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ORIGINAL WORK

Intravenous Milrinone for Cerebral Vasospasm in Subarachnoid Hemorrhage: The MILRISPASM Controlled Before–After Study

Karim Lakhal[1*], Antoine Hivert[1], Pierre-Louis Alexandre[2], Marion Fresco[1], Vincent Robert-Edan[1], Pierre-André Rodie-Talbere[1], Xavier Ambrosi[1], Romain Bourcier[2,3], Bertrand Rozec[1,3] and Julien Cadiet[1]

Abstract

Background: Intravenous (IV) milrinone, in combination with induced hypertension, has been proposed as a treatment option for cerebral vasospasm after aneurysmal subarachnoid hemorrhage (aSAH). However, data on its safety and efficacy are scarce.

Methods: This was a controlled observational study conducted in an academic hospital with prospectively and retrospectively collected data. Consecutive patients with cerebral vasospasm following aSAH and treated with both IV milrinone (0.5 µg/kg/min^{-1}, as part of a strict protocol) and induced hypertension were compared with a historical control group receiving hypertension alone. Multivariable analyses aimed at minimizing potential biases. We assessed (1) 6-month functional disability (defined as a score between 2 and 6 on the modified Rankin Scale) and vasospasm-related brain infarction, (2) the rate of first-line or rescue endovascular angioplasty for vasospasm, and (3) immediate tolerance to IV milrinone.

Results: Ninety-four patients were included (41 and 53 in the IV milrinone and the control group, respectively). IV milrinone infusion was independently associated with a lower likelihood of 6-month functional disability (adjusted odds ratio [aOR] = 0.28, 95% confidence interval [CI] = 0.10–0.77]) and vasospasm-related brain infarction (aOR = 0.19, 95% CI 0.04–0.94). Endovascular angioplasty was less frequent in the IV milrinone group (6 [15%] vs. 28 [53%] patients, $p = 0.0001$, aOR = 0.12, 95% CI 0.04–0.38). IV milrinone (median duration of infusion, 5 [2–8] days) was prematurely discontinued owing to poor tolerance in 12 patients, mostly ($n = 10$) for "non/hardly-attained induced hypertension" (mean arterial blood pressure < 100 mmHg despite 1.5 µg/kg/min^{-1} of norepinephrine). However, this event was similarly observed in IV milrinone and control patients ($n = 10$ [24%] vs. $n = 11$ [21%], respectively, $p = 0.68$). IV milrinone was associated with a higher incidence of polyuria (IV milrinone patients had creatinine clearance of 191 [153–238] ml/min^{-1}) and hyponatremia or hypokalemia, whereas arrhythmia, myocardial ischemia, and thrombocytopenia were infrequent.

Conclusions: Despite its premature discontinuation in 29% of patients as a result of its poor tolerance, IV milrinone was associated with a lower rate of endovascular angioplasty and a positive impact on long-term neurological and radiological outcomes. These preliminary findings encourage the conduction of confirmatory randomized trials.

*Correspondence: lakhal_karim@yahoo.fr
[1] Service d'Anesthésie-Réanimation, Hôpital Laënnec, Centre Hospitalier Universitaire, 44093 Nantes Cedex 1, France
Full list of author information is available at the end of the article

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Introduction

Among the complex mechanisms yielding poor outcomes following aneurysmal subarachnoid hemorrhage (aSAH), cerebral vasospasm is an important contributor, although the magnitude of this contribution is debated [1]. Vasospasm is the arterial narrowing that occurs a few days after aneurysm rupture and exposes to brain ischemia through decreased cerebral blood flow [2]. Induced systemic hypertension (including the maintenance of euvolemia) and endovascular angioplasty (with intraarterial vasodilators and/or balloon angioplasty) are the main proposed curative options, along with nimodipine as prevention [2, 3]. Endovascular angioplasty implies important healthcare resource utilization, may not be available 24 h a day, 7 days a week and bears specific risks: arterial wall rupture [4], other catheter-related complications (thrombosis, embolism, hematoma, infection) [5–7], cerebral hyperperfusion [8], intrahospital transport-related [9–11] and anesthesia-related complications. Furthermore, endovascular angioplasty may be inappropriate if the vasospasm is diffuse (i.e., involving several arteries) rather than focal. Last, the success of endovascular angioplasty is often only transient and iterative procedures are therefore required [12, 13].

Owing to the paucity of therapeutic options and despite very low quality evidence to support its use [14], intravenous (IV) milrinone (a phosphodiesterase-3 inhibitor with cerebral vasodilatory properties) is increasingly used, either following prior intraarterial administration in order to sustain its effects or even as first-line therapy (along with induced hypertension) [14–18]. Data about IV milrinone in this setting are limited to seldom case series with no control group [14]. Concerns about milrinone immediate tolerance encompass its systemic hypotensive effects (whereas induced hypertension is proposed as treatment cornerstone for symptomatic vasospasm [2, 3]), increase in glomerular filtration rate (GFR) and its related hydroelectrolytic disturbances (whereas aSAH and vasospasm are, per se, associated with augmented GFR [19] and hyponatremia [20]), myocardial ischemia (via an increase in myocardial workload related to both milrinone inotropic and chronotropic properties and systemic hypertension-induced increase in left ventricle afterload), arrhythmia (related to milrinone [21] and norepinephrine properties [22] on top of myocardial ischemia and electrolytic disturbances), thrombocytopenia, and worsening of intracranial hypertension via the vasodilation-induced increase in cerebral blood volume [23]. Furthermore, whether the use of IV milrinone safely permits to withhold some endovascular angioplasty procedures is unknown. Importantly, controlled data about long-term impact of the use of IV milrinone are lacking [14].

The objectives of this observational controlled before–after study which compared patients receiving both IV milrinone and induced hypertension with patients receiving hypertension alone were the assessment of (1) 6-month functional disability (defined as a score of 2 to 6 on the modified Rankin Scale [mRS] [24]) and vasospasm-related brain infarction on imaging studies, (2) the rate of first-line or rescue endovascular angioplasty for vasospasm, and (3) IV milrinone immediate tolerance.

Methods

Ethical Considerations

At Nantes University Hospital, we have used IV milrinone for the treatment of cerebral vasospasm since 2015, initially only for refractory cases then, since 2017, it has been incorporated into routine care, a dedicated institutional written procedure guiding its use for moderate/severe vasospasms. In patients who were included prospectively (IV milrinone group), consent to use the data for this observational study was obtained from all participants (patients or their next of kin then the patients themselves if they regained capacity) after oral and written reminding of their rights. For patients included retrospectively (historical control cohort), informed consent was waived. Anonymity was respected. This research has been approved by an independent ethical committee (Comité de Protection des Personnes Sud-Ouest & Outre-Mer III, march 2018, N° 2017-A03347-46, amended in march 2019).

Patients

Our hospital being a reference center for aSAH, all patients who were treated for vasospasm following aSAH were admitted to our intensive care unit during the two study periods:

- IV milrinone group: consecutive patients included from June 2018 to January 2020 if they received IV milrinone.
- Control group: consecutive patients (from April to December 2014) included if they received induced hypertension. None received IV milrinone.

Since IV milrinone was used occasionally, without strict protocol, in the January 2015–May 2018 period, this period was not considered.

We did not include pregnant women and patients under 18 years old, patients with vasospasm unrelated to aSAH, patients under guardianship, or patients with no French health insurance.

Management of aSAH

All patients were managed in accordance with international guidelines [2, 3]. For vasospasm prevention, nimodipine (Nimotop, Bayer Healthcare, Loos, France) was administered for 21 days (enteral route if possible: 60 mg every 4 h; otherwise IV: 2 mg H^{-1}).

Vasospasm detection relied on thorough clinical examinations, at least daily transcranial color-coded duplex Doppler of middle cerebral arteries (combining a dynamic approach [25] to the commonly retained velocity thresholds [2]). Vasospasm was confirmed by computed tomography (CT) angiography and classified as mild (arterial narrowing of < 25% as compared with the reference CT angiography), moderate (25–50%), and severe (> 50%) [26].

Across the two study periods, our policy was an early treatment of vasospasm, even though not associated with clinical deterioration. Once the diagnosis of angiographic vasospasm was established, the intensivist and the neuroradiologist jointly determined the therapeutic strategy, taking into account several parameters (severity of the arterial narrowing, its diffuse/focal nature, associated clinical deterioration and/or perfusion defects, and existence of contraindication for milrinone). Across the two study periods, there was no change with regard to induced hypertension: maintenance of a mean arterial blood pressure (BP) of 100–120 mmHg was the cornerstone of the treatment of vasospasm. To achieve this BP target, euvolemia was maintained, antihypertensive drugs (except for nimodipine) were withheld and, if necessary, norepinephrine was infused. In the second study period, IV milrinone—in combination with induced hypertension—has been added to our therapeutic options for moderate-to-severe forms of vasospasm.

Milrinone IV administration strictly followed our institutional written protocol. One hour after the attainment of a mean BP of 100–120 mmHg, milrinone (Medac, Lyon, France) IV infusion rate was initially set at 0.5 µg/kg/min^{-1} and, if well tolerated and deemed necessary, was increased to a maximum of 1.5 µg/kg/min^{-1}, as proposed by Fraticelli et al. [15]. No bolus was administered. Close monitoring looked for contra-indications for milrinone (aortic or pulmonary valve stenosis, hypertrophic obstructive cardiomyopathy, acute coronary syndrome, threatening arrhythmia) and for poor tolerance: echocardiography and repeated (at least on a daily basis) electrocardiogram and measurements of plasma troponin, potassium (target level: 4.0–4.5 mmol/l^{-1}), magnesium (0.80–1.2 mmol/l^{-1}), adjusted calcium (≈2.2 mmol/l^{-1}), creatinine (plasma and urine) and platelets count. Again, priority was given to the attainment of BP target: if mean BP was below 100 mmHg despite high dose (1.5 µg/kg/min^{-1}) of IV norepinephrine, IV milrinone infusion rate was first decreased to 0.5 µg/kg/H^{-1} (if the dose was higher) and, if BP target was not attained yet, IV milrinone was discontinued. Other signs of poor tolerance (life threatening arrhythmia or high intracranial pressure for instance) prompted immediate discontinuation of milrinone. Weaning from milrinone was left to the discretion of the attending intensivist.

Collection of Data

Data of the IV milrinone group were collected prospectively except for neurological outcomes, extracted from patients' charts. Data of the control group were extracted from patients' charts. One intensivist (AH) performed data extraction to limit interobserver variability. He was not blinded to group assignment. Radiological images were reassessed by a neuroradiologist (PLA) blinded to group assignment. After a careful analysis of all radiological images (including those from the digital subtraction angiography), vasospasm-related cerebral infarctions were adjudicated as secondary to vasospasm and not, for instance, as a complication of endovascular aneurysm treatment. For this adjudication, several parameters were taken into account, such as the existence of arterial occlusion events during the coiling procedure, cerebral infarctions on CT scan(s) performed before the occurrence of vasospasm, perfusion defects (if CT scan with perfusion analysis has been performed) in the brain territory involved by a moderate-to-severe vasospasm.

Objectives

We performed a between-group comparison of the following:

1. The incidence of functional disability (mRS ≥ 2) [24] and vasospasm-related brain infarction at 6 ± 1 months,
2. The rate of first-line and rescue use of endovascular angioplasty,
3. And features of poor immediate tolerance of the treatment for vasospasm.

BP Tolerance

Because induced hypertension was treatment cornerstone [2, 3], poor BP tolerance of the treatment for

vasospasm was a "non/hardly-attained induced hypertension" defined as sustained (> 2 h) mean BP below 100 mmHg at a norepinephrine infusion rate not higher than 1.5 µg/kg/min[1], IV milrinone, if any, being infused at 0.5 µg/kg/min^{-1}. We also specifically assessed the impact of IV milrinone on BP and heart rate (before/during milrinone infusion).

Other Features

Incidence of arrhythmia (refractory to simple correction of hypokalemia and requiring an antiarrhythmic agent and/or electric shock), myocardial ischemia (Tc troponin > 200 ng/l^{-1} along with its significant increase since the initiation of therapy for vasospasm and/or with electrographic and/or echocardiographic evocative signs), high GFR (creatinine clearance > 120 and > 130 ml/min^{-1} 1.73 m^2 in women and men, respectively [27]), hyponatremia (< 136 mmol/l^{-1}), hypokalemia (< 3.4 mmol/l^{-1}), thrombocytopenia (< 150 g.l^{-1}), dramatic increase in intracranial pressure (requiring specific change in therapy).

Statistical Analysis

Creatinine clearance was calculated ([urine creatinine × 24-h urine output]/serum creatinine).

Categorical variables were expressed as count (%) and compared using the χ^2 test. Continuous variables were expressed as median [interquartile range] and compared using the Mann–Whitney U or Friedman test. $p < 0.05$ was considered significant.

Direct logistic regression was performed to assess the respective impact of covariates on the likelihood of fulfilling the studied outcomes, i.e., 6-month functional disability, vasospasm-related brain infarction, and use of endovascular angioplasty for vasospasm. A specific model was determined for each outcome. The plausible covariates (listed in Supplemental Tables 1–3) which were associated with each outcome in the univariate analysis ($p < 0.20$) were entered into the model in one single step. If necessary, the World Federation of Neurosurgical Societies (WFNS) grade (for the 6-month functional disability outcome) and the modified Fisher grade (for the vasospasm-related brain infarction outcome), were forced into the model. The relationship between the explanatory variables and the outcome was assessed by Cox & Snell R^2 and Nagelkerke R^2. Goodness of fit for the model was assessed by Hosmer–Lemeshow test.

As additional analyses, patients from each group were matched (1:1) with respect to aSAH initial severity or vasospasm severity (please see corresponding Supplemental Tables legends for details).

Last, to delineate the respective impact of the study period and that of IV milrinone infusion we performed a post hoc analysis among the subgroup of patients who did not receive IV milrinone or less than 1 day.

There was no imputation of missing data. Analyses were performed with MedCalc19.4.1 (Ostende, Belgium). This manuscript is in accordance with the STROBE statement for the reporting of case–control studies (Supplemental Checklist).

Study Size

For this pilot study, no sample size has been determined a priori. All consecutive patients fulfilling the inclusion criteria were included over the two study periods that we arbitrarily set. Nearly 40 patients were expected to be included in each group.

Results

Ninety-four patients were included: 41 and 53 in the IV milrinone and the control group, respectively (Fig. 1, Table 1). In the IV milrinone group, there was a higher BP at the time of vasospasm diagnosis (Fig. 2), a higher rate of severe angiographic vasospasm and a longer duration of induced hypertension (Table 1 and Supplemental Table 5). All patients received nimodipine for the prevention of vasospasm (from day 1) and during its treatment.

6-Month Outcomes

Rates of resumption of work and mortality at 6 months were similar in the two groups. However, 6-month functional disability (mRS ≥ 2) was less frequent in the IV milrinone group (Table 1). After adjustment for other covariates (Fig. 3 and Supplemental Table 1), IV milrinone infusion was significantly associated with a lower likelihood of 6-month functional disability (mRS ≥ 2, which occurred in 47 [50%] patients): adjusted odds ratio (aOR) = 0.28 (95% confidence interval [CI] 0.10–0.77), Similarly, IV milrinone infusion was independently associated with a lower likelihood of vasospasm-related brain infarction on imaging studies (which occurred in 22 [23%] patients): aOR 0.19 (95% CI 0.04–0.94) [see Supplemental Fig. 1 and Supplemental Table 2 for detailed univariate and multivariable analyses].

Endovascular Angioplasty for Vasospasm

Endovascular angioplasty involved fewer patients in the IV milrinone group as compared with control patients: 6 [15%] vs. 28 [53%] patients ($p = 0.0001$), aOR = 0.12 (95% CI 0.04–0.38, see Supplemental Tables 3–4 for detailed univariate and multivariable analyses). The number of procedures of endovascular angioplasty was lower in the IV milrinone group: 0 [0;0] vs. 1 [0; 2] procedure per patient ($p = 0.0001$). This was true for first-line and second-line (rescue) endovascular procedures (Table 1).

Table 1 Patients' characteristics and outcomes

Variable	IV milrinone ($n=41$)	Control ($n=53$)	p
Female sex	24 (58%)	33 (62%)	0.72
Age (years)	52 [45; 61]	55 [46; 64]	0.46
Tobacco use	17 (41%)	22 (41%)	1
Causal aneurysm in the anterior circulation	30 (73%)	46 (89%)	0.06
Rebleeding prevention within 24 h, coiling/clipping	40 (98%)/1 (2%)	49 (93%)/4 (7%)	0.28
WFNS			0.22
I	10 (24%)	10 (19%)	
II	14 (34%)	15 (28%)	
III	3 (7%)	4 (7%)	
IV	9 (22%)	13 (25%)	
V	5 (12%)	11 (21%)	
Modified Fisher scale			0.82
I	2 (5%)	3 (6%)	
II	2 (5%)	2 (4%)	
III	10 (24%)	9 (17%)	
IV	27 (66%)	39 (74%)	
SAPS II	27 [17; 40]	26 [22; 36]	1
Time from aneurysm rupture to vasospasm detection (days)	7 [5; 7]	7 [5; 9]	0.48
Vasospasm severity on CT scan[a]			0.003*
Severe	19 (46%)	18 (34%)	
Moderate	17 (42%)	14 (26%)	
Mild	5 (12%)	19 (36%)	
Insignificant	0 (0%)	2 (4%)	
Duration of induced hypertension (days)	7 [4; 10]	5 [4; 6]	0.004*
Endovascular angioplasty			
n patients	6 (15%)	28 (53%)	0.0001*
n procedures per patient	0 [0; 0]; max = 2	1 [0; 2]; max = 5	0.0001*
As initial treatment	1 (2%)	20 (38%)	0.0001*
With IA milrinone	1 (2%)	14 (26%)	0.002*
With balloon	1 (2%)	10 (19%)	0.01*
As second-line therapy[b]	5 (12%)	20 (38%)	0.006*
n procedures per involved patient	1 [1; 1]	2 [1; 2]	0.053
With IA milrinone	1 [1; 1]	1 [1; 2]	0.09
With balloon	1 [0; 1]	0 [0; 1]	0.53
n patients receiving IA milrinone	5 (12%)	23 (43%)	0.001*
ICU length of stay (days)	21 [13; 28]	21 [9; 30]	0.81
Hospital length of stay (days)	27 [19; 36]	35 [19; 52]	0.07
Ischemic sequalae on CT scan at 6 months	15 (50%)	15 (50%)	1
Probably related to the vasospasm	4 (10%)	18 (34%)	0.006*
Modified Rankin scale (6 months) < 3	31 (76%)	29 (55%)	0.038*
Modified Rankin scale (6 months) < 2	27 (66%)	20 (38%)	0.007*
Mortality at 6 months	4 (10%)	8 (15%)	0.44
Resumption of work (or previous activity) at 6 months	15 (37%)	16 (30%)	0.52

Results are expressed as median [interquartile range] or count (%)

CT, computerized tomography, ICU, intensive care unit, IV, intravenous infusion, IA, intraarterial infusion, [35], Modified Fisher scale, a specific scale of SAH initial severity on the computerized tomography scan [36], SAH, subarachnoid hemorrhage, SAPS II, simplified acute physiology score (a nonspecific severity score calculated 24 h after the admission in the intensive care unit), WFNS, World Federation of Neurosurgical Societies grade (a specific scale of SAH initial clinical severity)

[a] The findings on this CT scan yielded the initiation of the treatment for vasospasm. Vasospasm was classified as mild (arterial narrowing of < 25% as compared with the reference CT angiography), moderate (25–50%), and severe (> 50%). After retrospective reanalysis of all CT scan by an expert in neuroradiology (blinded to group assignment), two patients were found to have insignificant vasospasm, contrary to what was alleged before the initiation of a treatment for vasospasm

[b] Because of first-line treatment failure, poor tolerance, or insufficiently sustained effect

*$p > 0.05$

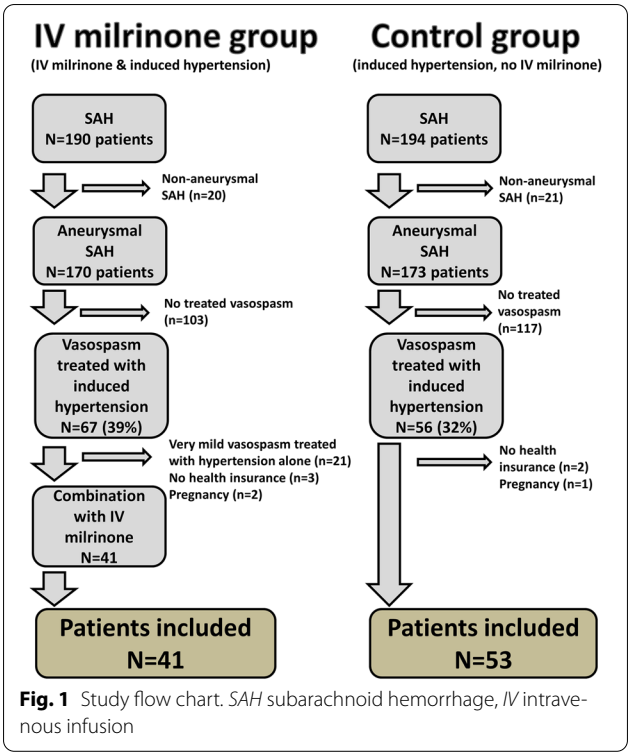

Fig. 1 Study flow chart. *SAH* subarachnoid hemorrhage, *IV* intravenous infusion

Search for Potential Biases

Patient matching with respect to aSAH initial severity or to vasospasm initial severity yielded similar findings (Supplemental Tables 5–6).

In addition, we attempted to delineate the respective impact of the study period and that of IV milrinone infusion. We focused on patients who were unlikely to have benefited from IV milrinone owing to short/lack of administration. Thus, among the 61 patients who either did not receive IV milrinone (53 patients from the first study period) or only less than 1 day (8 patients from the second study period), the study period was neither associated with 6-month functional disability nor with vasospasm-related brain infarction in multivariable analyses (Supplemental Tables 7–10). This suggests that IV milrinone rather than the study period could have determined 6-month outcomes.

Immediate Tolerance of IV Milrinone

Overall, 223 days of milrinone IV infusion were analyzed in 41 patients (median duration of infusion: 5 [2; 8] days/patient). In 12 patients (29%), IV milrinone was discontinued prematurely because of poor tolerance, mostly ($n=10$) for "non/hardly-attained induced hypertension" (Supplemental Fig. 2). In eight patients, poor tolerance occurred within the first day of infusion, in 11 patients before day 2.

Impact of IV Milrinone on BP

One (2%) and 14 (26%, $p=0.002$) IV milrinone and control patients, respectively, received intraarterial milrinone as first-line therapy and were excluded from this very specific analysis. After the induction of hypertension (before IV milrinone, if any), median BP was similar in the two groups as well as norepinephrine requirement. The initiation of IV milrinone was associated with a decrease in BP, partly counterweighted by an increase in norepinephrine dosage (Fig. 2). At day 1, volume expansion was more abundant in the IV milrinone group (1000 [375; 2000] vs. 0 [0; 1000] ml of crystalloid, $p=0.0002$).

The incidence of "non/hardly-attained induced hypertension," over the whole duration of treatment for vasospasm, was similar in the two groups (Table 2 and Supplemental Table 11). This event was often contemporaneous with sepsis.

Arrhythmias

The initiation of IV milrinone was associated with an increase in heart rate (Supplemental Fig. 3). During treatment for vasospasm, the incidence of arrhythmia was similar in the two groups (6 vs. 7%, Table 2). It was supraventricular arrhythmia (atrial fibrillation or frequent extrasystoles) except in one patient who experienced a transient (a few seconds) episode of ventricular tachycardia yielding, as a precaution, IV milrinone discontinuation. IV milrinone had to be stopped in another patient because of a poorly tolerated atrial fibrillation in a context of contemporaneous sepsis.

Myocardial Ischemia

Plasma troponin Tc increased by 14 [7;31] ng/l during IV milrinone infusion and peaked higher in the IV milrinone group than in control patients (Table 2). However, the incidence of troponin Tc level exceeding 200 ng/l^{-1} was low ($\leq 5\%$) and similar in the two groups (Table 2). IV milrinone was discontinued in two patients because of a high or a threateningly increasing troponin Tc level (Supplemental Fig. 2). In both patients, troponin decreased after milrinone discontinuation and coronary exploration was not deemed necessary by the attending cardiologist.

High GFR

In IV milrinone patients, creatinine clearance peaked at 191 [153; 238] ml min^{-1} and 31 patients (76%) experienced high GFR. In control patients, since urine creatinine was seldom available, creatinine clearance could not be analyzed. As a surrogate, daily urine output (mean per

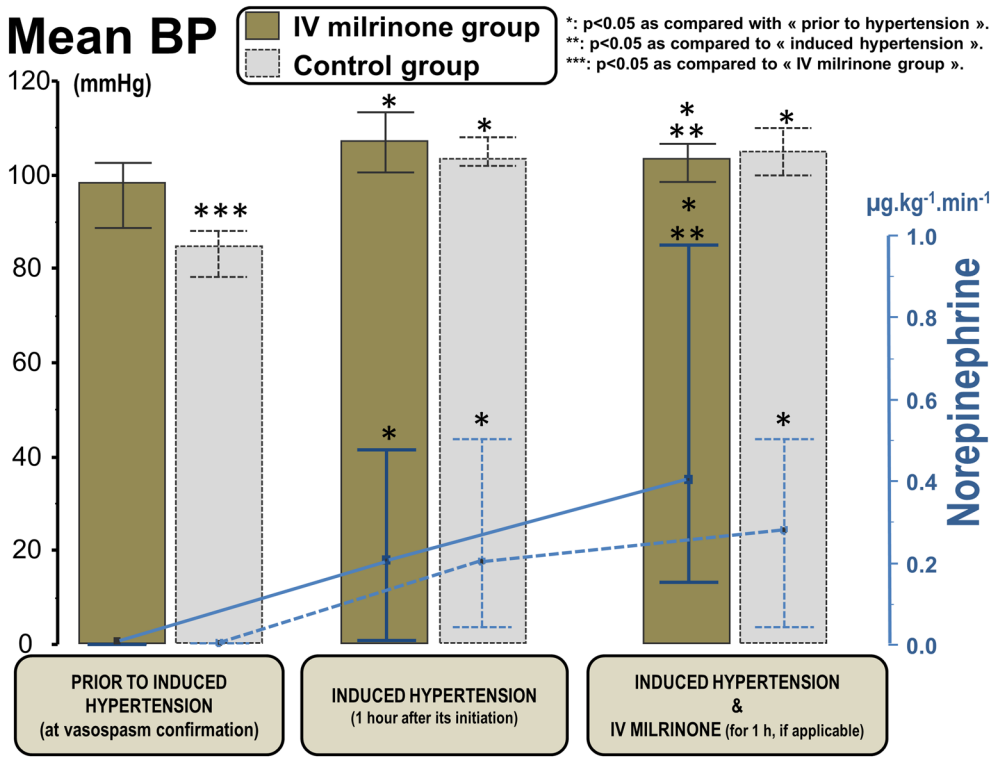

Fig. 2 Impact of IV milrinone on arterial blood pressure. Results are expressed as median [interquartile range]. After CT scan confirmation of vasospasm, induced hypertension (mean BP target of 100–120 mmHg) was started and followed (in the IV milrinone group only), one hour later, by the initiation of IV milrinone (0.5 µg kg H^{-1}). BP and norepinephrine requirements were collected one additional hour later. For this very specific analysis of IV milrinone effects on BP, patients who received intraarterial milrinone as initial therapy were excluded (1 [2%] and 14 [26%] patients of the IV milrinone and control group, respectively). At vasospasm confirmation, mean BP was higher in the IV milrinone group than in the control group, possibly because vasospasm was more severe in the former. The main message of this figure is that IV milrinone induced a decrease in BP which had to be counterweighted by an increase in norepinephrine dosage. *BP* arterial blood pressure, *CT* computerized tomography, *IV* intravenous infusion

patient over the duration of treatment for vasospasm) was higher in the IV milrinone group: 4155 [3058; 5244] vs. 2300 [1976; 2997] ml, $p < 0.0001$. Hyponatremia and hypokalemia occurred more frequently during IV milrinone infusion (Table 2).

Others

Thrombocytopenia did not occur (Table 2).

Intracranial pressure increase prompted IV milrinone discontinuation in one patient with impaired cerebral compliance.

Discussion

The main findings of this first controlled study assessing IV milrinone as treatment for cerebral vasospasm after aSAH are that, despite a higher degree of angiographic severity of vasospasm, despite premature discontinuation of IV milrinone because of poor tolerance in 29% patients and despite a higher incidence of polyuria and hydroelectrolytic disturbances as compared with induced hypertension alone, IV milrinone was associated with a lower rate of endovascular angioplasty and a lower likelihood of 6-month functional disability and vasospasm-related brain infarction.

A few published reports addressed the effects of intraarterial and/or IV milrinone as treatment for vasospasm [14, 26, 28]. Fewer articles reported its safety. These reports mostly consist in single-center case report/series including from 1 to 110 patients, most of them being retrospective [14, 26, 28]. For several reasons, a comparison of results across studies is tricky. First, milrinone modalities of IV infusion markedly vary from one study to another with respect to dosage (ranging from 0.5 [29] to 2.5 µg/kg/min^{-1} [26]), duration (from a few days to 2 weeks [15, 16, 30]) and combination or not with prior intraarterial administration [14]. The dose of IV milrinone we administered (0.5 µg/kg/min^{-1} possibly incremented progressively to 1.5 µg/kg/min^{-1}) was the one used in the hallmark case series by Fraticelli et al. [15] and lies

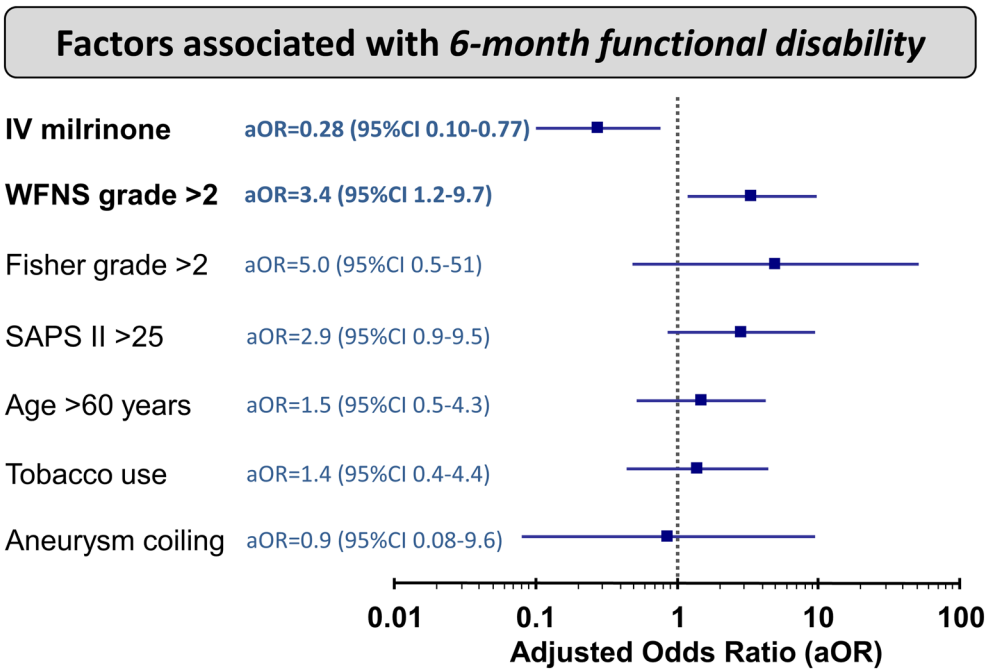

Fig. 3 Factors associated with 6-month functional disability (multivariable analysis). Six-month functional disability was defined as a score of 2 to 6 on the modified Rankin Scale. Factors associated with 6-month functional disability were assessed using logistic regression: clinically plausible variables associated with this outcome in the univariate analysis ($p < 0.2$ in Supplemental Table 2) were entered into the model in one single step. The adjusted odds ratios (ORs) and their respective 95% confidence interval (95%CI) represent the odds for 6-month functional disability after adjusting for the covariates listed in the figure. ORs to the right of midline (where OR = 1) indicate higher odds of 6-month functional disability while OR to the left of the midline indicate lower odds of this outcome. In this model, the IV milrinone study period and a WFNS grade of 3 to 5 were independently and significantly (95%CIs not crossing the midline) associated with favorable and unfavorable functional disability, respectively. The relationship between the explanatory variables and the outcome was assessed by Cox & Snell $R^2 = 0.28$ and Nagelkerke $R^2 = 0.37$. Goodness of fit for the model was assessed by Hosmer–Lemeshow test ($p = 0.20$). The model was associated with an honorable area under the receiver operating characteristics (ROC) curve of 0.80 (95% CI 0.71–0.88). IV, intravenous infusion, SAPS II, simplified acute physiology score II (a nonspecific severity score calculated 24 h after the admission in the intensive care unit), WFNS, World Federation of Neurosurgical Societies grade (a specific scale of SAH initial clinical severity) [35].

in the range used in several series [31]. Second, owing to the gap of knowledge about optimal BP in this setting [2, 32], between-study heterogeneity exists for BP targets, which range from no induced hypertension as first-line therapy [26] to mean BP of 100–120 mmHg in our study. This heterogeneity impacts norepinephrine requirements and the incidence of hemodynamic (BP, arrhythmia) and renal side effects. Third, between-study heterogeneity also exists for the criteria used to define poor tolerance of milrinone. Last, previous reports did not include a control group. Hence, attributing some observed side effects to milrinone is challenging. This is the first controlled study assessing IV milrinone as treatment for cerebral vasospasm after aSAH, whereas one previous study addressed preventive infusion of milrinone [29]. This previous study, not indexed in PubMed, was not devoid from important limitations, as recently underscored [14]. Overall, although most authors agreed that milrinone side effects were uncommon, our controlled study refines this statement: in 29% of patients, IV milrinone had to be discontinued prematurely. Importantly, this event frequently (8 out of 12 patients) occurred within the first day of infusion, enabling alternative therapeutic options to be considered. In addition, this study confirms that, even at low dose (0.5 µg/kg/min^{-1}), IV milrinone is associated with a decrease in BP and an increase in heart rate, a finding not consistently observed in previous studies [12, 15].

Importantly, besides safety findings, we herein report that IV milrinone was significantly associated with a reduction in the rate of endovascular procedures and, even more remarkably as angiographic vasospasm was more severe in the IV milrinone group, with a reduction of incidence of 6-month functional disability and vasospasm-related brain infarction.

Table 2 Incidence of adverse events during the treatment of vasospasm

Adverse event	IV milrinone group $n=41$	Control group $n=53$	p
Non/hardly-attained of induced hypertension[a]	10 (24%)	11 (21%)	0.68
Contemporaneous sepsis[b]	5/10 (50%)	8/11 (73%)	0.30
Arrhythmia	3 (7%)	3 (6%)	0.75
Thrombocytopenia (< 150 g/l^{-1})	0 (0%)	0 (0%)	1
Lower platelet count during vasospasm treatment (g/l^{-1})	237 (211; 302)	248 (205; 275)	0.76
Troponin Tc ≥ 200 ng/l^{-1}	1/41 (2%)	2/42 (5%)	0.57
Maximum troponin Tc (ng/l^{-1}) during vasospasm treatment	26 (16; 51), n = 41	13 (8; 30), n = 42	0.03*
Increase in troponin Tc from vasospasm diagnosis and its maximum level during treatment (ng/l^{-1})	14 (7 – 31)	–	–
Hyponatremia (< 136 mmol/l^{-1}) or hypokalemia (< 3.4 mmol/l^{-1})	27 (68%)	23 (43%)	0.02*
Hyponatremia (< 136 mmol/l^{-1})	19 (48%)	17 (32%)	0.13
Nadir level of plasma sodium (mmol/l^{-1})	136 (133; 138)	137 (134; 138)	0.14
Hypokalemia (< 3.4 mmol/l^{-1})	12 (30%)	12 (23%)	0.42
Nadir level of plasma potassium (mmol/l^{-1})	3.5 (3.3; 3.7)	3.7 (3.5; 3.8)	0.053
Daily urine output (ml, mean during treatment)	4155 (3058; 5244)	2300 (1976; 2997)	< 0.0001*
Creatinine clearance (maximum during treatment, ml/min^{-1}/1.73 m^2)	191 (153; 238)	–	–
High GFR[c]	31 (76%)	–	–

Troponin Tc has not been measured at the time of vasospasm diagnosis in the control group. Its variation was therefore not available in this group. Urine creatinine was not available in most patients of the control group. Results are expressed as median [interquartile range] or count (%)

BP blood pressure, *IV* intravenous infusion, *GFR* glomerular filtration rate

[a] Defined as a sustained (> 2 h) mean BP below 100 mmHg at a norepinephrine infusion rate not higher than 1.5 µg/kg/H^{-1} (a threshold we arbitrarily considered as reasonable), IV milrinone (if applicable) being infused at 0.5 µg/kg/H^{-1}

[b] Contemporaneous sepsis was defined as the initiation of an antimicrobial therapy 2 days before or 2 days after the initiation of the therapy for vasospasm

[c] High GFR was defined as creatinine clearance > 120 and > 130 ml/min 11.73 m^2 in women and men, respectively

*$p > 0.05$

Study Limitations

First, this is a single-center observational study of limited size combining retrospectively (control group) and prospectively collected data. Despite efforts (multivariable analyses, patients matching, attempt to delineate the impact of the study period) made to minimize potential biases, the observational before–after study design inherently precludes drawing definitive conclusions about causality between IV milrinone administration and outcomes. Indeed, uncaptured differences between the two study periods, i.e., between the IV milrinone and control groups, may have affected the differences in outcomes we observed. These potential differences encompass possible changes in neurocritical care across the two study periods at our institution.

Second, induced hypertension was the cornerstone of the treatment for vasospasm in our population, as recommended by international guidelines [2], although evidence on its effectiveness is limited [32].

Third, because half of control patients received endovascular angioplasty (only 15% in the IV milrinone group), this observational study did not specifically compare induced hypertension plus IV milrinone versus hypertension alone. Indeed, an influence on the novel regimen with IV milrinone on the policy to perform angioplasty is likely. Hence, except for the very specific analysis of the effects of IV milrinone on BP and heart rate, this study rather compared two strategies, in a pragmatic manner, one included IV milrinone and the other did not, both with an on-demand resort to endovascular angioplasty. This study is complementary to the retrospective study by Crespy et al. [28] which reported that intraarterial followed by IV milrinone ($n=24$ patients) was not superior to IV milrinone alone ($n=77$) in terms of reversion rate of vasospasm and neurological outcome.

Fourth, we arbitrarily set that, if norepinephrine dosage exceeded 1.5 µg/kg/min^{-1}, a decrease/withholding in/of milrinone dosage should be considered. However,

some patients may benefit from IV milrinone along with a higher dosage of norepinephrine. This would yield a lower rate of patients in whom IV milrinone have to be discontinued prematurely as compared with that reported in the present study (29%).

Fifth, data about 6-month neurological outcome were collected from patients' charts. Data abstractor was neither specifically trained for this purpose nor blinded to the study group. This could have introduced bias. However, the same investigator performed data collection in both groups, therefore preventing interobserver variability. In addition, for the control group, we herein report a neurological 6-month outcome similar to that reported in a study involving patients with aSAH admitted to our intensive care unit and who (or their relatives) were interviewed over the telephone [33]. Furthermore, there was no lost to follow-up.

Sixth, adjudicating cerebral infarctions as secondary to vasospasm and not as a complication of aneurysm treatment may be challenging. A brain imaging procedure performed in between is useful for this discrimination. Of note, a significant proportion of patients had at least one CT scan or magnetic resonance imaging in the period ranging from the day after the aneurysm treatment (coiling or clipping) to the day vasospasm was diagnosed (with exclusion of the CT scan which made the diagnosis of vasospasm) and, importantly, this proportion was not lower in the group of patients with the higher rate of cerebral infarctions adjudicated as vasospasm-related, i.e., the control group: 23/41 (56%) versus 35/53 (66%) in the IV milrinone and the control group, respectively ($p = 0.33$). In addition, some cerebral infarctions adjudicated as secondary to vasospasm could have been unrelated to vasospasm but rather caused by other mechanisms such as microthrombi, late embolic events, inflammation, or cortical spreading depolarization, whereas IV milrinone may be only effective on vasospasm. However, a cerebral infarction occurring in a brain area involved by a vasospasm seen on brain imaging is, to our opinion, unlikely to be fully unrelated to vasospasm. Importantly, this theoretical limitation of the study applies similarly to both patient groups.

Last, positive effects of IV milrinone on long-term neurological outcomes may encompass the avoidance of endovascular angioplasty-related specific complications, although not herein collected. Nor did we measure the cost savings associated with the reduction in both the rate of endovascular procedures and long-term functional disability which are expected to be substantial.

Conclusions

A strategy including IV milrinone may be regarded as a sufficiently safe option to conduct randomized controlled studies [34] aiming at confirming the promising findings of the present pilot study.

Supplementary Information

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Author details

[1] Service d'Anesthésie-Réanimation, Hôpital Laënnec, Centre Hospitalier Universitaire, 44093 Nantes Cedex 1, France. [2] Department of Diagnostic and Therapeutic Neuroradiology, University Hospital of Nantes, Nantes, France. [3] Institut du Thorax, Institut National de la Santé et de la Recherche Médicale (INSERM), Centre National de la Recherche Scientifique (CNRS), Université de Nantes, 44093 Nantes, France.

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Author Contributions

KL contributed to the conception and design of the study, the collection of clinical data, the statistical analysis, and the drafting and revision of the article. AH contributed to the conception and design of the study, the collection of clinical data, and the drafting and revision of the article. PLA contributed to the collection of radiological data and the revision of the article for its important intellectual content. MF contributed to the collection of clinical data and revision of the article for its important intellectual content. VRE contributed to the collection of clinical data and revision of the article for its important intellectual content. PART contributed to the collection of clinical data and revision of the article for its important intellectual content. XA contributed to the collection of clinical data and revision of the article for its important intellectual content. RB contributed to the interpretation of data and revision of the article for its important intellectual content. BR contributed to the interpretation of data and revision of the article for its important intellectual content. JC contributed to the conception and design of the study and the drafting and revision of the article. All authors approve of the final manuscript.

Source of Support

None.

Availability of data and materials

The datasets used and/or analysed during the current study areavailable from the corresponding author on reasonable request.

Conflicts of interest

KL has no conflict of interest in connection with the work submitted. In addition, KL received, during the past 3 years, congress registration fees from Sanofi Aventis (once in 2018), travel fees from Merck Sharp & Dohme (MSD) France (once, in 2017), Gilead Sciences (once, in 2017), pfizer (twice, in 2019 and 2020) and Correvio (twice, in 2020). BR has no conflict of interest in connection with the work submitted. In addition, BR received, during the past 5 years, lecture fees from Fisher&Paykel, Baxter, LFB, Aspen, research grants from Baxter and consulting fees from LFB, Astra Zeneca. None of the other authors has any financial or nonfinancial competing interest in connection with this study.

Ethical Approval/Informed Consent

This research involving human subjects complied with all relevant national regulations, institutional policies and is in accordance with the tenets of

the Helsinki Declaration (as revised in 2013). At our institution, intravenous milrinone has been incorporated into routine care several years ago, a dedicated institutional written procedure guiding its use for moderate/severe vasospasms. In patients who were included prospectively (IV milrinone group), consent to use the data for this observational study was obtained from all participants (patients or their next of kin then the patients themselves if they regained capacity) after oral and written reminding of their rights. For patients included retrospectively (historical control cohort), informed consent was waived. Anonymity was respected. This research has been approved by an independent ethical committee (Comité de Protection des Personnes Sud-Ouest & Outre-Mer III, March 2018, N° 2017-A03347-46, amended in march 2019).

Clinical Trials Registration
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