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Intraarterial Milrinone Therapy for Delayed Cerebral Ischemia: Impact on Functional Dependency and Mortality

Geç Serebral İskemide İntraarteriyel Milrinon Tedavisi: Fonksiyonel Bağımlılık ve Mortalite Üzerine Etkisi

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Abstract: Delayed cerebral ischemia (DCI) secondary to aneurysmal subarachnoid hemorrhage (aSAH) is a major contributor to morbidity and mortality. In addition to oral nimodipine, normovolemia, and induced hypertension, intra-arterial (IA) administration of vasodilators has been employed in DCI treatment. One such agent is milrinone, a phosphodiesterase-3 inhibitor. This study aimed to evaluate the long-term clinical outcomes of IA milrinone administration. In this retrospective controlled study, 60 patients diagnosed with DCI following aSAH and treated at our institution between January 2023 and June 2024 were analyzed. Of these, 35 received only standard DCI therapy, and 25 underwent IA milrinone administration in addition to standard treatment. No serious or permanent complications related to milrinone administration were observed. Clinical and radiological data were compared, and outcomes were assessed using the modified Rankin scale at 6 months postoperatively. The hypothesis that IA milrinone reduces mortality and functional dependency was tested. The univariate analysis showed a non-significant trend toward reduced dependency in the milrinone group (OR: 0.94, p = 0.945), and similar findings were observed in the multivariate analysis (OR: 0.56, p = 0.594). A nonsignificant increase in mortality was observed in the IA therapy group. Age was the only independent predictor of survival. In conclusion, although IA milrinone therapy appears to be safe, it does not confer a statistically significant benefit in terms of long-term survival or functional outcomes in patients with DCI. Further large-scale prospective multicenter studies are required to validate these findings.

Keywords: Delayed cerebral ischemia, Aneurysmal subarachnoid hemorrhage, Microsurgery, Endovascular treatment, Milrinone, Intraarterial vasodilator therapy.

Özet: Anevrizmal subaraknoid kanamaya (aSAK) bağlı geç serebral iskemi (GSİ) önemli bir mortalite ve morbidite etkenidir. GSİ tedavisinde oral nimodipin, normovolemi ve indüklenmiş hipertansiyon tedavilerinin yanı sıra endovasküler yöntemle intraarteriyel (İA) vazodilatörler kullanılmaktadır. Bu ajanlardan biri de fosfodiestera-3 inhibitörü olan milrinondur. Çalışmamızda İA milrinon verilen ve standart GSİ tedavisi uygulanan hastalar karşılaştırmalı analiz edilerek milrinon tedavisinin uzun dönem hasta sonuçlarına etkisi araştırılmıştır. Mevcut çalışmada Ocak 2023 ile Haziran 2024 tarihleri arasında merkezimizde tedavi edilen aSAK olguları arasından GSİ gelişen 60 hastanın retrospektif kontrollü analizi yapılmıştır. Hastaların 35'ine yalnızca standart GSİ tedavisi verilmiştir. 25 olguya standart tedaviye ek İA milrinon uygulanmıştır. Milrinon tedavisine bağlı ciddi ve kalıcı bir komplikasyon izlenmemiştir. Klinik ve radyolojik veriler karşılaştırılmış; fonksiyonel sonuçlar 6. ayda modifiye Rankin skalası skoru ile, sağkalım ise ölüm oranları ile değerlendirilmiştir. Milrinon tedavisinin mortalite ve fonksiyonel bağımlılık riskini azaltacağı hipotezi test edilmiştir. Bu amaçla, İA tedavi ile diğer klinik ve radyolojik değişkenlerin hasta sonuçlarına etkisi araştırılmıştır. Univariate analizde milrinon tedavisinin anlamlı olmamakla birlikte bağımlılık riskini azaltma eğiliminde olduğu görülmüştür (OR: 0.94, p = 0.945). Multivariate analizde de benzer bulgular görülmüştür (OR: 0.56, p = 0.594). İAT grubunda mortalitenin anlamlı düzeyde olmayan artış eğilimi dikkat çekmiştir. Multivariate regression analizinde mortalite riskini anlamlı düzeyde arttıran tek faktörün yaş olduğu saptanmıştır. Sonuç olarak, İA milrinon tedavisi güvenli bulunmakla birlikte, GSİ hastalarında uzun dönem sağkalım ve fonksiyonel sonuçlar üzerinde anlamlı bir fayda sağlamamıştır. Bulguların doğrulanması için daha büyük örneklemli, prospektif, çok merkezli çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Geç serebral iskemi, Anevrizmal subaraknoid kanama, Mikrocerrahi, Endovasküler tedavi, Milrinon, İntraarteriyel vazodilatör tedavi.

Ethics Committee Approval: The study was approved by the Ethics Committee of Ankara Etlik City Hospital (decision date30.04.2025:, number: 2025/0141).

Informed Consent: Patients signed informed consent regarding publishing their data and photographs.

Authorship, contributions: The authors confirm contribution to the paper as follows: Both of authors contributed to the study conception and design. Material preparation and data collection were performed by ÇE and GÜ. Data analysis and interpretation: ÇE. The first draft of the manuscript was written by ÇE. Study supervision and fundings materials were performed by GÜ and both of authors commented on previous versions of the manuscript. The authors read and approved the final manuscript

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1. Introduction

Aneurysmal subarachnoid hemorrhage (aSAH) is a severe neurosurgical emergency associated with high morbidity and mortality rates. One of the most critical complications of aSAH is delayed cerebral ischemia (DCI), which occurs in approximately 30% of patients with aSAH. DCI contributes to neurological deterioration and worsens long-term patient outcomes (26, 35, 44). Although its exact pathophysiology has not yet been fully elucidated, several mechanisms have been implicated in DCI development, including hemoglobin degradation products, endothelial dysfunction, free radicals, and inflammatory mediators (10, 15, 23, 38). In addition, cerebral vasospasm, which commonly occurs after aSAH, is considered to be closely associated with DCI development. Clinically, DCI typically presents with new-onset focal neurological deficits, deterioration in vital parameters, or infarcts due to cerebral ischemia, all of which are associated with poor long-term outcomes (7, 12, 40).

Given the unclear mechanisms underlying DCI, its treatment remains controversial. Several international guidelines have proposed recommendations for its management (8, 17, 34, 42). These guidelines generally recommend the continuation of nimodipine therapy initiated upon hemorrhage detection, along with maintaining a normovolemic state through careful fluid management and inducing hypertension (HT) using vasopressor agents, such as norepinephrine or dopamine (8, 17, 34). Intra-arterial therapy (IAT) using vasodilator agents is a suggested endovascular treatment option (17). Mechanical intervention devices, such as intraluminal balloons and stent retrievers, may also be used. However, these techniques are limited primarily to proximal arteries and are associated with the risk of arterial injury, particularly in the distal vascular segments (26, 39). In contrast, pharmacologic vasodilators can reach the distal vessels and are less invasive than mechanical devices. Nevertheless, vasodilator therapies also carry risks, including hemodynamic instability, arrhythmias, short duration of action, and the need for repeated administration of the drug. Furthermore, the availability of the technical infrastructure and endovascular expertise required to perform IAT and similar procedures remains limited to select specialized centers, posing an additional barrier to their widespread use in DCI treatment.

Among the vasodilators commonly used in IAT are nimodipine, verapamil, nicardipine, and milrinone. At our institution, milrinone is the preferred agent for intra-arterial (IA) use. Milrinone is a phosphodiesterase-3 inhibitor that increases intracellular cyclic adenosine monophosphate levels, resulting in vascular smooth muscle relaxation and vasodilation (5). Although systemic hypotension and positive inotropic effects are among its known pharmacological actions, they are generally considered controllable and limited, making milrinone a relatively safe option (5, 14, 25). Accordingly, IA milrinone represents a promising therapeutic strategy for restoring impaired cerebrovascular circulation in patients with DCI (3, 28, 30). Despite being included in recent guidelines, the efficacy of IATs is not well established because of the limited number of clinical studies (17, 22). In particular, there is a lack of data on the impact of milrinone therapy on patient-centered outcomes, highlighting the need for further investigation into its role in DCI management.

This study aimed to evaluate the effects of IA milrinone therapy on the clinical outcomes of patients with DCI. This study tested the hypothesis that IA milrinone may reduce DCI-associated adverse outcomes. The findings are expected to contribute to the existing body of literature and guide treatment strategies for DCI management.

2. Materials and methods

2.1. Study design and data collection

This retrospective study included 60 patients diagnosed with DCI among 209 patients treated for aSAH at our institution between January 2023 and June 2024. Hospital operating room and angiography unit records were reviewed to identify patients diagnosed with aSAH during the specified period of the study. For each eligible patient, physician notes, nursing records, flow sheets, radiological images, and discharge summaries were reviewed and analyzed. Demographic variables (age and sex) and comorbidities, including HT, diabetes mellitus (DM), and chronic obstructive pulmonary disease (COPD) were extracted. Ethical approval for the study was obtained from the Etlik City Hospital Ethics Committee (Decision No: 2025-0141, Date: 30.04.2025). This study was conducted in accordance with the principles of the Declaration of Helsinki. The authors declare that the patients provided informed consent for publication of their data.

2.1.1. Inclusion criteria

- ✓ Age >18 years
- ✓ Hospitalization and treatment in the neurosurgery department with a diagnosis of aSAH
- ✓ Aneurysm secured via endovascular or microsurgical methods
- ✓ Diagnosis of DCI following aSAH
- ✓ Minimum of 6 months of follow-up at our institution for surviving patients

2.1.2. Exclusion criteria

- ✓ Age <18 years
- ✓ Diagnosis of non-aneurysmal SAH
- ✓ Transfer to another center prior to treatment
- ✓ Unsecured ruptured aneurysm
- ✓ No clinical or radiological evidence of DCI

Among 209 patients with aSAH, 61 with DCI who met the inclusion criteria were identified. One patient was excluded from the study due to incomplete six-month follow-up at our institution.

2.2. General management principles for patients with aSAH

All patients with aSAH were monitored under normovolemic and normotensive conditions in the neurosurgical intensive care unit and received oral/enteral nimodipine at a dose of 15 mg every 4 h. Neurological status was assessed every 1–2 h, including the Glasgow Coma Scale (GCS) score (36), pupil size and reactivity, and vital signs. Oxygen support and mechanical ventilation were administered when necessary. Venous thromboembolism prophylaxis (mechanical or pharmacological) was administered after the aneurysm repair. Ruptured aneurysms were secured within the first 48 h using endovascular and microsurgical approaches.

2.3. Definition of DCI

The diagnosis of DCI was established retrospectively based on criteria adapted from the current guidelines and literature (2, 17, 41):

- ✓ Clinical deterioration beginning no earlier than 3 days after the initial hemorrhage
- ✓ Deterioration defined as new focal neurological deficit or a decrease of at least 2 points in the GCS score
- ✓ Symptoms persisting for at least 1 hour
- ✓ Exclusion of deterioration occurring immediately after aneurysm repair
- ✓ Exclusion of alternative explanations such as hydrocephalus, rebleeding, neurogenic pulmonary edema, hypo/hypernatremia, infection, or procedural complications
- ✓ Radiological evidence of cerebral infarction on brain computed tomography (CT) or magnetic resonance imaging (MRI) after clinical deterioration
- ✓ In patients where neurological assessment was unreliable (severe coma, sedation), the presence of ischemic findings on follow-up CT or MRI not attributable to other causes such as hematoma, procedural infarct, or catheter-related infarct

Patients who did not meet these criteria were not classified as having DCI.

2.4. Treatment protocol for DCI

- ✓ All patients with DCI received standard medical management, which included
- ✓ Avoidance of hypo/hypervolemia
- ✓ Maintenance of normovolemia through fluid balance monitoring
- ✓ Administration of vasopressors (norepinephrine or dopamine) for induced HT
- ✓ Continuation of oral/enteral nimodipine therapy
- ✓ IAT was performed in patients diagnosed with DCI according to the preference of the primary neurosurgeon.

2.5. IAT procedure

All IAT procedures were performed by hybrid neurosurgeons experienced in endovascular interventions and neurovascular surgeries. The number of milrinone infusion sessions administered to each patient was determined by consensus between the patient's primary neurosurgeon and the hybrid neurosurgeon responsible for performing IAT. While some patients received only a single session, others underwent up to five sessions of treatment. Due to the small sample size, the number of sessions administered was not included in the statistical analyses

Depending on the patient's level of consciousness and cooperation, the procedures were performed under local anesthesia, sedation, or general anesthesia. After bilateral groin sterilization, femoral artery access was achieved using the Seldinger technique under ultrasound guidance. A 5F introducer sheath was inserted, followed by selective catheterization of the bilateral internal carotid arteries and dominant vertebral artery using a 5F curved diagnostic catheter over a 0.035 in. hydrophilic J-tipped guidewire.

Anteroposterior and lateral angiographic images were obtained from each selectively catheterized artery, followed by IA infusion of milrinone. Post-infusion control angiograms were acquired with contrast injection to assess changes in the arterial diameter. The infusion protocol was adjusted by the performing neurosurgeon based on real-time hemodynamic monitoring. The maximum dose did not exceed 20 mg per session, infused at 1-3 mL/min with a dilution of 1 mg per 10-20 mL of normal saline. Transient arrhythmias and hemodynamic changes were observed during infusion; however, no life-threatening or permanent complications were noted in any patient.

2.6. Treatment related variables

Treatment-related variables included the method of aneurysm repair (endovascular coiling or microsurgical clipping) and IAT administration. Patients who received IA milrinone in addition to standard DCI treatment were included in the IAT group. The relationship between IAT and aneurysm treatment modalities was also examined. Patients who received standard DCI treatment were included in the non-IAT group. The effects of aneurysm treatment and IAT on patient outcomes were analyzed.

2.7. Clinical and radiological variables

Neurological status at admission was assessed using the GCS, Hunt-Hess (HH) (18), World Federation of Neurological Surgeons (WFNS) (1), and modified Rankin Scale (mRS) (24). Hemorrhage severity was quantified using the Fisher scale (13). These variables were compared between the IAT and non-IAT groups and analyzed for their influence on outcomes.

2.8. Complication related variables

The complications associated with aSAH include:

- ✓ Preoperative rebleeding
- ✓ Day of DCI onset after initial hemorrhage
- ✓ Intraoperative complications: including anesthesia-related issues, parent artery occlusion, distal embolism, vascular injury, and intracranial hemorrhage
- ✓ Postoperative severe complications: such as meningitis, intracranial abscess, pneumonia, sepsis, acute hydrocephalus, pulmonary thromboembolism, neurogenic pulmonary edema, stent thrombosis, and intracranial hematoma
- ✓ Owing to sample size limitations, intraoperative and postoperative complications were analyzed collectively rather than individually. The relationships between the complication types, IAT administration, and patient outcomes were evaluated.

2.9. Primary outcome

The primary outcome variable was the IAT administration. Comparative analyses were conducted to identify associations between IAT and demographic, clinical, and radiological variables.

2.10. Secondary outcomes

Long-term outcomes were assessed using the 6th month mRS score. To simplify the statistical analyses, patients with mRS scores of 0–2 were classified as functionally independent, while those with scores of 3–5 were classified as functionally

dependent. Patients with an mRS of 6 were categorized as deceased and excluded from the functional outcome analysis. It was determined that 18 cases represented in-hospital mortality.

Univariate and multivariate analyses were conducted to examine the effects of IAT and other independent variables (demographic, clinical, and radiological) on 6th month functional outcomes and mortality.

2.11. Statistical analysis

All statistical analyses were performed using R (version 4.5.1). Descriptive statistics are presented as mean ± standard deviation for continuous variables with normal distribution and as median [Q1-Q3] for non-normally distributed variables. Categorical variables were summarized using frequency and percentage. Comparisons between patients who underwent IAT and those who did not (non-IAT group) were conducted using the Wilcoxon rank-sum test and Welch's two-sample t-test for continuous variables, and Fisher's exact test for categorical variables. To assess the association between clinical, demographic, and radiological variables and secondary outcomes, including 6-month functional dependency and mortality, Firth's penalized logistic regression models were used because of the relatively small sample size and the presence of rare events. Both univariate and multivariate Firth logistic regression analyses were performed. In the multivariate analyses, potential confounders were included based on clinical relevance and p-values in the univariate analysis. Statistical significance was set at $p < 0.05$.

3. Results

3.1. Distribution of baseline characteristics by primary outcome

3.1.1. Patient demographics and comorbidities

A comparative analysis based on IAT status revealed that patients who received IAT were significantly younger than those who did not (IAT: 53.84 ± 11.65 years; Non-IAT: 59.89 ± 9.79 years; $p = 0.04$). No significant difference in sex distribution was observed between the treatment groups (Table 1).

Regarding comorbidities, no statistically significant associations were found between HT, DM, or COPD and IAT. However, the prevalence of DM (8%) and COPD (8%) was lower in the IAT group than in the non-IAT group (17% and 11%, respectively; Table 1).

3.1.2. Clinical and radiological parameters at admission

Although no significant differences were found between groups in terms of clinical grading scores, such as WFNS and HH scales, the initial neurological status, assessed using mRS, was significantly worse in patients who received IAT (median mRS: 4.0 [4.0–4.0]; $p = 0.02$). The proportion of patients with severe grades (scores 4–5) was slightly higher in the IAT group than in the non-IAT group for both WFNS (24% vs. 19.7%) and HH scores (20% vs. 14.3%) (Table 1).

The proportion of patients with Fisher Grade 4 hemorrhage, indicative of more extensive bleeding, was also higher in the IAT group (88%) than in the non-IAT group (60%). Additionally, the Fisher score was significantly higher in the IAT group (median, 4.0 [4.0–4.0]; $p = 0.02$; Table 1).

3.1.3. Complications

No statistically significant relationship was found between IAT administration and the occurrence of severe intraoperative or postoperative complications. Although the rate of preoperative rebleeding was higher in the non-IAT group (31% vs. 16%), the difference was not significant. The onset of DCI occurred later in the IAT group than in the non-IAT group (9.20 ± 4.61 vs. 7.34 ± 3.41 days); however, this difference was not statistically significant ($p = 0.10$; Table 1).

3.1.4. Treatment type of aneurysm

A statistically significant association was observed between the type of aneurysm treatment and the IAT ($p = 0.02$). The proportion of patients who underwent endovascular treatment was notably higher in the IAT group than in the non-IAT group (44% vs. 14%, respectively). This finding suggests a possible close relationship between the endovascular treatment approach and the preference for IAT (Table 1).

3.2. Effect of baseline variables and IAT on secondary outcomes

3.2.1. Effect of IAT

Comparative analysis of patient outcomes revealed that the 6-month modified Rankin Scale (mRS) scores were higher in the IAT group than in the non-IAT group (4.0 [1.0–6.0] vs. 2.0 [1.0–6.0]). Similarly, mortality was higher among patients who received IAT (48%) than among those who did not (34%). However, in contrast to these trends, the proportion of functionally dependent patients was comparable between the two groups (17% vs. 15%). Despite the apparent differences in the outcome

parameters, these findings were not statistically significant (Table 1).

In the univariate Firth logistic regression analysis, IAT was associated with a trend toward reduced 6-month functional dependency, although the effect was not statistically significant (OR: 0.94; 95% CI: 0.14–5.03; p = 0.945; Table 2). Similarly, multivariate analysis showed a negative but non-significant independent association between IAT and functional dependency (OR: 0.56; 95% CI: 0.04–4.25; p = 0.594; Table 3). The wide confidence intervals in both the univariate and multivariate models suggest a low reliability of these estimates.

Regarding mortality, the univariate analysis indicated a non-significant trend toward an increased risk associated with IAT (OR: 1.74; 95% CI: 0.62–4.95; p = 0.291; Table 4). The multivariate analysis yielded similar findings, with a non-significant positive correlation (OR: 1.89; 95% CI: 0.49–7.74; p = 0.353; Table 5).

3.2.2. Predictive role of patient characteristics in functional outcome

Univariate analysis of potential predictors of 6-month functional dependency revealed inverse associations for several variables: male sex, GCS score, microsurgical treatment, and presence of intraoperative or postoperative severe complications. In contrast, positive correlations were observed for WFNS, HH, Fisher grade, admission mRS score, and age, suggesting that these factors may be associated with worse outcomes, although none of these findings were statistically significant (Table 2).

Female sex was associated with slightly better functional outcomes, although this was not significant (OR 0.82 [95% CI 0.13–4.37]; p = 0.821). Higher GCS scores were predictably associated with reduced dependency risk; however, this trend did not reach significance (OR: 0.78; 95% CI: 0.51–1.07; p = 0.121). Clinical and radiological severity markers of aSAH, such as Fisher grade (OR: 1.5; p = 0.469), WFNS score (OR: 1.37; p = 0.331), and HH grade (OR: 1.6; p = 0.298), were positively associated with dependency but not at a statistically significant level.

Similarly, higher admission mRS scores were not significantly correlated with poorer functional outcomes (OR: 1.06; 95% CI: 0.53–2.17; p = 0.864). Although microsurgical treatment demonstrated a trend toward reduced dependency compared with endovascular treatment, this effect was marginally non-significant (OR, 0.17; 95% CI, 0.03–1.03; p = 0.054).

The positive association between preoperative rebleeding and functional dependency was also not statistically significant (OR, 1.03; 95% CI, 0.09–6.61; p = 0.978). Although intraoperative and postoperative severe complications showed inverse associations with dependency (OR: 0.6; p = 0.736 and OR: 0.82; p = 0.821, respectively), neither reached statistical significance (Table 2).

In the multivariate Firth logistic regression analysis, none of the variables emerged as independent predictors of functional dependency (Table 3). Age showed a positive trend with increasing dependency risk, although this was not statistically significant (OR, 1.05; 95% CI, 0.93–1.21; p = 0.428). In contrast, higher admission GCS scores and microsurgical treatment were associated with better functional outcomes, but these findings were not statistically significant. Contrary to expectations, GCS score improvement did not significantly reduce functional dependency (OR: 0.97; 95% CI: 0.61–1.5; p = 0.901). Similarly, the trend favoring microsurgery over endovascular treatment for reducing dependency was not statistically significant (OR, 0.18; 95% CI, 0.01–1.99; p = 0.159; Table 3).

3.2.3. Indicators of long-term mortality risk

It was determined that 24 patients died during the 6-month follow-up period. Of these, 18 deaths occurred during the initial hospital stay, and six patients died during post-discharge follow-up. In addition, univariate Firth logistic regression analysis was performed to identify demographic and clinical variables potentially associated with 6-month survival. Significant associations were found between the admission GCS score, Fisher grade, intraoperative severe complications, and the time interval between hemorrhage and DCI onset (Table 4). Higher GCS scores were associated with a reduced mortality risk (OR: 0.83; 95% CI: 0.67–0.98; p = 0.027), whereas a higher Fisher grade increased the risk of death (OR: 3.1; 95% CI: 1.27–11.25; p = 0.010). Mortality was approximately four times higher in patients with severe intraoperative complications (OR: 4.1 [95% CI: 1.07–18.73]; p = 0.039). Furthermore, a longer interval between hemorrhage and DCI onset was associated with a decreased mortality risk (OR: 0.87; 95% CI: 0.74–0.99; p = 0.038).

Other variables, such as age, preoperative rebleeding, admission WFNS, HH, and mRS scores,

showed positive but non-significant correlations with mortality. Male sex was associated with a non-significant trend toward reduced mortality (OR: 0.8; 95% CI: 0.27–2.29; p = 0.678). Although microsurgical treatment appeared to have a protective effect compared with endovascular treatment, this difference was not statistically significant (OR: 0.41; 95% CI: 0.13–1.29; $p = 0.127$; Table 4).

To identify independent predictors of 6-month mortality, multivariate Firth logistic regression analysis was performed. Notably, age, although non-significant in the univariate analysis, emerged as the only statistically significant predictor in the multivariate model (OR: 1.06; 95% CI: 1.00–1.13; $p = 0.048$), indicating that each additional year of age increased the mortality risk by approximately 6% (Table 5).

Other variables in the multivariate model, including GCS score (OR: 0.92; 95% CI: 0.74–1.1; $p = 0.354$), early DCI onset (OR: 0.88; 95% CI: 0.73–1.03; $p = 0.109$), and higher Fisher scores (OR: 2.03; 95% CI: 0.85–6.54; $p = 0.115$), demonstrated non-significant trends toward increased mortality. Intraoperative severe complications were also associated with a non-significant increase in mortality risk (OR: 3.85; 95% CI: 0.85–20.89; $p = 0.082$; Table 5).

Table 1. Baseline demographic and clinical characteristics of patients with delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage: Comparison between IAT and non-IAT groups

Variable		Non–IAT Group n (%) = 35	NIAT Group n (%) = 25	N p
Age	Mean ± SD	59.89 ± 9.79	53.84 ± 11.65	0.04[2]*
Female		25 (71)	13 (52)	0.18[1]
Male		10 (29)	12 (48)	
HT		17 (49)	14 (56)	0.61[1]
DM		6 (17)	2 (8.0)	0.45[1]
COPD		4 (11)	2 (8.0)	>0.99[1]
GCS Score at Ad.	Median [Q1–Q3]	14.0 [13.0–15.0]	14.0 [12.0–15.0]	0.30[3]
WFNS Score at Ad.	Median [Q1–Q3]	2.0 [1.0–2.0]	2.0 [1.0–3.0]	0.24[3]
	1	16 (46)	8 (32)	
	2	11 (31)	8 (32)	
	3	1 (2.9)	3 (12)	0.54[1]
	4	5 (14)	3 (12)	
	5	2 (5.7)	3 (12)	
HH Score at Ad.	Median [Q1–Q3]	2.0 [2.0–3.0]	3.0 [2.0–3.0]	0.27[3]
	1	3 (8.6)	1 (4.0)	
	2	17 (49)	10 (40)	
	3	10 (29)	9 (36)	0.84[1]
	4	3 (8.6)	2 (8.0)	
	5	2 (5.7)	3 (12)	
Fisher Score at Ad.	Median [Q1–Q3]	4.0 [3.0–4.0]	4.0 [4.0–4.0]	0.02[3]*
	1	1 (2.9)	0 (0)	
	2	5 (14)	1 (4.0)	0.13[1]
	3	8 (23)	2 (8.0)	
	4	21 (60)	22 (88)	
mRS Score at Ad.	Median [Q1–Q3]	3.0 [2.0–4.0]	4.0 [3.0–5.0]	0.02[3]*
	1	3 (8.6)	0 (0)	
	2	7 (20)	3 (12)	
	3	15 (43)	7 (28)	0.13[1]
	4	2 (5.7)	5 (20)	
	5	8 (23)	10 (40)	
Preop. Rebleeding		11 (31)	4 (16)	0.23[1]
Intraoperative Severe Complication		3 (8.6)	7 (28)	0.08[1]
Postop. Severe Complication without DCI		14 (40)	13 (52)	0.43[1]
Onset of DCI (Day)	Mean ± SD	7.34 ± 3.41	9.20 ± 4.61	0.10[2]
Treatment Type of Aneurysm	Endovascular	5 (14)	11 (44)	0.02[1]*
	Microsurgery	30 (86)	14 (56)	
6^{th} Month mRS Score	Median [Q1–Q3]	2.0 [1.0–6.0]	4.0 [1.0–6.0]	0.42[3]
	0	1 (2.9)	2 (8.0)	
	1	13 (37)	6 (24)	
	2	5 (14)	3 (12)	0.16[1]
	3	4 (11)	0 (0)	
	4	0 (0)	2 (8.0)	
	6	12 (34)	12 (48)	

Variable		Non–IAT Group n (%) = 35	NIAT Group n (%) = 25	N p
6th Month Mortality	Survived	23 (66)	13 (52)	0.30[1]
	Deceased	12 (34)	12 (48)	
6th Month Functional Outcome	Independent	19 (83)	11 (85)	>0.99[1]
	Dependent	4 (17)	2 (15)	

Note:[1]Fisher's Exact Test, [2]Welch Two Sample t-test, [3]Wilcoxon rank sum test. Percentages are column-based and reflect the proportion of each variable within the respective treatment group. Normally distributed variables are summarized using mean and SD, while non-normally distributed variables are summarized using median and interquartile range [Q1–Q3]. Dependency at 6th month defined as mRS score of 3–5 ("dependent" group) and 0–2 ("independent" group). A p value <0.05 was considered statistically significant and marked with an asterisk (*). Abbreviations: Ad, Admission; COPD, Chronic Obstructive Pulmonary Disease; DCI, Delayed Cerebral Ischemia; DM, Diabetes Mellitus; GCS, Glasgow Coma Scale; HH, Hunt Hess; HT, Hypertension; IAT, Intraarterial Therapy; mRS, Modified Rankin Scale; Postop, Postoperative; Preop, Preoperative; SD, Standard Deviation; WFNS, World Federation of Neurological Surgeons.

Table 2. Univariate Firth logistic regression analyses for predictors of 6 th month functional dependency following aneurysmal subarachnoid hemorrhage

Predictor	Beta	OR with 95% CI [Min–Max]	p
IAT (Ref. Non-IAT)	-0.06	0.94 [0.14–5.03]	0.945
Age	0.06	1.06 [0.96–1.2]	0.236
Male (Ref. Female)	-0.20	0.82 [0.13–4.37]	0.821
GCS Score at Ad.	-0.25	0.78 [0.51–1.07]	0.121
Fisher Score at Ad.	0.41	1.5 [0.54–6.75]	0.469
WFNS Score at Ad.	0.32	1.37 [0.71–2.62]	0.331
HH Score at Ad.	0.47	1.6 [0.64–3.98]	0.298
mRS Score at Ad.	0.06	1.06 [0.53–2.17]	0.864
Microsurgery (Ref. Endovascular)	-1.77	0.17 [0.03–1.03]	0.054
Preoperative Rebleeding (Ref. No Rebleeding)	0.03	1.03 [0.09–6.61]	0.978
Intraoperative Severe Complication (Ref. No Severe Complication)	-0.50	0.6 [0–7.49]	0.736
Postoperative Severe Complication (Ref. No Severe Complication)	-0.20	0.82 [0.13–4.37]	0.821
Onset Time of DCI (Day)	0.00	1 [0.79–1.22]	0.972

The table above presents the results of univariate Firth logistic regression analyses, investigating the association between several clinical and demographic predictors and dependency at 6 th month post-subarachnoid hemorrhage, defined as mRS score of 3–5 ("dependent" group) and 0–2 ("independent" group). None of the predictors reached statistical significance at p level of 0.05. Abbreviation: Ad, Admission; CI, Confidence Interval; DCI, Delayed Cerebral Ischemia; GCS, Glasgow Coma Scale; HH, Hunt-Hess; IAT, Intraarterial Therapy; mRS, modified Rankin Scale; OR, Odds Ratio; Ref, Referance; WFNS, World Federation of Neurological Surgeons.

Table 3. Multivariate Firth logistic regression analysis of predictors for 6 th month functional dependency after aneurysmal subarachnoid hemorrhage

Predictor	Beta	OR with 95% CI [Min–Max]	p
Age	0.05	1.05 [0.93–1.21]	0.428
IAT (Ref. non-IAT)	-0.58	0.56 [0.04–4.25]	0.594
GCS Score at Admission	-0.03	0.97 [0.61–1.5]	0.901
Microsurgery (Ref. Endovascular)	-1.72	0.18 [0.01–1.99]	0.159

Dependency defined as modified Rankin Scale score 3–5 at 6th month. No variable reached statistical significance at the p <.05 threshold. Abbreviations: CI, Confidence Intervals; GCS, Glasgow Coma Scale; IAT, Intraarterial Therapy; OR, Odds Ratio; Ref, Reference.

Table 4. Univariate Firth logistic regression analyses for predictors of 6 th month mortality following aneurysmal subarachnoid hemorrhage

Predictor	Beta	OR with 95% CI [Min–Max]	p
Age	0.04	1.04 [0.99–1.1]	0.080
IAT (Ref. non-IAT)	0.55	1.74 [0.62–4.95]	0.291
Male (Ref. Female)	-0.22	0.8 [0.27–2.29]	0.678
GCS Score at Admission	-0.19	0.83 [0.67–0.98]	0.027*
WFNS Score at Admission	0.37	1.45 [0.99–2.2]	0.058
Hunthess Score at Admission	0.39	1.48 [0.9–2.53]	0.126
Fisher Score at Admission	1.13	3.1 [1.27–11.25]	0.010*
mRS Score at Admission	0.33	1.39 [0.91–2.19]	0.126
Microsurgery (Ref. Endovascular)	-0.88	0.41 [0.13–1.29]	0.127
Preop. Rebleeding (Ref. No Rebleeding)	0.71	2.03 [0.64–6.58]	0.229
Intraoperative Severe Complication (Ref. No Severe Complication)	1.41	4.1 [1.07–18.73]	0.039*
Postop Severe Complication without DCI (Ref. No Severe Complication)	0.60	1.82 [0.66–5.18]	0.250
Onset Time of DCI (Day)	-0.14	0.87 [0.74–0.99]	0.038*

Univariate Firth logistic regression models for 6 th month mortality were summarized. A p value <0.05 was considered statistically significant and marked with an asterisk (*). Abbreviation: CI, Confidence Interval; DCI, Delayed Cerebral Ischemia; GCS, Glasgow Coma Scale; IAT, Intraarterial Therapy; mRS, modified Rankin Scale; OR, Odds Ratio; Postop, Postoperative; Preop, Preoperative; Ref, Referance; WFNS, World Federation of Neurological Surgeons.

Table 5. Multivariate firth logistic regression analysis for predictors of 6 th **month** mortality after aneurysmal subarachnoid hemorrhage

Predictor	Beta	OR with 95% CI [Min–Max]	p
Age	0.06	1.06 [1–1.13]	0.048*
IAT (Ref. non-IAT)	0.64	1.89 [0.49–7.74]	0.353
GCS Score at Admission	-0.09	0.92 [0.74–1.1]	0.354
Fisher Score at Admission	0.71	2.03 [0.85–6.54]	0.115
Intraoperative Severe Complication (Ref. No Severe Complication)	1.35	3.85 [0.85–20.89]	0.082
Onset Time of DCI (Day)	-0.13	0.88 [0.73–1.03]	0.109

A multivariate Firth logistic regression analyse for 6th month mortality was summarized. A p value <0.05 was considered statistically significant and marked with an asterisk (*). Abbreviation: CI, Confidence Intervals; DCI, Delayed Cerebral Ischemia; GCS, Glasgow Coma Scale; IAT, Intraarterial Therapy; OR, Odds Ratio; Ref, Reference.

4. Discussion

To the best of our knowledge, this study is among the limited number of investigations that exclusively utilized IA milrinone in its protocol and included a control group for comparison of outcomes. The principal finding of the present study was that IA milrinone therapy did not confer a statistically significant benefit in terms of long-term functional outcomes or mortality in patients who developed DCI. However, in the current study, the treatment appeared to be safe and was not associated with any serious complications. Based on the results obtained, it can be concluded that IA milrinone had no significant effect on clinical outcomes or mortality, although a trend toward improved functional outcomes was observed in the milrinone group. Notably, the treatment group showed a non-significant increase in mortality.

Another noteworthy observation was the apparent association of surgical clipping with lower dependency rates than endovascular aneurysm treatment, which was linked to increased patient dependency rates. Moreover, while the effect of advanced age on functional outcomes remains unclear, age has emerged as an independent predictor of postoperative mortality. Although severe intraoperative complications increased mortality, other perioperative variables, such as preoperative rebleeding and postoperative complications, did not significantly influence the risk of death.

The lack of a statistically significant interaction between IA milrinone and long-term patient outcomes indicates that our hypothesis could not be confirmed. Although a slight trend toward functional improvement was observed in patients receiving IAT, there is insufficient evidence to directly attribute this outcome to the pharmacological effect of milrinone. Several factors may have contributed to the lack of demonstrable therapeutic effect. First, irreversible ischemic injury may have already occurred by the time treatment was initiated, rendering the intervention less effective. Additionally, variations in dosage, treatment frequency, and timing may have limited their effectiveness. The heterogeneity of clinical conditions among patients and the inability to fully control for confounding variables may have further diluted potential treatment effects.

A review of the existing literature revealed that the largest series reported included only 14 patients, of whom nine had mRS scores below 4 and one died (30). In the study by Schmidt et al., only five of 160 endovascular procedures performed in 73 patients involved IA milrinone monotherapy (29). However, this study did not assess long-term outcomes, precluding any conclusions regarding milrinone efficacy. Another prospective study evaluating eight vasospasm cases refractory to IA papaverine reported a mean 3-month mRS score of 2 ± 1 (25). Notably, most studies examining milrinone in the treatment of vasospasm or DCI involved combinations with other agents, intravenous administration, or combined IV and IA protocols (3, 4, 6, 9, 11, 14, 16, 19, 31, 32, 43). In the first study to assess IV milrinone in aSAH-related DCI, Lannes et al. evaluated 88 patients and reported a 75% rate of functional independence (mRS <3) (19). However, owing to the standardized treatment protocol across all patients, no direct correlation between intravenous milrinone and clinical outcomes could be established (19).

In a randomized trial comparing intravenous milrinone and magnesium sulfate following aSAH, the milrinone group exhibited lower improvements in GCS scores and a higher risk of vasospasm (32). However, both agents were administered to all patients with subarachnoid hemorrhage (SAH), regardless of DCI development, and the results were not stratified by DCI status. Furthermore, the overall 21-day mortality rate was 13%, with a higher mortality rate in the milrinone group (18% vs. 9%). In our study, which included only DCI-positive patients, the 40% overall mortality rate was considered acceptable, particularly given that it was calculated over a 6-month follow-up period. Importantly, the milrinone group exhibited a relatively high mortality rate.

Some studies have examined the combined use of intravenous and IA milrinone. In one such study involving 34 vasospasm cases, IA nimodipine and milrinone were co-administered, followed by intravenous administration of milrinone. This approach achieved 92% angiographic resolution of vasospasm (16). However, this radiological outcome does not provide insight into long-term clinical recovery, and the lack of a control group precludes meaningful comparative analysis. Our study did not assess angiographic findings, which limited our ability to directly interpret the effects of the treatment on cerebral vasospasm. Although there is a consensus in the literature regarding the safety of IA therapy, evidence on its impact on long-term functional outcomes remains inconsistent, which is reinforced by our findings.

The higher mortality rate observed in the IAT group, along with the positive association detected in both univariate and multivariate analyses, raises concerns regarding the efficacy of this treatment. These findings contrast with those reported by Wambacher et al., who demonstrated low mortality in a retrospective series of 38 patients with refractory vasospasm (43). However, the absence of a control group and the lack of comparative or multivariate analyses in that study undermine the reliability of its conclusions. Additionally, the limited sample size of our study and the lack of statistical significance should be interpreted cautiously. Given the retrospective nature of this study, the tendency toward higher mortality in the IAT group may have been influenced by differences in baseline clinical characteristics or by selection bias. For instance, the higher Fisher and baseline mRS scores in the IAT group may explain the increased mortality risk, despite the control group comprising older patients, which was also identified as an independent predictor of mortality in our study.

Several variables associated with mortality were also investigated. Univariate analyses revealed significant associations between mortality and GCS and Fisher scores at admission, severe intraoperative complications, and DCI onset timing (Table 4). Age and initial WFNS scores were also near statistical significance. In the multivariate analysis, only age remained an independent significant predictor. This finding is consistent with previous studies, such as that by Said et al., who identified age and WFNS score as predictors of mortality in a large case series with a control group (27). While both variables in our study showed trends toward increased mortality, the WFNS score did not reach statistical significance. The GCS score showed a negative correlation with mortality in the univariate analysis, with lower scores associated with an increased risk of death. However, this finding was not supported by multivariate analysis. However, other studies, such as that by Mei et al., have shown that higher GCS scores predict lower mortality rates (21). Conversely, Terry et al. emphasized the GCS and WFNS scores and intraoperative complications as key predictors, without finding age to be significant (37). Stauning et al. identified high Fisher scores and age as important mortality predictors in patients with SAH, along with the WFNS score, preoperative rebleeding, and hydrocephalus (33). Although DCI is a known contributor to mortality in aSAH, this relationship could not be directly assessed in our study because only DCI-positive patients were included (20). Nonetheless, a significant correlation between earlier DCI onset and increased mortality was found in the univariate analysis, although this was not observed in the multivariate models (Table 5). This interesting finding could not be explored further because of the retrospective study design.

Baseline characteristics, such as age, aneurysm treatment modality, and initial Fisher and mRS scores, differed significantly between the IAT and control groups. Older patients were more prevalent in the control group, potentially confounding the association between mortality and functional outcomes. Conversely, the higher Fisher and mRS scores in the IAT group may have negatively impacted its outcome. These opposing effects may have obscured the true association between milrinone and the patient outcomes. Previous studies have shown that high hemorrhage severity, poor initial clinical condition, and advanced age are associated with poor outcomes in aSAH (33). Therefore, these variables may have acted as confounding factors in the present study. The unequal distribution of these variables likely limited our ability to accurately assess the true impact of the IAT.

In recent years, hybrid neurosurgery, in which the same neurosurgeon performs both microsurgical and endovascular procedures, has gained prominence (6, 16, 28). This approach allows for faster decision-making and more effective management of complex aneurysm cases that develop DCI. In this context, IA therapy is well suited to hybrid neurosurgical workflows because of its minimally invasive nature, repeatability, and efficacy against distal vasospasm. In our experience, these procedures were performed safely and without any major complications.

Moreover, our findings suggest that IA milrinone therapy in DCI cases is not superior to other non-endovascular measures such as induced hypertension or normovolemic fluid resuscitation. Although no serious or lasting complications occurred during IAT, this may reflect the small sample size and the limitations of retrospective data collection. Nonetheless, our findings indicate that IA milrinone is a safe intervention, although its efficacy in improving long-term functional outcomes or survival could not be demonstrated in this study.

The primary limitation of this study was its retrospective design, which may have inherently carried the risk of selection bias. Additionally, the single-center nature of the study may limit the generalizability of the findings to broader patient populations, as variations in treatment protocols,

surgical techniques, and patient management across centers could yield different outcomes. The absence of a prospective design precluded randomization in this study. Furthermore, the single-center structure constrained the sample size.

Another limitation is the treatment of patients by neurosurgeons with varying levels of experience and techniques, which, due to the small sample size, prevented stratification into surgeon-specific subgroups in this study. Only milrinone was used for IA therapy; hence, comparisons with other vasodilator agents such as nimodipine, nicardipine, verapamil, and papaverine could not be conducted. In addition, alternative approaches, such as balloon angioplasty or continuous infusion, were not included in the treatment protocol.

Despite these limitations**,** a key strength of our study lies in its distinction from many prior reports by demonstrating that IAT did not result in significant improvements in long-term mortality or functional outcomes. The inclusion of a control group further reinforced the objectivity of our findings.

5. Conclusion

In conclusion, IA milrinone therapy was safe for patients with delayed cerebral ischemia following aSAH. However, it did not significantly improve long-term survival or functional outcomes. Therefore, to better elucidate the potential role of milrinone in DCI treatment, prospective multicenter studies with larger sample sizes are required.

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