Cerebral vasospasm in the setting of aneurysmal subarachnoid hemorrhage (aSAH) may lead to delayed strokes. Current management options for the prevention and treatment of cerebral vasospasm and delayed cerebral ischemia (DCI) include hemodynamic therapy, nimodipine, intraarterial vasodilators, and angioplasty. However, these treatment modalities may not effectively treat severe and refractory vasospasm.

Milrinone, a bipyridine phosphodiesterase III inhibitor, is classified as an inodilator with both inotropic and vasodilator effects. Several clinical reports indicate that intraarterial or intravenous injection of milrinone directly reduces the severity of arterial vasospasm. However, an experimental study suggested that intracisternal injection of milrinone may be more efficacious than intraarterial injection for cerebral vasospasm, because intracisternal injection yields higher drug concentrations in vasospastic arteries. Questions about the safety and feasibility of intrathecal milrinone injections via lumbar catheters was addressed by Sadamasa et al. Due to the lack of a control group and selection bias, it was difficult to generalize that study’s findings related to the therapy’s effectiveness.

In this study, we evaluated the effectiveness of intrathecal injection of milrinone for prevention of DCI. Because
patients were not randomized into therapy or placebo arms, a propensity score–matching algorithm was used to balance selected covariates between the 2 patient cohorts.

**Methods**

This study is reported based on criteria from the STROBE (Strengthening the Reporting of Observational Study in Epidemiology) statement. The study protocol was approved by the institutional review board of the Kuroshiki Central Hospital Research Ethics Committee, and waiver of consent was sought and obtained for this cohort study with no unique patient identifiers.

**Patient Selection**

A prospectively maintained aSAH database at our institution was searched for patients who underwent clipping or endovascular treatment for ruptured cerebral aneurysms within 72 hours after onset between January 2010 and December 2015. Medical and surgical records of the 274 consecutive patients were retrieved and retrospectively reviewed.

**Radiological and Clinical Evaluation**

All patients underwent head CT scanning on admission. Subarachnoid clot burden was evaluated using the Hijdra scale, which accounts for the amount of clot in 10 basal cisterns and fissures by using a scoring system as follows: 0 (no blood); 1 (small amount of blood); 2 (moderately filled with blood); or 3 (completely filled with blood), for a range of scores from 0 to 30. Frequencies of intracerebral hemorrhage and intraventricular hemorrhage were also documented. The World Federation of Neurosurgical Societies (WFNS) grade on arrival was used for initial clinical grading, and WFNS Grades IV and V were designated as poor neurological status. In addition, contrast-enhanced head 3D CT angiography or catheter angiography studies were performed to localize the bleeding source, such as intracranial aneurysm.

**Management of SAH**

The choice of treatment (surgical clipping or endovascular coiling) was determined according to multidisciplinary discussions involving both surgical and endovascular teams. Younger patients with less comorbid burden, patients requiring clot removal or decompressive craniectomy, and patients with aneurysms < 3 mm were preferentially assigned to surgical clipping. Endovascular coiling was selected for elderly patients, those with posterior circulation aneurysms, patients who presented with poor initial neurological grade, and patients with severe comorbidities. External ventricular drainage was placed for acute hydrocephalus before endovascular coiling.

Baseline plain head CT scans were performed on the 1st postoperative day, after clipping or coiling. All patients received a prophylactic intravenous infusion of fasudil hydrochloride, in the absence of any contraindication, and were maintained euvoletic. A lumbar catheter was routinely inserted, in the absence of contraindications, for continuous CSF drainage and subarachnoid clot removal.

To assess for the presence of vasospasm and its severity, 3D CT angiography or conventional catheter angiography was performed.

**Intrathecal Milrinone Injection Therapy**

The clinical decision to treat with intrathecal milrinone injection was determined by our multidisciplinary team, who comprehensively considered a number of clinical and radiological factors that together influence the likelihood of development of vasospasm and delayed strokes. Patients with high WFNS and Hijdra scores with decreased capability for subarachnoid clot clearance were predominantly assigned to intrathecal milrinone injection therapy. On the other hand, elderly patients with severe comorbidities, delirious patients, and those with difficulty maintaining lumbar drainage were not selected for intrathecal milrinone injection therapy. The intrathecal milrinone injection protocol consisted of the following: 1) infusion rate of 0.87 mg milrinone (2.6 ml/day) per 7 ml normal saline for 2 hours via lumbar catheter; 2) clamped lumbar drain for 2 hours; followed by 3) drainage for 4 hours. This 8-hour cycle was repeated for 14 days post-SAH. In the presence of an external ventricular drain, cisternal milrinone irrigation was administered using the same 8-hour infusion cycle for 7 days post-SAH, followed by 7 days of lumbar cisternal milrinone injection.

**Clinical Outcome**

A delayed ischemic neurological deficit (DIND) was defined as neurological deterioration (altered consciousness, aphasia, and hemiparesis or hemiplegia) not attributable to rebleeding, postoperative complications, hydrocephalus, or systemic complications, with luminal narrowing of cerebral arteries confirmed with CT angiography or catheter angiography. Delayed cerebral ischemia was defined as newly developed cerebral infarction as a result of DIND on postoperative CT or MR images within 6 weeks after SAH that was not present on CT or MRI between 24 and 48 hours after early aneurysm occlusion, and that was not attributable to other causes such as surgical clipping or endovascular treatment. Functional outcome at 3 months after aSAH was assessed using the modified Rankin Scale (mRS).

**Propensity Score Matching and Statistical Analysis**

Primary outcomes included differences in incidences of DIND, DCI, and 3-month functional outcome between the control cohort and the treatment group receiving intrathecal milrinone injection therapy. Propensity score matching was performed using a multivariable logistic regression model, with exposure to intrathecal milrinone injection therapy as the dichotomous treatment variable. Given that patients were not randomized to receive intrathecal milrinone injection therapy, this approach balances selected pretreatment variables between the 2 treatment arms. Propensity score matching was performed with respect to age, sex, history of hypertension, WFNS scores, aneurysm location, treatment modality (clipping or coiling), Hijdra score, CSF drainage, presence of intracerebral hematoma, and presence of intraventricular hematoma. These vari-
ables were selected because they have previously been associated with DIND, DCI, and functional outcomes, or were deemed a priori to be important demographic characteristics. After propensity score generation, the cohort and treatment groups underwent 1:1 nearest-neighbor matching of the logit of the propensity score with a caliper width of 0.2 of the standard deviation of the score. Matching was performed without replacement, with treatment and control units not meeting matching criteria being excluded. We used the standardized difference to measure covariate balance. Imbalance of the covariate was defined as absolute value greater than 1.96 × √2/n.3

Continuous results are presented as the median and interquartile range (IQR) to account for nonparametric data distributions. Categorical results are presented as relative frequencies (%). Patient covariates were compared between control and treatment groups by using the Mann-Whitney test for continuous variables and Fisher’s exact test for categorical variables. The clinical outcome frequencies after propensity score matching were compared between control and treatment groups using Fisher’s exact test for categorical variables.3 Commercially available software (SPSS version 23, IBM Corp.) was used for all statistical analyses.

Results
Baseline Patient Characteristics
A total of 274 patients (64 men and 210 women) with a median age of 64 years were identified from our prospective aSAH database. In our cohort, 142 of 274 patients (52%) were treated with intrathecal milrinone injections prior to the onset of clinically symptomatic vasospasm. Ninety-four (34%) presented with poor neurological status (WFNS Grades IV and V) on admission. Of the 274 aneurysms, 240 (88%) were located in the anterior circulation and 34 (12%) were in the posterior circulation.

Analysis of patient baseline characteristics revealed that those who received intrathecal milrinone injections were 1) more likely to have presented with poor admission neurological grade (40% vs 28%, p = 0.042); 2) more likely to have aneurysms located in the anterior cerebral artery (ACA) territory (39% vs 24%, p = 0.013); 3) less likely to have aneurysms in the posterior circulation territory (7% vs 18%, p = 0.006); 4) more likely to have increased subarachnoid clot burden with higher presentation Hijdra scores (median score of 21 vs 17, p = 0.013); 5) more likely to have CSF drainage (100% vs 77%, p < 0.001); and 6) less likely to undergo coiling (22% vs 40%, p = 0.001) (Table 1).

Propensity Score–Adjusted Characteristics
The standard deviation of the logit of the propensity score was 0.64. Thus, a caliper width was set as 0.13. After 1:1 matching with a caliper width of 0.13, equal numbers of treatment and control group patients (n = 99 per group) were matched. Because the number of patients was 99 in each group, the cutoff value of absolute standardized difference for imbalance was 0.28. Across the baseline covariates, the absolute standardized differences ranged from a low of 0 to a high of 0.24, indicating that the means and prevalences of continuous and dichotomous variables were similar between treatment and control groups in the matched sample (Table 2).

Propensity Score–Adjusted Outcome Incidence Rates and Odds Ratios
Propensity score–adjusted outcome incidence rates and odds ratios are shown in Table 3. Matched cohorts exhibited significantly fewer DIND (8% vs 19%, p = 0.037) and DCI events (4% vs 14%, p = 0.024) when patients were treated with intrathecal milrinone injections compared with those without. However, there were no significant differences between the 2 groups with respect to their 90-day functional outcomes (46% vs 36%, p = 0.31). In addition, similar incidences of secondary chronic hydrocephalus, meningitis, and congestive heart failure were noted in both treatment and control groups, suggesting that intrathecal milrinone injections were not associated with higher incidences of specifically treatment-related complications.

Subgroup Analyses
Six patient subgroups exhibited baseline characteristic differences prior to propensity matching. Patients with poor WFNS grades, aneurysms in the ACA location, and higher subarachnoid clot burden were more likely to be treated with intrathecal milrinone, whereas those with posterior circulation aneurysms and treated with coiling were more likely to be treated without it. Cerebrospinal fluid drainage was more frequently observed in the milrinone treatment group, as it was routinely administered via lumbar catheter (Table 1).

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 TABLE 2. Demographic data and clinical and radiological characteristics in 198 propensity score–matched patients

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Milrinone</th>
<th>No Milrinone</th>
<th>p Value</th>
<th>Standardized Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>99</td>
<td>99</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median age in yrs (IQR)</td>
<td>62 (51–74)</td>
<td>65 (52–74)</td>
<td>0.42</td>
<td>0.10</td>
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<tr>
<td>Female</td>
<td>73 (74)</td>
<td>78 (79)</td>
<td>0.50</td>
<td>0.12</td>
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<tr>
<td>History of hypertension</td>
<td>40 (40)</td>
<td>37 (37)</td>
<td>0.77</td>
<td>0.041</td>
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<tr>
<td>WFNS Grades IV &amp; V</td>
<td>36 (36)</td>
<td>30 (30)</td>
<td>0.45</td>
<td>0.13</td>
</tr>
<tr>
<td>Aneurysm location</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACA</td>
<td>32 (32)</td>
<td>24 (24)</td>
<td>0.27</td>
<td>0.18</td>
</tr>
<tr>
<td>ICA</td>
<td>31 (31)</td>
<td>34 (34)</td>
<td>0.76</td>
<td>0.063</td>
</tr>
<tr>
<td>MCA</td>
<td>27 (27)</td>
<td>28 (28)</td>
<td>1</td>
<td>0.067</td>
</tr>
<tr>
<td>Posterior circulation</td>
<td>9 (9)</td>
<td>13 (13)</td>
<td>0.50</td>
<td>0.13</td>
</tr>
<tr>
<td>Subarachnoid clot burden</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median Hijdra score (IQR)</td>
<td>21 (14–25)</td>
<td>21 (11–26)</td>
<td>0.50</td>
<td>0.097</td>
</tr>
<tr>
<td>ICH</td>
<td>18 (18)</td>
<td>14 (14)</td>
<td>0.70</td>
<td>0.11</td>
</tr>
<tr>
<td>IVH</td>
<td>47 (47)</td>
<td>47 (47)</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Endovascular coiling</td>
<td>26 (26)</td>
<td>37 (37)</td>
<td>0.13</td>
<td>0.24</td>
</tr>
<tr>
<td>CSF drainage</td>
<td>99 (100)</td>
<td>99 (100)</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

Unless otherwise stated, values are expressed as number of patients (%).

2) patients with ACA aneurysms demonstrated fewer DCI events when treated with intrathecal milrinone (OR 0.10, 95% CI 0.002–0.98; p = 0.024); and 3) those with a higher subarachnoid clot burden, as demonstrated by Hijdra score, demonstrated fewer DCI events when treated with intrathecal milrinone (OR 0.13, 95% CI 0.013–0.66; p = 0.005). In addition, no significant differences were noted regarding DCI events in patients with posterior circulation aneurysms and those who underwent coil embolization and CSF drainage.

Discussion

Our study revealed that patients with aSAH who received intrathecal milrinone therapy were significantly less likely to develop DCI. The treatment cohort included patients with poor admission clinical states, those with increased subarachnoid clot burden, and those who were more likely to be treated with CSF drainage. In contrast, patients with posterior circulation aneurysms and those undergoing endovascular treatment were less likely to receive intrathecal milrinone. Propensity score adjustment of clinical covariates was performed to minimize the effects of selection bias on study outcomes based on imbalances in baseline patient characteristics. Subgroup analyses of outliers were also performed. Together, our study results suggest that intrathecal milrinone therapy may mitigate the development of delayed clinical deteriorations after aSAH.

Previous literature reports the use of intraarterial injections of vasodilators including papaverine, fasudil hydrochloride, calcium channel blockers, and milrinone for the treatment of arterial narrowing following aSAH. Although intraarterial injections deliver these drugs directly to narrowed vessels, these agents have relatively short half-lives, making repeated catheter injections mandatory, with the potential risk of procedure-related ischemia. Due to limitations posed by their transient effects and procedure-related risks, endovascular treatment is considered only for symptomatic, medically refractory vasospasm. Our method of intrathecal milrinone administration via lumbar catheter delivers the vasodilator agent directly to the subarachnoid space where cerebral arteries are situated, without increasing the risk of intrathecal catheter–related complications, such as meningitis or hydrocephalus.

In this study, we demonstrated that our intrathecal milrinone administration method was associated with significantly lower incidences of DCI. The DCI incidence in our control group was 14%, a figure that is comparable to previously reported incidences of 10%–21% in recent clinical series. In our study, the DCI incidence after aSAH was 4% in the intrathecal milrinone treatment group, which was significantly lower than the DCI incidence of 14% in the control group (p = 0.024).

First, our study suggests that intrathecal milrinone therapy may mitigate the development of DCI after aSAH and its associated neurological sequelae. However, statistical analysis of our cohort’s 90-day functional outcome did not reveal significant changes because outcome determination is multifactorial, with substantial influence by admission clinical status. A large proportion of our study cohort with poor admission status also had poor functional outcomes (52% of the intrathecal milrinone group and 48% of the control group had mRS scores between 3 and 6 at 90 days). In addition, we observed a discrepancy between the high incidences of poor admission clinical status (36% in the milrinone group vs 30% in the control group after propensity score matching) and low incidences of DCI (4% and 14%, respectively).

In comparison with previous literature, our study population had some distinct characteristics, as described. Poor initial clinical status (Hunt and Hess Grades IV and V) were observed in only 19.3% of the cohort in the Barrow Ruptured Aneurysm Trial (BRAT) study, with poor initial clinical status (Hunt and Hess grades > II) as an independent risk factor for poor outcome at 1 year (OR 3.51,
Intrathecal milrinone for vasospasm treatment

References


Conclusions

In propensity score–matched groups, intrathecal administration of milrinone via lumbar catheter resulted in significant reduction of DCI following aSAH without increasing the risk of complications.

Acknowledgments

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95% CI 2.21–5.68; p < 0.001). Further subgroup analyses in future studies may examine the positive influence of intrathecal milrinone on functional outcome in selected patients with aSAH who have better initial clinical grades. Second, there is growing evidence of a discrepancy between angiographic vasospasm and clinical outcomes. Although the severity of large-artery narrowing has been correlated to DCI, there exist patients with severe large-artery narrowing who have no symptoms and others with quite modest large-artery narrowing who have not only symptoms but also clinical infarction. In fact, large cerebral artery narrowing detected on angiography after aSAH results in DIND and DCI in only approximately 50% of cases, and some cases of DIND and DCI occur without angiographic vasospasm.9 Furthermore, even though oral administration of nimodipine was shown to reduce the risk of poor outcomes and secondary ischemia after aSAH, and has become a standard of care, nimodipine did not significantly reduce the frequency of angiographic vasospasm.24 On the other hand, recent clinical trials using clazosentan, an endothelin receptor antagonist, showed significant reduction of the incidence of vasospasm-related neurological morbidity but did not demonstrate significant clinical improvements.25 These observations suggest the presence of multiple pathophysiological mechanisms of secondary injury other than vasospasm, including cortical spreading ischemia,11 microthromboembolism,26 inflammation,10 and reperfusion injury18 contributing to poor outcomes. Together, these as well as other yet-to-be-elucidated mechanisms may shed some light on possible explanations for the discrepancy between angiographic vasospasm and functional outcomes.

Our study has several limitations. Selection bias exists in our observational study because patients were not randomly assigned to intrathecal milrinone therapy. Although propensity score adjustment minimized differences between treatment and control groups, other unmeasured variables exist, as well as interactions between several variables. A randomized trial would be necessary to definitively assess the efficacy of intrathecal milrinone therapy. In addition, the relatively small sample size analyzed in this study may have led to fewer perioperative factors being identified that could contribute to poor neurological outcomes after treatment. Also, our study sample size may be underpowered to detect differences in clinical outcome. Finally, all patients received intravenous fasudil hydrochloride, but not oral nimodipine, due to reimbursement-related issues. These medications might have differing additive influences on the pharmacological effects of milrinone.

Disclosures
The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

Author Contributions
Conception and design: Koyanagi, Fukuda. Acquisition of data: Fukuda, Uezato. Analysis and interpretation of data: Koyanagi, Fukuda, Lo, Uezato. Drafting the article: Koyanagi, Lo. Critically revising the article: Koyanagi, Fukuda, Lo, Kurosaki, Sadamasa, Handa, Chin, Yamagata. Reviewed submitted version of manuscript: Koyanagi, Fukuda, Lo, Kurosaki, Sadamasa, Handa, Yamagata. Approved the final version of the manuscript on behalf of all authors: Koyanagi. Study supervision: Chin, Yamagata.

Correspondence
Masaomi Koyanagi, Department of Neurosurgery, Kurashiki Central Hospital, 1-1-1 Miwa, Kurashiki City, Okayama 710-0052, Japan. email: koyanagm@gmail.com.