Seeking New Approaches: Milrinone in the Treatment of Cerebral Vasospasm

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Cerebral vasospasm and cerebral infarction is not only a potentially devastating complication after cerebral aneurysmal rupture, but because its mechanism is not completely understood, its prevention and treatment cannot be fully effective.

Apart from transluminal balloon angioplasty and induced hypertension and hypervolemia, several vasodilating drugs have been used to treat vasospasm, either by intravenous or intra-arterial route, and sometimes by intrathecal route: papaverine, nimodipine, nicardipine, verapamil, milrinone, magnesium, fasudil, colforsin daropate, and sildenafil. Among these available drugs, except for nimodipine, none has proved to be effective and several of these agents may have worrisome side effects [1–3]. Based on the currently available literature, it is not possible to recommend what would be the most effective intra-arterial therapy [4].

Hyperdynamic therapy by increasing cardiac output without increasing blood volume and blood pressure is considered the best available medical option for treatment of cerebral vasospasm [5, 6]. Among vasodilating agents, milrinone has the added effect of inotropy. Milrinone is a phosphodiesterase III inhibitor that affects cyclic adenosine

monophosphate (cAMP) pathways with both inotropic and vasodilatory effects. Its first use in the treatment of cerebral vasospasm after rupture of intracranial aneurysm has been reported in 2001 [7]. The intra-arterial infusion of milrinone was shown to reverse arterial spasm. Thereafter, its efficacy on vasospasm and hemodynamic safety has been established by several authors and intra-arterial milrinone has gained an increasing interest in cerebral vasospasm treatment [8–10].

In this issue of *Neurocritical Care*, Lannes et al. [11] from Neurological Hospital McGill University, Montreal, suggest a new approach that “moved away from volume expansion and routinely induced hypertension” and a focus on using of milrinone. They present a retrospective study of a series of 88 patients with symptomatic cerebral vasospasm after aneurysmal rupture, treated with continuous intravenous milrinone (and maintenance of normovolemia and homeostasis) as first line treatment (so called the Montreal Neurological Hospital protocol) [12, 13]. All patients received a standard course of prophylactic nimodipine and a short course of tranexamic acid until the aneurysm was secured. Monitoring of patients with symptomatic vasospasm included an arterial line, a central venous catheter for CVP monitoring, continuous electrocardiographic monitoring, daily electrolytes (that included phosphate and magnesium), complete blood counts and intracranial pressure monitoring if an external ventricular drain was present. The Montreal Neurological Hospital protocol stepwise approach was based on the maintenance of homeostasis and boluses of intravenous milrinone followed by intravenous infusion of milrinone. If neurological deficit persisted, doses of milrinone were increased, followed by norepinephrine continuous infusion to maintain MAP >90 mmHg. If symptoms still persisted, rescue therapy involves emergency angiography and the use of a

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repeat intravenous bolus of milrinone or the injection of intra-arterial milrinone with or without angioplasty. This protocol showed good overall outcome with only one case needing intra-arterial milrinone and none needing angioplasty and with good tolerance and safety of milrinone. Despite high doses of milrinone, more than one-third of the patients never received norepinephrine during their admission.

The mechanism of action of milrinone is not clear and the authors suggest an improvement of the cerebral microcirculation and not an increase in cardiac output (but they did not measure any of them). Moreover, milrinone may have some non hemodynamic interesting effects. Authors call attention to the noteworthy anti-inflammatory role of milrinone, since inflammation is one of the numerous factors of cerebral vasospasm occurrence [14]. This anti-inflammatory effects of milrinone had been suggested by some authors [15–18], but this remains controversial. Related advantages of intravenous treatment are avoidance of general anesthesia and balloon angioplasty and of their resulting risks. In addition, the treatment is easy to use and may bridge the time to cerebral angioplasty. This approach would be consistent with conceptional model voiced by the 2010 International Multi-disciplinary Consensus Conference on the Critical Care Management of Subarachnoid Hemorrhage that stated that endovascular intervention for clinically identified vasospasm is indicated as when medical management has failed or when there is a concern for complications from medical management [13].

Milrinone infusion may have some side effects, especially arterial hypotension. The risk is to thwart the favorable vasodilating effect on cerebral blood flow, since hemodynamic stability is an important criterion of safety. So, the paper stresses the importance of avoiding hypovolemia, i.e., maintaining euvolemia. Maintaining euvolemia is a laudable goal but difficult to achieve. A multimodal approach to volume monitoring might be useful and could include total blood volume measurement [19], thoracic fluid content (TFC) [20], and pulse oximetry waveform [21–23].

It is also highly advisable to exclude any myocardial dysfunction—possibly related to aneurysm rupture [2, 24–27]—before initiating the treatment and to monitor inotropic effect [28]. Since echocardiography becomes more and more routinely available in many intensive care units and is a non-invasive reliable and reproducible tool for cardiac output and hemodynamic condition monitoring, it enables initial evaluation and regular assessment. As the authors emphasize, cardiac output estimation would be also valuable to investigate any correlation with clinical improvement.

Some limitations of this study should be mentioned. Obviously, it is a single center retrospective study and, as

pointed out by the authors themselves, the study is intended “to act as hypothesis generator”. The subset of included patients may be regarded as moderately severe as most patients had a Hunt and Hess score between 1 and 3 and the overall mortality was 5.7 %. So the results may not be extrapolated to more severe affected patients for whom hemodynamic tolerance may be a concern.

More clinical randomized studies are needed with more precise assessment of volume status and standardized intravenous or/and intra-arterial administration protocols enabling comparison between drugs (i.e., milrinone vs. norepinephrine), administration routes, doses and duration of treatment and assessment of the clinical, radiological and cost-effectiveness. Other studies could specifically target comparing between balloon angioplasty with milrinone in proximal vasospasm treatment. Cerebral CT angiography, perfusion CT or MRI should also be used to investigate more accurately milrinone effects.

The Montreal Neurology Hospital protocol is a new and worthwhile effort to push the boundaries of cerebral vasospasm treatment. We may be stuck in our old habits and may have accepted a status quo that is far from satisfactory when it comes to management of severe cerebral vasospasm after subarachnoid hemorrhage.

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