Milrinone and Homeostasis to Treat Cerebral Vasospasm Associated with Subarachnoid Hemorrhage: The Montreal Neurological Hospital Protocol

**Marcelo Lannes · Jeanne Teitelbaum ·
Maria del Pilar Cortés · Mauro Cardoso ·
Mark Angle**

Abstract

Introduction For the treatment of cerebral vasospasm, current therapies have focused on increasing blood flow through blood pressure augmentation, hypervolemia, the use of intra-arterial vasodilators, and angioplasty of proximal cerebral vessels. Through a large case series, we present our experience of treating cerebral vasospasm with a protocol based on maintenance of homeostasis (correction of electrolyte and glucose disturbances, prevention and treatment of hyperthermia, replacement of fluid losses), and the use of intravenous milrinone to improve microcirculation (the Montreal Neurological Hospital protocol). Our objective is to describe the use milrinone in our practice and the neurological outcomes associated with this approach.
Methods Large case series based on the review of all patients diagnosed with delayed ischemic neurologic deficits after aneurysmal subarachnoid hemorrhage between April 1999 and April 2006.
Results 88 patients were followed for a mean time of 44.6 months. An intravenous milrinone infusion was used for a mean of 9.8 days without any significant side effects. No medical complications associated with this protocol were observed. There were five deaths; of the surviving patients, 48.9 % were able to go back to their previous baseline and 75 % had a good functional outcome (modified Rankin scale ≤2).
Conclusion A protocol using intravenous milrinone, and the maintenance of homeostasis is simple to use and requires less intensive monitoring and resources than the standard triple H therapy. Despite the obvious limitations of this study's design, we believe that it would be now appropriate to proceed with formal prospective studies of this protocol.

Keywords Subarachnoid hemorrhage ·
Cerebral vasospasm · Milrinone lactate ·
Phosphodiesterase inhibitors · Cerebrovascular circulation ·
Treatment outcome

Introduction

The main causes of mortality and poor neurological outcome after aneurysmal subarachnoid hemorrhage (SAH) are the direct effects of the hemorrhage, rebleed, and cerebral infarction associated with delayed ischemic neurological deficits (DINDs) secondary to cerebral vasospasm. In more recent patient series, it is obvious that despite advances in the monitoring and care of these patients, between 15 and 20 % will die or develop a stroke leading to increased morbidity and mortality [1]. Other than using nimodipine as a prophylactic agent, the mainstay of the treatment of symptomatic vasospasm is the so-called triple-H therapy, where varying degrees of induced hypertension, hypervolemia, and hemodilution are

M. Lannes (✉) · M. Angle
Department of Anesthesia, Faculty of Medicine McGill University, Montreal Neurological Hospital, Room 548, 3801 University Street, Montreal, QC H3A 2B4, Canada
e-mail: marcelo.lannes@mcgill.ca

J. Teitelbaum · M. Cardoso
Department of Neurology, Faculty of Medicine McGill University, Montreal Neurological Hospital, Montreal, QC, Canada

M. del Pilar Cortés
Department of Radiology, Faculty of Medicine McGill University, Montreal Neurological Hospital, Montreal, QC, Canada

used in an effort to increase perfusion to ischemic areas. This approach, although preferable to allowing uncorrected hypovolemia is fraught with difficulties. Its use is associated with a significant incidence of complications such as cardiogenic pulmonary edema, arrhythmias, myocardial ischemia and brain edema [2]. Furthermore, despite its wide acceptance in neurologic intensive care units (ICU), the evidence to support its use is controversial.

A Cochrane review published in 2004 found no beneficial effect of volume expansion and an increased rate of complications when compared to normovolemia [3]. A systematic review of the use of triple-H therapy to prevent vasospasm concluded that no recommendations could be made in view of the methodological flaws of previous studies and the paucity of information [4]. Other preventive and therapeutic modalities such as statins, magnesium infusions, tirilazad, and intra-arterial papaverine have produced negative or mixed results and did not challenge the current prevailing management; the interventions were used as add-ons to triple-H therapy [5–13].

In view of these concerns, the Montreal Neurological Hospital developed a protocol to manage patients with SAH that moved away from volume expansion and routinely induced hypertension. Milrinone is a selective inhibitor of the low-Km cAMP specific phosphodiesterase III that has both inotropic and vasodilatory effects. Animal and human studies have previously shown the efficacy of milrinone in reversing cerebral vasospasm. [14–17]. We present the largest case series published so far, where patients with DINDs are treated with intravenous milrinone by this new approach.

Materials and Methods

The Montreal Neurological Hospital protocol puts the emphasis on maintaining euvolemia [balanced fluid balance and a central venous pressure (CVP) ≥ 6], and normothermia, preserving electrolyte and metabolic balance, and the use of an intravenous milrinone infusion to treat patients with symptomatic vasospasm. After approval by the Research Ethics Board from the Montreal Neurological Hospital, we reviewed the charts of all the patients admitted to the Neuro ICU with a diagnosis of SAH from April 1999 to April 2006 to identify those diagnosed with DINDs secondary to cerebral vasospasm. We retained only the charts of those with aneurysmal SAH.

All patients received a standard course of prophylactic nimodipine and a short course of tranexamic acid until the aneurysm was secured. Monitoring of patients with symptomatic vasospasm included an arterial line, a central venous catheter for CVP monitoring, continuous electrocardiographic monitoring, daily electrolytes (that included

phosphate and magnesium), complete blood counts, and intracranial pressure monitoring if an external ventricular drain was present. Troponins were not routinely assessed and were measured only in the presence of new EKG changes or symptoms suggesting myocardial ischemia.

The Montreal Neurological Hospital protocol followed an algorithmic approach using as the initial step the maintenance of homeostasis and boluses of intravenous milrinone, followed by escalating doses of an intravenous infusion of milrinone according to the patient's clinical response (Fig. 1). A satisfactory clinical response consisted of the resolution of the new neurological deficits and the return to the baseline mental status. Vasopressors were not routinely used. Augmentation therapy with norepinephrine or neosynephrine is used to restore the mean arterial pressure (MAP) to its previous values if there is a drop following milrinone administration. Another indication for the use of vasopressors would be to achieve a higher MAP in the event of poor clinical response despite a repeat intravenous bolus of milrinone and an increase in the infusion dose. Studies have not yet identified the optimal target for BP augmentation in this population and we chose to maintain a MAP ≥90 mmHg.

If there was no recurrence of symptoms after 72 h, we decreased the milrinone infusion by 0.25 mcg/kg/min every 24 or 48 h until discontinuation. If deterioration occurred, the protocol was restarted and the weaning process instituted at a slower rate. Finally, rescue therapy
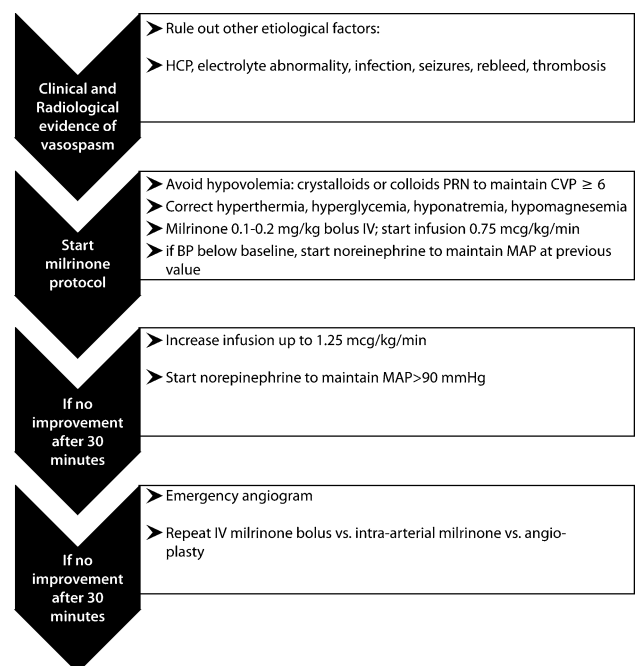

Clinical and Radiological evidence of vasospasm
➤ Rule out other etiological factors:
➤ HCP, electrolyte abnormality, infection, seizures, rebleed, thrombosis

Start milrinone protocol
➤ Avoid hypovolemia: crystalloids or colloids PRN to maintain CVP ≥ 6
➤ Correct hyperthermia, hyperglycemia, hyponatremia, hypomagnesemia
➤ Milrinone 0.1-0.2 mg/kg bolus IV; start infusion 0.75 mcg/kg/min
➤ if BP below baseline, start noreinephrine to maintain MAP at previous value

If no improvement after 30 minutes
➤ Increase infusion up to 1.25 mcg/kg/min
➤ Start norepinephrine to maintain MAP>90 mmHg

If no improvement after 30 minutes
➤ Emergency angiogram
➤ Repeat IV milrinone bolus vs. intra-arterial milrinone vs. angioplasty

Fig. 1 Flowchart illustrating the Montreal Neurological Hospital protocol. *HCP* hydrocephalus, *CVP* central venous pressure, *BP* blood pressure, *MAP* mean arterial pressure

Fig. 2 Cerebral angiogram of a patient with severe symptomatic vasospasm before (**a**) and after (**b**) therapy with the Montreal Neurological Hospital protocol
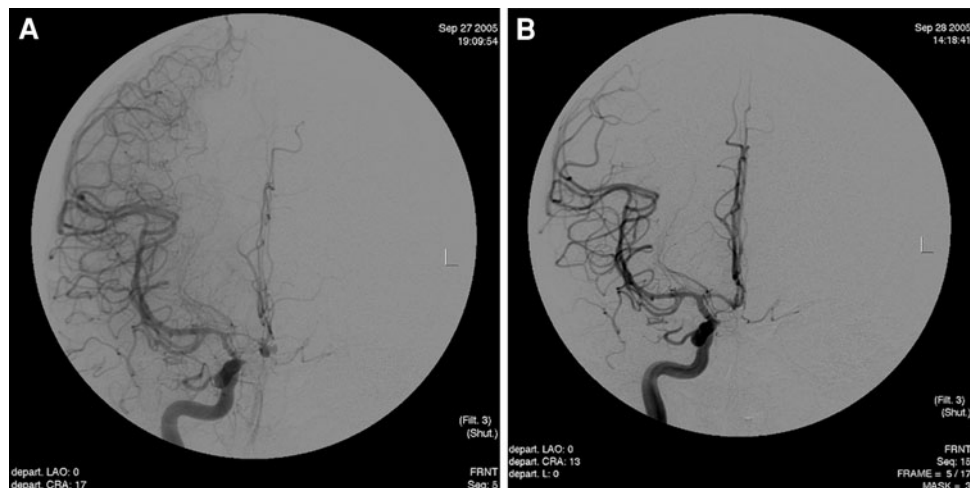
involves emergency angiography and the use of a repeat intravenous bolus of milrinone or the injection of intra-arterial milrinone with or without angioplasty. The dose of intra-arterial milrinone used was of 2–3 mg injected over 2 min. Figure 2 shows the angiogram of a patient with severe symptomatic vasospasm and the follow-up image performed about 19 h later showing a good response after an intravenous bolus dose of 8 mg of milrinone followed by a continuous intravenous infusion.

Symptomatic vasospasm was defined as follows: angiographic or transcranial Doppler (TCD) results consistent with vasospasm and the appearance of a new focal neurological deficit or a change in mental status or both that could not be explained by other factors such as new hydrocephalus, electrolyte abnormality, medication effect, rebleed, surgical or coiling complications such as thrombosis, and new-onset infection. All the patients who were diagnosed with vasospasm according to the criteria described above received intravenous milrinone. We excluded two patients who were comatose on admission and who did not improve after initial medical and surgical therapies. One of the patients was comatose on admission, had hemorrhagic brain contusions and severe left carotid stenosis that required an urgent carotid endarterectomy following the clipping of an anterior communicating aneurysm. The second patient also was comatose and intubated on admission, and the initial CT scan of the head revealed bilateral subacute ischemic changes indicating a late presentation.

Another patient who was transferred to her native country in Europe and whose follow-up was shorter than 28 days was also excluded from the analysis. 12 patients who received intravenous milrinone because of significant signs and symptoms, but who had not undergone either a cerebral angiogram or a TCD were not included in the analysis. Severity of radiological vasospasm was based on the radiologist's assessment and categorized as mild,

moderate, or severe. TCD results were classified as mild, moderate, and severe based on the mean velocities and the ratio between the velocities in the intracranial vessel studied and the extra-cranial portion of the internal carotid artery as described elsewhere [18].

Besides age, sex, and severity of vasospasm, other variables collected included Hunt and Hess grade on admission, modified Fisher grade on initial head CT scan, length of stay in the ICU, whether clipping, coiling, and external ventricular drainage were performed, day of onset of symptomatic vasospasm, duration in days of the intravenous milrinone infusion, presence of significant adverse reactions attributable to milrinone (these being hypotension requiring discontinuation of treatment and the presence of sustained arrhythmias), concomitant use of vasopressors (norepinephrine or neosynephrine), the presence of hypertension and previous neurological deficits in the past medical history, the presence of congestive heart failure on admission, year of admission, and the number of patients who developed ischemic changes on the CT scan in the territories affected by vasospasm. Clinical outcome was assessed by the modified Rankin scale (mRS) and classified as a binary variable; good (scores 0–2) versus bad (scores 3–6). A good outcome was defined as a mRS of 0 (absence of symptoms) to 2 (mild disability) and was ascertained by reviewing the follow-up notes and evaluations performed by the occupational therapists, and if the documented follow-up had been shorter than 1 month by telephone contact. The last day of follow-up was considered to be the date of the detailed exam available in the patient's chart, the date of the telephone interview, or the date of death.

Since this is a large case series where all patients received the same treatment, we cannot establish an association between the intervention described here (the Montreal Neurological Hospital protocol) and patient outcome. We performed statistical analyses related to the binary clinical

outcome (good versus bad) only with the goal of better characterizing the population described here. Patient's characteristics were described and grouped for identification of potential determinants of better outcomes. Univariable statistical analysis used simple χ^2 tests and Fisher's exact tests for categorical variables and two-sample t tests for interval variables. Those patient characteristics found to be associated with the outcome at a P value <0.15 were studied with a multivariable logistic regression using a forward stepwise selection. Significance was assessed with Wald tests and the overall fit of the model to the data was determined by likelihood ratio tests. The variables were tested also for possible interaction by likelihood ratio tests as well. Again, these are only descriptive analyses, performed here only to verify whether this series of patients is comparable with the ones used in previously published prospective studies. One would expect that the common factors associated with poor outcome, such as Hunt and Hess grade would also play a significant role in this series.

Results

There were 502 patients in total admitted to the Montreal Neurological Hospital between 1999 and 2006 with the diagnosis of aneurysmal SAH. We studied 88 patients with cerebral vasospasm after the exclusion of the patients mentioned above. All patients had been treated according to the Montreal Neurological Hospital protocol based on the use of escalating doses of intravenous milrinone and the maintenance of homeostasis.

Patients' demographics, Hunt and Hess grades, modified Fisher grades, the frequency of intraventricular hemorrhage, ICU length of stay, and the treatment duration are summarized in Table 1. Mean age was 53.4 years (range 34–78) and over 78 % of patients were female. Most patients (75 %) had a Hunt and Hess score between 1 and 3. Modified Fisher grades of 3–4, indicating significant filling of the basal cisterns with blood, were observed in over 80 % of cases.

Early securing of the aneurysm (within 48 h) either by clipping or by coiling was achieved in 79 patients. The other nine patients had a delayed procedure because they presented to the hospital days after the initial bleeding. Immediate complications resulting from either procedure occurred in <7 % of cases. Vasospasm was diagnosed after a mean of 5.2 days after admission ($\pm$SD 2.7). Severe vasospasm was demonstrated in more than 44 % of the patients. Figure 3 summarizes the anatomic location of the aneurysms.

All patients were treated with a milrinone intravenous bolus followed by an infusion according to the Montreal Neurological Hospital protocol. The mean duration of the intravenous infusion was of 9.8 days and there was no

Table 1 Patients' demographic and clinical characteristics

Age	
Range	34–78
Mean (SD)	53.4 (11.45)
Gender	
Female	69 (78.4 %)
Male	19 (21.6 %)
Hunt and Hess grade	
1–3 N (%)	66 (75 %)
4–5 N (%)	22 (25 %)
Modified fisher score	
1 N (%)	4 (4.6 %)
2 N (%)	10 (11.5 %)
3 N (%)	33 (37.9 %)
4 N (%)	40 (46.0 %)
History of hypertension N (%)	16 (18.2 %)
CHF on admission N (%)	4 (4.6 %)
Presence of IVH on admission N (%)	44 (50 %)
Use of Norepinephrine N (%)	60 (68.2 %)
External ventricular drain N (%)	70 (79.6 %)
Treatment duration (days)	
Mean (SD)	9.8 (5.1)
Deaths N (%)	5 (5.7 %)

IVH intraventricular hemorrhage, *CHF* congestive heart failure
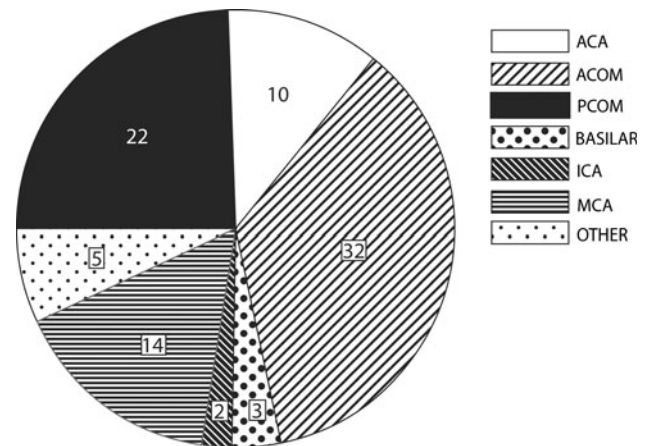

Fig. 3 Location of aneurysms. *Numbers* indicate number of patients. *ACA* anterior cerebral artery, *MCA* middle cerebral artery, *PCOM* posterior communicating artery, *ACOM* anterior communicating artery, *ICA* internal carotid artery. Total sample 88 patients

difference between the outcome groups at 1 month and at 12 months as indicated by a P value >0.005 (t test). There were no significant side effects associated to its use. In addition, there were no instances either of pulmonary edema or cardiac ischemia caused by the Montreal Neurological Hospital protocol. Norepinephrine for augmentation therapy was required in 68 % (60/88) of

patients. Only one patient received intra-arterial milrinone. No angioplasties were performed either because the vasospasm was diffuse without a target stenotic area or because there was a significant improvement in the radiological picture after a repeat intravenous bolus dose of milrinone during the angiogram.

Mean follow-up time was 44.6 months and 74 % (65/88) of patients were followed for 12 months and more. There were a total of five deaths (5.7 %): one of the patients died 20 months later from a lung cancer after being discharged from the hospital with a mRS score of 2. The other four patients left the hospital with an initial mRS score ≥4 and died after 24 months or more.

Outcomes are summarized on Figs. 4, 5 and 6. Overall 43 patients (48.9 %) were able to return to all their previous activities and 66 patients (75 %) had a good outcome (mRS ≤ 2). At 1 month after the initial event all the patients were accounted for and 34 (38.6 %) had a good outcome. 66 of the 88 patients were followed for 12 months or more. Of those 66 patients, 53 had a good outcome (60.2 % of the initial sample or 80.3 % of the
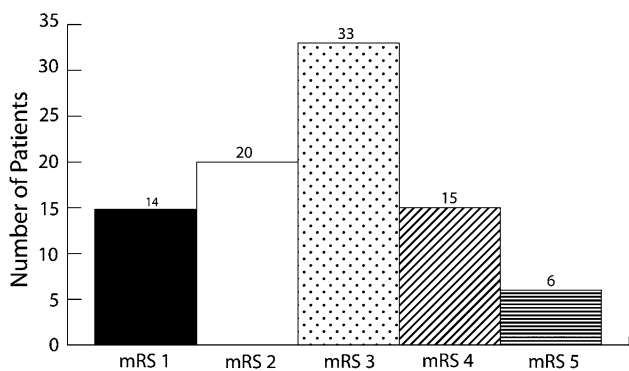

Fig. 6 Neurological outcomes of patients with follow-up times shorter than 12 months and of variable follow-up lengths. Population sample = 23 patients. Each *dot* represents one patient *mRS* modified Rankin scale

patients who had a longer follow-up) and 34 of them had no significant disability and were able to return to all their previous activities (mRS ≤ 1).

There were 23 patients who had follow-ups shorter than 12 months. There was no difference between these patients and those who had follow-ups of 12 months or longer with respect to age (P = 0.22), gender (P = 0.57), and Hunt and Hess grade (P = 0.84). The distribution of the mRS scores across the different lengths of follow up is depicted on Fig. 5. In those patients with a shorter follow-up, over 65 % (15/23) had a good outcome and 43.5 % (10/23) were able to return to all their previous activities.

Univariable and multivariable analyses showed that, as in other series of patients presented in previous studies, older age and a higher Hunt and Hess were associated with an increased likelihood of worse outcome. Table 2 summarizes the findings of the univariable analysis. The multivariable logistic regression model only tested age, Hunt and Hess grade (summarized as a binary variable grades 3–5 versus grades 1–2) and aneurysm location because those were the only variables that reached the cut-off specified a priori of a P < 0.15. The analysis showed that aneurysm location had no confounding effect and a likelihood ratio test demonstrated that its addition did not add significantly to the model. The final model included only age and Hunt and Hess grade. At 1 month, the odds ratio for a bad outcome for each year increase in age was 1.05 (95 % CI = 1.01–1.10) with a P = 0.02 and at 12 months and more it was 1.11 (95 % CI 1.03–1.20) with a P = 0.005. Higher Hunt and Hess grades [3–5] had an odds ratio of 6.0 (95 % CI 2.23–16.14) and P < 0.001 at 1 month, and an odds ratio of 4.14 (95 % CI 0.93–18.51) and a P = 0.063 at 12 months.

Fig. 4 Neurological outcomes at 1 month after the initial event. Total sample = 88 patients. *mRS* modified Rankin scale
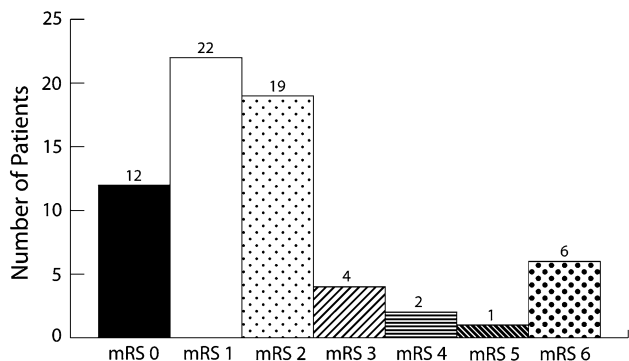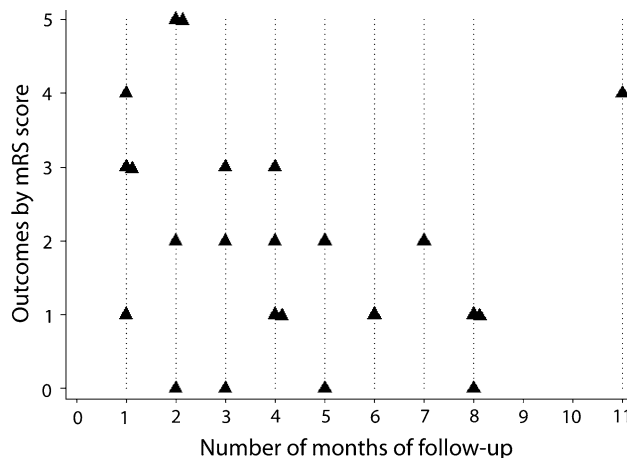

Fig. 5 Neurological outcomes of patients who had a follow-up assessment 12 or more months after the initial bleed. Population sample = 66 patients *mRS* modified Rankin scale

Table 2 Comparison of patients with good and bad outcomes at 1 month (sample population 88) and at 12 months and more of follow-up (sample population 66)

	Outcome at 1 month			Outcome at ≥12 months		
	Good	Bad	P value	Good	Bad	P value
Age (years)						
Mean	50.2	55.5	0.04[†]	50.8	60.8	0.003[†]
±SD	1.50	1.70		1.42	3.13	
Gender						
Female n (%)	28 (31.8)	41 (46.6)	0.48	41 (62.1)	10 (15.2)	0.97
Male n (%)	6 (6.8)	13 (14.8)		12 (18.2)	3 (4.5)	
H&H ≥ 3 (n)	10	37	<0.001	9	25	0.15
OR (95 % CI)	5.2 (2.1–13.3)		0.001	2.52 (0.7–9.2)		0.16
Norepinephrine						
Yes n (%)	22 (25)	38 (43.2)	0.58	39 (59.1)	8 (12.1)	0.50[‡]
No n (%)	12 (13.6)	16 (18.2)		14 (21.2)	5 (7.6)	
OR	1.30		0.39	0.58		0.39
95 % CI	0.52–3.23			0.16–2.05		
IVH						
Yes	28 (31.8)	16 (18.2)	0.66	25 (42.4)	8 (12.1)	0.35
No	26 (29.5)	18 (20.5)		28 (37.9)	5 (7.6)	
OR	1.21		0.66	1.79		0.36
95 % CI	0.51–2.56			0.52–6.20		
Ischemic changes						
Yes n (%)	13 (14.8)	19 (21.5)	0.77	19 (28.8)	3 (4.5)	0.52[‡]
No n (%)	21 (23.9)	35 (39.8)		34 (51.5)	10 (15.2)	
OR	0.88		0.77	0.54		0.39
95 % CI	0.36–2.15			0.13–2.23		
Fisher ≥ 3						
Yes n (%)	27 (30.8)	46 (52.3)	0.68[‡]	45 (69.2)	11 (16.9)	1.00[‡]
No n (%)	6 (6.9)	8 (9.1)		7 (10.8)	2 (3.08)	
OR	1.28		0.68	0.86		0.86
95 % CI	0.40–4.11			0.15–4.77		
Vasospasm severity (angio)						
Severe n (%)	21 (32.3)	32 (48.5)	0.51[‡]	30 (65.2)	7 (15.2)	1.00[‡]
Mild-mod. n (%)	3 (4.62)	9 (13.6)		8 (17.4)	1 (2.2)	
OR	0.51		0.35	1.87		0.58
95 % CI	0.12–2.14			0.19–18.03		
Admission year	P = 0.22			P = 0.92		
Aneurysm location	P = 0.98[‡]			P = 0.04[‡]		

All differences are significant at P < 0.05

[†] Two sample t test, [‡] Fisher's test; otherwise χ² tests were used

In more than 36.4 % of patients, new ischemic lesions which were not associated with surgery or coiling could be detected on a head CT corresponding to the territory of the vasospasm. The presence of these lesions was not statistically associated with a bad outcome as shown by the results on Table 2.

Discussion

Cerebral vasospasm remains as a common complication of SAH and constitutes an important predictor of outcome together with the severity of the initial bleed, the patient's age, the presence of medical co-morbidities, hyperglycemia, and hyperthermia [1, 19, 20]. The established approach to treat cerebral vasospasm is to use a combination of hypervolemia, hemodilution, and hypertension, the so-called hemodynamic or triple-H therapy, with the importance of each component varying according to the treating center [21, 22]. In most articles and textbooks on the subject, this therapy consists in administering crystalloids and colloids to maintain a CVP between 8 and 12 mmHg or a pulmonary arterial occlusion pressure between 15 and 18 mmHg, a systolic blood pressure

above 120–150 mmHg and a hematocrit of 30–35 % [23–26].

Despite its widespread acceptance, this therapy has never been validated in a randomized controlled trial looking at clinical outcomes [25, 27]. Even if we examine only the investigations where the outcome consisted of changes in the cerebral blood flow (CBF), the existing studies are too heterogeneous in design, lack a proper control group, use different measures of CBF, and often have very small sample sizes. A recent systematic review concluded that the evidence that hemodynamic intervention improves CBF in patients with vasospasm was very weak with only hypertension showing some promise [27]. There is, on the other hand, good evidence that triple-H therapy has no benefits when used prophylactically [28, 29], and that its use is costly, labor intensive, and associated with significant side effects, such as pulmonary edema, cardiac arrhythmias, increased brain edema, hemorrhagic infarction, and myocardial infarction among others [2, 24, 30–32]. Hypervolemia is its most controversial component and has been shown to be ineffective and possibly harmful, increasing the rate of complications by almost twofold [3]. Despite this, a survey of 167 members of the Neurocritical Care Society in the USA published in 2010 revealed that 27 % of respondents used hypervolemia prophylactically and 100 % used it to treat symptomatic vasospasm with an average CVP value of 10 mmHg [33].

Milrinone is a potent selective phosphodiesterase III (PDE III) inhibitor that affects cyclic adenosine monophosphate (cAMP) pathways with both inotropic and vasodilatory effects [34]. The cerebrovascular smooth muscle contains large amounts of PDE III making it an important target for milrinone actions. In isolated arteries of dogs with chronic vasospasm, milrinone decreased wall thickness, reduced corrugation of the elastic lamina and increased the amount of cAMP within the vessel walls [14]. Milrinone has also anti-inflammatory effects through the inhibition of interleukin 1B and interleukin 6 [35]. Initial investigations in an animal model of SAH and in a small series of patients showed rapid reversal of cerebral vasospasm [15, 16].

More recently, its efficacy and safety was demonstrated in the treatment of 22 patients with angiographically proven vasospasm. A protocol using intra-arterial injection followed by a prolonged intravenous infusion was used in another study [17].

In this series of 88 patients with vasospasm, we used a protocol that abandons hypervolemia altogether focusing on the use of primarily intravenous milrinone and maintenance of normovolemia and homeostasis. The standard therapy included also initial blood pressure control and the early and short-term use of tranexamic acid to prevent

rebleed only till the aneurysm was secured [36], early intervention to secure the aneurysm, and the use of nimodipine. A recent review of general mortality and morbidity in patients who survived the initial episode of SAH revealed a case fatality rate between 17 and 45 % and a good functional outcome (mRS ≤ 2) in up to 43 % of patients [37]. This, however, are the outcomes described for all patients with SAH, whereas this case series describes only patients with symptomatic vasospasm. Outcomes cited for a group of patients who survived the initial event and went on to develop cerebral vasospasm indicate a mortality of 17.5 % despite triple-H therapy [5].

In this series, there were no cases of pulmonary edema, cardiac arrhythmias, myocardial ischemia, or severe hypotension associated with the Montreal Neurological Hospital protocol. Norepinephrine was not routinely used [28 patients (31.8 %) never received it], being given only to restore blood pressure to baseline values if there was a drop associated with milrinone or if patients were judged not to be improving fast enough, which always carries an element of subjective analysis from the treating physician. No angioplasties were deemed necessary. In most cases, the angiographic picture improved after a second and larger intravenous bolus dose of milrinone was used. Only one patient also received intra-arterial milrinone. During angiography we also observed at times that, after a milrinone intravenous bolus, there was an improvement in the overall CBF as shown by a faster venous phase, even though there was no significant change in the caliber of the larger vessels. This suggests that at least in those cases, a more important role was being played by changes in the microcirculation, which were corrected by an increase in the intravenous milrinone dose.

There are several limitations to large case series such as the one described here. The main purpose of such investigations is to act as hypothesis generators. There are obvious problems in attributing outcome retrospectively including observer bias and incomplete information from the charts. We tried to minimize those by a standard and validated scoring system (mRS) and by contacting the patients by phone interview whenever the follow-up provided in the records was too short. All patients who were diagnosed with vasospasm during the study period received the milrinone protocol, which decreases the impact of selection bias.

The doses used were based on those administered as infusions in cardiac patients, whereas the doses used as intravenous boluses were much larger. Despite that they were well tolerated in this series of patients with no subjects experiencing arrhythmias or hypotension requiring the discontinuation of the drug. Another limitation is the lack of cardiac output measurement which would have allowed us to investigate any possible correlation between

the magnitude of a positive inotropic effect of milrinone and the degree of clinical improvement observed. However, in two studies where this measurement was performed, there was no significant effect on the cardiac output of subjects who had a normal or increased function before starting milrinone suggesting that its effect on reversing vasospasm of intracerebral vessels was not due to its systemic hemodynamic effects [15, 38].

Conclusion

We describe a protocol to treat cerebral vasospasm associated with SAH using primarily intravenous milrinone, normovolemia, and general measures to maintain homeostasis and the occasional use of vasopressors (the Montreal Neurological Hospital protocol). In this retrospective large case series, we did not observed any significant deleterious effects suggesting that this approach could be safely investigated at the doses employed here. The protocol was also much simpler to use than treatments that use primarily hypertension and higher fluid volumes.

We believe that this protocol should be evaluated by a pilot prospective study, where more precise dose determination and a better outcome evaluation could be performed.

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