

The Effect of a Single dose Dantrolene in Patients with Vasospasm Following Aneurysmal Subarachnoid Hemorrhage

Abstract

Background: Cerebral vasospasm is a prolonged, occasionally severe, but reversible narrowing of the cerebral arteries that begins 3 to 5 days after the hemorrhage becomes maximal at 14 days. This study is designed to evaluate the effect of dantrolene on the reduction of vasospasm following aneurysmal subarachnoid hemorrhage (SAH). **Materials and Methods:** This randomized controlled clinical trial was conducted on 32 patients with proven aneurysms in AL-Zahra hospital during 2011-2013. They were randomly divided into two groups. In all patients, daily transcranial Doppler sonography was performed and as soon as the diagnosis of vasospasm onset in the first group, in addition to conventional treatment of vasospasm 2.5 mg/kg Dantrolene infusion within 60 minutes and while the blood pressure and heart rate of patient monitored, and arterial flow velocity changes such as PSV and MFV were measured by transcranial Doppler sonography in 45, 90 and 135 minutes. Data was analyzed by SPSS 22 and Chi-square, Student *t*, Mann-Whitney and ANOVA tests with repeated observations. **Results:** There was no significant difference in the site of the aneurysm in the two groups. The mean of PSV index prior to treatment and the 45th minute was not different but at 90th and 135th minutes it was significantly lower in the Dantrolene receiving group ($P < 0.05$). The mean of MFV index prior to intervention and in the 45th minute was not different between two groups, but at 90th and 135th minutes was significantly lower in the target group **Conclusion:** Using dantrolene in patients with artery vasospasm significantly reduced artery spasm and increased the patient recovery.

Keywords: Cerebral aneurysm, dantrolene, subarachnoid hemorrhage, vasospasm

Introduction

Subarachnoid hemorrhage (SAH) is one of the most devastating forms of stroke affecting primarily young patients before the age of 65 and has a fatality of 50% in the first 30 days.^[1,2]

For survivors of the initial insult, cerebral vasospasm is the leading cause of disability and death.^[2] Cerebral vasospasm in 70% of patients with SAH, and one-third have neurological deficits develop.^[3]

Cerebral vasospasm is a prolonged, occasionally severe, but reversible narrowing of the cerebral arteries that begins 3 to 5 days after hemorrhage become maximal at 14 days and gradually resolves over 2 to 4 weeks.^[4,5]

The risk of vasospasm depends on blood thickness in the subarachnoid space, ventricles and history of hypertension, smoking, cocaine use and other factors.^[4] Following vasospasm, stenosis is seen

in cerebrovascular and its prevalence in cerebral angiography after aneurysm rupture is about 50-90% in which half of the patients have symptoms of cerebral ischemia and 24-32% of these patients have serious neurologic complications.^[4,6] Diagnosis of vasospasm is based on neurologic symptoms, blood flow velocity >200 cm/s that occurs during the stenotic vessels which is detectable by transcranial Doppler sonography and eventually angiography or CT angiography used to confirm the stenosis of cerebral vessels.^[4,5] Although cerebral vasospasm is a multi-factorial process and some causes such as vasoconstriction and inflammatory changes (lymphocytic infiltration) are involved in its creation, the most common pathway of vasoconstriction is the continuous elevation of intracellular Ca level attributable to a combination of influx from extracellular Ca and release from the largest intracellular Ca store,

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the endoplasmic/sarcoplasmic reticulum mediated by the ryanodine receptor.^[7-9] Nowadays, calcium blockers e.g., Nifedipine and Nicardipine are used to vasospasms with blocking calcium entrance but their effectiveness is limited since they have no effect on the release of calcium from intracellular sources. Therefore, according to the mechanism of muscle contraction in vasospasm, using a drug which inhibits the release of calcium from intracellular sources is necessary. Although many studies have been conducted on the effect of this drug on the reduction of artery vasospasm,^[10-12] the result are not the same. available treatments for cerebral vasospasm are limited, consisting of hypervolemic hypertensive therapy and cerebral angiography with intervention, which have the risks of pulmonary edema, myocardial infarction, stroke, vessel rupture with death and are labor-intensive and expensive.^[13] Alternative treatments for cerebral vasospasm offer the hope of improving outcome. there is evidence that dantrolene is neuroprotective.^[9]

On the other hand, there is no internal study that has examined the effects of these drugs in native patients. Therefore, the present study aimed to evaluate the effect of dantrolene on the reduction of vasospasm following from subarachnoid hemorrhage (SAH) caused by cerebral aneurysm in AL-Zahra educational and medical center.

Materials and Methods

This randomized double-blinded clinical trial study was conducted in AL-Zahra educational and medical center during 2011-2013 Isfahan/Iran. The studied population included patients with cerebral aneurysms who were admitted to the ICU. Inclusion criteria were all patients with cerebral aneurysms confirmed by angiography or CT angiography along with vasospasm conditions (these conditions include as follows (a) 50% increase in MFV (mean flow velocity (cm/s) is calculated as EDV (end diastolic velocity) plus one-third of the difference between PSV and EDV. the EDV lies between 20% and 50% of the PSV values) than basis MFV which is achieved in the first 24 hours of admission; (b) PSV (peak systolic velocity (cm/s) is the first peak on a transcranial Doppler wave form from each cardiac cycle) 200 cm/s or greater in MCA or ACA artery or $3 < \text{Lindegard (V MCA/V ICA)} > 3$ consistent with vasospasm) (17); (c) Psv ≥ 120 cm/s in the basilar or PCA artery; (d) any daily 100 cm/s PSV increase from the previous day; (e) a linear increase in MFV ≥ 80 cm/s, older than 18 years, no pregnancy, no use of verapamil, no history of cirrhosis and negative hepatitis B and C. Also, patients with SAH caused by trauma and those who have high level of liver enzymes (alanine transferase greater than 165 units per liter, aspartate transferase greater than 120 units per liter and alkaline phosphatase greater than 345 units per liter) were excluded from the study. Sample

size of the study was estimated through the Gehan sample size estimation table by considering the confidence level of 95%, test power of 80% and the consideration of 80% least significant difference at PSV before and after the injection of dantrolene which was considered and estimated in 16 patients in each group. The procedure was in a way that 32 patients with proven aneurysms who were admitted to the intensive care unit and had inclusion criteria were selected and randomly divided into two groups. Randomization of the samples was in this way that a ballot was taken in order to place the first patient in the first group and the next patients sequentially were distributed in the second until achieving the sufficient sample size. In all patients, daily transcranial Doppler sonography was performed and as soon as the diagnosis of vasospasm onset in the first group (target group), in addition to conventional treatment of vasospasm (infusion of normal saline 150-200 cc per hour, %5 albumin 250 cc every 6 hours, Nifedipine 60 mg tablets every 4 hours, and maintain the mean arterial blood pressure >100 mmHg and in the case of any need Dopamine and phenylephrine was used) 2.5 mg/kg Dantrolene was infused within 60 minutes and while the blood pressure and heart rate of patient were monitored and, arterial flow velocity changes i.e. PSV and MFV were measured by transcranial Doppler sonography in 45, 90 and 135 minutes. In the second group, which was considered as the control group, the conventional treatment of vasospasm was given to the patient and arterial flow velocity changes i.e., MFV and PSV were measured by transcranial Doppler sonography by the same technician and the results of two groups were compared. After the collection, data were entered into the computer and analyzed by SPSS version 22 and Chi-square, Student t, Mann-Whitney and ANOVA tests with repeated observations.

Results

In this study, 32 patients with vasospasm were randomly distributed into two groups of 16; target group received dantrolene and the control group didn't receive dantrolene. The mean age of the patients in target and control groups was respectively 56.4 ± 12.2 and 52 ± 6.3 years; according to the T-test there was no significant difference between the age of groups ($P = 0.11$). The female/male ratio in the target group was 10/6 and in the control group was 9/7 and according to the Chi-square test gender distribution was not significantly different in the two groups ($P = 0.68$). According to the results obtained, the aneurysm site in nine patients (28.1%) MCA, in seven patients (21.9%) ACOM, in nine patients (28.1%) PCOM, in three patients (9.4%) A1 in one patient (3.1%) carotid bifurcation, in two patients (6.3%) cavernos carotid and in one patient (3.1%) was A2. Frequency of aneurysm site in both target and control groups is shown in Figure 1. Fisher's exact test on the data showed no significant difference in the site

of the aneurysm in these two groups ($P = 0.89$). The mean and SD of PSV and MFV parameters prior to treatment up to 135th minute in both target and control groups are shown in Table 1. According to Table 1, the mean of PSV index prior to treatment and the 45th minute was not different between two groups, but at 90th and 135th minutes, the mean of this index was significantly lower in the dantrolene receiving group ($P < 0.05$) but according to ANOVA with repeated observations, the change process of this index during the intervention period was not different between two groups ($P = 0.11$). The mean of MFV index prior to intervention and in the 45th minute was not different between two groups, but at 90th and 135th minutes was significantly lower in the target group. ANOVA with repeated observations showed that the change process of this index during the intervention period has found significant different between these two groups ($P = 0.021$). The change process of two mentioned parameters in both intervention and control groups are shown in Figures 2 and 3.

Discussion

The overall aim of this study was to determine the effect of a single-dose dantrolene in patients with vasospasm following aneurysmal SAH. According to the results, the most common site of aneurysm in our study was PCOM, MCA and ACOM aneurysm (%78.1) but site distribution of aneurysm in these two groups was not significant. The age and sex distribution of patients in both groups had no significant difference; thus, the confounding effect of above factors in this study was neutralized and the

observed results most likely related to the effect of the drug. According to the results obtained, the PSV index was not different between the two groups before treatment and amount of its changes was not significant up to 45 minutes between two groups, but in the 90th minute the difference between two groups reached to the significant level so that its average in the dantrolene receiving group was 120 ± 27.4 and in the control group was 139 ± 21 and this difference also existed in 135th minute but at the same time, the change process of PSV index while intervening period between two groups was not different. On the other hand, MFV index at the beginning of treatment and up to 45 minutes was not significant between two groups but at 90 and 135 minutes in the Dantrolene receiving group a more favorable decrease and changes between two groups were significant. In other words, the use of dantrolene in patients with cerebrovascular vasospasm can significantly affect the PSV and MFV patients. Other studies have also shown the anti-spasmodic nature of dantrolene and its impact on sarcoplasmic reticulum that inhibits the release of calcium from intracellular sources and thus reduces the contraction of vessel wall of muscle cells.^[10,14-16] Soydan *et al.* study in an *ex vivo* rat model showed that the use of dantrolene with nimodipine, inhibits the vasoconstriction and significantly increases the efficacy of Dantrolene.^[11] Also, in Muehschlegel study it was observed that the use of dantrolene reduces the vasospasm resulting from SAH.^[6,14]

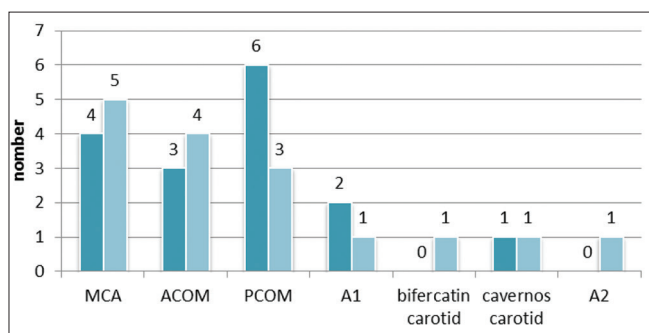


Figure 1: The frequency of aneurysm in the two study groups

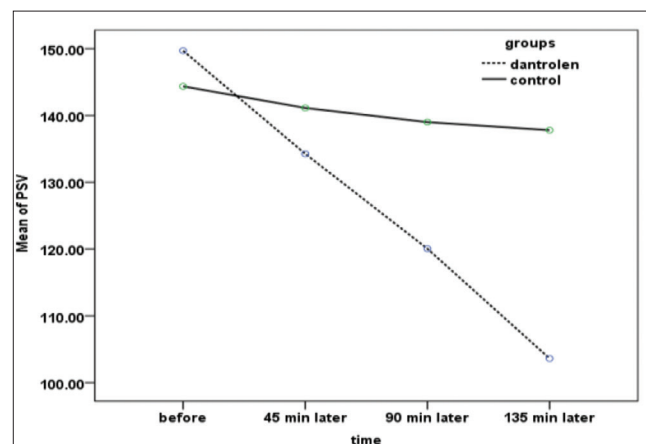


Figure 2: PSV index changes in both groups

Table 1: Mean and SD of PSV and MFV during intervention in both groups

Group time	PSV			MFV		
	Intervention	Control	P	Intervention	Control	P
Min 0	149/7±24/4	144/4±21/6	0.56	79/5±12/1	79/8±11/1	0.99
Min 45	134/3±22/8	14/1±20/7	0.59	73/9±9/5	79/5±11/7	0.18
Min 90	120±27/4	139±21	0.032	66/1±11/9	78/8±11/8	0.01
Min 135	103/6±39	137/8±21/9	0.021	57/4±17	76/7±11/9	0.002
P value	0.11			0.021		

SD: Standard deviation, PSV: Peak systolic velocity, MFV: Mean flow velocity

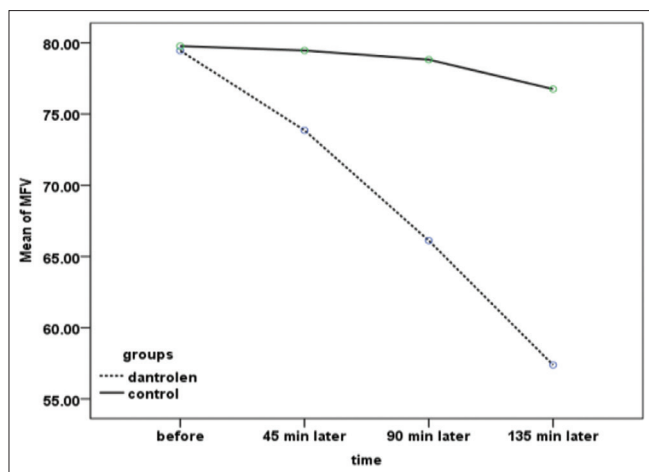


Figure 3: MFV index changes in both groups

The result of our study were in line with the results obtained by Muehlschlegel *et al.* in which it showed that the use of dantrolene can significantly reduce the MFV and PSV.^[10]

Conclusion

Therefore, the overall conclusion that can be derived from this study is that using of dantrolene in patients with artery vasospasm significantly reduced artery spasm and increased the patient recovery; therefore, if there is not contraindication for its use, according to the medical discretion its use in patients with vasospasm resulting from SAH caused by cerebral aneurysm is recommended.

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Conflicts of interest

There are no conflicts of interest.

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