evidence for all these treatment options is weak and is based on case reports, case series, and expert's opinion. We report a case of severe postpartum RVCS complicated by ICH successfully treated with IV milrinone infusion.

## Case Report

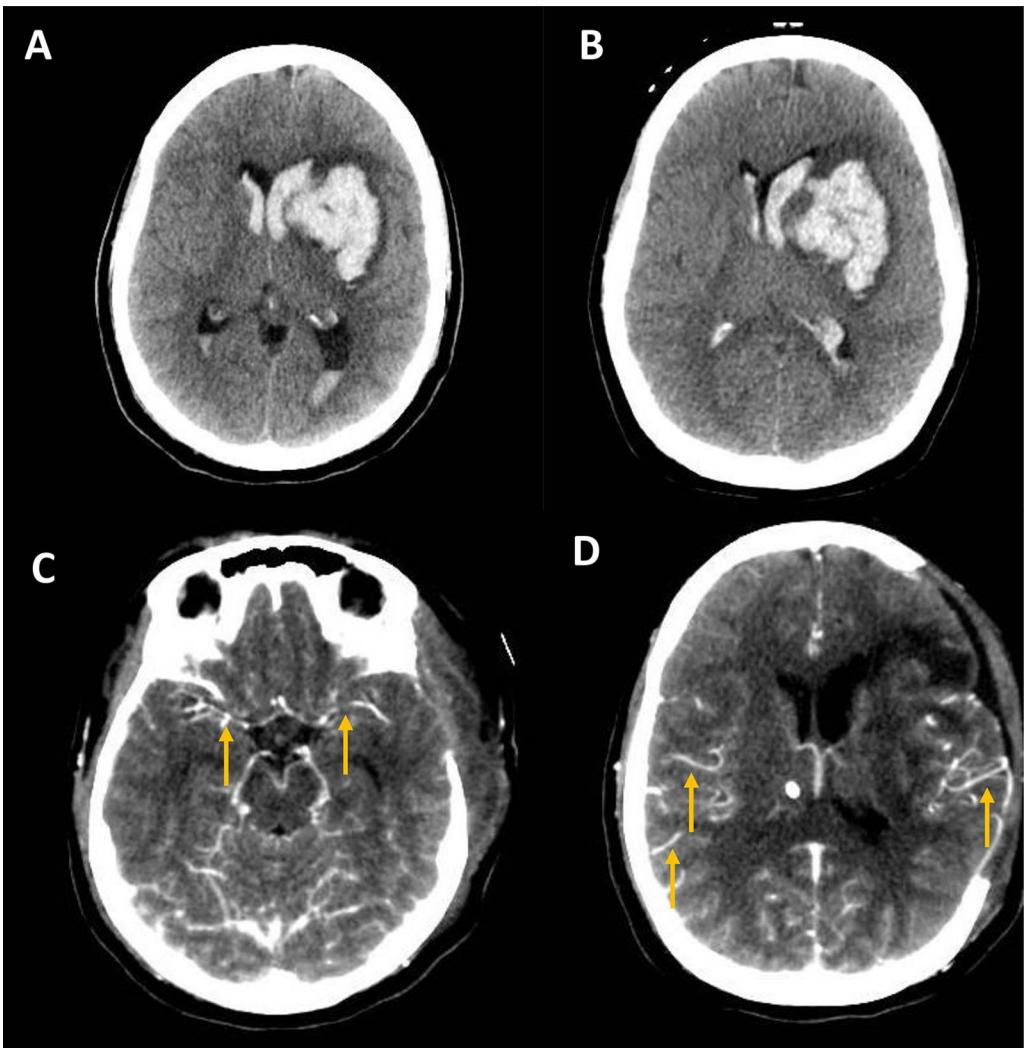
A 30-year-old woman with no past medical history developed sudden onset headache, vomiting, and a tonic-clonic seizure 6 days after delivery of a healthy child. The pregnancy and delivery had been uncomplicated. She was initially evaluated by the Emergency Medical Services at home. On initial assessment, the patient had a non-focal neurological examination, and her blood pressure was 160/100 mmHg. She was transferred to a local hospital, where she then developed a breakthrough of seizures shortly after arrival, requiring orotracheal intubation and mechanical ventilation. She received IV magnesium sulfate and a 20 mg/kg phenytoin load. The initial computed tomography (CT) scan revealed a 40-cc ICH within the

basal ganglia causing 8-mm midline shift with ventricular extension and acute hydrocephalus (Fig. 1a). An external ventricular drain (EVD) was emergently placed, and the patient was transferred to us for further management. At arrival, she was somnolent with global aphasia and right-sided paralysis. A digital subtraction angiogram (DSA) showed diffuse vasospasm (Fig. 2). With diagnosis of postpartum RVCS, she was started on nimodipine 60 mg Q6H through a nasogastric tube. On admission day 3, the patient presented neurological deterioration and intracranial hypertension at 25 cmH<sub>2</sub>O. She received osmotic therapy with 1 g/kg of mannitol and sedation for intracranial pressure control. An emergent brain CT revealed an increase in the size of the hematoma with progression of the vasogenic edema and midline shift (Fig. 1b). She was taken to the operating room for hematoma evacuation and hemicraniectomy with no complications. A brain CT done on postoperative day (POD) 1 showed successful hematoma evacuation with centered midline and no hydrocephalus (Fig. 1c, d). On POD 2, a transcranial Doppler (TCD) revealed hyperemia and mild vasospasm on the left middle cerebral artery (MCA) (Table 1) [3]. Repeated TCD on POD days 3 and 4 confirmed persistent hyperemia and worsening vasospasm on the left middle cerebral artery (MCA), as well as the development of hyperemia and vasospasm on the right MCA. On POD 5, the patient remained comatose despite weaning of sedatives. A CT angiogram (Fig. 1d) revealed severe narrowing of both MCA with collateral flow through leptomeningeal arteries (Fig. 1c, d). A new TCD confirmed worsening vasospasm in both MCA, particularly on the left (Table 1). At this point, milrinone was started at 1 mcg/kg/min and up titrated to 3 mcg/kg/min with no substantial change in the mean arterial blood pressure, which remained stable between 80 and 90 mmHg. A low dose of norepinephrine was preemptively started to strictly avoid hypotension. Within the

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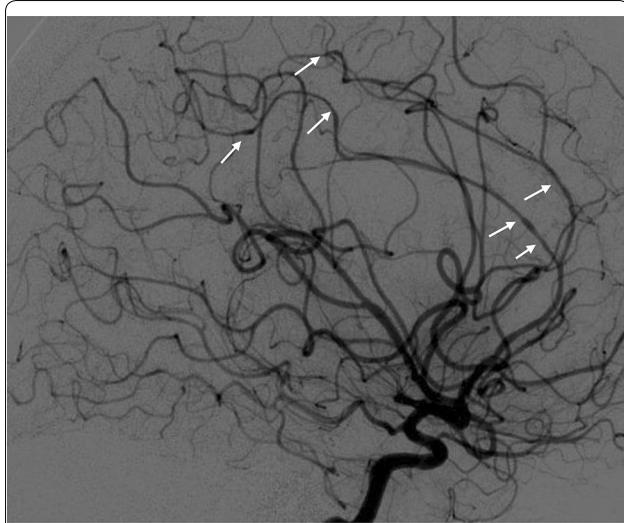
**Fig. 1** Serial brain CT. Initial brain CT (a): 40-cc ICH within the striatum with ventricular extension, 8-mm midline shift, and early obstructive hydrocephalus. Brain CT prompted by clinical deterioration on admission day 3 (b): Increased sized hematoma, with vasogenic edema and worsened midline shift. Brain CT-CTA prompted by persistent coma on postoperative day 5 (c, d): successful hematoma evacuation and decompressive craniectomy. Severe narrowing of both MCA (c, arrows) and brain perfusion through leptomeningeal arteries (d, arrows)

next 3 days, the patient recovered alertness and started following one-step commands. The MCA velocities measured by TCD rapidly normalized (Table 1). Milrinone was slowly weaned within 2 days with stable TCD values. The EVD was successfully retired and the patient discharged from the intensive care unit with global aphasia and severe right-sided weakness (National Institute of Health Stroke Scale [NIHSS] 16, modified Rankin scale [mRs] 5). Nine months later, the patient's neurological examination is remarkable for mild expressive aphasia, dysprosody, and moderate right arm and mild right leg

paresis, respectively (NIHSS 5). She continues outpatient rehabilitation and requires minimal assistance with daily living activities (mRs 2).

### Discussion

We present a well-documented case of severe postpartum RCVS successfully treated with IV milrinone. Our patient had multifocal distal vasoconstriction on initial DSA that progressed to severe MCA narrowing despite appropriate treatment. Her neurological status improved and the proximal vasospasm completely resolved within



**Fig. 2** Digital subtraction angiogram (DSA). DSA performed on admission day 2. Arrows point multiple foci of arterial vasoconstriction

**Table 1** Serial transcranial Doppler

POD#	TCD variable	Right MCA	Left MCA
1	Mean velocity (cm/s)	52	215
	Pulsatility index	0.7	0.6
	Lindergard ratio	0.8	3.3
2	Mean velocity (cm/s)	62	220
	Pulsatility index	0.7	0.74
	Lindergard ratio	0.8	4.13
3	Mean velocity (cm/s)	174	228
	Pulsatility index	0.93	0.71
	Lindergard ratio	4	5
5	Mean velocity (cm/s)	187	279
	Pulsatility index	0.66	0.60
	Lindergard ratio	4.14	6.17
6	Mean velocity (cm/s)	156	161
	Pulsatility index	0.9	0.8
	Lindergard ratio	4.2	4.3
7	Mean velocity (cm/s)	71	63
	Pulsatility index	1.1	1.4
	Lindergard ratio	1.6	1.4

Milrinone infusion initiated on POD#5

MCA middle cerebral artery, POD postoperative day, TCD transcranial Doppler

3 days of the initiation of milrinone infusion. Four points deserve special mention. First, our patient received full-dose nimodipine for 8 days before milrinone was initiated. Second, arterial vasospasm progressed for 5 days

after hemicraniectomy [4]. Third, our patient received milrinone on admission day 8, while the natural history of RCVS suggests that arterial narrowing peaks around day 16 [5]. And fourth, sonographic and clinical responses were evident at 24 h of milrinone initiation. This suggests that milrinone, rather than the effect of other therapies, was more directly responsible for the clinical improvement observed in our patient. Our observation is clinically relevant because we describe a potentially useful therapeutic intervention for a clinical situation with little supporting evidence.

RCVS describes a group of disorders characterized by reversible multifocal constriction of cerebral arteries [1, 6, 7]. The exact pathophysiologic mechanism of RCVS remains unclear, but the lack of histologic changes on biopsy samples suggests a deregulation of cerebral vascular tone [8]. Sympathetic overactivity, endothelial dysfunction, blood-brain barrier breakdown and oxidative stress may potentially explain for the former [1, 8]. Available treatment options for this condition are supported by observational studies, case series, and expert opinion [2]. The early identification and suspension of the precipitating agent are probably the highest yield interventions for all patients. Avoidance of headache triggers, proper analgesia, and bed rest are additional recommendations until clinical stability has been achieved [2]. Oral nimodipine (30–60 mg every 4 h) is the most commonly prescribed treatment in our center and previous reports [9, 10]. In two prospective observational studies, oral nimodipine was associated with resolution of thunderclap headache in up to 84% of patients with an acceptable safety profile [11, 12]. Since RCVS usually has a self-limited course and complications are infrequent, most patients respond well to supportive treatment and oral nimodipine. Long-acting verapamil appeared to be more effective to reverse arterial narrowing compared to shorter-acting calcium channel blockers in case series [13]. Yet, the use of long-acting drugs may be suboptimal in the more critically ill patients with severely threatened brain perfusion and polypharmacy.

Patients who develop refractory vasospasm, ischemic stroke, or ICH may require further interventions. Intra-venous nimodipine has been used in severe cases of RCVS [5, 14, 15]. Endovascular treatments, either mechanical or pharmacological, appear as attractive options for refractory cases. Intra-arterial nimodipine infusion has been reported successful for normalizing vessel caliber in refractory RCVS [16, 17]. Intra-arterial milrinone and balloon angioplasty are less commonly reported therapeutic approaches [18, 19]. Milrinone is a

phosphodiesterase-3 inhibitor that combines vasodilatory and inotropic properties, resulting from the increase in cyclic adenosine monophosphate in the cytosol of vascular smooth muscle cells and cardiomyocytes [20]. Beyond its vasodilatory effect, milrinone may improve cerebral perfusion through augmentation of the cardiac output. Milrinone has good safety profile and can be easily titrated. Yet, its main adverse effect, hypotension, should be strictly avoided since patients with severe MCA narrowing compensate brain perfusion through leptomeningeal collaterals. Failure of collateral flow puts them at a high risk of hemodynamic stroke. For this reason, we started milrinone at the lowest dose (1 mcg/kg/min) and to titrated it up slowly in combination with vasopressors. In the recent years, IV milrinone has been increasingly reported as a suitable treatment option for refractory vasospasm in patients with subarachnoid hemorrhage [21, 22]. Two previous case reports have described the potential effectiveness of IV milrinone for the treatment of RCVS. In the first one, a post-transplant patient on tacrolimus developed progressive arterial narrowing despite intravenous nicardipine, argatroban, magnesium sulfate, dextran, and verapamil. Neurological symptoms and brain imaging "dramatically improved" hours after starting IV milrinone. Of note, there is no mention of treatment duration and side effects. Also, it is difficult to isolate the effect of milrinone from other five agents being concomitantly administered [23]. More recently, Lakhal et al. reported a case of postpartum RCVS complicated with ICH resistant to intravenous nimodipine that responded to intravenous milrinone. In this case, milrinone was used for 7 days, and responsiveness was evaluated with serial CT angiograms. There were no serious side effects [24].

Unlike subarachnoid hemorrhage, conditions with multifactorial disorders leading to delayed cerebral ischemia [21], cerebral vasoconstriction seems to be the main pathophysiological derangement of RCVS. Hence, milrinone may be particularly useful for the treatment of this condition from a mechanistic standpoint. Also, compared to endovascular treatments, IV infusions have no risks of stroke or arterial rupture due to insertion of microcatheters and adverse events during transport to the angiography suite or administration of anesthetics [20]. Avoiding transfers and polypharmacy is particularly important in critically ill patients.

## Conclusion

Milrinone appears as a potentially useful therapeutic option for patients with severe RCVS resistant to conventional therapies. The combination of direct arterial vasodilation and cardiac output augmentation may explain its benefits on brain perfusion. Since the best treatment for

severe RCVS remains unknown, our report may help to guide clinical decisions in the individual patient.

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### Author Contributions

MAH data adquisition and drafting of the manuscript. All authors study design and review of the manuscript.

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### Conflict of interest

The authors declare that they have no conflicts of interest.

### Informed Consent

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