Milrinone for the Treatment of Cerebral Vasospasm After Aneurysmal Subarachnoid Hemorrhage

Amanda Tarabini Fraticelli, MD; Bernard P. Cholley, MD, PhD; Marie-Reine Losser, MD, PhD; Jean-Pierre Saint Maurice, MD; Didier Payen, MD, PhD

Background and Purpose—Attempts to reverse cerebral vasospasm (CVS) after aneurysmal subarachnoid hemorrhage (aSAH) rely on a limited number of treatments. Calcium channel blockers have proven a benefit but their vasodilating effect on spastic cerebral arteries is relatively modest. Milrinone, a phosphodiesterase inhibitor, combines vasodilating and inotropic properties, but limited data exist to support its use for the treatment of CVS. We assessed the efficacy and tolerance of milrinone in patients with CVS secondary to aSAH.

Methods—Twenty-two consecutive patients with angiographically-proven CVS (arterial diameter reduction >40%) have been studied. Intraarterial milrinone was infused in the cerebral territory(ies) involved and followed by continuous intravenous infusion until Day 14 after initial bleeding. We evaluated angiographic reversal of CVS, hemodynamic tolerance, and neurological outcome 1 year after aSAH.

Results—Thirty-four selective intraarterial infusions of milrinone were required to treat 72 vasospastic territories. Intraarterial milrinone resulted in 53±37% increase in arterial diameter (P<.0001). Milrinone infusion resulted in moderately increased heart rate, but systemic arterial pressure remained unchanged. Five patients (23%) had angiographically-proven vasospasm recurrence within 48 hours after the procedure. Two of them were successfully reversed after another intraarterial infusion of milrinone. The remaining 3 underwent mechanical angioplasty. Two patients (9%) died in ICU, and 2 were lost to follow-up. All other patients had very good neurological outcome (modified Rankin scale: 0.8±1.0; Barthel index: 100 [95–100]).

Conclusion—This study suggests that milrinone is effective and safe for reversal of CVS after aSAH and should be tested in a large randomized trial. (Stroke. 2008;39:893-898.)

Key Words: angioplasty and stenting ■ outcome ■ subarachnoid hemorrhage ■ vasospasm ■ phosphodiesterase inhibitors

Cerebral vasospasm (CVS) is present in up to 70% of patients suffering from aneurysmal subarachnoid hemorrhage (aSAH) and is symptomatic in nearly half of cases with subsequent increased morbidity, mortality, and cost of care.1 Up to now, there is no satisfactory therapy to prevent this complication. Various cerebral protectants have been tested in patients with aSAH, but only calcium channel blockers have demonstrated a beneficial effect on outcome, especially oral nimodipine.2,3 Attempts to reverse CVS rely on a limited number of treatments. “Triple H” (hypervolemia, hypertension, hemodilution) never demonstrated any benefit in outcome and is associated with numerous side effects. Intraluminal balloon angioplasty (also called mechanical angioplasty) has been introduced in the late 80’s.4-5 Although very effective on angiographically proven CVS, this technique is associated with a high risk of arterial damage such as wall rupture or dissection.5-7 Chemical angioplasty, consisting in intraarterial infusion of vasodilators at the time of cerebral arteriography, is a less aggressive procedure. Papaverine was used first, but this agent has only transient efficacy and is sometimes responsible for serious adverse events.8-10 Intraarterial calcium channel blockers have also been tested, but only nonrandomized studies support their efficacy.11-14 Inhibitors of the phosphodiesterase III isoenzyme have vasodilating properties combined with inotropic effects and are currently used for heart failure treatment. Few investigators have tested intraarterial infusion of these agents to treat CVS secondary to aSAH in experimental models (Khajavi, 1997)15 and in selected patients (Arakawa, 2001).16 Their results indicated a good efficacy, which prompted us to perform a pilot trial in patients with CVS secondary to aSAH despite maximum...
conventional treatment. The goal of this prospective study was to assess the efficacy and tolerance of intraarterial milrinone, followed by a prolonged intravenous infusion, in patients with CVS after aSAH.

Methods

Patients

Twenty-two consecutive patients suffering from aSAH with angiographically-proven CVS have been prospectively studied from February 2002 to April 2004 after approval of the local Ethics Committee. All patients underwent endovascular treatment of their cerebral arterial aneurysm under general anesthesia within 24 hours after admission. The following standard protocol of care was applied to all patients on admission: oral Nimodipine (360 mg/d) was given orally or in the gastric tube if patients remained ventilated; analgesic treatment consisted in IV paracetamol (4 g/d) and IV or subcutaneous opioids (fentanyl or morphine sulfate, respectively); antiepileptic treatment (valproate acid 2g/d) if required. In addition, patients received fluids: normal saline 30 to 40 mL/kg/d and gelatin 10 mL/kg/d. When mean arterial pressure (MAP) was less than 90 mm Hg, norepinephrine infusion was started using incremental doses until the 90 mm Hg threshold was reached. In 7 patients who had external ventricular drainage to treat hydrocephalus, cerebral perfusion pressure (CPP) was directly monitored and the end point of resuscitation was to maintain CPP above 75 mm Hg.

The early detection of cerebral vasospasm was based on repeated neurological examination in intensive care unit and on body temperature monitoring. Routine transcranial Doppler velocimetry of cerebral arteries was performed at least daily, or more if required. CVS was suspected when patients exhibited neurological alteration, hyperthermia, or suggestive Doppler changes, either separately or in combination. The diagnosis of CVS was confirmed by a new cerebral angiography, performed using the exact same incidence as that used for admission angiography. CVS was defined as a reduction in vessel diameter greater than 40% with respect to admission diameter. The magnitude of reduction was used to grade the severity of CVS as moderate (40% to 60%) or severe (>60%).

Cerebral Arterial Dilatation Procedure

Patients who developed CVS despite the standard preventive treatment were eligible for active arterial dilatation therapy using milrinone, occasionally associated with mechanical angioplasty. Patients themselves, or next of kin when neurological status was altered, were informed of the procedure. Patients with CVS were treated openly with the following method: (1) Intraarterial milrinone was infused (8 mg over 30 minutes) in the main artery dedicated to the vasospastic territory (internal carotid, dominant vertebral artery). Infusion could be repeated once in the same territory if an incomplete reversal was observed. Intraarterial milrinone infusion could also be repeated in a different territory in situation of extensive vasospasm, with a maximum milrinone dose of 24 mg. An independent radiologist assessed the efficacy of intraarterial injection by measuring angiographic enlargement of the vessel diameter. (2) Mechanical angioplasty was performed only if vasospasm persisted after 2 intraarterial milrinone challenges, or if severe CVS occurred before Day 5 (suggesting a high risk of recurrence). (3) All patients received a prolonged continuous intravenous infusion of milrinone. If well tolerated, the dose was progressively incremented from 0.5 μg/kg/min to 1.5 μg/kg/min (i.e.: twice the regimen recommended for heart failure patients) to maintain relatively high plasma concentrations of the drug after intraarterial infusion. This dose incrementation was stopped when tachycardia (HR >100 bpm) or blood pressure reduction (>20%) occurred. Intravenous milrinone infusion was maintained during the entire “high risk” period, i.e.: up to Day 14 after the initial bleeding. When CVS recurrence was suspected, a new angiogram was performed and the procedure could be repeated. Patients remained in ICU until Day 14 and were then transferred to the ward in the absence of other ICU complication.

Parameters collected included the following clinical data and radiological findings: Age, gender, SAPSII score, World Federation of Neuro Surgeons (WFNS) score (= clinical severity of aSAH), Fisher score (= CT scan severity of aSAH), radiological characteristics of intracranial aneurysm on admission angiogram (location, number, and size) angiographic characteristics of CVS (severity, arterial territories involved); delay between CVS detection and initial hemorrhage, arterial diameter variation after intraarterial milrinone infusion, number of CVS recurrences, number of mechanical angioplasties, clinical tolerance of intraarterial and IV milrinone infusion (systemic arterial pressure, heart rate, peripheral oxygen saturation, and end-tidal CO₂ in ventilated patients), and occurrence of hypokalemia. In addition, long-term neurological outcome was assessed 12 to 18 months after aSAH by telephone interview using modified Rankin score (0 to 6 points) and Barthel index (0 to 100 points).

Data Analysis

The vasodilating response to intraarterial milrinone infusion was assessed by referring to premilrinone arterial diameter, and was also compared between the different arterial territories: anterior cerebral artery (ACA), middle cerebral artery (MCA), internal carotid artery (ICA), and basilar artery (BA).

Statistical Analysis

Data were expressed as mean±SD, or as median [extremes] when distribution was not normal. Data were analyzed using Student’s t test, signed rank test, or 2-way ANOVA as appropriate.

Results

Twenty-two patients were studied over a 2-year period, from February 2002 to April 2004. Demographic data, WFNS score, Fisher score, and number and location of intracranial aneurysm on initial angiography are presented in Table 1. The day of occurrence of CVS after initial hemorrhage, number of arterial territories involved in each patient, and the severity of vasospasm are described in Table 2. Seventy-two vasospastic territories were treated using the procedure described above, requiring a total of 34 selective intraarterial infusions of milrinone (mean dose=12±6 mg). The anatomic distribution of vasospastic vessels was: internal carotid artery (n=25); middle cerebral artery (n=21); anterior cerebral artery (n=19); and basilar artery (n=7). Intraarterial milrinone infusion resulted in a 53±37% overall increase in vessel diameter (P<0.0001; Figure). There was a greater vessel diameter increase after milrinone when vasospasm was “severe” with respect to “moderate”: 73±23% versus 40±46%, respectively, P=0.0001. The response to milrinone did not differ among the different territories (ANOVA, P=0.6).

Hemodynamic Tolerance

Two patients received norepinephrine infusion (0.3±0.05 μg/kg/min) to maintain mean arterial pressure (or cerebral perfusion pressure) within the predefined range. Intraarterial milrinone infusion resulted in increased heart rate (75±14 versus 89±21 beats per min, P=0.002), but systolic (SBP) and diastolic (DBP) blood pressures did not change significantly (SBP: 135±30 versus 131±29 mm Hg, NS; DBP: 65±14 versus 63±14 mm Hg, NS). End-tidal CO₂ was monitored in a subgroup of 11 mechanically ventilated patients and remained unchanged (32±4 versus 32±4 mm Hg, NS). Intraarterial milrinone infusion did not alter peripheral arterial oxygen saturation (99±1% versus 99±1%, NS). The average dose of intravenous milrinone was 1±0.55 μg/kg/
min, for a duration of 7±3 days, and this infusion was well tolerated. After IV milrinone introduction 2 more patients required IV norepinephrine (0.25±0.04 μg/kg/min) during less than 24 hours. Heart rate increased after IV milrinone infusion, with higher minimum and maximum values over 24 hours: 66±8 versus 72±11 bpm, \( P = 0.03 \), and 81±10 versus 90±12 bpm, \( P = 0.003 \), respectively. Five patients had a low serum potassium (\( \leq 3.5 \) mEq/L) while receiving IV milrinone.

**CVS Recurrence**

Twelve patients of 22 had a control angiography between the first and the fourth day after intraarterial milrinone for suspicion of CVS recurrence. Five patients (23%) had angiographically-proven CVS recurrence, which occurred within 48 hours after the procedure. Two CVS recurrences were successfully reversed after another intraarterial infusion of milrinone. The remaining 3 patients underwent mechanical angioplasty.

**Mechanical Angioplasty**

In our series, a total of 8 patients underwent mechanical angioplasty. As mentioned above, 3 patients had this procedure to treat CVS recurrence whereas 5 patients had it initially, when CVS was first recognized. For those 5 patients, mechanical angioplasty was associated to intraarterial milrinone because the vasospasm persisted after 2 intraarterial milrinone challenges, or because severity and precocity (before Day 5) suggested a high risk of recurrence.

**Outcome**

Only 2 patients died in ICU (9%) as a consequence of extensive cerebral ischemia associated with intracranial hypertension. We calculated outcome scores 12 to 18 months after aSAH. Two patients were lost to follow-up; the remaining 18 patients had a modified Rankin score of 0.8±1.0, and a Barthel index of 100 [95–100] (median [extremes]). Nine patients (41%) were able to resume all their anterior activities, including their professional life. For the 9 other patients disability was minimal and mainly related to memory deficits and speech disorders, which did not limit their autonomy. These patients were all able to care for themselves, and 4 were able to drive an automobile and practice sports. There was no outcome difference, neither for modified Rankin score nor for Barthel index (\( P = 0.28 \) and \( P = 0.60 \), respectively), when comparing patients who underwent mechanical angioplasty and those who did not.

**Discussion**

The present study suggests that an arterial dilatation procedure based on a combination of intraarterial milrinone infusion followed by intravenous administration (up to Day 14 after initial bleeding) can be effective and safe for cerebral vasospasm (CVS) treatment. A third of our patients also...
required a mechanical angioplasty in addition to milrinone infusion to treat their CVS. In our cohort, mortality was only 9% and patients who survived had very mild disability scores at one year after aneurysmal subarachnoid hemorrhage.

Subarachnoid hemorrhage secondary to intracranial aneurysm rupture occurs with a worldwide incidence of 10.5 new cases per 100,000 persons-year.20 According to recent publications, half of patients who sustain aSAH die, one third of survivors need lifelong care, and only 20% to 35% attain a good recovery.20,21 One of the major causes of disabilities and death after aSAH is cerebral ischemia secondary to cerebral vasospasm. Despite recommended treatment, one third of patients experiencing aSAH develop neurological impairment, and up to 70% have angiographically-proven vasospasm within the first week.1 The poor prognosis associated with CVS after aSAH has prompted the search for therapeutic strategies aiming at reversing arterial vasoconstriction and avoid, or limit, subsequent cerebral ischemia.

Mechanical angioplasty is very effective to reverse CVS, but this procedure can generate physical damage to intracranial arteries and may worsen CVS per se.6,7 Moreover, the use of this technique is limited by the localization of CVS, because smaller distal arteries are not accessible to angioplasty. Therefore, this technique should be complementary with chemical angioplasty. In the present study, mechanical angioplasty was performed in selected patients with early (i.e., high risk of recurrence) or recurrent CVS limited to the terminal segment of carotid siphon, M1 segment of MCA, intracranial vertebral arteries, and basilar artery. In our experience, the benefit/risk ratio may be favorable in this subgroup of patients.

Intraarterial infusion of vasodilators (or “chemical” angioplasty) is therefore an important alternative for CVS treatment, and different pharmacologic agents have been tested including papaverine and calcium channel antagonists. Intraarterial papaverine was the first drug to be tested and has been widely used in patients with symptomatic CVS, but no outcome improvement could be demonstrated in comparison to standard medical treatment.9 Moreover, papaverine is associated with serious neurotoxic side effects including: severe brain stem depression, increased intracranial pressure, mydriasis, neurological deficits, seizures, and coma,10 possibly related to precipitation of papaverin hydrochloride crystals.8 Various calcium channel blockers have also been administered as intraarterial infusion. Intraarterial verapamil was found to increase vessel diameter, and the authors suggested that it could also improve immediate clinical status.11 Nicardipine and nimodipine have also been shown to reverse CVS after intraarterial infusion.12 Subsequent immediate clinical improvement was documented in 76% of patients receiving intraarterial nimodipine, and a similar proportion had favorable outcome at 6 months.13 Some of these preliminary trials showed encouraging results, but randomized and adequately powered studies are still warranted to demonstrate the impact of intraarterial infusion of

Table 2. Characteristics of Cerebral Vasospasm (CVS)

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calcium channel blockers on CVS, and its impact on outcome. Phosphodiesterase III inhibitors combine vasodilating and inotropic properties, resulting from the increase in cAMP in the cytosol of vascular smooth muscle cells and cardiomyocytes. Among these agents, milrinone is widely used to treat patients with acute heart failure. The combination of potent vasodilatation with reinforcement of inotropy is also very attractive to treat aSAH. Milrinone has similar systemic hemodynamic effects as the beta-agonist dobutamine in patients with altered left ventricular function after aSAH.22 The potential role of increased cardiac output in improving cerebral tissue perfusion independently of mean arterial pressure has been suggested by several authors.23,24 The first and unique clinical study using intraarterial milrinone showed angiographic effectiveness to reverse CVS in patients with aSAH.16 In this study, intraarterial milrinone was also followed by an intravenous infusion for up to 2 weeks after initial bleeding. Another recent study by the same authors reported their initial experience with cisternal irrigation using lactated Ringer’s solution containing urokinase and milrinone in 12 aSAH patients with WFNS grade 4 or 5.25 The authors reported good results in these patients presenting very severe aSAH: few CVS and only 1 new permanent ischemic deficit related to CVS. The patients also had better outcome than historical controls receiving the same treatment except for cisternal irrigation.

Our findings confirmed the preliminary observations by Arakawa et al., demonstrating a significant enlargement in diameter of vasospastic intracranial arteries. This effect was independent from location of CVS. The vessel diameter enlargement was more pronounced in severe than in moderate CVS. Because CVS remains a threat during approximately 2 weeks after initial bleeding, milrinone infusion was maintained intravenously until Day 14 after the onset of aSAH. Intraarterial infusion was very well tolerated and no serious adverse reaction was observed on standard hemodynamic and gas exchange parameters. In 2 patients receiving intravenous milrinone and sedation, mean arterial pressure dropped below the predefined threshold (90 mm Hg). This hypotension was corrected using norepinephrine infusion during less than 24 hours. The increase in heart rate was moderate and never required milrinone discontinuation. Hypokalemia is known to occur in subjects treated with phosphodiesterase inhibitors, but only 5 patients required potassium supplementation to maintain a normal kalemia. Overall, milrinone was effective to reverse CVS and well tolerated during both intraarterial and intravenous infusions in our cohort of patients.

The observed outcome in this population of consecutive patients was surprisingly good. A 9% in-hospital mortality was far less than the 40% mortality reported for similar patients in recent reviews.20,21 However, other authors have already reported a low mortality rate in similar patients,26,27 but Rabinstein A et al observed 52% of permanent deficits attributable to CVS in survivors in a series of aSAH patients of comparable severity (WFNS IV or V: 35%; WFNS I, II, and III: 65%) treated with intraarterial papaverine or angioplasty. In our series, among patients discharged from the hospital, 2 were lost to follow-up, but none of the 18 remaining was severely disabled 1 year after aSAH. Nine of them attained full recovery and returned to their professional life, whereas 9 had minimal neurological impairment (mainly speech disorders and memory deficits), which did not limit their autonomy. In a systematic review of mortality and functional outcome, Hop et al reported that 10% to 20% of patients remain severely disabled after aSAH,28 whereas Suarez et al estimate that almost one third of survivors need lifelong care.20 The proportion of patients with good neurological outcome in the present series is at least 81%, clearly more than 35%, the figure that is usually accepted.

**Limitations of the Study**

This pilot study was performed to test the efficacy of milrinone to reverse CVS in patients with aSAH and to evaluate its tolerance. We did not obtain systematic cardiac output measurements in these patients and were therefore unable to quantify the effects of milrinone on hemodynamic targets such as cardiac output and systemic vascular resistance. The lack of control group does not allow to conclude on the impact of milrinone in the observed favorable outcome. However, the angiographically-proven reversal of CVS after intraarterial milrinone infusion suggests a positive role of this agent in preventing CVS-related brain ischemia.

To summarize, intraarterial milrinone infusion was found to be safe and very effective to reverse CVS secondary to aSAH. Milrinone should be compared randomly and blindly to another vasodilator such as nimodipine to evaluate which drug is the best for chemical angioplasty in aSAH patients.

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**Disclosures**

None.

**References**


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