Université de Poitiers
Faculté de Médecine et Pharmacie

ANNEE 2024

THESE
POUR LE DIPLOME D'ETAT
DE DOCTEUR EN MEDECINE
(décret du 25 novembre 2016)

Présentée et soutenue publiquement
le 14 octobre 2024 à Poitiers
par Madame Chloé VILLARET

COROSPASM

Interest in the use of milrinone in secondary prevention of cerebral vasospasm in patients with aneurysmal subarachnoid hemorrhage.

COMPOSITION DU JURY

Président : Monsieur le Professeur Rémy GUILLEVIN

Membres :

Monsieur le Professeur Marc PACCALIN

Monsieur le Docteur Stéphane VELASCO

Directeur de thèse : Monsieur le Docteur Samy BOUCEBCI

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UNIVERSITE DE POITIERS

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Je vous aime.

Table des matières

ABBREVIATIONS

(A)SAH : (Aneurysmal) subarachnoid hemorrhage

CVS : Cerebral vasospasm

DCI : Delayed cerebral ischemia

EVT : Endovascular treatment

RI : Resistance index

CT : Computed tomography

MRI : Magnetic resonance imaging

CTA : Computed tomography angiography

CTP : Computed tomography perfusion

MTT : Mean transit time

CBF : Cerebral blood flow

CBV : Cerebral blood volume

TCD : Transcranial doppler

mRS : Modified Rankin scale

IA : Intra-arterial

IV : Intravenous

ICA : Internal carotid artery

MCA : Middle cerebral artery

ACA : Anterior cerebral artery

PCA : Posterior cerebral artery

PICA : Posterior inferior cerebellar artery

INTRODUCTION

Subarachnoid hemorrhage (SAH) caused by aneurysm rupture is a serious condition with mortality exceeding 30% (1). The global incidence of SAH, considering all causes, is approximately 9 cases per 100,000 people annually, primarily affecting individuals aged 40 to 60 (1,2).

Among survivors, the most concerning complication is cerebral ischemia which occurs in about 30% of patients, mainly between the 4^{th} and 10^{th} days after the initial hemorrhage (3). While some signs of cerebral ischemia are reversible, it can progress to cerebral infarction, leading to severe disability or death (3).

Due to its late onset, this complication is often called “delayed cerebral ischemia” (DCI). It is mostly associated with cerebral vasospasm (CVS), which affects 30 to 40% of patients and is the primary cause of DCI in 20 to 30% of cases (4). Despite various therapeutic efforts, the management of vasospasm and DCI remains challenging.

Intraluminal balloon angioplasty, introduced in the late 1980s, is highly effective at reversing CVS but carries risks such as arterial damage and wall rupture (5). Chemical angioplasty, involving intra-arterial infusion of vasodilators, is a less but still an invasive alternative (5).

Therefore, a multitude of studies are focused on identifying secure pharmacological treatments for the prevention of cerebral vasospasm.

Phosphodiesterase III inhibitors, like milrinone, commonly used for heart failure, have shown promising results in treating CVS in both experimental models and selected patients, providing vasodilation and inotropic benefits (6–8).

Since 2015 at the University Hospital of Poitiers, we have been using milrinone to alleviate CVS. However, due to its side effects and the lack of extensive studies on the subject, milrinone is not yet considered a standard treatment for patients with aneurysmal SAH (ASAH) (9).

It seemed interesting to us to compare patients with ASAH before and after the introduction of milrinone into our monitoring protocol, to see if it influenced their outcomes.

In this study, we hypothesized that the use of milrinone for secondary prevention of CVS could reduce the incidence of endovascular treatment (EVT) and prevent the onset of cerebral ischemia in patients who experienced an ASAH.

MATERIALS AND METHODS

Study design

We made an observational and single-center study and our data were retrospectively gathered from electronic files and images.

We screened our hospital records for patients admitted in our center after ASAH between January 2012 and December 2023, who underwent computed tomography perfusion (CTP).

Patients were divided into two groups: one before the use of milrinone, prior to 2015, and another group since the use of milrinone, starting in 2015.

Definition of outcomes

The primary endpoint was the treatment of CVS by EVT.

The secondary outcome was the onset of DCI during these two eras.

Patient identification

Inclusion criteria

All adult patients (> 18 years old) with ASAH who underwent a CTP at the University Hospital of Poitiers between January 2012 and December 2023 were included.

Non-inclusion criteria

Patients with subarachnoid hemorrhage of unknown etiology, mycotic or traumatic-induced pseudoaneurysms, and aneurysms associated with arteriovenous malformations were not included.

Exclusion criteria

Patients with an uncomplete follow-up, insufficient quality of CTP and those who were initially managed in another center were excluded.

Local protocol

According to our institutional policy, all patients with ASAH, treated either by endovascular or open surgery, received intensive care and the standard medical treatment for the prevention of vasospasm. These patients were monitored clinically and by daily transcranial doppler (TCD) for impending signs of vasospasm. On suspicion on any of the two, the vasospasm was further confirmed by CTP. In case of absence of clinical, biological, or TCD abnormalities, a follow-up CTP was performed

on day 6. If there was no vasospasm, another scan was repeated 4 days after; in case of vasospasm, a follow-up scan was repeated 2 days after. Monitoring concludes on day 14 post-hemorrhage or when two consecutives CTP were normal (Appendix 1).

In case of vasospasm with an impact on perfusion mapping, a diagnostic and potentially therapeutic arteriography was indicated, followed by IV milrinone therapy. If there was no impact on perfusion mapping, the initiation of IV milrinone alone was discussed between the neurointensivists and interventional neuroradiologists.

Regarding the usage protocol of milrinone in the neurointensive care unit of the University Hospital of Poitiers, milrinone was administered intravenously by bolus via a central venous line on a dedicated line separate from the norepinephrine line, 100 µg/kg over 30 minutes, which is 8 mg over 30 minutes for a 70 kg adult. A maintenance treatment via syringe pump was started after the bolus at a dose of 0.5-1 µg/kg/min. Dosages should be reduced by one-third if creatinine clearance is between 30-50 ml/min, and by half if clearance is less than 30 ml/min.

Imaging method

TCD allows us the study of blood flow velocities (cm/s) and the resistance index (RI) of intracranial vessels, subject to an adequate acoustic window in the temporal region and a trained operator (10). In practice at the University Hospital of Poitiers, a CTP was recommended if transcranial Doppler showed average velocities above 150 cm/s or a variation in average velocity greater than 50 cm/s within 24 hours.

Before 2019, most of CTP scan was performed using a 40-slices computed tomography (CT) scan (BRILLANCE 40, Philips) and a 640-slices CT scan (Aquilion ONE Genesis, Canon).

After 2019, most of CTP was performed using a 128-slices CT scan (Somatom Go-Top, Siemens) and some were performed using another 640-slices CT scan (Aquilion ONE Genesis, Canon).

Using the 128-slices CT scan, first a non-contrast encephalic CT was performed with the following parameters: caudal-cranial direction, gantry rotation time of 1 second, detector collimation of 64 x 0,60 mm, tube voltage of 120kV, pitch of 0,55. The scanning time was 9,3 seconds.

Then, a CT angiography (CTA) was performed after injecting iodine-based contrast media: 45ml of intraveinous contrast agent (Iomeron 400, Bracco) injected through an

antecubital vein at 4ml/s followed by 40ml of isotonic saline solution at 4ml/s. The scanning time was 4,8 seconds.

A CTP was performed injecting 50ml of intravenous contrast agent at 5ml/s followed by 45ml of isotonic saline solution at 5ml/s, starting 5 minutes after the CTA, acquisition window of 40mm. The scanning time was 44 seconds.

For the 640-slices CT scan, the same protocol was used with the following parameters: caudal-cranial direction, gantry rotation time of 0,75 second, detector collimation of 40 x 0,5 mm, tube voltage of 120kV, acquisition window of 140mm. The scanning time was 10 seconds.

Non-contrast head CT was done to reassess the bleeding, look for other complications (hydrocephalus, etc.), verify the positioning of probes (intracranial pressure, drainage catheter, etc.), CTA to look for arterial narrowing and CTP to look for perfusion evidence of vasospasm.

The interpretation of perfusion maps is primarily based on mean transit time (MTT), which is the average time it takes for blood to pass through the capillary network, on cerebral blood volume (CBV), which is the fraction of cerebral parenchyma occupied by blood vessels, and on cerebral blood flow (CBF). 'Perfusion' vasospasm was defined by an increase of MTT in the territory of an arterial narrowing and was considered compensated in the absence of an impact on CBV and CBF and no longer compensated if these parameters decreased.

To identify infarctions related to DCI, patients underwent a follow-up brain magnetic resonance imaging (MRI) at 3 months, or a cerebral CTA in cases where MRI was not possible. In the absence of imaging at 3 months, we relied on the patient's most recent brain imaging.

Statistical analysis

Descriptive analysis of the incidence rates

We first studied the occurrence of EVT events and DCI incidence in patient who presented an aneurysm rupture. The frequency of events (%) and the incidence rate (%) were graphically inspected for their change across the years.

Risk modeling

Endovascular treatment

Multivariable Cox proportional hazard model (MCPM) was used to model the hazard rate of getting an endovascular treatment. We used the terminology of survival to refer to the chance of not undergoing endovascular treatment and/or not getting a DCI at 3 months. We verified beforehand the assumption of proportional hazard which supposes that the ratio of hazard between the two groups (before 2015 and after 2015) was constant over time. In case a patient had multiple endovascular treatments, only the first occurrence was set to be the event of interest. The Logrank Test was used to compare the survival distribution of two groups of patients.

DCI

DCI risk before and after 2015 was estimated using a Multivariable Weighted Logistic Regression (MWLR) incorporating spasm levels, age and sex as covariates in the model.

The odd ratios estimated from the MWLR were used to determine the odds of having a DCI in period where milrinone was used (after 2015) versus when it wasn't yet instaured (before 2015). For this analysis, because we observed years of vacillation in the introduction of milrinone, complete years of data were selected: from 2012 to 2014 representing the sample before milrinone and 2018 to 2023 representing the sample after milrinone.

Statistical-test and software

Cox model was implemented in R using *survival* package.

Baseline characteristics and demographics were summarized with descriptive statistics; mean value and Standard Deviation (SD). Group comparison was assessed using Chi-square test for qualitative variables and Wilcoxon-test or student t-test for quantitative variables. Statistical significance level was set at 0.05 and all analysis was performed using R Statistical Software (R version 4.3.2, R Core Team 2023).

RESULTS

Study sample

From January 1, 2012, to December 31, 2023, 482 patients were studied, 73 in the group before the introduction of milrinone in 2015 and 409 in the group after.

A total of 33 vasospastic territories were treated using endovascular method before 2015 (over 73 patients) and 108 after (over 409 patients). 93 patients were treated using milrinone only after 2015.

We noticed 21 DCI before 2015 and 71 after.

Patient characteristics and selection

Table 1. Demographics – Period Before 2015 and After 2015

	Before (n=73)	After (n=409)	*p*
Population Characteristics			
Mean Age (sd)	63.14 (10.55)	61.12 (11.34)	0.14
Female, n (%)	46 (63.01)	265 (64.79)	0.79
Aneurysm Location n, (%)			0.472
Anterior circulation	66 (90,42)	344 (84,75)	
Posterior circulation	7 (9,59)	62 (15,27)	
Aneurysm Treatment n, (%)			0.98
Coiling	67 (91.78)	376 (91.93)	
Surgical	2 (2.74)	9 (2.20)	
WEB	0 (0.00)	5 (1.22)	
Flow Diverter	3 (4.11)	12 (2.93)	
0	1 (1.37)	7 (1.71)	
Radiological Status, initial CT			0.233
Modified Fisher Scale, n (%)			
IV	63 (86.30)	359 (87.78)	
III	10 (13.70)	34 (8.31)	
II	0 (0.00)	10 (2.44)	
I	0 (0.00)	6 (1.47)	
Vasospasme Treatment n, (%)			< 0.001
Endovascular	33 (45.21)	108 (26.41)	
Milrinone	0 (0.00)	93 (22.74)	
No Treatment	40 (54.79)	208 (50.86)	
Delayed Cerebral Ischemia n, (%)			0.05
DCI event	21 (29.17)	71 (18.49)	

Demographics data, aneurysm location, aneurysm treatment, Fisher score, vasospasm treatment and DCI events are presented in Table 1.

The anatomic distribution of aneurysms was: Anterior circulation which includes anterior communicating artery, the internal carotid artery (ICA), posterior

communicating artery, anterior, middle and posterior cerebral artery (ACA, MCA and PCA); Posterior circulation which includes vertebrobasilar circulation and its branches such as the posterior inferior cerebellar artery (PICA) (11).

Modified Fisher Scale was determined based on the initial scan.

Patients in both groups were statistically comparable, with a median age of around 60 years old, and a majority of women, anterior circulation aneurysms, aneurysm treatment by coiling and Fisher scale IV subarachnoid hemorrhage in both groups.

Procedural characteristics

After the year 2015, all patients undergoing either chemical or mechanical angioplasty received adjunctive maintenance milrinone via syringe pump.

Only one patient in 2016 required discontinuation of milrinone therapy due to poor clinical tolerance (hemodynamic failure).

Outcome

Descriptive analysis

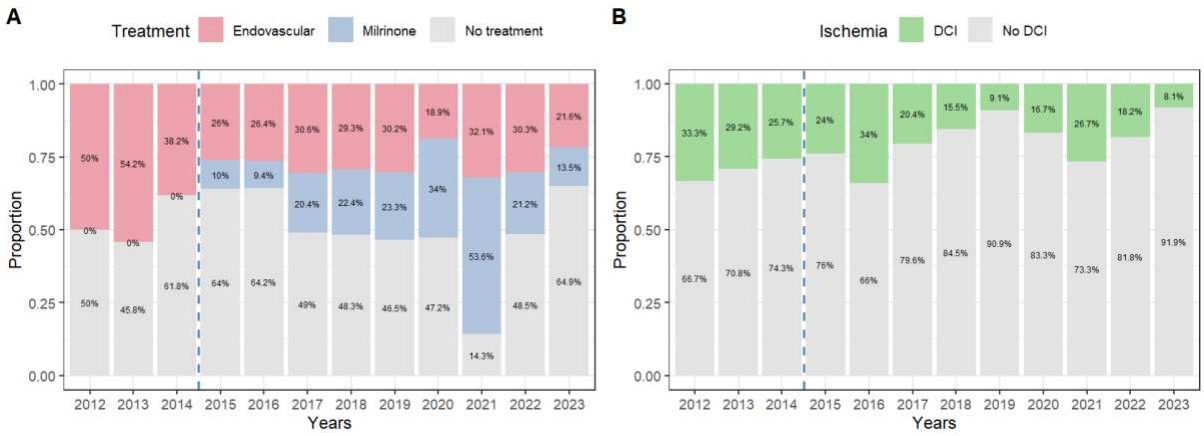

Figure 1. Percentage of Patients (A) by treatment, (B) by DCI events. Dashed line indicates the initiation of milrinone.

In Figure 1A, we observe a trend towards a decrease in EVT over the years, particularly since the introduction of milrinone at the end of 2014. In Figure 1B, there is also a noticeable trend towards a reduction in the incidence of DCI over the years.

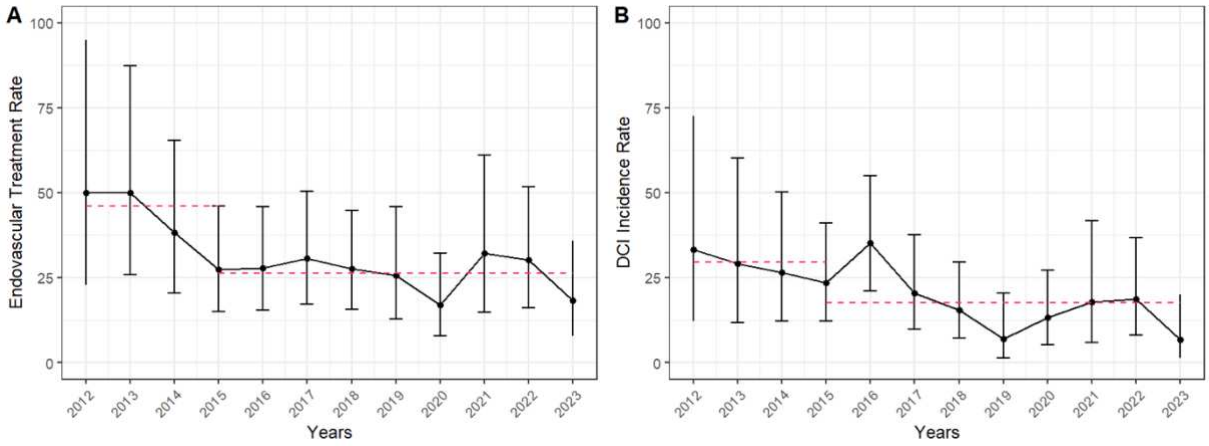

Figure 2. Time Series of the Incidence rates. **(A)** Endovascular Treatment cases, **(B)** DCI events. Dashed line represents mean level for each period.

Figure 2 shows a decrease in the mean level of the incidence rates of EVT and DCI between the two study periods, before and after 2015. This suggests a possible effectiveness of milrinone in the prevention of DCI.

Risk modeling

Samples characteristics summary is reported in Table 3.

Table 3. Comparison of characteristics and outcomes of patients before 2015 (2012 to 2014) and after 2015 (2018 to 2023).

	Before (n=65)	After (n=139)	*p*
Covariates			
Mean Age (sd)	63.00 (10.31)	58.23 (10.44)	0.003
Female, n (%)	40 (61.54)	99 (71.22)	0.19
Vasospasm severity n, (%)			
No Spasm of T-carotid*	43(66.15)	77(55.40)	
<50%	10(15.38)	41(29.50)	0.09
>50%	12(18.46)	21(15.11)	
Outcomes			
Endovascular Treatment n (%)			
Yes	32 (49.23)	41 (29.50)	0.008
No	33 (50.77)	98 (70.50)	
DCI n (%)			
Yes	21 (31.25)	19 (16.67)	0.03
No	44 (68.75)	95 (83.33)	

*carotid termination

Overall, patients from both groups had similar sex ratio (p=0.19), and similar severity of vasospasm (p=0.09). However, patients from milrinone group were slightly younger (p=0.003).

As seen in table 3, we observed that a significantly lower proportion of patients treated with milrinone required EVT (29,50% vs 49,23%; p=0.008) and that the incidence of DCI was significantly lower in patients who received milrinone too (16,67% vs 31,25%; p=0.03).

Endovascular treatment

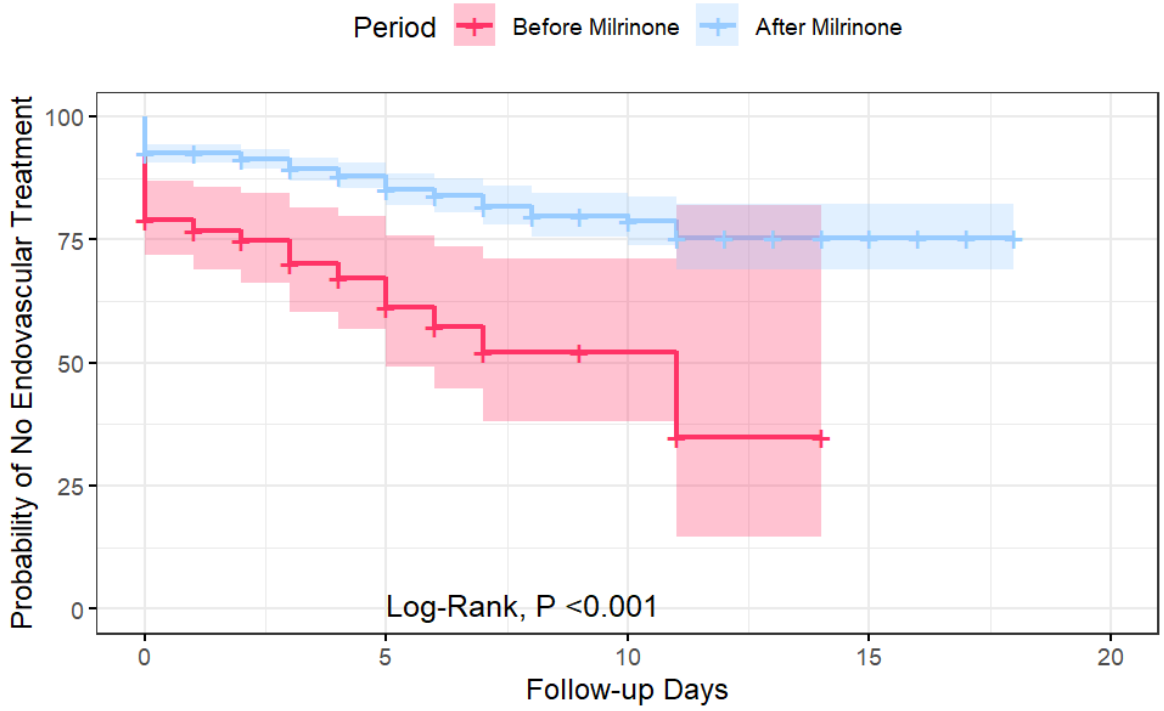

Figure 3. Probability of Not undergoing Endovascular Treatment during follow-up period before and after instauration of Milrinone.

In Figure 3, the shaded areas around the curves represented the 95% confidence intervals. The blue curve (after milrinone) was significantly higher than the red one, indicating a higher probability of not undergoing endovascular treatment after the introduction of milrinone.

We could noticed that the follow-up period of the post milrinone group is longer, that could be explained by the actual algorithm of monitoring patients with ASAH which was instituted in 2015.

Table 2. Cox Proportional Hazard Model of Endovascular Treatment Risk before and after milrinone instauration.

Covariates	Coefficient	*P*-value
Period After 2015		
Hazard (±se)	-0.81 (±0.22)	< 0.001
Hazard Ratio [95% CI]	0.44 [0.28 to 0.68]	
Age		
Hazard (±se)	0.01 (±0.01)	0.15
Hazard Ratio [95% CI]	1.0 [0.99 to 1.03]	
Sex		
Hazard (±se)	-0.10 (±0.21)	0.63
Hazard Ratio [95% CI]	0.90 [0.59 to 1.37]	
Spasm levels <50%		
Hazard (±se)	0.91(±0.24)	< 0.001
Hazard Ratio [95% CI]	2.48[1.53 to 4.01]	
Spasm levels >50%		
Hazard (±se)	2.17(±0.25)	< 0.001
Hazard Ratio [95% CI]	8.82 [5.38 to 14.46]	
Comparison Tests		
Logrank test	140.7	< 0.001

The proportional hazard assumption holds for our data (χ^2 = 1.10, df=5, *P = 0.95).*

Patients examined during the period when milrinone was used experienced a significant 56% reduction in the risk of undergoing EVT (p <0.001).

Age and sex do not appear to have a statistically significant influence on risk.

Spasm severity when the carotid termination was involved, especially when it exceeded 50%, was strongly associated with an increased risk of undergoing EVT.

DCI

Table 4. Multivariate Analysis of the probability of DCI events according to the grouping variable (Before and after 2015) and other covariates.

Covariates	Coefficient (±se)	p
After 2015	-0.85 (±0.40)	0.03
Age	0.01 (±0.02)	0.45
Sex	-0.09 (±0.42)	0.83
Spasm levels <50%	0.74(±0.49)	< 0.001
Spasm levels >50%	1.84(±0.52)	< 0.001

The multivariate analysis also shows a significant decrease of DCI risk in patient group with milrinone (odd ratio = exp(-0.85) = 0.42 , p <0.001) (Table 4).

We observe that age and sex do not have significant effects on DCI occurrence and that patients with more severe vasospasm (>50%) are at a much higher risk of developing DCI, highlighting vasospasm severity as an important risk factor of DCI.

DISCUSSION

The present study focuses on the secondary prevention of CVS in patients who have experienced an ASAH.

In the last decade, neurosurgeons, intensivists and neuroradiologists focused on CVS, and specifically on how to prevent it (12). Although this phenomenon considered reversible, it significantly worsens the patient's prognosis and negatively affects the use of healthcare resources (4). In 20 to 40% of cases, it precedes the onset of neurological symptoms (13).

CVS refers to a transient and self-limited narrowing of the intracranial arteries several days after an SAH. The diagnosis of vasospasm is primarily based on clinical examination, transcranial doppler and perfusion imaging but the gold standard remains cerebral angiography (14).

It’s the main cause of DCI which is defined as the presence of a focal neurological deficit or a decrease of at least 2 points on the Glasgow Coma scale. This condition must persist for at least 1 hour, should not occur immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, computed, CT or MRI scanning of the brain, and appropriate laboratory studies (14,15). From an imaging perspective, DCI is identified by the appearance of cerebral infarctions on follow-up MRI or CT, as hypodensities localized to a specific vascular territory, while on MRI, it presents as hyperintense areas on FLAIR sequence, potentially accompanied by ischemic lacunes (3).

The pathogenesis of vasospasm is poorly understood and likely involves a multitude of intertwined phenomena within a metabolic cascade, including Nitrogen Monoxide (NO) depletion (vasodilator), the presence of extravascular hemoglobin, production of endothelin-1, subendothelial fibrosis, media remodeling, and endothelial edema (13). Its complexity makes its management difficult.

We also know risk factors for CVS such as a large amount of extravasated blood, poor clinical condition upon admission, smoking, hyperglycemia, hydrocephalus, diabetes, systemic inflammatory response syndrome and a history of hypertension (16). The amount of extravasated blood is the most important risk factor for vasospasm and is assessed by the modified Fisher scale (Appendix 2), which has predictive value for delayed ischemia and prognosis. Other factors have been studied and considered to

be potentially related to the risk of vasospasm, such as female gender, young age of the patient, and distal anterior location of the aneurysm (10,17).

Indeed, in accordance with the literature, our study identified a majority of women, anterior circulation aneurysms, and Fisher grade IV hemorrhages among patients who experienced CVS.

Mechanical angioplasty is one of the best-documented therapies in the literature for refractory vasospasm following ASAH, however there is still a potential serious life-threatening complication including vessel rupture, branch occlusion, displacement of surgical clips and rupture of untreated aneurysms (18,19). It is responsible for 5 to 10% of serious complications (20). Moreover, angioplasty is generally applicable only to proximal segmental vasospasm in the ICA, M1 segment of MCA and rarely to A1 segment of ACA (20). This is why a large number of studies have been performed to establish a safe and effective treatment for vasospasm (12).

Currently, only one drug, nimodipine, is approved by the Food and Drug Administration for improving ischemic deficits in patients with CVS after SAH (9). There is no clear evidence that nimodipine reduces the incidence of angiographic or symptomatic CVS, but several studies, including those by Allen and al in 1983 (21) and Pickard and al (22), have shown that it improves neurological outcomes and reduces mortality in patients with SAH (9).

Milrinone is a specific phosphodiesterase type 3 inhibitor with vasodilatory, positive inotropic and some anti-inflammatory properties (9), which make it a molecule of major interest for the treatment of vasospasm (6,23). The vasodilatation results from an increase of cAMP in vascular smooth muscle that facilitates calcium uptake into the sarcoplasmic reticulum, reducing the amount of calcium available for contraction and thus relaxing vascular tone. It is supposed to alleviate CVS by relaxing the cerebral vascular system, thereby restoring vessel diameter, and improving CBF. Moreover, animal models have suggested that inotropic treatment with milrinone improves cerebral perfusion pressure after a SAH (9). Intravenous milrinone was first shown to be useful in preventing chronic CVS in a canine model of experimental chronic CVS (23).

Since 2001, the use of milrinone has been reported for treatment of vasospasm. One of the first studies to report the use of IV milrinone as a treatment for CVS was conducted at the Montreal Neurological Hospital: this study focused on patients presenting clinical or radiographic signs of vasospasm and used a standardized

algorithm correcting volume and electrolyte abnormalities along with the administration of IV milrinone while maintaining baseline mean arterial pressure with norepinephrine. Among the 88 patients, the authors identified only one patient requiring rescue treatment with intra-arterial milrinone, and no transluminal angioplasty was performed. Good functional outcomes, defined as an mRS score of 2 or less, were observed in 75% of the patients (9).

Moreover, the pilot study of Fraticelli et al in 2008 (6) suggests that milrinone was effective and safe for reversal of CVS after ASAH. However, only 22 consecutive patients with angiographically-proven cerebral narrowing (defined as a reduction in vessel diameter greater than 40% with respect to admission diameter) have been studied and they did not work on perfusion maps but only on the diameter of the spasmed vessels, which is known that it can't be a good target treatment, if isolated.

Although we did not reach the very low rates of the Montreal team (1 patient out of 88) (24), the use of EVT in our study tends to decrease steadily since the introduction of milrinone in the management of CVS.

Indeed, in our study, we observed that since the introduction of milrinone for managing CVS, we employed EVT in just over 25% of cases (Figure 2), which is lower than the 35% reported in the literature (25).

Introducing milrinone was significantly associated with a reduction of the need of EVT; avoiding patients potentially life-threatening situation because of risk of arterial damage or rupture.

Currently, this treatment is indicated when a focal deficit attributable to vasospasm persists after medical treatment and in the absence of confirmed cerebral infarction on CT. After arterial catheterization, dilatation is performed either mechanically by balloon angioplasty or by intra-arterial injection of a vasodilatory agent (23). It is use as a first-line option in certain specific situations (motor deficit attributable to vasospasm, incomplete circle of Willis…) when the vasospasm is proximal, allowing endovascular dilation.

We also observed a statistically significant decreasing in the onset of DCI incidence over the years since the introduction of milrinone in the management of ASAH. This suggests that the reduction in therapeutic angioplasties did not come at the expense of an increased incidence of DCI.

Lastly, we noticed a fluctuation in DCI in 2016 (Figure 1) with a peak at 26,7%. However, it is noted that 2016 was the year with the lowest percentage of milrinone use (9,4%) since its introduction. This further supports our findings regarding the role of milrinone in preventing the onset of DCI.

However, this study has several limitations.

First, the presented data are retrospective and derived from a single care center, limiting generalizability.

Moreover, this is an observational study, which makes the comparison of results with other studies difficult due to multiple differences such as inclusion criteria, initial severity of patients, diagnostic criteria for vasospasm, follow-up time, and so on.

Another limitation is that some extraneous factors have not been investigated for their potential effect on DCI outcome for example. Indeed, DCI is most often due to a vasospasm, but it can also be due to the formation of microthrombi in relation to the activation of coagulation cascades in the days following SAH and can also be linked to cortical spreading depolarization: cortical depolarization which, through an astrocytic and microglial action, could be responsible for vasoconstriction of small arteries, leading to the occurrence of cortical infarcts. Finally, inflammation can also contribute to delayed cerebral ischemia and thus offer other therapeutic targets (26).

CONCLUSION

These findings suggest a crucial role for milrinone in preventing secondary CVS following ASAH.

Indeed, we found a statistically significant decrease in EVT for CVS complicating ASAH since the introduction of milrinone as a secondary prevention treatment at the University Hospital of Poitiers. Moreover, this decrease in EVT was associated with a significant reduction in DCI.

As a result, by reducing the need for EVT and reducing the onset of neurological deficits, milrinone may improve outcomes for these patients.

A randomized controlled trial is warranted to further investigate these promising results.

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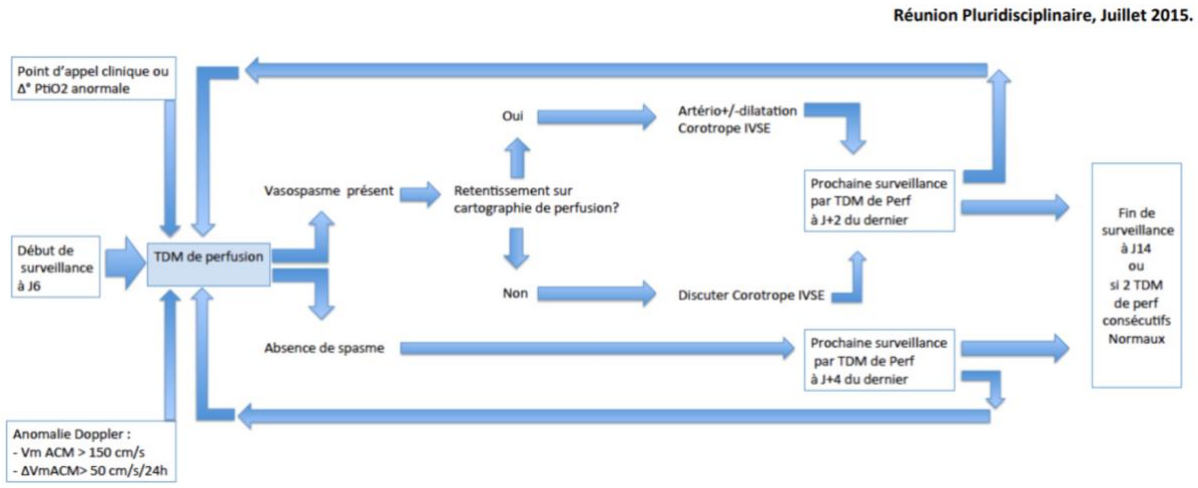
APPENDIX

Appendix 1. Algorithm for the diagnosis and monitoring of cerebral vasospasm by CTP in patients with severe meningeal hemorrhage at the University Hospital of Poitiers.



Appendix 2. Modified Fisher Scale and probability of symptomatic vasospasm (27)

Grades	Scanning appearance	Probability of symptomatic vasospasm
Grade 0	No SAH, no intraventricular hemorrhage	0%
Grade 1	Thin SAH, no intraventricular hemorrhage	24%
Grade 2	Thin SAH, intraventricular hemorrhage	33%
Grade 3	Thick SAH, no intraventricular hemorrhage	33%
Grade 4	Thick SAH, intraventricular hemorrhage	40%

ABSTRACT

Introduction: Cerebral vasospasm (CVS) following aneurysmal subarachnoid hemorrhage (ASAH) is a significant cause of morbidity and mortality. We decided to study the benefit of milrinone in the secondary prevention of CVS in patients who have experienced an ASAH.

Materials and methods: We performed a retrospective review of patients with ASAH admitted in the University Hospital of Poitiers between January 2012 and December 2023. We decided to study patients in two groups: one before the implementation of milrinone in our monitoring protocol in 2015, and another group after. Baseline characteristics, treatment and radiological outcomes were compared between the two groups. A multivariable Cox proportional hazard model was used to model the hazard rate of getting an endovascular treatment and a multivariable weighted logistic regression incorporating spasm levels, age and sex as covariates in the model was used to estimate DCI risk before and after 2015.

Results: 73 patients were included in the group before milrinone and 409 in the group after. We observed a significant reduction of endovascular treatment rate since the introduction of milrinone in our protocol (reduction of 56%, $p < 0.001$). Moreover, we found a statistically significant decreasing in the onset of DCI over the years, which shows that the fall in the use of endovascular treatment has not led to an increase in ischemic complications.

Conclusion: This study suggests that milrinone can reduce the incidence of therapeutic angiographies for CVS and prevent the onset of cerebral ischemia after ASAH.

KEY WORDS

Aneurysm, Subarachnoid hemorrhage, Cerebral vasospasm, Angioplasty, Milrinone, Delayed cerebral ischemia.

SERMENT

En présence des Maîtres de cette école, de mes chers condisciples et devant l'effigie d'Hippocrate, je promets et je jure d'être fidèle aux lois de l'honneur et de la probité dans l'exercice de la médecine. Je donnerai mes soins gratuits à l'indigent et n'exigerai jamais un salaire au-dessus de mon travail. Admis dans l'intérieur des maisons mes yeux ne verront pas ce qui s'y passe ; ma langue taira les secrets qui me seront confiés, et mon état ne servira pas à corrompre les mœurs ni à favoriser le crime. Respectueux et reconnaissant envers mes Maîtres, je rendrai à leurs enfants l'instruction que j'ai reçue de leurs pères.

Que les hommes m'accordent leur estime si je suis fidèle à mes promesses ! Que je sois couvert d'opprobre et méprisé de mes confrères si j'y manque !

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