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SCIENTIFIC ARTICLE

Effect of magnesium sulphate and milrinone on cerebral vasospasm after aneurysmal subarachnoid hemorrhage: a randomized study

Rabie Soliman*, **Gomaa Zohry**

Cairo University, Department of Anesthesia, Cairo, Egypt

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KEYWORDS
Magnesium sulphate;
Milrinone;
Aneurysmal subarachnoid hemorrhage;
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Abstract
Background: Aneurysmal subarachnoid hemorrhage is an important cause of premature death and disability worldwide. Magnesium sulphate is shown to have a neuroprotective effect and it reverses cerebral vasospasm. Milrinone is also used in the treatment of cerebral vasospasm. The aim of the present study was to compare the effect of prophylactic magnesium sulphate and milrinone on the incidence of cerebral vasospasm after subarachnoid hemorrhage.
Methods: The study included 90 patients with aneurysmal subarachnoid hemorrhage classified randomly (by simple randomization) into two groups: magnesium sulphate was given as an infusion of 500 $mg.day^{-1}$ without loading dose for 21 days. Group B: milrinone was given as an infusion of 0.5 $\mu g.kg^{-1}.min^{-1}$ without loading dose for 21 days. The cerebral vasospasm was diagnosed by mean cerebral blood flow velocity in the involved cerebral artery (mean flow velocity $\geq$ 120 $cm.s^{-1}$), neurological deterioration by Glasgow coma scale, or angiography (the decrease in diameter of the involved cerebral artery >25%).
Results: The mean cerebral blood flow velocity decreased significantly in the magnesium group compared to milrinone group through Day 7, Day 14 and Day 21 ($p < 0.001$). The incidence of cerebral vasospasm decreased significantly with magnesium compared to milrinone ($p = 0.007$). The Glasgow coma scale significantly improved in the magnesium group compared to milrinone group through Day 7, Day 14 and Day 21 ($p = 0.036$, $p = 0.012$, $p = 0.016$, respectively). The incidence of hypotension was higher with milrinone than magnesium ($p = 0.012$).
Conclusions: The incidence of cerebral vasospasm after aneurysmal subarachnoid hemorrhage was significantly lower and Glasgow coma scale significantly better with magnesium when compared to milrinone. Milrinone was associated with a higher incidence of hypotension and requirement for dopamine and norepinephrine when compared to magnesium.

* Corresponding author.
E-mail: rabiesoliman@hotmail.com (R. Soliman).

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PALAVRAS-CHAVE
Sulfato de magnésio;
Milrinona;
Hemorragia subaracnoidea por aneurisma;
Vasoespasmo cerebral

Efeitos do sulfato de magnésio e da milrinona sobre o vasoespasmo cerebral após hemorragia subaracnoidea por aneurisma: estudo randômico

Resumo
Justificativa: A hemorragia subaracnoidea por aneurisma é uma importante causa de morte prematura e de incapacidade em todo o mundo. O sulfato de magnésio mostra um efeito neuroprotetor e reverte o vasoespasmo cerebral. A milrinona também é usada no tratamento de vasoespasmo cerebral. O objetivo do presente estudo foi comparar o efeito profilático do sulfato de magnésio e da milrinona sobre a incidência de vasoespasmo cerebral após hemorragia subaracnoidea.
Métodos: O estudo incluiu 90 pacientes com hemorragia subaracnoidea por aneurisma randomicamente distribuídos (randomização simples) em dois grupos: sulfato de magnésio foi administrado em infusão de 500 $mg.dia^{-1}$ sem dose de ataque durante 21 dias. O Grupo B recebeu milrinona em infusão de 0,5 $\mu g.kg^{-1}.min^{-1}$ sem dose de ataque durante 21 dias. O vasoespasmo cerebral foi diagnosticado pela velocidade média do fluxo sanguíneo cerebral na artéria cerebral envolvida (velocidade média do fluxo $\geq$ 120 $cm.s^{-1}$), a deterioração neurológica por escala de coma de Glasgow ou angiografia (diminuição do diâmetro da artéria cerebral envolvida >25%).
Resultados: A velocidade média do fluxo sanguíneo cerebral diminuiu significativamente no grupo magnésio em comparação com o grupo milrinona nos dias 7, 14 e 21 ($p < 0,001$). A incidência de vasoespasmo cerebral diminuiu significativamente com o magnésio em comparação com milrinona ($p = 0,007$). A escala de coma de Glasgow melhorou significativamente no grupo magnésio em comparação com o grupo milrinona nos dias 7, 14 e 21 ($p = 0,036$, $p = 0,012$, $p = 0,016$, respectivamente). A incidência de hipotensão foi maior com milrinona do que com magnésio ($p = 0,012$).
Conclusões: A incidência de vasoespasmo cerebral após hemorragia subaracnoidea por aneurisma foi significativamente menor e a escala de coma de Glasgow significativamente melhor com magnésio em comparação com milrinona. A milrinona foi associada a uma maior incidência de hipotensão e necessidade de dopamina e norepinefrina em comparação com o magnésio.

Introduction

The incidence of cerebral vasospasm after aneurysmal subarachnoid hemorrhage (aSAH) is about 70% and is symptomatic in nearly 50% of the patients.[1] It is the major cause of morbidity and mortality in patients suffering from aSAH.[2]

Recent studies showed that magnesium sulphate therapy is safe and reduces the incidence of delayed cerebral ischemia and subsequent poor outcome after aSAH.[3,4] The mechanism of action of magnesium sulphate includes an inhibition of the release of excitatory amino acids and blockade of N-methyl-D-aspartate–glutamate receptors.[5] Magnesium is also a noncompetitive antagonist of voltage-dependent calcium channels and has a dilatory effect on cerebral arteries. In addition, magnesium attenuates the effect of various potent vasoconstrictors, such as endothelin 1, and blocks the formation of reactive oxygen species.[6] Hypomagnesaemia occurs in more than 50% of patients with aSAH.[7]

Milrinone is a phosphodiesterase III inhibitor that affects cyclic adenosine monophosphate (cAMP) pathways producing both inotropic and vasodilator effects. It has been used in the treatment of cerebral vasospasm in Asah.[8,9] It was hypothesized that the milrinone will improve the neurological outcome in patients with aSAH, therefore this study was to compare the effect of magnesium sulphate and milrinone on the incidence of cerebral vasospasm after aSAH.

Methods

After obtaining informed consent (on admission to neurosurgical ICU) and approval of local ethics and research committee (14/10/2013. 229/2013), a double-blinded randomized study included ninety patients with angiographic proof of cerebral aneurysm and computed tomography (CT) evidence of aSAH with Fisher Grade II–III,[10] and admitted to the neurosurgical Intensive Care Unit (ICU) within 24 h of the onset of aSAH in preparation for surgical management. The exclusion criteria included aSAH with Fisher Grade I and IV, non-aneurysmal SAH, no informed consent, imminent death, patients with cardiac disease (a pre-operative second or third degree heart block, severe valvular stenosis, hypertrophic obstructive cardiomypathothy (HOCM), ejection fraction <30%), renal impairment (serum creatinine $\geq$ 1.4 $mg.L^{-1}$), or hemodynamic instability. In the ICU, pulse oximeter,

electrocardiogram (ECG), non-invasive arterial blood pressure and nasopharyngeal temperature monitoring was performed. Under local anesthesia, central venous and radial artery cannulation was performed. The patients with preoperative Glasgow coma scale (GCS) score $\leq$8 were intubated and placed on mechanical ventilation to maintain oxygenation and to control the arterial partial pressures of carbon dioxide $PaCO_2$ between 30 and 35 mmHg. The included patients were classified into two groups (each = 45) and the study medication was prepared by a staff-nurse in the central pharmacy and given to the anesthetist blindly. The concealment of allocation was done by using random numbers generated through Excel. The Group MG received magnesium sulphate as an infusion of 500 mg over 24 h (daily) without a loading dose after the diagnosis of aSAH for 21 days. The serum magnesium concentration was measured daily. The Group ML received milrinone as an infusion of 0.5 $\mu g.kg^{-1}.min^{-1}$ (for 24 h daily) without a loading dose for 21 days. For all patients of the two groups, oral 360 mg of nimodipine (60 $mg.4\,h^{-1}$) was given after aneurysmal clipping either orally or through the nasogastric tube.

The anesthesia was induced with thiopental sodium, and fentanyl and atracurium were administered for analgesia and neuromuscular blockade respectively. Anesthesia was maintained with sevoflurane, atracurium and fentanyl infusion. Corticosteroids, diuretics and mannitol were administered according to the need. The monitors used during anesthesia included ECG, pulse oximetry, invasive blood pressure, core temperature, central venous pressure (CVP), end-tidal CO_2, urine output and arterial blood gases. After surgery, patients were readmitted to the neurosurgical ICU. Patients with good GCS postoperatively were extubated and patients with postoperative GCS $\leq$ 8 were maintained on mechanical ventilation. The patients were monitored clinically and radiologically by transcranial Doppler (TCD) (right or left middle, anterior or posterior cerebral arteries, according to the site of cerebral aneurysm, mean flow velocity was monitored using a 2 mHz pulsed range-gated Doppler ultrasound probe; TC 2000; EME, Uberlingen, Germany), to determine the effects of intravenous administration of magnesium and milrinone on the incidence of cerebral vasospasm. The cerebral vasospasm was diagnosed by mean cerebral blood flow velocity in the involved cerebral artery (mean flow velocity $\geq$ 120 $cm.s^{-1}$), where the mean flow velocity equal to (peak systolic velocity + (end-diastolic velocity $\times$ 2)/3),[11] or angiography (the decrease in diameter of the involved cerebral artery > 25%). The neurological assessment by GCS was done during transcranial Doppler examination. For patients with deteriorated conscious level by GCS, brain CT scan was done to exclude the presence of hydrocephalus, subarachnoid or intracerebral hemorrhage.

For all patients and after surgical clipping, the arterial blood pressure was targeted >150/90 mmHg and hypervolemia was induced by fluids administration to maintain the CVP around 12–14 mmHg and to induce hemodilution to maintain the haematocrit between 30% and 33% according to the triple H therapy protocol. Hypertensive patients were controlled by antihypertensive drugs (Beta-antagonist and nitroglycerin infusion 0.5–10 $\mu g.kg^{-1}.min^{-1}$). Blood pressure below 150/90 mmHg was elevated by inotropic drugs dopamine infusion (0.5–10 $\mu g.kg^{-1}.min^{-1}$) and/or norepinephrine infusion (0.01–0.2 $\mu g.kg^{-1}.min^{-1}$) and correction of intravascular volume. Daily measurements of serum sodium, potassium, magnesium, liver enzymes, albumin, urea and creatinine were done. For patients with deteriorated conscious levels post-operatively, brain CT-scan was done to exclude hydrocephalus or brain edema and four vessels cerebral angiography was done to diagnose cerebral vasospasm.

The primary outcome was the incidence of cerebral vasospasm based on the transcranial Doppler (mean cerebral blood flow velocity in the involved cerebral artery $\geq$ 120 $cm.s^{-1}$), neurological deterioration by GCS, or angiography (the decrease in diameter of the involved cerebral artery > 25%). The secondary outcome was the safety of the study medications. The safety was assessed by the occurrence of any adverse events to the patients.

Power analysis was performed using the Chi square test for independent samples on incidence of cerebral vasospasm after aSAH in patients undergoing clipping of cerebral aneurysm, because it was the main outcome variable in the present study. A pilot study was done before starting this study (14 patients in each group), because there are no available data in the literature that compared the effect of magnesium and milrinone on the cerebral vasospasm. The results of the pilot study showed the incidence of cerebral vasospasm was 22% in magnesium group, and 50% in the milrinone group. Taking power 0.8 and alpha error 0.05, Beta 0.2, a minimum sample size of 45 patients was calculated for each group.

Data were statistically described in terms of mean $\pm$ standard deviation ($\pm$SD), frequencies (number of cases), and median interquartile range (IQR). Comparison of numerical variables between the study groups was done using one way analysis of variance (ANOVA) test with post hoc multiple 2 group comparisons. Exact test was used instead when the expected frequency was less than 5. A *p*-values less than 0.05 were considered statistically significant. All statistical calculations were done using computer programs SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 15 for Microsoft Windows.

Results

All patients completed the study. There was no statistical difference regarding the demographic data, preoperative co-morbidities, the anatomical location of the cerebral aneurysms, and Fisher grade ($p > 0.05$) (Table 1).

There was no statistical difference between the two groups regarding heart rate, mean arterial blood pressure and arterial partial pressure of carbon dioxide ($p > 0.05$) (Table 2). On admission to the ICU, the heart rate and mean arterial blood pressure were elevated (the heart rate > 100 pm and mean arterial blood pressure > 110 mmHg), and managed by beta-blockers, calcium channel blockers, and volume replacement. The comparison of CVP between the two groups was statistically insignificant ($p > 0.05$). The CVP was managed with fluid administration to induce hypervolemia according to the triple H therapy protocol after surgical clipping of a cerebral aneurysm (Table 2). The comparison of the haematocrit values between the two groups was statistically insignificant ($p > 0.05$) (Table 2). The

Table 1 Demographic data of patients. Values are expressed as mean ± SD, number.

Variables	Group MG ($n = 45$)	Group ML ($n = 45$)	p-Value
Age (year)	51.10 ± 8.31	50.62 ± 9.30	0.796
Gender			
Male/female	23/22	26/19	0.525
Body weight (kg)	77.63 ± 8.70	78.22 ± 9.59	0.749
Hypertension	7	9	0.581
Anatomical location of aneurysms			
Middle cerebral artery	11	14	0.581
Anterior cerebral artery	7	4	0.334
Anterior communicating artery	15	17	0.659
Posterior communicating artery	12	10	0.623
Fisher grade			
Grade II/III	29/16	34/11	0.250

Group MG, magnesium group; Group ML, milrinone group.

Table 2 Heart rate, mean arterial blood pressure, central venous pressure, arterial partial pressure of carbon dioxide, haematocrit value and magnesium level of patients. Values are expressed as mean ± SD (%).

Variable	Timepoints	Group MG ($n = 45$)	Group ML ($n = 45$)	p-Value
Heart rate (bpm)	Day 1	109.45 ± 8.61	108.61 ± 7.04	0.613
	Day 7	93.71 ± 7.39	92.37 ± 4.61	0.305
	Day 14	87.84 ± 6.46	85.00 ± 7.58	0.059
	Day 21	82.75 ± 8.12	84.07 ± 6.16	0.387
Mean arterial blood pressure (mmHg)	Day 1	119.16 ± 7.60	120.54 ± 6.43	0.369
	Day 7	114.21 ± 6.31	113.10 ± 7.46	0.448
	Day 14	113.40 ± 5.91	112.72 ± 6.26	0.597
	Day 21	111.52 ± 6.31	110.61 ± 6.57	0.504
Central venous pressure (mmHg)	Day 1	7.27 ± 1.44	7.03 ± 1.30	0.408
	Day 7	13.60 ± 1.13	13.42 ± 1.14	0.453
	Day 14	13.91 ± 1.01	13.83 ± 0.94	0.698
	Day 21	13.33 ± 1.21	13.40 ± 1.30	0.792
Arterial partial pressure of carbon dioxide (mmHg)	Day 1	37.00 ± 2.64	37.25 ± 2.29	0.632
	Day 7	36.72 ± 1.78	37.30 ± 1.60	0.107
	Day 14	37.11 ± 1.54	37.52 ± 1.46	0.198
	Day 21	36.83 ± 1.43	36.94 ± 1.41	0.714
Haematocrit value (%)	Day 1	39.32 ± 3.15	38.94 ± 3.32	0.578
	Day 7	32.36 ± 1.53	31.74 ± 1.66	0.068
	Day 14	32.76 ± 1.42	33.28 ± 1.60	0.106
	Day 21	32.91 ± 1.80	33.43 ± 1.72	0.164
Magnesium level (mmoL/L)	Day 1	1.13 ± 0.17	1.15 ± 0.21	0.620
	Day 7	2.42 ± 0.33[a]	1.23 ± 0.18	0.001[b]
	Day 14	2.34 ± 0.23[a]	1.19 ± 0.21	0.001[b]
	Day 21	2.37 ± 0.28[a]	1.24 ± 0.20	0.001[b]

Group MG, magnesium group; Group ML, milrinone group.
Day 1, the 1st day from the onset of subarachnoid hemorrhage; Day 7, the 7th day from the onset of subarachnoid hemorrhage; Day 14, the 14th day from the onset of subarachnoid hemorrhage; Day 21, the 21st day from the onset of subarachnoid hemorrhage.
[a] $p < 0.05$ versus baseline.
[b] Statistically significant ($p < 0.05$) between the two groups.

haematocrit values decreased to 30–35% by haemodilution according to the triple H therapy protocol. The blood magnesium level was higher in magnesium group at Day 7, Day 14 and Day 21 than milrinone group ($p < 0.001$) (Table 2).

Table 3 shows the changes in the mean cerebral blood flow and GCS of the patients. The mean cerebral blood flow velocity decreased in the patients of the magnesium group and increased in the patients of the milrinone group

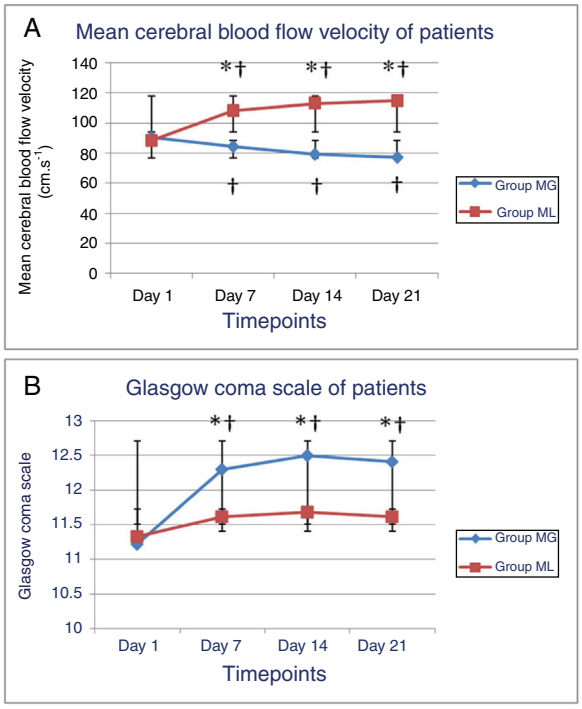

Figure 1 (A) Mean cerebral blood flow velocity of patients and (B) Glasgow coma scale of patients. Day 1, the 1st day from the onset of subarachnoid hemorrhage; Day 7, the 7th day from the onset of subarachnoid hemorrhage; Day 14, the 14th day from the onset of subarachnoid hemorrhage; Day 21, the 21st day from the onset of subarachnoid hemorrhage. Group MG, magnesium group; Group ML, milrinone group.
*Statistically significant ($p < 0.05$) between the two groups.
†$p < 0.05$ versus baseline.

through Day 7, Day 14 and Day 21 and the comparison between the two groups was significant ($p < 0.001$) (Fig. 1A). The mean cerebral blood flow velocity increased more than 120 cm.s^{-1} in 5 patients in the magnesium group and 13 patients in the milrinone group ($p = 0.035$) (Table 4). The GCS significantly improved in magnesium group more than the milrinone group through Day 7, Day 14 and Day 21 (Fig. 1B). The variation in the GCS (median interquartile range) was less in Group M than Group ML, and the comparison between the two groups was significant ($p < 0.05$) (Table 3), but the GCS decreased below 8 in 3 patients in the magnesium group and 10 patients in the milrinone group ($p = 0.036$) (Table 4) and the decrease in the GCS was through 5–10 days from the onset of SAH and the patients had to be mechanically ventilated.

The angiographic vasospasm (the decrease in diameter of the involved cerebral artery > 25%) was positive in these cases. Also, the new neurological symptoms were found in 9 patients in the magnesium group and 21 patients in the milrinone group ($p = 0.007$) (Table 4). The incidence of rebleeding after surgical clipping of the aneurysm was insignificant between the two groups ($p = 0.764$) (Table 4). The incidence of hypotension (systolic arterial blood pressure < 20% below baseline) was 14 patients in milrinone group and 5 patients in the magnesium group ($p = 0.012$) (Table 4), therefore, the requirement for dopamine and norepinephrine to maintain an elevated blood pressure was higher in the milrinone group compared to the magnesium group ($p = 0.034$, $p = 0.027$, respectively). The incidence of bradycardia was insignificant between the two groups ($p = 0.936$) (Table 4). The requirement of postoperative mechanical ventilation as a result of low GCS was less in the magnesium group than milrinone group ($p = 0.035$). The incidence of respiratory complication (pneumonia) was insignificant between the two groups ($p = 0.783$). The incidence of mortality decreased in the magnesium group compared to the milrinone group, but it was statistically insignificant ($p = 0.352$) (Table 4). The mortality happened after the Day 21 as a result of severe pneumonia and cerebral vasospasm.

Discussion

Magnesium decreased the incidence of cerebral vasospasm compared to the milrinone. The neurological outcome (GCS) was better with magnesium than milrinone group. Also, the incidence of hypotension was lower in the magnesium group compared to the milrinone group.

Table 3 Glasgow coma scale and mean cerebral blood flow velocity of patients. Values are expressed mean ± SD.

Variable	Timepoints	Group MG ($n = 45$)	Group ML ($n = 45$)	p-Value
Mean cerebral blood flow velocity (cm·s^{-1})	Day 1	90.24 ± 15.52	88.36 ± 13.75	0.544
	Day 7	84.38 ± 12.68[a]	108.15 ± 19.28[a]	0.001[b]
	Day 14	79.30 ± 9.25[a]	112.97 ± 22.76[a]	0.001[b]
	Day 21	77.14 ± 7.46[a]	114.71 ± 25.15[a]	0.001[b]
Glasgow coma scale	Day 1	11.22 ± 1.69	11.33 ± 1.84	0.768
	Day 7	12.30 ± 1.49[a]	11.62 ± 1.55	0.036[b]
	Day 14	12.50 ± 1.38[a]	11.68 ± 1.66	0.012[b]
	Day 21	12.41 ± 1.48[a]	11.62 ± 1.58	0.016[b]

Group MG, magnesium group; Group ML, milrinone group.
Day 1, The 1st day from the onset of subarachnoid hemorrhage; Day 7, the 7th day from the onset of subarachnoid hemorrhage; Day 14, the 14th day from the onset of subarachnoid hemorrhage; Day 21, the 21st day from the onset of subarachnoid hemorrhage.
[a] $p < 0.05$ versus baseline.
[b] Statistically significant ($p < 0.05$) between the two groups.

Table 4 Postoperative outcomes. Values are expressed as number.

Variables	Group MG ($n=45$)	Group ML ($n=45$)	p-Value
Glasgow coma scale ≤ 8	3	10	0.036[b]
Mean flow velocity increased $\geq 150\,cm.s^{-1}$	5	13	0.035[b]
Cerebral vasospasm			
Incidence			
Total	9	21	0.007[b]
Mild	2	3	0.645
Moderate	2	5	0.237
Severe	5	13	0.035[b]
Symptomatic	5	13	0.035[b]
Rebleeding	6	7	0.764
Hypotension	5	14	0.012[b]
Bradycardia	6	4	0.936
Dopamine	8	17	0.034[b]
Norepinephrine	4	12	0.027[b]
Postoperative mechanical ventilation	3	10	0.035[b]
Respiratory complication (pneumonia)	7	9	0.783
Mortality	4	8	0.352

Group MG, magnesium group; Group ML, milrinone group.
[a] $p<0.05$ versus baseline.
[b] Statistically significant ($p<0.05$) between the two groups.

The present findings correlate with a study by Westermaier et al.[12] which found that the transcranial Doppler-detected vasospasm significantly decreased in the magnesium group compared with placebo ($p=0.028$), and the incidence of delayed ischemic infarction was significantly lower in magnesium-treated patients ($p=0.002$) with a good neurological outcome. In a study involving 283 patients, 139 received magnesium infusion 64 $mmoL.L^{-1}$ per day within 4 days after SAH and continued for 14 days after occlusion of an aneurysm. Magnesium sulphate reduced the delayed cerebral ischemia and improved the neurological outcome,[3] and other studies showed similar results.[13–17]

Against our results, Dorhout Mees et al.[18] found in a large study involving 8 centers with 1204 patients (606 patients were assigned to the magnesium group; 598 to the placebo, the patients did not receive magnesium sulphate), that magnesium was not superior to placebo for reduction of poor outcome after aSAH, but this study included only patients with SAH after rupture of posterior circulation aneurysms. These types of the aneurysms have poor prognosis from the beginning in addition to the difficult surgical techniques.[19–21]

Meta-analyses of studies investigating the role of magnesium showed that despite decreasing the incidence of delayed cerebral ischemia in patients with aSAH, prophylactic intravenous magnesium does not improve neurologic outcome or decrease cerebral infarction, radiographic vasospasm, or mortality.[22] Most of the studies included in this meta-analysis used magnesium orally or small dose of magnesium (360 $mg.day^{-1}$), and magnesium was started within 48–94 h after the onset of aSAH. Similar results were shown by other studies.[3,5,23–26]

The present study showed that milrinone has no effect on the incidence of cerebral vasospasm and the milrinone was associated a significant hypotension, therefore the dopamine and norepinephrine were required more in patients of milrinone group than the magnesium group. But against the present findings, Arakawa et al.[8] used milrinone in seven patients with clinical and angiographic vasospasm. They used an intra-arterial milrinone infusion (5–15 mg) followed by an intravenous infusion (0.50–0.75 $\mu g.kg^{-1}.min^{-1}$) for 2 weeks. After the intra-arterial infusion, they observed a statistically significant cerebral vasodilatation. Fraticelli et al.[27] documented that milrinone reversed the cerebral vasospasm after intra-arterial administration in the cerebral territory involved followed by continuous intravenous infusion until Day 14 after initial bleeding. Ghanem and his colleague et al.[28] reported that milrinone with norepinephrine decreased the incidence of cerebral vasospasm after aSAH with improvement in the GCS and neurological outcome and similar results were shown by other studies.[9,29–35]

Most of the previous studies used the milrinone either through intra-arterial or subarachnoid cistern route followed by intravenous infusion to prevent and decrease the cerebral vasospasm, but the present study started the milrinone as an intravenous infusion without intra-arterial or subarachnoid cisterns administration.

There are some limitations of the present study. First, this study was done in a single center with a limited number of patients. Second, the blood level of milrinone was not measured, as the kits for milrinone were not available during the study.

Conclusion

Magnesium decreased the incidence of cerebral vasospasm after aSAH and significantly improved the Glasgow coma scale compared to milrinone. Milrinone was associated with

increased incidence of hypotension and requirement for dopamine and norepinephrine compared to magnesium.

Editor in chief

This research was done in Cairo University, Egypt. The authors are interesting to publicate this article in the Brazilian Journal of Anesthesiology. The authors agree with and are responsible for the data presented. The authors also describe or deny any potential conflicts of interest, including commercial relationships, such as consultation and equity interests. The manuscript is not under consideration for publication elsewhere.

Conflicts of interest

The authors declare no conflicts of interest.

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