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POINT OF VIEW

Milrinone in cerebral vasospasm secondary to aneurysmal subarachnoid hemorrhage: real therapeutic alternative or rescue option?

Milrinona en el vasoespasmo cerebral secundario a hemorragia subaracnoidea aneurismática: ¿alternativa terapéutica real o recurso de rescate?

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Delayed cerebral ischemia (DCI) is the most important preventable cause of mortality and poor functional outcome after aneurysmal subarachnoid hemorrhage (aSAH), affecting 20%–40% of patients. Although approximately 70% of patients with aSAH develop angiographic narrowing of cerebral arteries or cerebral vasospasm, traditionally considered the primary cause of DCI, additional pathophysiological mechanisms — including blood–brain barrier disruption, microthrombosis, cortical spreading depolarization/ischemia, and impaired cerebral autoregulation — also contribute to its development. This multifactorial pathogenesis may explain why current therapeutic strategies — induced systemic hypertension, euvolemia, and endovascular procedures — targeting only large-vessel vasospasm have had limited impact on DCI, functional outcomes, or mortality, thereby justifying the search for novel therapeutic alternatives.

In this context, intravenous (IV) and intra-arterial (IA) milrinone has emerged as a potentially useful therapy, supported by its dual inotropic and vasodilatory effects mediated by phosphodiesterase III inhibition, its endothelial-protective properties, and its ability to modulate the inflammatory response.[1]

However, available evidence comes primarily from observational studies, suggesting that milrinone — administered in variable doses (initial bolus of 0.1–0.2 mg/min followed by IV infusion of 0.5–2.5 μg/kg/min) — produces direct vasodilation of spastic cerebral arteries, without definitive proof that this translates into improved functional outcomes. This evidence remains insufficient to support prophylactic use. Consequently, its clinical role has progres-

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sively shifted toward rescue therapy in cases of refractory vasospasm, where conventional treatments have failed.

Among existing protocols, the Montreal Neurological Hospital protocol[2] is particularly notable. Based on IV milrinone administration after correction of homeostatic disturbances, it demonstrated a favorable safety profile and significant functional improvement, positioning milrinone as a viable alternative to traditional triple-H therapy. Subsequent studies[3] suggest that IV milrinone alone may be as effective and safe as combined IV–IA therapy, facilitating broader clinical implementation.

Nevertheless, the drug's safety profile is not without concern. Hypotension, often requiring vasopressor support even at high doses, and electrolyte disturbances are particularly relevant adverse effects, especially in hemodynamically fragile neurocritical patients.

To date, only 1 randomized controlled trial[4] has compared prophylactic administration of magnesium sulfate and milrinone. The magnesium group exhibited a lower incidence of vasospasm, better neurological outcomes, and fewer adverse effects (hypotension and vasopressor requirement), thereby challenging the preventive role of milrinone and necessitating reconsideration of its therapeutic position. In contrast, the MILRISPASM study published in 2021[5] remains the only controlled observational study demonstrating statistically significant functional improvement in patients with aSAH-related cerebral vasospasm on IV milrinone. However, its small sample size, single-center observational design, lack of direct comparisons and variable control, potential outcome-measurement bias, diagnostic uncertainty, and absence of economic analysis limit causal inference and generalizability.

Systematic reviews[1,6] evaluating IV milrinone for aSAH-related vasospasm report clinical and angiographic benefits with favorable functional outcomes in most patients, but also highlight high adverse-event rates and significant methodological limitations, concluding that current evidence is insufficient to recommend routine use. Consistently, clinical guidelines reflect this uncertainty: the Neurocritical Care Society[7] discourages its use due to the lack of controlled trials, whereas the AHA/ASA[8] recognizes milrinone as a promising option pending validation by higher-quality studies.

Nonetheless, given the strong pathophysiological rationale and cumulative clinical experience, compassionate use of milrinone as rescue therapy for refractory vasospasm may represent a reasonable therapeutic approach, provided it is implemented within well-defined protocols and under strict hemodynamic monitoring. Typical IV dosing ranges from 0.5 to 1.5 μg/kg/min, with vasopressor support as tolerated, while IA administration is reserved for severe focal cases or nonresponders, depending on institutional resources and patient condition.

Currently, 2 randomized trials — OPTIMIL[9] and MIVAR[10] — are ongoing, and their results will be pivotal in establishing the efficacy and safety of IV milrinone for the prevention and treatment of cerebral vasospasm and DCI after aSAH.

In conclusion, although milrinone therapy for prevention of DCI after aSAH is supported by sound pathophysiological rationale and encouraging clinical experience, the available evidence remains insufficient to recommend its routine use. Until future randomized trials clearly define its role, milrinone should be limited to clinical research settings or, exceptionally, used as compassionate rescue therapy for refractory vasospasm after careful risk–benefit assessment and under close monitoring.

CRediT authorship contribution statement

All listed authors meet authorship criteria and certify substantial contribution to the conception, design, analysis, drafting, critical revision of the intellectual content, and final approval of the submitted version, assuming public responsibility for the work.

Ethical considerations

This work did not involve patient data or human participants and therefore did not require approval from an Institutional Review Board or Ethics Committee.

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