ORIGINAL ARTICLE

The Use of Milrinone in Patients with Delayed Cerebral Ischemia Following Subarachnoid Hemorrhage: A Systematic Review

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ABSTRACT: ***Objective:*** The purpose of this article is to provide a systematic review of the evidence supporting the use of milrinone for the management of delayed cerebral ischemia (DCI) following subarachnoid hemorrhage (SAH). ***Design:*** Primary outcomes were functional neurological status and the incidence of cerebral infarction. Search strategies adapted to the different databases were developed by a professional librarian. Medline, EMBASE, the Cochrane Library database, Web of Science, SCOPUS, BIOSIS, Global Health, Health Star, Open SIGLE, Google Scholar and the New York Academy of Medicine Gray Literature were searched as well as clinical trials databases and the proceedings of several scientific meetings. Quality of the evidence for these outcomes across studies was adjudicated using the GRADE Working Group criteria. ***Results:*** The search resulted in 284 citations after elimination of duplicates. Of those 9 conference proceedings and 15 studies met inclusion criteria and consisted of case reports, case series and two comparative studies: one non-randomized study with physiological outcomes only and a case series with historical controls. There was considerable variation in dosing and in co-interventions and no case control or randomized controlled studies were found. ***Conclusion:*** There is currently only very low quality evidence to support the use of milrinone to improve important outcomes in patients with delayed cerebral ischemia secondary to subarachnoid hemorrhage. Further research is needed to clarify the value and risks of this medication in patients with SAH.

RÉSUMÉ: Utilisation de la milrinone chez les patients présentant de l'ischémie cérébrale retardée suite à une hémorragie sous-arachnoïdienne. ***Objectif:*** Le but de cet article est de présenter une revue systématique des données en faveur de l'utilisation de la milrinone dans le traitement de l'ischémie cérébrale retardée (ICR) suite à une hémorragie sous-arachnoïdienne (HSA). ***Méthodologie:*** L'état neurologique fonctionnel et l'incidence de l'infarctus cérébral étaient les critères d'évaluation primaires. Un bibliothécaire a élaboré des stratégies de recherche adaptées aux différentes bases de données. Nous avons mené des recherches dans les bases de données *Medline, EMBASE, Cochrane Library, Web of Science, SCOPUS, Medicine Gray Literature* ainsi que dans les bases de données portant sur les essais cliniques et les comptes rendus de réunions scientifiques. Nous avons déterminé la qualité des données concernant les résultats rapportés dans les différentes études au moyen des critères du *GRADE Working Group*. ***Résultats:*** Nous avons identifié 284 citations après avoir éliminé les publications redondantes. Parmi les publications retenues nous avons identifié 9 comptes rendus de réunions scientifiques et 15 études qui rencontraient les critères d'inclusion. Ces publications comportaient des études de cas et des séries de cas, et deux études comparatives : une étude non randomisée rapportant seulement l'impact physiologique du traitement et une série de cas avec témoins historiques. Il existait une variation considérable dans le dosage et les coïnterventions, et nous n'avons retrouvé aucune étude cas-témoin ou étude contrôlée et randomisée. ***Conclusion:*** Il existe actuellement seulement des données de très faible qualité à l'appui de l'utilisation de la milrinone pour améliorer l'issue d'une ischémie cérébrale retardée secondaire à une hémorragie sous-arachnoïdienne. Des études plus poussées devront être réalisées pour élucider quelle est l'efficacité et quels sont les risques que comporte cette médication chez les patients atteints d'une HSA.

Keywords: Cerebral vasospasm, subarachnoid hemorrhage, delayed ischemia milrinone
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Introduction

For patients who survive the initial episode of aneurysmal subarachnoid hemorrhage, clinical or symptomatic vasospasm, also known as delayed cerebral neurological deficit (DIND) occurs in 28.5%, according to more recent series,[1] and subsequent cerebral infarction correlates strongly with a poorer outcome.[2] Indeed, the risk of death and disability from vasospasm remains a leading cause of poor outcome after SAH.[3]

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The pathogenesis of vasospasm remains poorly understood, and the various theories have been extensively reviewed in a recent article.[4] Potential mechanisms include smooth muscle contraction that becomes chronic and inflammation that can lead to vessel remodeling. Milrinone is a phosphodiesterase (PDE) 3 inhibitor. PDEs, including PDE3, are present in cerebral smooth muscle[3,4] and are involved in the regulation of smooth muscle function. Their inhibition leads to vasodilation by increasing the levels of intracellular cyclic adenosine monophosphate (cAMP).[5] Milrinone's anti-inflammatory effects may inhibit the abnormal proliferation of the vascular smooth muscle and remodeling observed in patients with DCI through its effect on interleukin 6.[6]

Several centers in different countries have reported the use of milrinone in patients with SAH. A survey of 268 practitioners in neurocritical care from 172 institutions in 12 European countries revealed that already in 2012 milrinone was the second most common intra-arterial vasodilator agent used to treat symptomatic cerebral vasospasm.[7] Despite its increasing use there has been no systematic review of the literature to help inform this practice. We thus undertook a systematic review to determine the quality of the existing evidence supporting the use of milrinone in the management of patients suffering from subarachnoid hemorrhage with the specific goal of preventing or treating delayed cerebral ischemia.

Methods

This review was designed following the PRISMA statement for systematic reviews.[8] A study protocol was written before developing the search strategies specifying the objectives and methods of this systematic review.

Design and Search Strategy

We conducted a systematic review of the pertinent literature without time or language limitations. The search was designed to retrieve publications on cerebral vasospasm and milrinone using a combination of relevant subject headings and text. A search strategy was initially developed and applied to Medline via OvidSP (1945 to April 27, 2016) with the assistance of a qualified librarian. This strategy was adapted to take into consideration the different characteristics of other databases: EMBASE via OvidSP (1974 to April 27, 2015), PubMed (only for records "as supplied by publisher"), the Cochrane Library (via Wiley), Web of Science, SCOPUS, and BIOSIS Previews via OvidSP (1969 to 2016 week 20). Searches were run on April 27, 2016 for all databases. Open SIGLE, Google Scholar, and the New York Academy of Medicine Gray Literature were used for the gray literature. References from review articles were scanned in an attempt to identify studies that could have been missed in the original search. The search was also extended to clinical trials databases (Clinicaltrials.gov, International Clinical Trials Registry Platform Search Portal). No limitation was placed on language or time. Furthermore we reviewed the proceedings for the past 5 years of the following scientific societies: The Canadian Neurological Sciences Federation (CNSF), the American Association of Neurological Surgeons (AANS), the Congress of Neurological Surgeons (CNS), the European Neurosurgical Society (ENSS), the World Federation of Neurological Surgeons (WFNS), the American Neurology Association (ANA), the American Academy of Neurology (AAN), the European Federation of Neurological Science (EFNS), the World Congress of Neurology (WCN), the Neurocritical Care Society, the European Society of Intensive Care Medicine (ESICM), the Society of Critical Care Medicine (SCCM), and the annual Vasospasm Conference.

Study Selection

Following the study protocol we tried to identify any human study evaluating the efficacy of milrinone in patients with aneurysmal subarachnoid hemorrhage who were at risk of developing DCI or who were diagnosed with DCI. The search and the evaluation of potential studies were performed independently by three reviewers (ML, FZ and CG); differences of opinion were resolved by discussion and consensus. We included studies that used amrinone, a bipyridine with PDE 3 inhibition properties that is very similar to milrinone.

Data Collection

Data was extracted from identified studies using a standardized form. The primary outcomes of interest were functional status (from asymptomatic and independent to dead, irrespective of the clinical scale used), and the incidence of cerebral infarction. Outcomes of secondary interest were the occurrence of DCI or symptomatic vasospasm in patients receiving any type of milrinone therapy prophylactically; serious side effects resulting from the intervention (arrhythmias, severe hypotension requiring discontinuation or increased vasopressor support, pulmonary edema, myocardial ischemia); surrogate measures of cerebral oxygen delivery; and reversal of angiographic vasospasm. Data extracted included patient population, patient characteristics, study design, description of measured outcomes, follow-up characteristics, statistical analysis used, and results reported for the outcomes of interest.

Quality Assessment

The quality of the body of evidence for the outcomes of interest across studies was rated by using the GRADE Working Group criteria.[9-11] GRADE identifies 4 levels of evidence for quality assessment conducted in the context of a systematic review: high quality, moderate, low, and very low, based on how confident we are that the true effect lies close to the estimate of effect derived from the studies. The GRADE categories do not refer to individual studies, but to the body of evidence for each outcome.

Results

Search Results

We retrieved a total of 284 records from bibliographic databases after duplicate references were identified and removed (Figure 1). We eliminated 181 articles after screening their abstracts because they were unrelated to our search or because they were letters to the editor or editorial comments. We examined the full text of 103 studies and excluded another 79 because they were animal studies, practice surveys, review studies, or abstracts that were a repetition of other full text articles. We also eliminated 2 case series that were published in Japanese for which only a very short abstract was available. 24 studies featuring 957 patients were used to evaluate the evidence for the outcomes described above.

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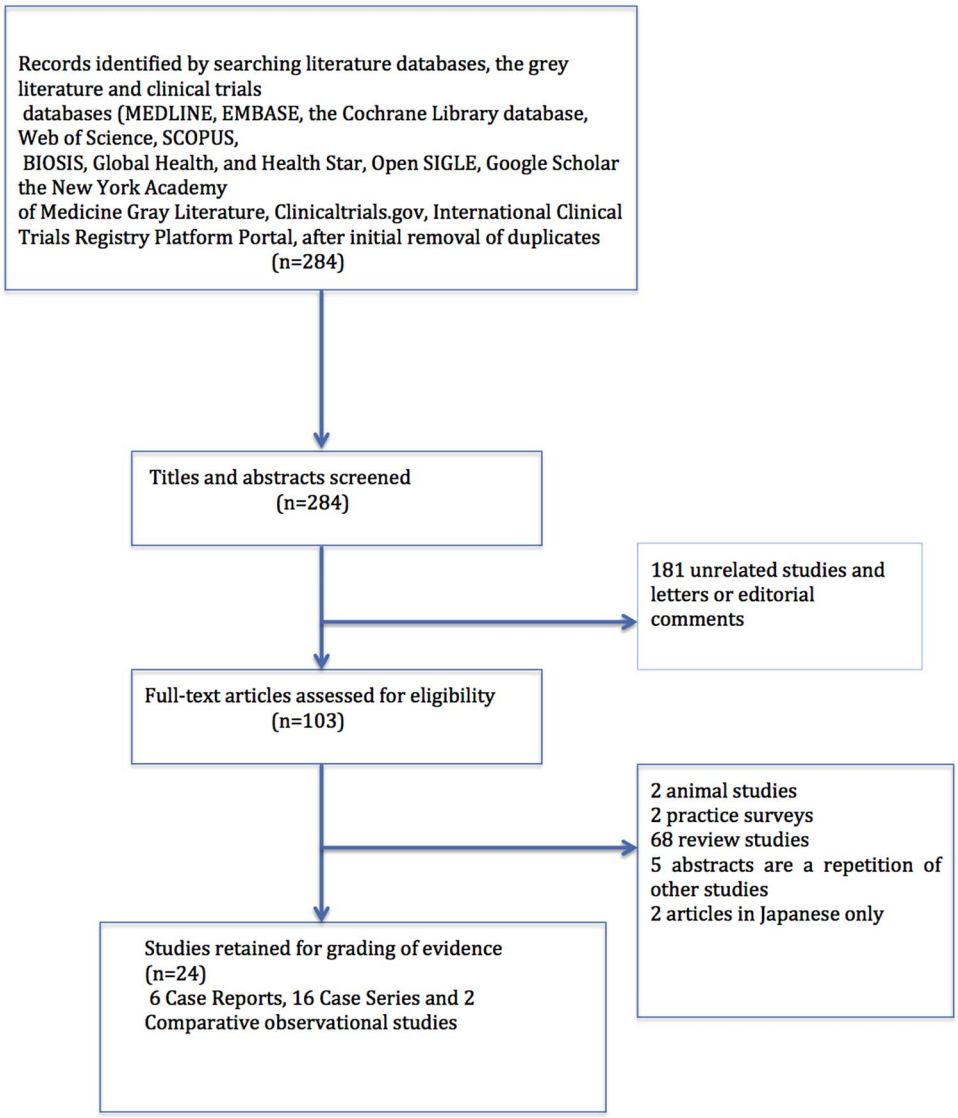

Figure 1: *Flow diagram of search results*

Study Characteristics

The 24 studies consisted of 9 abstracts (7 conference abstracts and 2 theses) and 15 full-text journal articles (Table 1).

There were 16 case series without a comparison group, 5 being prospectively acquired and 11 built from chart reviews. Moreover, 8 of those case series were published in abstract form only. The remaining citations consisted of 6 case reports, one prospective case series with a comparison group built with historical controls,[23] and one prospective non-randomized unblinded comparative study.[12] In this latter study there is no mention of how the control group was selected and it is unclear whether allocation concealment was maintained. The primary outcome in this one study was the non-invasive measurement of transcranial mixed venous oxygen saturation during therapy. Other outcomes described in the methodology are cerebral perfusion pressure (CPP), dose of norepinephrine used, Glasgow Coma Scale, mean arterial pressure, markers of renal and liver function, and occurrence of vasospasm on computerized tomographic imaging with contrast. Although this study reports an increase in the cerebral oxygen saturation and an increase in CPP in the intervention group, these patients also received higher norepinephrine doses, and no statistical analysis attempting to control for this and other confounders is described.

All articles use adults with post aneurysmal subarachnoid hemorrhage except for one that investigates patients with traumatic subarachnoid hemorrhage.[13] However, some include only patients with diagnosed angiographic or clinical vasospasm while others include only patients who did not yet develop vasospasm. The interventions are very heterogeneous and include intra-arterial milrinone combined or not with another intra-arterial vasodilator and followed or not by intravenous milrinone; continuous intra-arterial milrinone; cisternal milrinone irrigation; continuous intra-thecal lumbar milrinone; and continuous intravenous milrinone combined or not with vasopressor therapy.

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Table 1: Characteristics of milrinone studies. SAH: subarachnoid hemorrhage; WFNS: World Federation of Neurosurgical Societies scale; IA: intra-arterial; pts: patients; H&H: Hunt and Hess scale. NA: not available

Study	Design	Publication type	Study setting	Number of patients	Patients' characteristics	Disease severity	Intervention	Doses used	Duration of treatment
Yoshida et al. 1997	Case report	Journal article	Single center	2	SAH with symptomatic vasospasm	H&H 1 and 3	IA amrinone	200 and 400 mg	Single injections
Arakawa et al. 2001	Prospective case series	Journal article	Single center	7	SAH with symptomatic vasospasm	WFNS I-II	IA milrinone + IV infusion	5-15mg IA 0.5-0.75 mcg/kg/min IV	Up to 2 weeks
Arakawa et al. 2004	Prospective case series with historical controls	Journal article	Single center	12	SAH	WFNS IV-V	Cisternal irrigation with milrinone	108 mcg/h	11 to 18 days
Fraticelli et al. 2008	Prospective case series	Journal article	Single center	22	SAH with symptomatic vasospasm	WFNS I-IV	IA milrinone + IV infusion	8 mg IA; 0.5-1.5 mcg/kg/min IV	14 days
Heintzelmann 2009	Retrospective cases series	Thesis	Single center	30	Angiographic vasospasm	NA	IA milrinone + IV infusion	NA	14 days
Romero et al. 2009	Prospective case series	Journal article	Single center	8	SAH with symptomatic vasospasm	WFNS I-III	IA milrinone	10-15 mg	Single injection repeated once PRN
Schmidt et al. 2010	Retrospective case series	Journal article	Single center	73	SAH with symptomatic vasospasm	Moderate to severe radiographic vasospasm (82%)	IA injection of nicardipine e ± milrinone	10-17.5 mg	Single injection
Lecat 2011	Retrospective case series	Thesis	Single center	15	SAH with symptomatic vasospasm	NA	IA milrinone + IV infusion	NA	NA
Shankar et al 2011	Retrospective case series	Journal article	Single center	14	SAH with symptomatic vasospasm	WFNS I-V	IA milrinone + IV infusion	2.5-15 mg IA	NA
Mutoh et al 2011	Prospective case series	Conference abstract	Single center	110	SAH with symptomatic vasospasm	NA	Milrinone IV infusion	NA	NA
Lannes et al 2012	Retrospective case series	Journal article	Single center	88	SAH with symptomatic vasospasm	H&H 1-4	Milrinone IV infusion	01-0.2 mg/kg bolus Up to 1.25 mcg/kg/min	Mean duration 9.8 days
Elayoubi et al 2013	Retrospective case series	Conference abstract	Single center	21	SAH with symptomatic vasospasm	NA	IA milrinone	NA	Single injection

Table 1. *Continued*

Study	Design	Publication type	Study setting	Number of patients	Patients' characteristics	Disease severity	Intervention	Doses used	Duration of treatment
Vas et al 2013	Retrospective case series	Conference abstract	Single center	5	SAH with Refractory symptomatic vasospasm	NA	IA milrinone	NA	Single injections
Lasry et al 2014	Case report	Journal article	Single center	2	Traumatic SAH with symptomatic vasospasm	NA	IV milrinone infusion	0.1 mg/kg bolus 0.75 mcg/kg/min	6 and 9 days
Ghanem et al 2014	Comparative non-randomized study	Journal article	Single center	30	SAH	WFNS I-III	IV milrinone and norepi vs norepi alone	50 mcg/kg bolus and 0.5-0.75 mcg/kg/min	7 days
Anand et al 2014	Case report	Journal article	Single center	1	SAH with refractory vasospasm	Severe diffuse vasospasm	Continuous IA milrinone	1 mg/h infusion	72 hours
Zeiler et al 2014	Case report	Journal article	Single center	2	SAH with symptomatic vasospasm	H&H 2	IV milrinone	5 mg bolus 1.5 mcg/kg/min	8 days in one patient
Sadamasa et al 2014	Retrospective case series	Journal article	Single center	425	SAH	WFNS I-V	Cisternal and lumbar intrathecal milrinone	2.6 mg/day for lumbar milrinone	Until day 14 post SAH
Sherif et al 2015	Prospective cases series	Journal article	Single center	16	SAH with symptomatic vasospasm	H&H 1-4	IA milrinone combined with IA nimodipine	4-8 mg	Single injections
Zeiler et al 2015	Case report	Journal article	Single center	1	SAH with symptomatic vasospasm	H&H 4 WFNS IV	IV milrinone	5 mg bolus 0.75 mcg/kg/min	5 days
Osgood et al 2015	Case report	Conference abstract	Single center	2	SAH with symptomatic vasospasm	NA	Intrathecal milrinone	0.87mg Q 8 hours	NA
Alamri et al 2015	Retrospective case series	Conference abstract	Single center	17	SAH with refractory vasospasm	H&H 3 (median score)	IA milrinone	1-10 mg	Single injections
Thaher et al 2015	Retrospective case series	Conference abstract	Single center	36	SAH with symptomatic vasospasm	NA	IA milrinone	8 mg	Single injection
Alamri et al 2016	Retrospective case series	Conference abstract	Single center	18	SAH with refractory vasospasm	NA	IV milrinone	8 mg bolus + up 2.75 mcg/kg/min	NA

Measured outcomes and follow-up times were also very diverse: angiographic response,[14-21] Neurological exam,[13,17,22-26] Glasgow Outcome scale (GOS),[27] modified Rankin Scale (mRS),[18,20,21,28-33] cerebral infarction,[31] Barthel index,[28] and TCD values.[34,35] In 7 studies only data on immediate results were available,[14,15,17,19,23,34,35] and in one publication the follow-up time was not specified.[24] All reviewed articles except for 7[17,19,20,23-25,35] reported information on the occurrence of adverse effects associated with milrinone: 12 of the 17 studies reported that no adverse hemodynamic changes were observed[13,14,21,22,26,27,29-34] while the other 5[12,15,16,18,28] reported only mild increases in heart rate and a decreased blood pressure that in some cases required institution of vasopressors or an increase in the dose of preexisting vasopressors. No instances of severe hypotension requiring discontinuation of therapy or severe arrhythmias or other significant side effects were described.

Using the Clinicaltrials.gov database we were able to identify one registered randomized single-center double blind control trial of the use of milrinone to treat delayed cerebral ischemia in patients with subarachnoid hemorrhage. Patients in the intervention group will receive intravenous milrinone in addition to standard hyperdynamic therapy, while the control group will receive placebo plus standard therapy (https://clinicaltrials.gov/ct2/show/NCT02712788?term=milrinone+AND+vasospasm&rank=1+AND+vasospasm&rank=1). Starting date was April 2016.

Outcome Measures and Quality rating

In the GRADE approach to rating the quality of the evidence available one must define which outcomes are relevant for the specific question that guides a systematic review. This is an "outcome centric" approach, where the quality of the evidence is evaluated for each outcome across different studies.[9,10] The present question is "does the use of milrinone to treat patients with symptomatic vasospasm or delayed cerebral ischemia improve outcomes when compared to current standard therapy?" Outcomes may be clinical (e.g. neurological function), physiological (e.g. cerebral blood flow), societal (e.g. shortened hospital stay), or negative (e.g. adverse events, costs). These outcomes are then ranked by their impact on clinical decision making as critical, important, or unimportant. The quality assessment of the evidence for important outcomes can then be used by guideline panels that will formulate practice recommendations.

A multidisciplinary research group recommended that observational studies and clinical trials investigating new therapies for patients with SAH should use, as main outcomes, only patient functional neurological status and cerebral infarction identified on CT, MRI or autopsy after exclusion of procedure-related ischemic lesions.[36] Clinical deterioration due to DCI should be a secondary outcome measure, and cerebral vasospasm identified on angiogram or TCD, if used as an outcome at all, should be interpreted in conjunction with DCI. This recommendation was also emphasized in a 2011 multidisciplinary consensus conference.[37] Table 2 summarizes the outcomes and follow-up times for the included studies.

Functional Status

Functional neurological status can be ascertained by means of established scales (mRS, GOS) or by detailed follow-up neurological examination (usually at 3 and 6 months), and is usually described as "good" or "bad." A total of 9 studies including 632 patients reported mRS scores[18,20-21,28-33] and GOS scores[14,27] in patients with DCI treated with milrinone, with follow-up times that varied from "at discharge" to a mean of 44.6 months. Good outcomes (mRS ≤ 2 or GOS ≥ 4) were seen in 57-82% of patients. One article[20] reported 80% good outcomes, but included patients with a mRS ≤ 3. The case reports also describe good outcomes, but with very small numbers and in less descriptive terms. These results are better than what has been usually reported in the literature describing usual care with hypertensive or triple H therapy.[38,39] However, because of the absence of a comparison group, this collection of case series constitutes only a very low quality of evidence for this outcome.

Cerebral Infarction

Cerebral infarction associated with DCI and not caused by parenchymal hematoma or procedures such as clipping, coiling or insertion of external ventricular drains is another important outcome that generally correlates with functional neurological status.[36] In one study reviewing only patients who had developed delayed neurological deficits associated with radiological vasospasm (total sample 88) the proportion of patients with new ischemic lesions on CT not associated with procedures was of 36.4%.[30] The only other study that described this outcome used a combination of cisternal and lumbar irrigation with a solution containing milrinone.[31] The subjects were patients with SAH, both with and without DCI; 7.1% developed cerebral infarction. The difference in treatment approach and the study design make it impossible to determine the significance of these results and their association with the milrinone therapy.

Angiographic Response

We identified 12 studies, containing 191 patients, that described the use of intra-arterial milrinone and measured the change in vessel caliber as an outcome. There was a high degree of heterogeneity regarding the intervention. Some studies used only intra-arterial milrinone while others used a combination of papaverine followed by milrinone,[14] nicardipine combined or not with milrinone,[16] nimodipine followed by milrinone,[21] and intra-arterial amrinone.[22]

Changes in vessel diameter were analyzed as "before and after." Only one retrospective observational study had a comparison group.[19] The study targeted arteries, but the allocation to the intervention was not through randomization, and the control group included vessels that had no vasospasm. All articles observed an improvement in vessel caliber in most or all arteries studied, varying from "mild" to "excellent." In the study with a comparison group 90% of vessels treated with milrinone had improved diameter compared to 11% in the control group. There is no data to suggest that immediate changes in vessel caliber correlate with long term outcome.

Symptomatic Vasospasm or Delayed Ischemic Neurologic Deficits

There are several problems in using the occurrence of ischemic events as an outcome, due to wide variations in its definition, and in the use of radiological means to corroborate its presence because it is a diagnosis of exclusion. For this reason, it is difficult to compare results across studies and to reliably evaluate whether

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Table 2: Outcomes and follow-up times. AEs adverse effects; VSP vasospasm; mRS modified Rankin scale; HR heart rate; BP blood pressure; NR not reported; CO cardiac output; rSO2 regional cerebral oxygen saturation; DIND delayed ischemic neurologic deficit; TCD transcranial doppler.

Study	Outcomes	AEs milrinone	Follow-up
Yoshida 1997	Neurological examination	None	2 months 1 year
Arakawa 2001	Glasgow Outcome score Angiographic response	No hemodynamic changes	Immediate results
Arakawa 2004	Glasgow Outcome Scale Occurrence symptomatic VSP	No hemodynamic changes	3 months
Fraticelli 2008	mRS and Barthel index, angiographic response	Mild increase in HR; need for pressors	12 and 18 months
Heintzelmann 2009	Angiographic change	Mild increase in HR	Immediate results
Romero 2009	mRS and Barthel index angiographic response	No hemodynamic changes	3 months
Schmidt 2010	Angiographic change, need for vasopressors, surrogates for organ ischemia, 30-day in-hospital mortality and disposition at discharge	Decreased BP, higher vasopressor dose	30 days Discharge
Lecat 2011	Neurological examination, Angiographic change	NR	Immediate results
Shankar 2011	Angiographic response, mRS	Mild hypotension not treated	Immediate and at discharge
Mutoh 2011	CO, changes in rSO2, neurological examination	NR	Immediate
Lannes 2012	mRS Cerebral infarction	None	Mean = 44.6 months
Elayoubi 2013	Angiographic response	NR	Immediate response
Lasry 2014	Neurological examination	None	At discharge
Vas 2013	Angiographic response, mRS	NR	I6-12 months
Ghanem 2014	Changes in rSO2, occurrence angio spasm	higher vasopressor dose	1 week
Anand 2014	Neurological examination	NR	Not reported
Zeiler 2014	Neurological examination	NR	Days 22 and 25
Sadamasa 2014	DIND, infarction, mRS at 3 months	None	3 months
Sherif 2015	Angiographic response, TCD, mRS	None	4.5 months (mean)
Zeiler 2015	Neurological examination	None	Discharge to ward
Osgood 2015	TCD, angiographic appearance	None	Immediate effect
Alamri 2015	Median mRS	None	At discharge and at 3 months
Thaher 2015	TCD and brain tissue oxygenation	NR	Immediate response
Alamri 2016	mRS on discharge	None	At discharge

the ascertainment of its frequency has been unbiased. Only two studies described this outcome and the occurrence of "symptomatic vasospasm" varied from 16 to 25% of treated patients.[27,23]

Adverse Effects of Milrinone/Amrinone

The presence of adverse effects is an important outcome, particularly because most studies used doses of milrinone that are well above those recommended in the treatment of heart failure (50 mcg/kg IV bolus and maintenance of 0.125–0.75 mcg/kg/min for milrinone; 750 mcg/kg IV bolus for amrinone). In 12 publications with a total sample of 288 patients, doses up to 400 mg intra-arterially for amrinone and up to 15 mg intra-arterially and 0.2 mg/kg intravenously of milrinone were used.[13,14,16,18,22,28-30] In 8 of those, no hemodynamic changes were observed, while in the other 4 the authors describe only mild tachycardia or a decrease in blood pressure that did not need to be treated or that required the institution or the increase in the dose of vasopressors to maintain the mean arterial pressure at pre-specified levels. No patients developed severe adverse effects such as severe hypotension requiring the discontinuation of therapy or ventricular and supraventricular arrhythmias. This excellent safety profile occurred despite the fact that in two studies milrinone was given in combination with another vasodilator, either nicardipine or nimodipine.[16,21] One must, however, keep in mind the heterogeneity of the studies and the mostly retrospective design of the data acquisition.

Discussion

Until recently the suggested approach to treating episodes of DCI following subarachnoid hemorrhage was based on the induction of varying degrees of hypertension, hypervolemia and hemodilution–the so-called triple-H therapy–in an effort to increase perfusion to ischemic areas of the brain. The American Heart Association (AHA) Guidelines for the management of aneurysmal SAH published in 2009 still stated that "volume expansion, induction of hypertension and hemodilution (triple-H therapy)" was a reasonable approach.[40] This recommendation, however, was based on scant evidence, and there were no controlled randomized trials to support it. Furthermore, the hypervolemia and hemodilution components do not appear to offer any additional benefits to induced hypertension

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alone.[41-43] In the 2012 revision of the same guidelines, only euvolemia and induction of hypertension are recommended.[44] Consistent with these findings, a Neurocritical Care Society multidisciplinary consensus conference from 2011 recommended to treat DCI following SAH with euvolemia, stepwise increase in MAP titrated to effect, and inotropic therapy if no clinical improvement was seen with blood pressure augmentation.[37] Endovascular therapies with intra-arterial vasodilators and/or angioplasty were recommended in cases that remained refractory to medical treatment. The authors of these guidelines make it clear in their review of the subject that there is a disturbing dearth of high-quality data to support their recommendations.

Despite a thorough search with no limitations of language (both Japanese articles were case series) and the inclusion of the grey literature databases, conference abstracts and trials databases, we were unable to identify any randomized controlled trials of the use of milrinone or amrinone in the management of patients with subarachnoid hemorrhage. Only case reports, case series, and two non-randomized comparative studies were found. There were differences in the study populations as well: some included SAH patients without vasospasm and others only SAH patients who had already developed delayed cerebral ischemia either untreated or refractory to initial therapy. Treatment protocols were also quite different in their duration, manner of administration (intra-arterial, intravenously, cisternal, lumbar), and adjunct therapy. One comparative study used arteries as study targets and the other had a surrogate measure of cerebral oxygen delivery as its main outcome, and a short follow-up time.

The results in these series appear encouraging, with functional neurological outcomes that are better than those traditionally cited in the literature. Of particular interest is the apparent lack of observed side effects, even with the high doses used in most studies. Furthermore, the serious side effects frequently associated with traditional therapy, such as pulmonary edema and myocardial ischemia, could potentially be obviated if the main treatment goals were not guided chiefly by augmentation therapy with vasopressors and fluids.

An obvious limitation of our study, however, is the absence of randomized control trials and the wide variation in regimens used. The exclusion of the two articles written in Japanese with only very short abstracts is another limitation, but the final rating of the evidence would not have changed since both were case series. Even if from a physiological point of view milrinone appears as a possible therapeutic choice in the treatment of DCI, its expanding use has not been followed by well-designed trials to corroborate its efficacy. This carries the risk of an intervention becoming so deeply rooted in an institution's practice that it becomes very difficult to perform a randomized study. Physicians may become so convinced of its efficacy that they refuse to enroll their patients, fearing they may be allocated to a treatment that they consider less beneficial.

Conclusion

Since the first reports of its use to treat patients with DCI secondary to SAH in the late 1990s and early 2000s,[14,22] milrinone has been included as a therapeutic option using different protocols in several hospitals across the world.[7] However, in this systematic review and using the GRADE system we determined that there is currently only very low quality evidence to support an effect on important outcomes such as functional neurological status and the incidence of cerebral infarction and adverse effects. The same applies to physiological outcomes such as angiographic response and changes in cerebral oxymetry. Because of the expanding use of milrinone to treat delayed cerebral ischemia in patients with subarachnoid hemorrhage, there is an urgent need for a randomized control trial investigating its effects on clinically relevant outcomes.

Disclosures

The authors do not have any competing interests to disclose. All authors have completed the Unified Competing interest form. This study was supported by personal funds.

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