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Research Article

Effects of Milrinone continuous intravenous infusion on global cerebral oxygenation and cerebral vasospasm after cerebral aneurysm surgical clipping

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KEYWORDS

Cerebral;
Oximetry;
Norepinephrine;
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Abstract *Background:* Cerebral vasospasm (CVS) is a disabling disease with high morbidity and mortality risk. Milrinone (phosphodiesterase III inhibitor) has inotropic and vasodilator effects, noninvasive transcranial cerebral oximetry (rSO**2**%) useful in estimating the effect of triple-H therapy preventive measures against CVS.

Objective: **The objective** of the study is to clarify the value of the use of Milrinone continuous IV infusion as a cerebral vasodilator in post-clipping spasm prevention during the period of maximum vasospasm incidence, guided by noninvasive rSO**2**%.

Methods: Post-clipping all patients extubated in the operative room, shifted to Neurosurgical ICU, and fully monitored. Then, in the period from 4th till the 11th day post-clipping, they were divided into two groups 15 patients each: Group 1: control group, given Norepinephrine continuous IV infusion alone in a dose ranges from 0.05 to 0.2 μg/kg/min. Group 2: given Norepinephrine continuous IV infusion 0.05–0.2 μg/kg/min, Plus Milrinone starting with 50 μg/kg bolus dose, followed by IV infusion at a rate of [0.5–0.75 μg/kg/min]. IMAP, ICP **and** CPP, GCS, Norepinephrine dose, rSO2%, were recorded every 6 h for the next 168 h. Any attack of cerebral vascular spasm recorded as number and % in each group as an incident.

Results: MBP, rSO2%, ICP, CPP, Norepinephrine Infusion dose, and GCS were significantly increased in Group (2) in comparison with Group (1) mostly during the period of the study. CVS

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occurrence was significantly lower in group (2), i.e., (20%) cases compared to (46.6%) in group (1).
Conclusions: Milrinone improved significantly the global cerebral oxygenation and reduced the incidence of cerebral vasospasm during the dangerous period of cerebral spasm after cerebral aneurysm clipping.

1. Introduction

Cerebral vasospasm (CVS) secondary to aneurysm induced subarachnoid hemorrhage (SAH) is a disabling disease with high risks of morbidity and mortality even after successful surgical clipping. CVS is the most common cause of delayed neurological deficit affecting up to 30% of patients who survive the initial hemorrhage, current therapy for prevention and treatment of symptomatic vasospasm includes hypertensive, hypervolemic hemodilution (triple-H therapy), calcium channel antagonists, and early surgery with clot removal. [1] The clinical CVS syndrome starts with an inclination to sleep, confusion, and stupor. Normally, the symptoms appear between the 5th to the 7th day of an SAH and rarely occur after 2 weeks. The pathophysiology of vasospasm is not totally understood [2].

Milrinone, a phosphodiesterase III inhibitor that affects CAMP pathways producing both inotropic and vasodilator effects, also was first used in the treatment of CVS after rupture of intracranial aneurysm in 2001 [3]. Constantoyannis and his colleagues 2007 [4] documented that noninvasive transcranial cerebral oximetry may be useful in estimating the clinical impact of triple-H therapy as a preventive measures against arterial CVS in aneurysm induced SAH patients.

Antoine and his colleagues 2012 [5] recommended that there is great need for more clinical studies on standardized intravenous and/or intra-arterial administration protocols enabling comparison between drugs (i.e., Milrinone vs. Norepinephrine). On this future vision, ***the aim of this study was to*** clarify the value of the use of Milrinone continuous IV infusion as a cerebral vasodilator in post-clipping spasm prevention during the period of maximum vasospasm incidence (between the 4th and the 11th day post-clipping) in the neurosurgical ICU, guided by noninvasive transcranial cerebral mixed venous oxygen saturation (rSO2). All patients must have continuous normovolemic state simultaneously with sufficient cerebral perfusion level utilizing Norepinephrine that provides safe supporting effective systemic hypertension.

1.1. Patient and methods

After protocol approval by local ethics committee, written informed consent was taken from each patient or relatives. In this present study, patients were selected depending on a merge of clinical and radiological grading and classification, respectively; 1st clinical grade patients were selected of grade 1 or 2, or 3 according to ***world federation of neurosurgeon grading scale***, [22] shown in Table 6, and 2nd by radiological classification using ***modified Fissure classification*** only class 2, 3, and 4 only if associated with good clinical grading 1, 2, or 3 world federation grades. (Fissure classification was modified by Claassen and coworkers classifies the appearance of subarachnoid hemorrhage on CT scan and reflects the additive risk from SAH size and associated with intraventricular hemorrhage as following: 0 – none; 1 – minimal SAH without IVH; 2 – minimal SAH with IVH; 3 – thick SAH without IVH; 4 – thick SAH with IVH) [23]. In this present study, Patients were divided in two groups each 15 patients, all patients, aged from 25 to 60 years old, of either male or female.

Exclusion criteria: Evident vasospasm with trans-cranial Doppler or CT angiography, peripheral vascular disease, preoperative cognitive dysfunction, neuromuscular, primary cardiac, pulmonary, hepatic, renal and endocrine disorders, Glasgow Coma Scale GCS $\leqslant$ 12, preoperative ventilatory or circulatory (pharmacological and mechanical) support, pulmonary edema, also aneurismal rebleeding after surgical clipping patients, maintaining endotracheal intubation, delayed recovery after surgical clipping, and obese.

In this study, hypothesis was that addition of continuous IV infusion Milrinone to IV infusion norepinephrine after clipping of cerebral aneurysms (during the period of maximum cerebral arterial spasm incidence) will improve rSO2.

The primary outcome: Changes in rSO2 (each 6 h for post-clipping for 168 h = 1 week).

The secondary outcome: measurement of mean arterial blood pressure, cerebral perfusion pressure, intracranial pressure, doses of norepinephrine, conscious level GCS (each 6 h for post-clipping 168 h = 1 week) and organ functions once/day for 7 successive days (Serum ALT, serum AST, Serum bilirubin, Serum albumen, Serum Cr, and serum urea).

Group patients sample size: A pilot study showed that the normally distributed mean transcutaneous cerebral mixed oxygen saturation (rSO2) after start of norepinephrine infusion during the postoperative period after aneurismal clipping was 61% (SD of 10), with type I error of 0.05 and a power of 90%. A priori power study indicated a sample size of **15 patients** for each group was sufficiently large to detect a 20% differences in the mean rSO2 after the start of norepinephrine infusion.

Anesthesia during surgery: (All aneurysms were clipped within 24 h of the onset of SAH) was induced with Fentanyl 1 μg/kg, then lidocaine 1 mg/kg, then Propofol 2 mg/kg, and ETT facilitated using 0.1 mg/kg Cisatracurum then maintained with total intravenous anesthesia of continuous IV infusion drugs [Remifentanil 0.05–2 μg/kg/min, Propofol 50–200 μg/kg/min, and muscle relaxant Cisatracurum infusion of 0.1 mg/kg/h]. After surgical clipping, an open and surgically functioning external ventricular devise catheter (EVD) [6] was then connected to the pressure transducer fixed 1 cm above the level of temporomandebular joint via which the intracranial pressure (ICP) will be recorded and then cerebral perfusion pressure (CPP) was calculated (utilizing the famous equation CPP = mean arterial blood pressure MBP-ICP) [7].

Post-surgical clipping extubation just after operation in the operative room, conscious and spontaneously breathing, protocol criteria for extubation on table after clipping; fully conscious and oriented, GCS > 13, Obey commands, no new motor deficits, noncomplicated surgery, stable vitals, temp. > 36 C, FiO2 < 0.5, PEEP $\leqslant$ 5 cm H2O, Pa/FiO2 ra-