Egyptian Journal of Anaesthesia (2014) **30**, 73–82

Egyptian Society of Anesthesiologists

**Egyptian Journal of Anaesthesia**

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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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Received 8 April 2013; revised 14 July 2013; accepted 19 July 2013
Available online 16 August 2013

**KEYWORDS**

Cerebral;
Oximetry;
Norepinephrine;
Milrinone;
Aneurysm

**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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Peer review under responsibility of Egyptian Society of Anesthesiologists.

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http://dx.doi.org/10.1016/j.egja.2013.07.006

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-

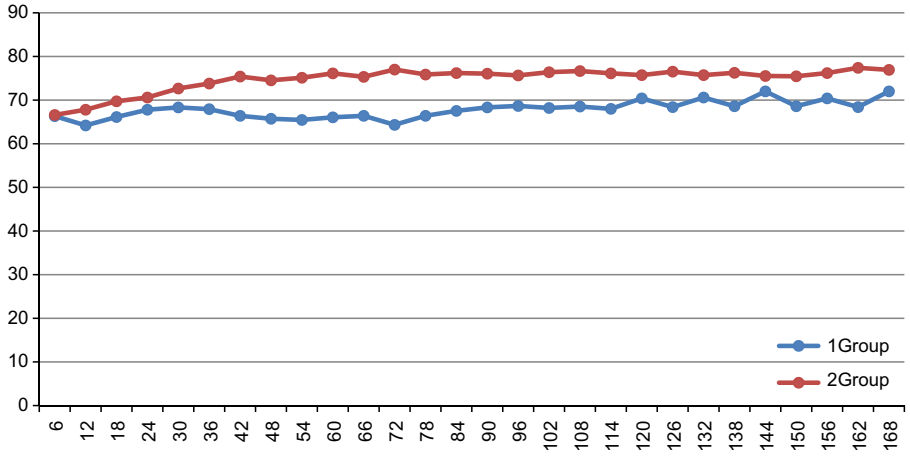


**Chart 1** Transcranial Noninvasive O2 saturation of the studied groups in% related to time in hours.

tio > 300, PaO2 > 60 mmHg, PaCO2 35–45 mmHg, pH > 7.3, TOF > 0.9, VTe > 5 ml/kg, UOP > 0.5 and < 3 ml/kg.

Then, patients shifted directly to the Neurosurgical ICU and connected to full monitoring system including HR, ECG leads, arterial oximetry probe, invasive arterial blood pressure via pre-inserted arterial 18 gage cannula, CVP monitoring, and the transcutaneous cerebral mixed oxygen saturation forehead bilateral interconnected adhesive probes (CASMED-FORE-S. GHT noninvasive cerebral oximetry monitoring devise).

Then, for all patients: 1-Both groups 1 and 2 were kept normovolemic utilizing the isotonic normal saline 0.9% solution rates between 80 and 100 cc/h (Mayer and his colleagues 2005) [8] as a basic hourly infusion solution. The goal is to maintain the patient normovolemic by keeping the central venous pressure (CVP) 5–8 mmHg in the patient recovering from a SAH with normal hourly urine output for all patients of the study.

2-Both groups 1 and 2 started Norepinephrine (levofed) vasopressor infusion support in an IV infusion dose ranges from 0.05 to 0.2 μg/kg/min [effective doses of norepinephrine were defined as doses required to increase mean arterial pressure (MAP) by 20 mmHg] [9]. MAP was maintained at between 100 and 120 mmHg targeting CPP (MAP-ICP) > 80 mmHg.

Then, after passage of 96 h (4 days) (as the 5th day is the start of the period of highest incidence of cerebral vasospasm after cerebral aneurismal clipping) [2] postoperatively in the neurosurgical ICU, patients were divided into two groups 15 patients in each group as follow:

Group 1 = Norepinephrine alone group (Control group): *Norepinephrine* continuous infusion alone in a dose range 0.05–0.2 μg/kg/min to keep MAP between 100 and 120 mmHg targeting CPP (MAP-ICP) > 80 mmHg .

Group 2 = Norepinephrine plus Milrinone (Milrinone group): *Norepinephrine* continuous infusion in a dose range 0.05–0.2 μg/kg/min to keep MAP between 100 and 120 mmHg. targeting CPP (MAP-ICP) > 80 mmHg, Plus *Milrinone* (cerebral arterial vasodilator and +ve inotropic) starting with 50 μg/kg bolus dose [4], followed by intravenous infusion at a rate of [0.5–0.75 μg/kg/min] [3], according to the rSO2% monitoring starting by 0.5 μg/kg/min and increase up to 0.75 μg/kg/min if rSO2% dropped under 60%.

Data recording of GCS, norepinephrine infusion dose, rSO2%, IMAP, ICP and CPP calculated (MAP-ICP), all were recorded every 6 h for the next seven successive postoperative days = 168 h. Organ functions (Serum ALT, serum AST, Serum bilirubin, Serum albumen, Serum Cr, and serum urea) the once daily measurement (for seven successive days).

Any attack of cerebral vascular spasm (CT angiographic-proven arterial diameter reduction > 40%) [10]), these cases will be recorded as number and % in each group as an incident and soon start the management of cerebral arterial spasm in the form of oral or via nasogastric tube 60 mg Nimodipine every 4 h and continued for up to 21 day, Hetastarch (6%) 500 ml bolus infusion added to the basic hourly 0.9% normal saline fluid infusion to maintain the central venous pressure CVP of 8–10 mmHg (during spasm as a treatment). Simultaneously, milrinone 50 μg/kg bolus then intravenous infusion of a higher rate than prevention rate already used in this study [0.75–1.25 μg/kg/min] then gradually reduce the dose according to the rSO2% monitoring down to a rate of 0.75 μg/kg/min if rSO2% improves over 70%, plus Norepinephrine infusion rate up to[ 0.2 μg/kg/min] to maintain invasive MAP between 100 and 130 mmHg, targeting CPP (MAP-ICP) > 80 mmHg .

## 2. Statistical analysis

Data of the study were collected and entered into computer. Statistical analysis was done by using statistical package for social science version 16 (SPSS). The data were normally distributed by using Kolmogrov–smirnov test. The data were presented in the form of mean and standard deviation. Student's *t*-test was used to compare between quantitative data of two groups. Significance was considered at p value less than 0.05.

According to the pilot study done before this study to detect the sufficient number of patients of each group of the study showed that the normally distributed mean rSO2 after start of norepinephrine infusion during the postoperative period after aneurismal clipping was 61% (SD of 10). A prior 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, with type I error of 0.05 and a power of 90%. We added 10% more to compensate for the dropped out cases.

**Table 1** Transcranial noninvasive O2 saturation and mean arterial blood pressure of the studied groups.

| Group | Time | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6 h | 12 h | 18 h | 24 h | 30 h | 36 h | 42 h | 48 h | 54 h | 60 h | 66 h | 72 h | 78 h | 84 h |
| *Cereb. Transcr. Noninvv. O2 saturation* | | | | | | | | | | | | | | |
| Group1 Mean ± SD | 66.33 ± 1.71 | 64.20 ± 5.72 | 66.13 ± 3.20 | 67.80 ± 1.37 | 68.33 ± 2.58 | 67.93 ± 1.03 | 66.40 ± 1.54 | 65.73 ± 4.13 | 65.46 ± .51 | 66.06 ± 1.03 | 66.40 ± 1.54 | 64.33 ± 2.58 | 66.40 ± 1.54 | 67.53 ± 2.87 |
| Group2 Mean ± SD | 66.60 ± 2.64 | 67.80 ± 3.34 | 69.73 ± 1.71 | 70.60 ± 3.48 | 72.66 ± 2.35 | 73.80 ± 1.26 | 75.40 ± 1.59 | 74.53 ± 1.50 | 75.13 ± 2.38 | 76.13 ± .99 | 75.33 ± 2.52 | 77.0 ± 2.26 | 75.86 ± 1.64 | 76.20 ± 1.61 |
| *T* test | −.32 | −2.10 | −3.83 | −2.89 | −4.80 | −13.91 | 15.67 | −7.75 | −15.33 | −27.24 | −11.67 | −14.27 | −16.24 | −10.18 |
| *P* value | .74 | * | * | * | * | * | * | * | * | * | * | * | * | * |
| *Mean Arterial Blood Pressure* | | | | | | | | | | | | | | |
| Group1 Mean ± SD | 105.53 ± 0.83 | 106.47 ± 1.30 | 106.33 ± 1.23 | 106.20 ± 1.37 | 106.33 ± 1.23 | 106.47 ± 1.30 | 106.33 ± 1.23 | 106.93 ± 2.01 | 106.87 ± 2.0 | 106.40 ± 1.54 | 106.93 ± 2.01 | 106.00 ± 2.00 | 106.07 ± 1.03 | 1.0647 ± 1.6 |
| Group2 Mean ± SD | 108.40 ± 1.24 | 110.47 ± 1.64 | 112.00 ± 2.82 | 113.27 ± 1.57 | 112.87 ± 3.06 | 113.73 ± 2.73 | 113.80 ± 3.16 | 114.47 ± 2.89 | 114.60 ± 2.19 | 115.40 ± 1.18 | 115.33 ± .89 | 115.73 ± 1.03 | 115.33 ± 1.11 | 114.33 ± 2.05 |
| *T* test | −7.42 | −7.39 | −7.11 | −13.07 | −7.65 | −9.28 | −8.50 | −8.26 | −9.93 | −17.88 | −14.73 | −16.74 | −23.64 | −11.57 |
| *P* value | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| | Time | | | | | | | | | | | | | |
| | 90 h | 96 h | 102 h | 108 h | 114 h | 120 h | 126 h | 132 h | 138 h | 144 h | 150 h | 156 h | 162 h | 168 h |
| *Cereb. Transcr. Noninvv. O2 saturation* | | | | | | | | | | | | | | |
| Group1 Mean ± SD | 68.33 ± .48 | 68.66 ± 2.43 | 68.20 ± 2.11 | 68.53 ± 2.23 | 68.0 ± 0.00 | 70.40 ± 2.22 | 68.40 ± .50 | 70.60 ± .50 | 68.60 ± .50 | 72.000 ± 0.00 | 68.60 ± .50 | 70.40 ± .50 | 68.40 ± .50 | 72.00 ± .00 |
| Group2 Mean ± SD | 76.06 ± 1.53 | 75.66 ± 3.13 | 76.40 ± 2.74 | 76.66 ± 1.75 | 76.13 ± 2.79 | 75.73 ± 2.15 | 76.53 ± 2.55 | 75.73 ± 1.98 | 76.26 ± 2.28 | 75.53 ± 2.74 | 75.46 ± 1.76 | 76.20 ± 2.75 | 77.40 ± 2.61 | 76.93 ± 1.62 |
| *T* test | −18.6 | −6.82 | −9.16 | −11.08 | −11.25 | −6.66 | −12.07 | −9.72 | −12.7 | −4.98 | −14.46 | −8.01 | −13.09 | −11.76 |
| *P* value | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| *Mean Arterial Blood Pressure* | | | | | | | | | | | | | | |
| Group1 Mean ± SD | 106.40 ± 1.54 | 107.3 ± 0.72 | 106.33 ± 1.23 | 106.73 ± 1.70 | 106.33 ± 1.23 | 106.33 ± 1.44 | 115.33 ± 1.04 | 107.47 ± .51 | 106.33 ± 2.58 | 105.93 ± 1.03 | 106.80 ± 3.09 | 107.53 ± .51 | 106.67 ± 2.58 | 105.93 ± 1.03 |
| Group2 Mean ± SD | 114.53 ± 1.12 | 115.53 ± 1.59 | 115.47 ± 1.40 | 115.00 ± 1.13 | 115.13 ± .990 | 114.80 ± 1.32 | 106.33 ± 1.23 | 114.47 ± 1.18 | 115.20 ± 1.26 | 115.40 ± 1.18 | 114.47 ± 1.30 | 114.33 ± 2.22 | 114.20 ± 2.78 | 114.47 ± 2.89 |
| *T* test | −16.45 | −18.10 | −18.89 | −15.60 | −21.53 | −16.73 | −21.53 | −20.94 | −11.94 | −23.34 | −8.835 | −11.52 | −7.68 | −10.73 |
| *P* value | * | * | * | * | * | * | * | * | * | * | * | * | * | * |

Significant increase **(*)** in cerebral transcranial noninvasive mixed venous O2 saturation (%) in Group 2 in comparison with Group 1: from hour 12 till hour 168 of this study in the Neurosurgical ICU. Significant increase**(*)** in Invasive Mean Arterial Blood Pressure(mmHg) in Group 2 in comparison with Group 1 from hour 6 till hour 168 of this study in the Neurosurgical ICU.

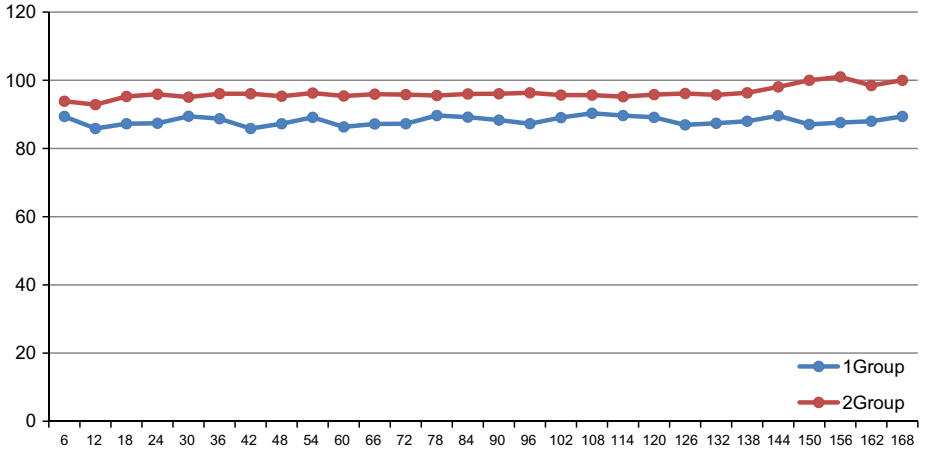


**Chart 2** Cerebral perfusion pressure of the studied groups in mmHg in relation to time in hours.

## 3. Results

- As regard gender distribution, mean patients age and weight. There was no significant ($p < 0.05$) difference between groups (Table 5).
- Global cerebral oxygenation using noninvasive cerebral mixed venous O2 saturation shown in Table 1 shows significant increase in Group (2) in comparison with Group (1) from hour 12 till hour 168 of this study in the NICU. (Chart 1 clarify the numerical result in a clear graph).
- Invasive Mean Arterial Blood Pressure Table 1 shows significant increase in Group 2 in comparison with Group 1 from hour 6 till hour 168 of this study in the Neurosurgical ICU.
- The calculated cerebral perfusion pressure Table 2 shows significant increase in Group 2 in comparison with Group 1 from hour 6 till hour 168 of this study. In the Neurosurgical ICU. (Chart 2 clarify the numerical result in a clear graph).
- Intracranial pressure (ICP) Table 2 shows significant increase in Group 2 in comparison with Group 1 from hour 18 till hour 168 of this study in the Neurosurgical ICU.
- Glasgow Coma score Table 3 shows significant increase in Group 2 in comparison with Group 1 from hour 6 till hour 168 of this study in the Neurosurgical ICU.
- Norepinephrine Infusion dose Table 3 shows significant increase in Group 2 in comparison with Group 1 from hour 42 till hour 144 of this study in the Neurosurgical ICU.
- As regard organ functions Table 4 shows no significant changes between both groups 1 and 2 as regard Serum ALT, serum AST, Serum bilirubin, Serum albumen, Serum Cr, and serum urea during the 7 days of the study.
- As regard cerebral arterial Spasm accidents in each group was recorded as follows: 3 cases of 15 = (20%) cases in group 2 (Norepinephrine plus Milrinone group) compared to 7 cases of 15 = (46.6%) cases in group 1 (Norepinephrine alone group).

## 4. Discussion

Noninvasive monitoring of cerebral oxygenation *not only* used to determine the underlying regional cerebral parenchymal oxygen saturation (rSO2) utilizing tissue oxygen index (oxyhemoglobin divided by the total hemoglobin) *but also* as an early detection monitor of hematoma formation. Keeping regional oxygen saturation greater than 55% is the goal in clinical management. Baseline number is obtained, and any significant change (reduction of 20% from this defined baseline) is indicative for active management of cerebral hypoxia. Cerebral oxymetry has numerous problems that have limited its usefulness in the Neurosurgical ICU (NICU), and the percentage distribution of venous, capillary, and arterial blood representing the cerebral oxymeter signal is undefined [11].

After successful surgical aneurismal clipping, a great challenge starts in the NICU due to the high incidence of post-clipping critical cerebral arterial spasm (typically occurs within 4–14 days following hemorrhage in the case of virgin bleeds and earlier with recurrent hemorrhage, management is by inducing iatrogenic therapeutic hypertension, hypervolemia, and hemdilution the previously known (triple-H), but according to (Mayer and his colleagues 2005) [8], it is enough to achieve a normovolemic controlled hypertensive state (CVP of 5 mmHg) for cerebral aneurysm spasm prevention, so in this present study, the aim is to induce therapeutic basal normovolemic controlled hypertensive state for all patients, then to evaluate the effect of Milrinone as a cerebral vasodilator on the global cerebral oxygenation using the noninvasive transcutaneous cerebral oxymetry.

Milrinone, a phosphodiesterase III inhibitor, affects cAMP pathways with both inotropic and vasodilator effects. Milrinone was first used in the treatment of cerebral vasospasm after rupture of intracranial aneurysm in 2001 [3]. According to (Fraticelli and his colleagues 2008) [12], intra-arterial Milrinone infused in the cerebral territory is effective and safe for reversal of cerebral vasospasm after a subarachnoid hemorrhage and should be tested in a large randomized trial and still not widely used as a continuous IV infusion protecting drug against post-surgical cerebral aneurysm spasm.

In this study, we reported significant increase in global cerebral oxygenation using noninvasive cerebral mixed venous O2 saturation Group (2) in comparison with Group (1) from hour 12 till hour 168 of this study in the NICU**,** this could be attributed to the combined Milrinone cerebral arterial vasodilator (VD) and the cardiac +ve inotropic effects that leads to subsequent increase in the oxygenated arterial cerebral blood flow

**Table 2** Cerebral perfusion pressure and Intracranial pressure of the studied groups.

| Group | Time | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6 h | 12 h | 18 h | 24 h | 30 h | 36 h | 42 h | 48 h | 54 h | 60 h | 66 h | 72 h | 78 h | 84 h |
| *Cerebral perfusion pressur* | | | | | | | | | | | | | | |
| Group 1 Mean ± SD | 89.4 ± 4.5 | 85.9 ± .74 | 87.3 ± .79 | 87.4 ± 1.9 | 89.5 ± 2.9 | 88.7 ± 3.7 | 85.9 ± .74 | 87.3 ± .79 | 89.1 ± 2.06 | 86.3 ± 1.98 | 87.2 ± 0.77 | 87.3 ± 1.94 | 89.7 ± 2.76 | 89.2 ± 3.76 |
| Group 2 Mean ± SD | 93.9 ± 1.7 | 92.9 ± 1.8 | 95.3 ± 2.54 | 95.9 ± 2.98 | 95.1 ± 3.01 | 96.1 ± 2.25 | 96.1 ± 2.52 | 95.3 ± 2.09 | 96.3 ± 1.43 | 95.4 ± 1.72 | 95.9 ± 2.71 | 95.8 ± 2.93 | 95.5 ± 2.19 | 96.0 ± 2.47 |
| *T* test | −3.60 | −13.62 | −11.60 | −9.30 | −5.23 | −6.56 | −15.03 | −13.94 | −10.97 | −13.34 | −11.99 | −9.39 | −6.42 | −5.84 |
| *P* value | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| *Intracranial pressure* | | | | | | | | | | | | | | |
| Group1 Mean ± SD | 17.00 ± 1.19 | 17.00 ± .92 | 17.3 ± 0.97 | 16.7 ± .70 | 16.7 ± .72 | 16.9 ± 1 .3 | 17.0 ± 1.36 | 18.2 ± .85 | 17.2 ± .414 | 17.8 ± .93 | 17.2 ± 1.08 | 16.5 ± .639 | 16.8 ± .51 | 17.1 ± 1.09 |
| Group 2 Mean ± SD | 17.00 ± .00 | 16.9 ± 1.0 | 16.5 ± .51 | 17.3 ± .72 | 17.3 ± .90 | 18.1 ± .25 | 18.2 ± 1.65 | 17.1 ± 1.00 | 17.9 ± 1.03 | 18.6 ± .81 | 18.5 ± .51 | 18.5 ± .51 | 18.4 ± 1.18 | 18.5 ± 1.18 |
| *T* test | .00 | −.18 | −2.80 | 2.30 | 2.12 | 3.50 | 2.16 | −3.58 | 2.55 | 2.47 | 4.09 | 9.42 | 4.78 | 3.35 |
| *P* value | 1.000 | .854 | * | * | * | * | * | * | * | * | * | * | * | * |
| | Time | | | | | | | | | | | | | |
| | 90 h | 96 h | 102 h | 108 h | 114 h | 120 h | 126 h | 132 h | 138 h | 144 h | 150 h | 156 h | 162 h | 168 h |
| *Cerebral perfusion pressur* | | | | | | | | | | | | | | |
| Group 1 Mean ± SD | 88.3 ± 1.95 | 87.3 ± 1.27 | 89.1 ± 3.05 | 90.3 ± 4.33 | 89.7 ± 4.33 | 89.1 ± 2.32 | 86.9 ± 1.03 | 87.4 ± 1.54 | 88.0 ± 0.0 | 89.6 ± 1.54 | 87.1 ± 1.03 | 87.6 ± 1.54 | 88.0 ± 0.0 | 89.4 ± 1.54 |
| Group 2 Mean ± SD | 96.1 ± 2.52 | 96.3 ± 1.95 | 95.7 ± 1.23 | 95.7 ± 2.79 | 95.2 ± 2.07 | 95.8 ± 2.93 | 96.1 ± 1.64 | 95.7 ± 1.22 | 96.3 ± 1.23 | 98.1 ± 2.68 | 1.00 ± 3.60 | 1.01 ± 3.22 | 98.5 ± 1.88 | 1.00 ± 2.66 |
| *T* test | −9.39 | −15.04 | −7.75 | −4.00 | −4.45 | −6.89 | −18.37 | −16.35 | −26.14 | −10.57 | −13.91 | −14.93 | −21.50 | −14.39 |
| *P* value | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| *Intracranial pressure* | | | | | | | | | | | | | | |
| Group1 Mean ± SD | 16.9 ± .51 | 17.5 ± .99 | 17.2 ± .414 | 16.8 ± .94 | 17.2 ± 1.08 | 17.3 ± 1.29 | 17.0 ± .65 | 17.4 ± 1.05 | 17.3 ± 1.16 | 17.2 ± 1.20 | 17.3 ± .96 | 17.4 ± .63 | 17.1 ± .91 | 17.3 ± 1.16 |
| Group 2 Mean ± SD | 18.5 ± 1.18 | 18.8 ± .41 | 17.9 ± 1.032 | 17.6 ± .82 | 18.5 ± .51 | 18.9 ± 1.55 | 19.0 ± .00 | 18.9 ± 1.03 | 19.5 ± .51 | 19.5 ± .516 | 19.0 ± .00 | 19.1 ± 1.03 | 19.5 ± .516 | 19.5 ± .51 |
| *T* test | 4.78 | 4.57 | 2.55 | 2.47 | 4.09 | 2.94 | 11.83 | 4.02 | 6.69 | 6.88 | 6.98 | 5.33 | 8.84 | 6.69 |
| *P* value | * | * | * | * | * | * | * | * | * | * | * | * | * | * |

Significant increase (∗) in Calculated cerebral perfusion pressure in(mmHg) in Group 2 in comparison with Group 1: from hour 6 till hour 168 of this study in the Neurosurgical ICU. Significant increase (∗) in Intracranial pressure (ICP) in mmHg in Group 2 in comparison with Group 1: from hour 18 till hour 168 of this study in the Neurosurgical ICU.

**Table 3** Glasgow Coma score and Noradrenalin infusion dose of the studied groups.

| Group | Time | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 6 h | 12 h | 18 h | 24 h | 30 h | 36 h | 42 h | 48 h | 54 h | 60 h | 66 h | 72 h | 78 h | 84 h |
| *Glasco Coma score* | | | | | | | | | | | | | | |
| Group1 Mean | 13.00 | 13.13 | 13.33 | 13.66 | 13.33 | 13.13 | 13.33 | 13.66 | 13.33 | 13.66 ± .48 | 13.13 | 13.33 | 14.13 ± .35 | 14.46 |
| ± SD | ± .00 | ± .35 | ± .48 | ± .48 | ± .48 | ± .35 | ± .48 | ± .48 | ± .48 | | ± .35 | ± .48 | | ± .51 |
| Group2 Mean | 13.3333 | 13.6667 ± .48795 | 14.0000 ± .00000 | 14.0000 | 14.0000 | 13.6667 | 14.000 | 14.000 | 14.000 | 14.000 | 13.6667 ± .48795 | 14.000 | 14.8667 | 15.0000 |
| ± SD | ± .48795 | | | ± .00000 | ± .00000 | ± .48795 | ± 0 .00000 | ± 0 .00000 | ± 0 .00000 | ± 0 .00000 | | ± 0.00000 | ± 14.8667 | ± .00000 |
| *T* test | −2.64 | −3.43 | −5.29 | −2.64 | −5.29 | −3.43 | −5.29 | −2.64 | −5.29 | −2.64 | −3.43 | −5.29 | −5.70 | −4.00 |
| *P* value | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| *Noradrenalin Inf. dose Inf..fdosedose* | | | | | | | | | | | | | | |
| Group1 Mean | 05 | 05 | .05 | .07 | .07 | .07 | .07 | .07 | .07 | .08 | .08 | .08 | .08 | .08 |
| ± SD | ± .00 | ± 00 | ± .00 | ± .005 | ± .005 | ± .005 | ± .005 | ± .010 | ± .010 | ± .010 | ± .010 | ± .005 | ± .005 | ± .00 |
| Group2 Mean | 05 | 05 | 05 | .08 | .08 | .08 | .08 | .08 | .08 | .09 | .09 | .09 | .09 | .09 |
| ± SD | ± 0.0 | ± 0.0 | ± 0.0 | ± 0.01 | ± 0.01 | ± 0.01 | ± 0.01 | ± 0.01 | ± 0.01 | ± .005 | ± .005 | ± .005 | ± .005 | ± .005 |
| *T* test | .00 | .00 | .000 | 1.93 | 1.93 | 1.93 | 3.83 | 2.16 | 2.70 | 4.09 | 4.09 | .00 | .00 | −3.50 |
| *P* value | 1.000 | 1.000 | 1.000 | .064 | .064 | .064 | * | * | * | * | * | * | * | * |

| | Time | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 90 h | 96 h | 102 h | 108 h | 114 h | 120 h | 126 h | 132 h | 138 h | 144 h | 150 h | 156 h | 162 h | 168 h |
| *Glasco Coma score* | | | | | | | | | | | | | | |
| Group1 Mean | 14.06 ± .25 | 14.06 | 14.13 | 14.13 | 14.06 | 14.13 ± .35 | 14.46 | 14.06 ± .25 | 14.46 | 14.46 | 14.46 | 14.46 | 14.46 | 14.46 |
| ± SD | | ± .25 | ± .35 | ± .35 | ± .25 | | ± .51 | | ± .51 | ± .51 | ± .51 | ± .51 | ± .51 | ± .51 |
| Group2 Mean | 14.4667 ± .51640 | 14.4667 | 14.8667 | 14.8667 | 14.4667 | 14.8667 | 15.0000 | 14.4667 | 15.0000 | 15.0000 | 15.0000 | 15.0000 | 15.0000 | 15.0000 |
| ± SD | | ± .51640 | ± 14.8667 | ± 14.8667 | ± .51640 | ± 14.8667 | ± .00000 | ± .51640 | ± .00000 | ± .00000 | ± .00000 | ± .00000 | ± .00000 | ± .00000 |
| *T* test | −2.68 | −2.68 | −5.70 | −5.70 | −2.68 | −5.70 | −4.00 | −2.68 | −4.00 | −4.00 | −4.00 | −4.00 | −4.00 | −4.00 |
| *P* value | * | * | * | * | * | * | * | * | * | * | * | * | * | * |
| *Noradrenalin Inf. dose Inf..fdosedose* | | | | | | | | | | | | | | |
| Group1 Mean | .08 | .08 | .08 | .08 | 09 | 09 | 09 | 09 | 09 | 09 | 16 | .16 | 16 | 17 |
| ± SD | ± .004 | ± .01 | ± .01 | ± .01 | ± .01 | ± .01 | ± .01 | ± .01 | ± .01 | ± .01 | ± .00 | ± .00 | ± .005 | ± .21 |
| Group2 Mean | .09 | 0.10 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 11 | 16 | 16 | 16 | .18 |
| ± SD | ± .005 | ± .00 | ± .03 | ± .03 | ± .03 | ± .03 | ± .03 | ± .03 | ± .03 | ± .03 | ± .25 | ± .25 | ± .25 | ± .29 |
| *T* test | .00 | 3.05 | 2.55 | 2.55 | 2.25 | 2.25 | 2.25 | 2.25 | 2.25 | 2.25 | 1.55 | 1.55 | 1.49 | 042 |
| *P* value | * | * | * | * | * | * | * | * | * | * | .130 | .130 | .145 | .967 |

Significant increase (*) in Glasgow Coma score in Group 2 in comparison with Group 1: from hour 6 till hour 168 of this study in the Neurosurgical ICU. Significant increase (*) in Noradrenalin Infusion dose (μg/kg/min) in Group 2 in comparison with Group 1: from hour 42 h 144 of this study in the Neurosurgical ICU.

**Table 4** Liver and kidney function of the studied groups.

| Org. function | Gr | Day | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | | 1st | 2nd | 3rd | 4th | 5th | 6th | 7th |
| Serum ALT U/L | Group 1 | 39.8 ± 1.8 | 41.7 ± 4.04 | 38.6 ± 1.5 | 37.93 ± 1.03 | 39.6 ± 1.5 | 43.13 ± 1.59 | 37.93 ± 1.03 |
| | Group 2 | 40.1 ± 1.5 | 41.4 ± 2.13 | 37.3 ± 2.41 | 38.6 ± 3.8 | 38.3 ± 2.41 | 40.6 ± 2.8 | 38.6 ± 3.8 |
| | *T* test | −0.561 | −0.282 | 1.73 | −0.719 | 1.71 | 3.06 | −0.72 |
| | *P* value | 0.579 | 0.78 | 0.14 | 0.478 | 0.1 | * | 0.48 |
| Serum AST U/L | Group 1 | 20.5 ± 5.6 | 22.4 ± 5.34 | 21.0 ± 4.0 | 24.2 ± 6.1 | 22.53 ± 2.7 | 25.4 ± 4.9 | 24.07 ± 4.41 |
| | Group 2 | 21.4 ± 4.6 | 24.0 ± 5.74 | 23.06 ± 4.26 | 24 ± 4.7 | 23.6 ± 4.8 | 24.7 ± 5.4 | 24.3 ± 5.8 |
| | *T* test | −.465 | −.790 | −1.297 | 100 | −.751 | .390 | −.141 |
| | *P* value | 0.645 | 0.436 | 0.205 | 0.921 | 0.459 | 0.700 | 0.88 |
| S. albumen g/L | Group 1 | 30.66 ± 3.26 | 30.46 ± 3.13 | 30.73 ± 3.26 | 31.20 ± 3.80 | 32.20 ± 3.00 | 31.26 ± 2.49 | 32.06 ± 2.71 |
| | Group 2 | 30.26 ± 2.89 | 30.93 ± 3.88 | 31.60 ± 3.60 | 33.20 ± 2.78 | 31.80 ± 2.27 | 30.60 ± 3.92 | 31.73 ± 2.84 |
| | *T* test | .355 | −.362 | −.691 | −1.644 | .411 | .555 | .329 |
| | *P* value | .725 | .720 | .495 | .111 | .684 | .583 | .745 |
| S. bilirubin μmol/L | Group 1 | 6.73 ± 1.75 | 5.73 ± 2.18 | 4.46 ± 2.13 | 6.33 ± 1.63 | 5.86 ± 1.92 | 4.60 ± 2.09 | 4.46 ± 2.13 |
| | Group 2 | 5.86 ± 2.44 | 5.13 ± 2.19 | 5.78 ± 2.45 | 5.21 ± 2.22 | 4.92 ± 1.89 | 4.85 ± 1.79 | 3.85 ± 1.65 |
| | *T* test | 1.116 | .749 | −1.547 | 1.552 | 1.321 | −.354 | .855 |
| | *P* value | .274 | .460 | .133 | .132 | .198 | .726 | .400 |
| Serum urea Mmol/L | Group 1 | 4.7 ± 0.3 | 4.4 ± 0 .4 | 4.53 ± 0.5 | 4.0 ± 0.4 | 4.5 ± 0.5 | 4.7 ± 0.3 | 4.8 ± 0 .4 |
| | Group 2 | 4.7 ± 0.3 | 4.2 ± 0.3 | 4.62 ± 0 .4 | 4.4 ± 0.6 | 4.6 ± 0 .4 | 4.7 ± 0.3 | 4.8 ± .3 |
| | *T* test | * | 0.83 | −.99 | −2.6 | −.99 | * | * |
| | *P* value | 1.0 | 0.415 | 0.32 | 0.16 | 0.32 | 1.0 | 0.96 |
| Serum Cr μmol/L | Group 1 | 66.86 ± 5.19 | 66.80 ± 4.03 | 72.00 ± 6.95 | 76.06 ± 6.62 | 78.40 ± 6.98 | 78.73 ± 7.07 | 76.86 ± 8.07 |
| | Group 2 | 68.73 ± 5.83 | 69.73 ± 5.53 | 68.13 ± 6.47 | 71.93 ± 2.37 | 74.20 ± 6.58 | 80.80 ± 3.27 | 76.73 ± 8.19 |
| | *T* test | −.925 | .363 | −1.575 | −2.274 | −1.695 | 1.026 | 1.026 |
| | *P* value | −1.658 | .108 | .126 | * | .101 | .313 | .317 |

No significant changes between groups 1 and 2 as regard organ functions Serum (ALT, AST, albumen, bilirubin, Creatinine, and urea) during the 7 days of the study.

**Table 5** Age, gender, and body weight.

| Patient data | Group | |
|---|---|---|
| | Group 1 | Group 2 |
| Age (years) | 41.44(14.3) | 43.16(13.9) |
| *Gender* | | |
| (Male) | 8 | 8 |
| (Female) | 7 | 7 |
| Body weight (kg) | 75.34(9.1) | 78.65(7.4) |

No significant difference between the two groups as regard age, gender and body weight; values are in mean and standard deviation (SD).

**Table 6** World Federation of Neurological Surgeons Grading System for Subarachnoid Hemorrhage (WFNS) scale.

| Grade | Motor deficit | Glasgow Coma score |
|---|---|---|
| 1 | Absent | 15 |
| 2 | Absent | 13–14 |
| 3 | Present | 13–14 |
| 4 | Present or absent | 7–12 |
| 5 | Present or absent | 3–6 |

Where a motor deficit refers to a major focal deficit interpretation:

- Maximum score of 15 has the best prognosis.
- Minimum score of 3 has the worst prognosis.
- Scores of 8 or above have a good chance for recovery.
- Scores of 3–5 are potentially fatal, especially if accompanied by fixed pupils.

(CBF) improving the global cerebral oxygenation. In line with this result (Yoshiki and his colleagues 2004), [13] suggested that Milirinone cerebral cisternal irrigation has an effective cerebral arterial VD effect is sufficient enough to reduce the occurrence of vasospasm in patients with poor grade aneurismal SAH. Also, in accordance to our result, (Shankar and his colleagues 2011) [14] documented that milirinone intra-arterial infusion increased the cerebral blood flow via reversing the arterial spasm. Thereafter, Milrinone can improve the global cerebral oxygenation during the serious period of post-cerebral aneurismal clipping in the ICU.

As regard to the Milrinone cardiac +ve inotropic mechanism (Alousi and his colleagues 1986) [15] suggested that Milrinone may stimulate the influx of Ca + + into the cardiac cell. As phosphodiesterase inhibitor that increase cardiac cAMP levels. However, analyzing a time-course of the changes in cAMP levels during the inotropic response to bipyridines indicated that the isometric tension elevation development preceded the increase in cAMP level. Lastly, Alousi concluded that more than one mechanism may be involved in the initiation and maintenance of the inotropic response to the Milrinone.

A co-link in our results between invasive Mean Arterial Blood Pressure and norepinephrine infusion dose documented as significant increase in invasive Mean Arterial Blood Pressure in Group 2 in comparison with Group 1 from hour 6 till hour 168 of this study as shown in Table 1 associated with increased IV infusion dose of norepinephrine in group 2 in comparison with group 1 from hour 42 till hour 144 of this study Table 3, this can be explained by the combined effects of the potent VC effect of norepinephrine in addition to the + ve inotropic effect of Milrinone. Considering the infusion dose of norepinephrine shown in Table 3 that we got most significantly increased IV infusion dose of norepinephrine in group 2 in comparison with group 1 explained by the increased need in group 2 to counteract the systemic peripheral VD effect of the simultaneously IV infused Milrinone. In opposition to this explanation, Liu and his colleagues 1997 [16] concluded that the vasodilator effect of Milrinone is strong enough to abolish the vasoconstrictor effect of norepinephrine and in the same line (Jeon and his colleagues 2006) [17] used the same Milrinone infusion dose of our study and found that vasopressin is better than norepinephrine in counteracting the post-infusion Milrinone hypotension, but we can argue that opposing opinions by the significant increase in the continuous IV infusion dose of the supporting norepinephrine.

Value of including the 6 hourly recording of the Noradrenaline infusion dosing was to detect if there is need to increase the needed infusion dose after adding the peripheral VD Milrinone in group 2 to counteract this milrinone VD effect on the IMAP and in turn on the CPP.

As regard Calculated CPP and ICP shown in Table 2: in this present study, CPP was calculated from the famous formula CPP = MBP-ICP Table 2 showed significant increase in CPP in Group 2 in comparison with Group 1 from hour 6 till hour 168 of this study, also Table 2 showed significant increase in ICP in Group 2 in comparison with Group 1 from hour 18 till hour 168. These co-linked two results are dependent on each other and can not be explained separately and can be explained by the combined effects of the potent VC effect of norepinephrine in addition to the + ve inotropic effect of Milrinone have increased the MBP and subsequently increased the CPP, and ICP (within the normal range) in group (2) compared to group (1). In opposition to this explanation, (Fraticelli and his colleagues 2008) [12] studied twenty-two consecutive patients with angiographically proven CVS (arterial diameter reduction > 40%) intra-arterial Milrinone was infused in the cerebral territory involved and followed by continuous intravenous infusion until day 14 after initial bleeding and recorded improving cerebral tissue perfusion independently of mean arterial pressure.

As regard Glasgow Coma score (GCS) shown in Table 3: shows significant increase in Group 2 in comparison with Group 1 from hour 6 till hour 168. The GCS was recorded starting from the 1st hour after surgical clipping, and according to this present study rules, it was decided for all cases of both groups to be fully conscious and of GCS > 12 in order to detect any deterioration of conscious level with all signs of newly developing cerebral spasm. The significantly increased GCS in group 2 in comparison with group 1 can be explained by the increased cerebral arterial vasodilator Milrinone effect added to that milrinone + ve inotropic effect augmented by the effective supporting systemic arterial vasoconstrictor vasopressor effect of the norepinephrine maintaining increased effective MABP&CBF enriching the vasodilated cerebral arterial tree with effective CPP and CBF enough to maintain effective brain perfusion, and also conscious level seen as a mirror image for cerebral oxygenation shown in the significantly increased noninvasive cerebral O2 saturation in (norepinephrine plus Milrinone group 2) than (norepinephrine alone group 1).

According to organ functions shown in Table 4, no significant changes between both groups 1 and 2 as regard Serum ALT, serum AST, Serum bilirubin, Serum albumen, Serum Cr, and serum urea during the 7 days of the study. All recorded organ function were routinely done as a guard against any organ blood perfusion deterioration can happen with the continuous IV infusion of VC norepinephrine (i.e., renal artery spasm) putting in mind the fact that autoregulation is essentially maintained independent of nervous and humeral stimuli documented by (Kiil and his colleagues 1969) [18] who infused norepinephrine continuously into the renal artery. In line with our result (Anderson and his colleagues 1981) [19] who infused norepinephrine intravenously at 0.2–0.4 μg/kg/min in conscious dogs, did not decreased the renal function even found renal vasodilatation that could be attributed to the increase in systemic blood pressure which in turn decreases renal sympathetic tone. In opposition to this result, the old theory that norepinephrine infusions have been reported to decrease splanchnic and renal blood flow, under normal circulatory conditions, as well as during essential hypertension and hypovolemic hypotension. These reports have significantly inhibited the clinical use of norepinephrine, but if it is used to support a vasodilated circulation with a normal or increased cardiac output, it is likely to be the kidney's friend not its foe [20].

Arterial Spasm accidents in each group were recorded as follows: 3 cases of 15 = (20%) cases in group 2 (Norepinephrine plus Milrinone group) compared to 7 cases of 15 = (46.6%) cases in group 1(Norepinephrine alone group) indicating significant decrease in the occurrence of spasm during continuous IV infusion of Milrinone with norepinephrine than norepinephrine alone that can be explained by the continuous effective cerebral arterial VD effect of the continuous IV infusion of Milrinone and its + ve inotropic effect added to the effective vasoconstrictor norepinephrine augmenting effect on MABP which in turn increased the CPP and CBF, all these effects are very important factor in preventing the occurrence of cerebral arterial spasm during the period of highest incidence of cerebral vasospasm after cerebral aneurismal clipping. In line with this result, Khajavi and his colleagues (1997) [21] proved that experimental chronic cerebral vasospasm in canine model can be prevented by intracisternal Milrinone injection with no significant changes in systemic hemodynamic, and 4 years later, Arakawa and his colleagues (2001) [3]'s study suggests that cisternal irrigation with Milrinone is safe and effective and reduces the occurrence of vasospasm in patients aneurismal SAH. Very few or even nil number of studies were done on the effect of intravenous infusion of Milrinone on preventing post-aneurysmal clipping cerebral arterial spasm for example; Fraticelli and his colleagues (2008) [12] mixed local intra-arterial Milrinone infusion in the affected cerebral territory, then followed by continuous intravenous infusion until day 14 after 1st bleeding, and concluded that Milrinone is safe and effective for reversal of CVS after aneurismal SAH and should be examined in a large randomized trial.

In conclusion, Milrinone continuous intravenous infusion improved significantly the global cerebral oxygenation and re-

duced the incidence of cerebral vasospasm during the dangerous period of cerebral spasm after cerebral aneurysm clipping surgery in the neurosurgical ICU.

## Conflicts of interest

None.

## References


[1] James K, Liu, William T, Could well. Intra-arterial papaverine infusions for the treatment of cerebral vasospasm induced by aneurismal subarachnoid hemorrhage. Neurocrit Care 2005;2:124–32.

[2] Wilkins RH. Cerebral vasospasm. Crit Rev Neurobiol 1990;6:51–77.

[3] Arakawa Y, Kikuta K, Hojo M, et al. Milrinone for the treatment of cerebral vasospasm after subarachnoid hemorrhage: report of seven cases. Neurosurgery 2001;48(4):723–8.

[4] Constantoyannis C, Sakellaropoulos GC, Kagadis GC, et al. Transcranial cerebral oxymetry and transcranial doppler sonography in patients with ruptured cerebral aneurysms and delayed cerebral vasospasm. Med Sci Monit 2007;10:35–40.

[5] Baumann Antoine, Derelle Anne-Laure, Mertes Paul-Michel, et al. Seeking new approaches: milrinone in the treatment of cerebral vasospasm. Neurocrit Care 2012;16:351–3.

[6] Hoefnagel D, Dammers R, Ter Laak-Poort MP, et al. Risk factors for infections related to external ventricular drainage. Acta Neurochirurg 2008;150(3):209–14.

[7] Steiner, Luzius A, Czosnyka. Continuous monitoring of cerebrovascular pressure reactivity allows determination of optimal cerebral perfusion pressure in patients with traumatic brain injury. J Crit Care Med 2002;30(4):733–8.

[8] Mayer SA, Bernardini GL, Solomon RA. Subarachnoid hemorrhage. In: Rowland LP, editor. Merritt's neurology. Philadelphia: Lippincott Williams and Wilkins; 2005. p. 28–338.

[9] Monique Pharm D BCPS Richer, Sylvie MSc Pharm D Robert, Marcel MD FRCP Lebel. Renal hemodynamics during norepinephrine and low-dose dopamine infusions in man. Crit Care Med 1996;24(7):1150–6.

[10] Ruengsakulrach Permyos, MarkBrooks, David L, Hare, et al. Preoperative assessment of hand circulation by means of Doppler ultrasonography and the modified Allen test. J Thorac Cardiovasc Surg 2001;121:526–31.

[11] David P, Adelson MD. Cerebral oximetry in the head-injured patient: is it time for widespread application? Clin Neurosurg 2007;54:58–63.

[12] Fraticelli AT, Cholley BP, Losser MR, et al. Milrinone for the treatment of cerebral vasospasm after aneurysmal subarachnoid hemorrhage. Stroke 2008;39(3):893–8.

[13] Arakawa Yoshiki, Kikuta Ken-ichiro, Hojo Masato, et al. Milrinone reduces cerebral vasospasm after subarachnoid hemorrhage of WFNS grade IV or V. Neurol Med-Chirurg 2004;44(8):393–401.

[14] Shankar JJ, dos Santos MP, Deus-Silva L, et al. Angiographic evaluation of the effect of intra-arterial milrinone therapy in patients with vasospasm from aneurismal subarachnoid hemorrhage. Neuroradiology 2011;53(2):123–8.

[15] Alousi AA, Johnson DC. Pharmacology of the bipyridines: Amrinone and Milrinone. Circulation 1986;73(3 Pt 2), III10-24.

[16] Liu JJ, Doolan LA, Xie B, et al. Direct vasodilator effect of milrinone, an inotropic drug, on arterial coronary bypass grafts. FANZCA. J Thorac Cardiovasc Surg 1997;113(1):108–13.

[17] Jeon Y, Ryu JH, Lim YJ, et al. Comparative hemodynamic effects of vasopressin and Norepinephrine after Milrinone-induced hypotension in off-pump coronary artery bypass surgical patients. Eur J Cardiothorac Surg 2006;29(6):952–6.

[18] Kiil F, Kjekshus J, Loyning E. Renal autoregulation during infusion of Noradrenalin. Angiotensin Acetyl Acta Physiol Scand 1969;76(1–2):10–23.

[19] Anderson WP, Korner PI, Selig SE. Mechanisms involved in the renal responses to intravenous and renal artery infusions of noradrenaline in conscious dogs. J Physiol 1981;321:21–30.

[20] Bellomo Rinaldo, Di Giantomasso David. Noradrenalin and the kidney: friends or foes? Crit Care 2001;5:294–8.

[21] Khajavi, Kaveh MD, Ayzman, et al. Prevention of chronic cerebral vasospasm in dogs with milrinone. Neurosurgery 1997;40(2):354–63.

[22] Teasdale G, Drake C, Hunt W, et al. A universal subarachnoid hemorrhage scale: report of a committee of the World federation of neurosurgical Societies. J Neurol, Neurosurg, Psychiat 1988;51(11):1457.

[23] Claassen J, Bernardini GL, Kreiter K, et al. Effect of cisternal and ventricular blood on risk of delayed cerebral ischemia after subarachnoid hemorrhage: the Fisher scale revisited. Stroke 2001;32(9):2012–20.