The Effect of Milrinone on the Cerebral Vasospasm in Patients with Subarachnoid Hemorrhage

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Abstract

Introduction: Cerebrovascular diseases are called brain blood vessel problems. The prevalence of brain aneurysms has been reported to be between 6% and 10%. In cerebral aneurysm, vasospasm is known to be the most important curable cause of mortality. Milrinone is used as inotropic drug to dilate vessels via phosphodiesterase inhibition. Therefore, the purpose of this study was to compare the effectiveness of milrinone for treatment of cerebral vasospasm in patients with subarachnoid hemorrhage.

Materials and Methods: This is a clinical and double-blind clinical trial performed on all patients with SAH who formed the target population. Furthermore, CT scans and angiography were performed for all patients. 50 µg/ml milrinone was injected initially during digital subtraction angiography (DSA) for patients in intervention group, and followed by an infusion of 0.5 to 0.75 µg / kg / min. Angiography was repeated 10 minutes after injection. In the control group, the milrinone drug was not injected. Data was analyzed by software spss 20. Descriptive statistics and t-test were used to analyze the parametric data and, the Chi-square test was used for non-parametric masters.

Results: The mean age of patients in the two groups did not show a significant difference (P = 0.974). There was no significant difference between the two groups in terms of GCS, at first (P = 0.809). There was a statistically significant difference between the two groups (GCS) after 24 hours and 14 days, respectively (P = 0.004 and P = 0.011), and GCS in the milrinone group improved over 24 hours and 14 days, indicating a positive effect of milrinone on patients with brain aneurysm. A significant difference was found between the two groups in terms of vasospasm treatment (P = 0.033), where the milrinone group showed better improvement of vasospasm. Regarding the overall improvement, the milrinone group had a better treatment when comparing with the control group, but this difference was not found to be statistically significant (P = 0.078).

Conclusion: Milrinone was effective in improving vasospasm in patients, but did not improve the patients' neurological status. Furthermore, GCS in the milrinone group was better than the other group after 24 hours and 14 days.

Keywords: Milrinone, Cerebral Vasospasm, Subarachnoid Hemorrhage.

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Introduction

Cerebrovascular diseases are called brain blood vessel problems, which are among the most common deadly diseases worldwide, leading to high rates of stroke, cerebral hemorrhage and other complications. Although the mortality rate has slowed down by 35% during the last decade, but the amount of disability and complications imposes a heavy burden on the health system of the community (1).

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The cerebrovascular lesions include aneurysm, arteriovenous malformation (AVMs), Arteriovenous Fistula (AVFs), intracranial hematoma, embolism, stenosis and vascular thrombosis. Meanwhile, aneurysms are particularly important because of their most common manifestation of subarachnoid hemorrhage (SAH). In the past, the presence of calcification of the aneurysm wall in a simple image was the only symptom of aneurysm, but this sign was extremely rare, which its cause in linked to the long-term clotting (2). Today, the appropriate method for the detection of aneurysms is MRI and spiral CT scanning, with focus on the circle of Willis and Bifurcation Cerebral-Mid, which often causes bleeding of aneurysms. In cases where these methods are not available, direct angiography is used (3).

The prevalence of multiple aneurysms is between 6% and 6%, and in most cases, the largest aneurysm often shows bleeding. The most common place of occurrence of cerebral aneurysms is around the circle of Willis, but it can occur in any part of the brain's circulatory system. Upper stentorian aneurysms are often seen at the site of the PCA, at junction of the anterior cerebral artery and anterior communicating artery, at the branches of the middle cerebral artery (MCA), at the end of the internal carotid (4).

Vasospasm is known to be the curable cause of mortality in cerebral aneurysms (5). Many causes are involved in the pathogenesis of brain vasospasm. Previous studies have identified the main components of its pathogenesis, including apoptosis, oxyhemoglobin, ischemia and inflammation (6). Although many studies have been done on the vasospasm pathogenesis, but there is still a controversy about this in terms of age below 65 years old, having blood pressure, smoking, and hemorrhage in the CT scan, that are among the risk factors for developing cerebrovascular vasospasm (7). Of the 70% of patients who have vasospasm, 20 to 30% have neurological deficits (8,9). Clinical and cellular studies have been conducted on cerebral vasospasm, but there are still many unknown aspects in pathophysiology and its effective treatment. Currently, treatment consists of care measures to prevent or minimize secondary damage to the brain, as well as hemodynamic control and endovascular treatment (10). There are some medicines that have been shown to reduce the mortality rate, such as papaverine injection by angioplasty (11). However, defects such as damage to the cerebral cortex have also been reported for this drug (12). Milrinone is one of the other medicines that can enhance vasospasm by vasodilation (13). Milrinone is a phosphodiesterase-3 inhibitor that is effective on the CAMP pathway and has inotropic and vasodilatory effects (14). Most studies have been limited to small sample size for assessing milrinone, where a strong clinical trial has not been conducted. Therefore, the aim of this study was to investigate the effect of milrinone on the elimination of cerebrovascular vasospasm in patients with subarachnoid hemorrhage.

Materials and Methods

This double blind clinical trials were performed on all SAH patients who formed the target population. All patients with cerebrovascular aneurysm referred to Valiasr hospital in Arak, Iran were enrolled in the study. All patients with inclusion conditions were randomly selected and entered the study.

The sample size is calculated by the following formula:

$$N = \frac{\left(Z_{1-\frac{\alpha}{2}}\right)^2 (\delta_1)^2}{(\mu_1)^2} = 14$$

$$Z_{1-\frac{\alpha}{2}} = 1/96$$

$$\delta_1 = 0.37$$

$$\mu_1 = 0.12$$

Inclusion criteria: 1- Age between 30-80 years, 2- Patients with subarachnoid hemorrhage and vasospasm, 3. Getting informed consent

Exclusion criteria: 1. Age under 30 and over 80 years, 2. Patient dissatisfaction, 3. Patients with subarachnoid hemorrhage and lack of diagnosis of vasospasm with TCD (TransCranial Doppler), 4. Cardiovascular disease with contraindication for the use of milrinone

Finally, an informed consent form was received after approving and receiving the ethics code from Arak University of Medical Sciences. At the time of admission, demographic information, history, history of the disease, neurological examinations and Glasgow Coma Scale/Score (GCS) were recorded.

Conventional CT scan and angiography were performed for all patients. 50 µg / ml milrinone was injected initially during digital subtraction angiography (DSA) for patients in intervention group, and followed by an infusion of 0.5 to 0.75 µg

/ kg / min. Angiography was repeated 10 minutes after injection. In the control group, the milrinone drug was not injected.

The severity of subarachnoid hemorrhage was determined by Fisher scale for all patients including Score 1: Absence of blood in CT Scan, Scale 2: the presence of diffuse blood without formation of a dense, thick, big or thick cloth (< 1 mm). Scale 3: Blood accumulation (> 3 mm) indicating the presence of clots in the groove between the hemispheres, Insular cistern and ambient cistern in the vertical view and the presence of clots in the roots of the Sylvian groove.

The cistern sylvian and the interpeduncular cistern are in the horizontal view, Scor 4: The presence of intracerebral clot or intra-ventricular clot without blood in the basal cisterns.

The location of aneurysm was recorded in both groups. The neurological condition was recorded precisely after injection and 24 hours after injection according to Glasgow scale (GCS),

The deterioration of the patient's condition was defined as a reduction in more than two cases with the Glasgow scale, and an increase of more than 2 symptoms in the Glasgow's Scale or more than one in the muscle test were considered as improvement.

Changes in level of consciousness were evaluated using GCS criteria until the 14th day after surgery.

Table 1. Glasgow Coma Scale for Assessment of Coma and Impaired Consciousness

Eye Opening	Best Motor Response	Best Verbal Response
4=Spontaneous	6=Obeying	**5=Oriented**
3=To speech	5=Localizing	**4=Confused**
2=To pain	4=Withdrawing	**3=Inappropriate**
1=None	2=Extending	**1=None**
	1=None	

Data Analysis

Data is provided by software spss 20. Descriptive statistics and t-test were used to analyze the parametric data. For non-parametric data, chi-square test was used.

Ethical Considerations

1- A letter was sent to the university's authorities to be introduced to the research centers. 2. A letter was received from the officials of selected research centers. 3. The purpose of the study was described for all research units and written consent was obtained from them. 4. The information of all patients remained confidential 5. All ethical statements in the Helsinki Research Committee and the research committees in the ethics of Arak University of Medical Sciences were considered. 6. This research has been registered with the ethic code (IR.ARAK.MU.REC.1396.2).

Results

A total of 32 patients with aneurysm were entered the study with inclusion criteria. The minimum age was 38 years and the maximum age was 75 years. Of the patients, 12 (36.4%) were male and 20 (60.6%) were women. The mean age of patients in the milrinone group was recorded to be 52.81± 11.29 years and in the control group was 52.06 ± 10.76 years.

There was no significant difference in mean age between the two groups (P = 0.974), and the average age of the patients was 52.43 ± 10.86 years. The comparison of the frequency of gender in the control and intervention group showed that 10 (62.5%) were women and 6 (37.5%) were male, where no statistically significant difference was found (P > 0.05). The number of people in both groups was found to be equal in sex. The mean and standard deviation of GCS in the two groups of milrinone and control were evaluated in Table 2. According to the results of the GCS, no statistically significant difference was observed between the two groups (P = 0.809), but a statistically significant difference was found between the two groups in terms of GCS in 24 hours (P = 0.004), and 14 days later (P = 0.011), indicating positive effect of milrinone on patients with cerebral aneurysm.

Table 2. Comparison of mean and standard deviation of GCS in two groups of milrinone and control

Group GCS	Milrinone Mean ±SD	Control Mean±SD	p-value
Primary	9.00±2.44	8.75±3.27	0.809
24 h next	11.37±3.00	8.12±2.87	0.004
14days next	11.18±3.5	8.00±3.11	0.011

Table 3 shows the frequency and percentage of Fisher grading scale among the two groups. The results demonstrated that there was no statistically significant difference between the two groups of in terms of Fisher grading scale (P = 0.713).

Table 3. Frequency and percentage of Fisher grading scale in two groups

Group Variable		**Milrinone** Number (%)	Control Number (%)	p-value
Fisher grading scale	1	3 (18.75)	2 (12.5)	0.713
	2	9 (62.25)	8 (50)	
	3	4 (25)	5 (31.25)	
	4	0 (0)	(16.25)	

The frequency of aneurysm location between the two groups was shown in Table 4. There was no significant difference between the two groups based on the results (P = 0.821).

Table 4. Frequency and percentage of location of aneurysm in two groups

Group Variable		**Milrinone** Number (%)	Control Number (%)	p-value
aneurysm Place	MCA	4 (25)	3 (18.75)	0.821
	ACOM	8 (50)	9 (62.25)	
	Carotid	2 (12.5)	2 (12.5)	
	PCOM	1 (6.25)	0 (0)	
	MCA-ACOM	1 (6.25)	1 (6.25)	
	DACA	0 (0)	1 (6.25)	

Table 5 shows frequency of vasospasm removal between the two groups of milrinone and control. A significant statistical difference was observed between the two groups (P = 0.033), indicating that the treatment of vasospasm was better in the milrinone group. As e matter of fact, vasospasm was treated in more cases.

Table 5. Comparison of frequency and percentage of vasospasm treatment between the two groups

Group Variable		**Milrinone Number (%)**	**Control Number (%)**	**p-value**
vasospasm treatment	Treated	(81.25) 13	.43) 7 (75	0.033
	No treated	3 (18.75)	(62.25) 9	

The frequency of recovery between the two millerinone groups and controls is listed in Table 6 below. In the Milrinone group, out of 16 patients, 11 (68.75%) patients were treated, and 5 (31.25%) did not show improvement. In the control group, out of a total of 16, 6 (37.5%) patients were treated and 10 (62.5%) did not show improvement. Taken together, the milrinone group had more improvement than the control group, but this difference was not statistically significant (P = 0.078).

Table 6. Comparison of frequency and percentage of improvement between two groups

Group Variable		**Milrinone** Number (%)	Control Number (%)	p-value
improvement	Yes	(68.75) 11	(37.5) 6	0.078
	No	5 (31.25)	(62.5) 10	

Table 7 shows the mean and standard deviation of heart rate after angiography in two groups, there was no statistically significant difference between the two groups (P-pain = 0.69), indicating that the mean heart rate in the two groups did not have a significant difference by angiography.

Table 7. Comparison of mean and standard deviation of heart rate after angiography in two groups

Group Variable	**Milrinone** Mean±SD	Control Mean±SD	p-value
heart rate	66.93±15.03	64.75±15.73	0.69

The mean and standard deviation of blood pressure after angiography were assessed in the two groups of milrinone and control, and the systolic pressure in the milrinone group and the control group were recorded as 150.62± 15.26 and 148.38±,14.52, but the difference was not statistically significant (p= 0.672). Diastolic pressure in the milrinone and control group was determined to be 72.5± 8.75 and ± 70.93±9.52. However, no significant difference was found between the two groups in this regard (P = 0.633), demon stating that blood pressure was almost equal in the two groups after angiography.

Discussion

Brain vascular disease, in particular brain aneurysm rupture, is one of the most important causes of mortality and disability in humans. Brain aneurysms are congenital in most cases, and part of the artery wall is expanded in the form of a balloon-like bulge. As an aneurysm grows, it does not have the normal elements of the cerebrovascular wall; puts pressure on adjacent structures, and tends to rupture.

The aneurysm may appear in different forms, but the saccular or berry aneurysm is the most common type. Brain aneurysm rupture and the onset of bleeding in the arachnoid mater is prevalent in younger people than other cases of cerebrovascular disease, Which accounts for the most common type of stroke until the 5th-6th decades of life (15).

In cerebral aneurysm, vasospasm was recognized as the leading cause of death. Therefore, we

decided to investigate the effect of milrinone on the cerebrovascular vasospasm in patients with subarachnoid hemorrhage.

A total of 32 patients were included in the study. The minimum age was 38 years and the maximum age was 75 years. Of the patients, 12 (36.4%) were male and 20 (60.6%) were women. The mean age of patients in the two groups did not show a significant difference (P = 0.974).

In terms of GCS, there was no significant difference between the two groups at first (P = 0.809). There was a statistically significant difference between the two groups (GCS) after 24 hours and 14 days, respectively (P = 0.004 and P = 0.011), and GCS in the milrinone group improved over 24 hours and 14 days, indicating a positive effect of milrinone on patients with brain aneurysm.

There was no statistically significant difference between the two groups in terms of Fisher scale (P = 0.713). Regarding the improvement of vasospasm, there was a significant difference between the two groups (P = 0.033), where the milrinone group showed better improvement of vasospasm. Regarding the overall improvement, the milrinone group had a better treatment as compared to the control group, but this difference was not found to be statistically significant (P = 0.078).

The results from this study were consistent with previous studies. Ghanem et al. (2014) examined the effect of the use of Milrinone continuous IV infusion on post-clipping spasm prevention. They said that melirinone was capable of reducing the cerebral vasospasm during a dangerous period of cerebral spasm after cerebral aneurysm clipping (16). Their results coincided with this study.

Sadamasa et al. in 2014 evaluated he effects of intrathecal milrinone infusion through lumber subarachnoid catheter for managing delayed ischemic neurological deficit after neurysmal subarachnoid hemorrhage, they indicated that its used was feasible, but suggested a need for more randomized prospective investigations (17), However, the results of which were in line with this study.

Another study was conducted to investigate effect of intra-arterial injection of milrinone on vasospasm. Aforementioned study indicated that intra-arterial milrinone could improve cerebral vasospasm after aneurysmal SAH (18). In the current study, milrinone improved the vasospasm after 24 hours and 14 days, which were consistent with aforementioned study.

Arakawa assessed the safety and effectiveness of intra-arterial and subsequent intravenous milrinone on cerebral vasospasm after subarachnoid hemorrhage. Seven patients received 0.25 mg/min of milrinone intra-arterially by catheter. vasospastic vessels dilatation was observed in all patients and cerebral blood flow increased in 6 patients. They stated that milrinone was capable of improving vasospasm after subarachnoid hemorrhage and recommends further studies with more samples (19). Their results were also consistent with our study.

Conclusion

Milrinone was effectivelly capable of treating cerebral vasospasm, but did not improve the patients' neurological status. On the other hand, GCS in the milrinone group was better than the other group over a 24 hours and 14 days period.

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