

The Use of Milrinone in Extracranial to Intracranial Bypass Surgery: A Review of the Literature

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Background

Extracranial to intracranial (EC-IC) bypass surgery is a revascularization procedure used to augment or replace cerebral blood flow in patients at risk of developing cerebral ischemia. Its primary indication nowadays remains patients with moyamoya disease¹. It is not without risk, however; perioperative and postoperative cerebral ischemia has been reported to be approximately 3.5% in post-operative adults, with increased risk in patients with severe disease, a history of TIAs, and patients undergoing an indirect bypass². Milrinone, a selective phosphodiesterase III inhibitor, has seen potential use in the treatment of cerebral vasospasm in both animal³ and human studies^{4,5}. However, data has been primarily focused on its use in subarachnoid hemorrhage; its use in patients undergoing neurosurgery and specifically, EC-IC bypass, has not been well-established. This paper looks to review the existing literature on the potential risks and benefits of milrinone in EC-IC bypass surgery.

Methods

Systematic literature search was conducted through MEDLINE, EMBASE, and Cochrane Database of Systematic Reviews. Year of publication, language, and geographic location were not restricted. Primary search terms were mapped to include milrinone with one of the following: cerebral revascularization, extracranial intracranial bypass, intracranial bypass, and extraintracranial anastomosis. Due to a lack of publications, search terms were then expanded to include moyamoya disease, neurosurgical procedures, neurosurgery, neuroanesthesia, and cerebral ischemia.

Results

The search strategy identified only two initial citations prior to expansion of search terms, of which one was excluded as it was unrelated. Secondary search terms identified a further 120 citations, of which all were excluded as they were either unrelated or duplicates. Most of the excluded publications focused on the use of milrinone specifically in patients with subarachnoid hemorrhages and its potential to decrease cerebral vasospasm, which although relevant to the discussion did not address the initial review question.

Discussion

Since the first successful EC-IC bypass surgery in 1967, cerebral revascularization has seen continued use especially in patients with moyamoya disease⁶. Although landmark studies—namely the 1985 EC/IC Bypass Study Group⁷ and the 2011 Carotid Occlusion Surgery Study⁸—concluded that its use may be somewhat more limited in patients with occlusive cerebrovascular disease, potential indications on a case-by-case basis remain. As these patients are already vulnerable to cerebral ischemia, and may have altered hemodynamics in response to adaptation, care must be taken to avoid cerebral ischemia and stroke. The use of pharmacologic and non-pharmacologic measures allow for manipulation of the patient's cerebral blood flow and volume, perfusion pressures, and metabolic rate.

Milrinone is one such drug that has seen use in neurocritical care, although not specifically for neurosurgical procedures. First studied in 1997 by Khajavi et. al. in dogs with chronic cerebral vasospasm³, further human case series^{4,5} showed potential benefit in reversing angiographically proven cerebral vasospasm. The theoretical benefits over other vasodilators include an increase in inotropy, decreased wall

thickness, and anti-inflammatory effects through the inhibition of interleukins⁹. In 2012, the Montreal Neurological Hospital published a case series of 88 patients diagnosed with delayed ischemic neurologic deficits after aneurysmal subarachnoid hemorrhage¹⁰. Using a protocol of titrated intravenous milrinone therapy, maintenance of homeostasis, and avoidance of induced hypervolemia and hemodilution, only one patient in the cohort needed intra-arterial milrinone as a rescue therapy, and no patients required angioplasty.

Unfortunately, no other studies have been published regarding the use of milrinone in neurosurgical procedures. On review, the only relevant citation is a conference abstract by Fenner et. al. in 2018, which describes a five patient case series in which intravenous milrinone was used to reverse vasospasm and symptoms of cerebral ischemia in the context of EC-IC bypass¹¹. From the abstract, all patients treated with milrinone underwent a complete recovery to baseline neurological status, and acute hemiparesis was reversed in three patients. Given the limited sample size, however, it would be difficult to draw conclusions over its potential benefits.

Conclusion

Although the successful use of milrinone has been well documented in neurocritical care for patients with aneurysmal subarachnoid hemorrhages, limited data exists to support its use in routine neurosurgical care. Further evaluation is recommended.

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