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Role of Magnesium Sulfate in Preventing Vasospasm and Maintaining Hemodynamic Stability in Patients Undergoing Endovascular Coiling for Brain Aneurysm

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ABSTRACT

Introduction: The maintenance of hemodynamic stability in brain aneurysm surgery has paramount clinical significance in order to prevent vasospasm in the patients with aneurysmal subarachnoid hemorrhage. Regarding this, the present study was conducted to assess the role of magnesium sulfate in preventing vasospasm and maintaining hemodynamic stability during endovascular coiling procedure for brain aneurysm.
Material and Methods: This double-blind clinical trial was conducted on 60 patients who were candidates for undergoing endovascular coiling for brain aneurysm. The patients were subjected to angiography through femoral artery catheterization. Then, they were randomly assigned into two treatment groups of case receiving magnesium sulfate and control administered normal saline. The vasospasm and hemodynamic status were measured and recorded during and following the surgery.
Results: According to the results, no significant difference was observed between the two groups in terms of heart rate (p=0.98) and mean arterial pressure (p=0.089) one hour post-surgery. Furthermore, there was no statistical difference between the two groups regarding the use of nimodipine (p=0.11). Nevertheless, the frequency of vasospasm was significantly lower in the patients receiving magnesium sulfate, during surgery (p=0.037) and after surgery (p=0.02), compared to those administered normal saline.
Conclusion: As the findings indicated, magnesium sulfate could lower the incidence of vasospasm during and following the endovascular coiling procedure for brain aneurysm. Moreover, it resulted in no adverse effects on the hemodynamic status of the patients.

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Introduction

Cerebrovascular conditions, particularly brain aneurysms, can result in serious complications,

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leading to severe morbidity and mortality. The tendency of congenital brain aneurysms to dilation makes them prone to rupture as the anomaly lacks normal vascular elements (1). Therefore, they should be excised and surgically removed to prevent from any cerebrovascular catastrophe.

Surgical procedures have witnessed substantial improvements in the field of cerebrovascular interventions over the past decades (2). Endovascular procedures have been indicated as a less invasive and less life-threatening approach resulting in low morbidity and mortality rates. There are a number of factors determining the prognosis in aneurysmal cases undergoing surgical interventions. These factors include clinical, surgical, and individual parameters, namely bleeding severity, aneurysmal grading, size, and location, as well as the surgeon's experience and expertise (3).

Delayed ischemic neurological deficit is known as a grave complication, which may lead to both mortality (two weeks post-surgery) and morbidity in one-third of the cases. This complication often occurs as a consequence of vasospasm in the context of subarachnoid hemorrhage (4, 5). It is of paramount significance to maintain hemodynamic stability throughout the aneurysm surgery.

A number of measures, including the administration of vasodilators, calcium channel blockers, alfa- and beta-adrenergic blockers, and anesthetic inhalers, are routinely taken to minimize the causative factors, such as intubation and surgery-induced pain. Nevertheless, based on the evidence, the concomitant administration of these drugs is not risk-free and may occasionally lead to cardiac arrhythmia, namely atrial fibrillation (6).

Magnesium sulfate is demonstrated to be relatively safe and effective in stabilizing the hemodynamics in patients with eclampsia. This can be explained by the curtailment of catecholamines release during intubation and/or induction (7, 8). Magnesium sulfate has also been known for its anticonvulsant effects (9).

There are a number of accounts delineating the mechanism of action of this substance. For instance, magnesium sulfate acts directly as a vasodilator or functions indirectly through interaction with potent vasoconstrictors (10). It also functions as an NMDA(N-methyl-D-aspartate) antagonist, as well as a calcium channel blocker (11). The latter role accounts for the negative inotropy as magnesium inhibits calcium reabsorption by troponin C in cardiac myocytes (7).

With this background in mind, the present study was conducted with the aim of assessing the efficacy of magnesium sulfate in preventing vasospasm and maintaining hemodynamic stability during and following coiling procedure in patients with brain aneurysm.

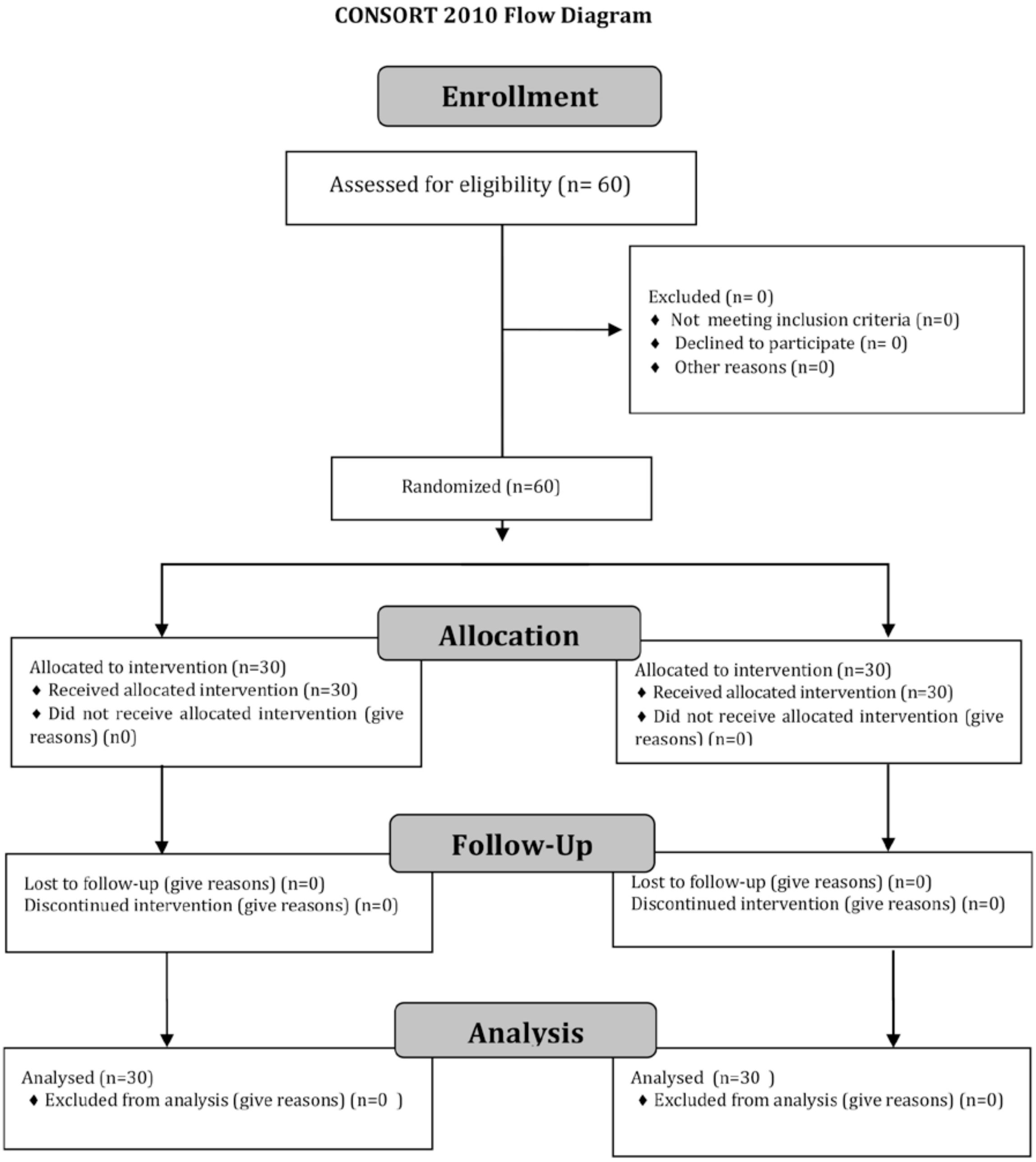
Materials and Methods

The randomized controlled trial was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (IRCT: 2013042813159N1). This study was conducted on 60 patients diagnosed with grades II and III brain aneurysm who underwent coiling procedure within three days after aneurysmal bleeding. The exclusion criteria were: 1) age of > 70 years, 2) body mass index of > 30 kg/m^2, 3) ejection fraction of < 40%, 4) serum creatinine level of > 2.5 mg/dL, 5) abnormal liver function tests, 6) glomerular filtration rate of < 50, 7) coagulopathy, and 8) history of allergic reactions to any agents.

After obtaining an informed written consent, Patients were randomly allocated to receive magnesium sulfate (study group) and normal saline (control group) on a 1:1 ratio before the procedure. A researcher who had not any responsibility in the study protocol, did the randomization. The randomization sequence was created by computer-generated random number. For this purpose, the numbered envelopes that contained the name of the agents (magnesium sulfate or normal saline) were used. Moreover, all the baseline characteristics including age, body mass index, surgery duration, and outcomes were recorded by the researcher without the knowledge to groupings. Patients were not aware about their agents. It was a double blinded placebo controlled clinical trial. Prior to anesthesia induction, the patients were subjected to routine electrocardiography monitoring, pulse oximetry, blood pressure assessment through arterial line, and intravenous line placement (18 gauge needle).

Fluid compensation was commenced using isotonic normal saline 0.9% following the standard guidelines of 4-2-1, which mandates a three-fold replacement of the lost blood volume with isotonic normal saline. The case group received 20 mg/kg of a 50% solution of magnesium sulfate, manufactured by the Pasteur Institute of Iran. To this end, magnesium sulfate was diluted in 100 cc normal saline in a 15-minute time period, and the infusion was maintained at a constant rate of 10 mg/kg/hour to the end of the coiling procedure.

The control group was treated similarly, but with normal saline rather than magnesium sulfate. In the control group, anesthesia induction was performed using Propofol (2 mg/kg), Sufentanil (0.2 μg/kg), Atracurium (0.5 mg/kg), and Lidocaine (1.5 mg/kg). The patients in both



CONSORT flow diagram: A comparative clinical study to receive magnesium sulfate (study group) and normal saline (control group)

groups were intubated utilizing the appropriate size of endotracheal tube. In the control group, anesthesia was maintained by administering 6 L oxygen per minute plus Propofol infusion at 50-150 μg/kg/min and a repeated dose of Atracurium (0.15 mg/kg) every 20 min. The same process was conducted for the case group, considering a 10% reduction in induction and maintenance doses to compensate for the drop in blood pressure as a result of magnesium sulfate administration.

In case the blood pressure or heart rate recorded by intra-arterial cannula exceeded 20% of the basal rates, a bolus shot of 5-15 μg Sufentanil was administered. All patients underwent the same surgical procedure (i.e., coiling for brain aneurysm through femoral artery angiography port), applying the same method conducted by a single surgeon.

Systolic blood pressure should remain constant in a range of 80-100 mmHg. Regarding this, infusions (i.e., Propofol, Sufentanil, and Magnesium Sulfate) had to be lowered or even ceased in case there were readings of less than 80 mmHg. At the end of the procedure, patients received Atropine (0.02 μg/kg) and Neostigmine (0.04 μg/kg) to reverse muscle relaxation. Once respiration was restored to normal status, the patients were extubated.

Solutions were all prepared and administered by an anesthesiologist and his assistant, both of whom were aware of patients' group allocation. The mean arterial pressure (MAP) and heart rate were recorded 5 min after anesthesia induction and every 15 min during the coiling process, as well as during recovery following extubation. These measures were recorded by an anesthesiology resident who was blind to the patients' group assignment. Similarly, the surgeon was unaware of the group allocation.

Vasospasm was to be detected by the surgeon throughout the procedure and subsequently recorded by the anesthesiology resident, who infused nimodipine for controlling the condition. A dose of 60 mg nimodipine was given via nasogastric tube in case of detecting vasospasm during the procedure.

Vasospasm was defined as elevated mean flow velocities exceeding 200 cm/s in the bilateral middle cerebral arteries. This condition was assessed via transcranial Doppler following the surgery by a neurologist, blind to the patients' assignment assignment (study group or control group). Furthermore, morbidity was defined as lowered Glasgow coma scale (9-14) or a decline in muscle strength and movement after coiling.

Statistical analysis

Statistical analysis was performed in SPSS software for windows, version 16. Chi-square or Fisher's exact test was used to analyze the qualitative variables. The normality of all variables was checked using the Kolmogorov-Smirnov test. Furthermore, the comparison of the quantitative variables was accomplished using the t-test or Mann-Whitney U test. The repeated measures analysis of variance (ANOVA) was used to compare the different time points of heart rate and mid arterial pressure variations. In addition, Mauchly's test was run to ensure the sphericity of the data. Where sphericity was not met, the Greenhouse-Geisser correction was employed. Additionally, logistic regression analysis was used to adjust probable confounders. P-value less than 0.05 was considered statistically significant.

Results

A total of 60 patients with ASA (American Society of Anesthesiology) physical status II and III who were candidates for brain aneurysm surgery were enrolled in this study (with 30 patients in each of the case and control groups). The results revealed no significant difference between the two groups regarding the demographic characteristics, frequency of emergency surgery, and the frequency of intubation (Table 1). The two groups also showed no significant difference in terms of Glasgow coma scale (P=0.25). However, there was a significance difference between the two groups in terms of the operative duration (P=0.005) and coiling duration (P=0.04). In this regard, these procedures were longer in the case group, compared to those in the control group (Table 1).

Figure 1 illustrates the trend of heart rate variations in both case and control groups. In the case group, the results of the repeated measures ANOVA showed no significant changes in the heart rate in the first hour post-surgery (F=2.436, df=2.22, P=0.09). In addition, there was no significant difference with the heart rate before anesthesia induction (P=0.65). Similarly, the control group showed no statistically significant changes in the heart rate (F=0.292, df=2.15, P=0.76), and there was no significant difference with the heart rate before anesthesia induction (P=0.067). Accordingly, there was no significant difference between the two groups in terms of heart rate variability during the first hour post-surgery (P=0.98).

Figure 2 depicts the MAP changes in the study groups. Regarding the case group, MAP changes were not statistically significant (F=2.153, DF=2.66, P=0.108), and showed no significant difference with the MAP recorded before anesthesia induction (P=0.076). On the other hand, the control group demonstrated significant changes in MAP (F=3.07, DF =2.18, P=0.049) in the first hour post-surgery due to the difference between MAP recorded 45 and 60 min after the induction of anesthesia (P=0.035). Furthermore, the MAP changes in the control group showed no

Table 1. Patient demographics and surgical characteristics

Characteristic	Groups		P value
	Control	Magnesium sulfate	
Age #	53.47±12.78	52.60±13.46	0.79
Sex (male)*	15 (50)	11 (36.67)	0.29
ASA (II/III)*	5/25	7/23	0.52
Weight (kg)#	70.66 ± 14.37	68.56 ± 14.50	0.57
Operative time (min)&	105 (60-300)	135 (90-300)	0.005
Coil time&	30 (15-200)	45 (15-240)	0.04
Emergency surgery*	14 (46.7)	17 (56.7)	0.44
Intubation*	6 (20)	2 (6.7)	0.25

mean ± SD,Independent T test; *Frequency (percentage), Chi-Square Test; & Median (Range), Mann-Whitney U test

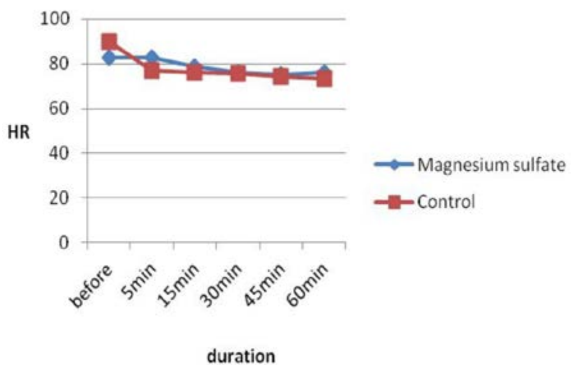


Figure 1. Illustrates the trend of heart rate variations in both case and control groups

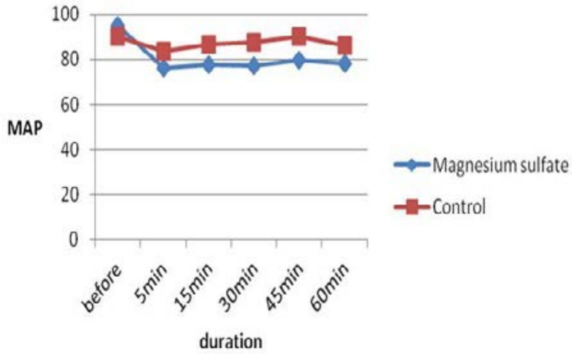


Figure 2. Depicts the mean arterial pressure (MAP) changes in the study groups

Table 2. The frequency (percentage) of vasospasm, mortality and morbidity in magnesium sulfate and control groups

		Group		P value
		Control	Magnesium Sulfate	
Vasospasm	Before Surgery*	3 (10)	2 (6.7)	0.99
	During Surgery*	11 (36.7)	4 (13.3)	0.037
	After Surgery*	9 (30)	2 (6.7)	0.02
Mortality*		3 (10)	1 (3.3)	0.61
Morbidity**		16 (53.3)	13 (43.3)	0.43

*Fisher Exact Test
** Chi-square Test

significant interaction with the MAP recorded before anesthesia induction (P=0.095). As the results indicated, during the first hour post-surgery, the two groups were not significantly different in terms of MAP changes (P=0.89).

The frequency of Nemodipine administration (P=0.11) showed no significant difference between the two groups. Table 2 presents the frequency of vasospasm before, during, and after the surgery, the frequency of mortality and morbidity, and their comparison between the two groups. According to the results, the case group had a lower frequency of vasospasm during (P=0.037) and after the surgery (P=0.02), compared to the control group.

The results of logistic regression analysis revealed that after the adjustment of such factors as operative and coiling durations, magnesium sulfate was found as a protective factor against vasospasms during (OR: 0.27, 95% CI: 0.07-0.96) and after the procedure (OR: 0.17, 95% CI: 0.03-0.85).

Discussion

The current study aimed to assess the efficacy of magnesium sulfate in preventing vasospasm and maintaining hemodynamic stability during and following coiling procedure in patients with brain aneurysm. Given the lack of any disparity between the groups in terms of their mean age and gender, these two variables can be ruled out as intervening variables.

According to our findings, magnesium sulfate was not effective in reducing heart rate and the need for inotropes in the first hour post-surgery. Nonetheless, it could effectively prevent from vasospasm during and after coiling for brain aneurysms. There was no significant difference between the two groups in terms of the morbidity and mortality rates. This may be attributed to small sample size.

There are a few studies sharing the same or similar objectives with ours. James et al. claimed that magnesium sulfate, when applied at a dose of 60 mg/kg, can effectively reduce catecholamines release after surgery (12). In another study performed by Jee et al., a bolus shot of 50 mg/kg magnesium sulfate administered prior to laparoscopic cholecystectomy was reported to effectively decrease vital signs (i.e., heart rate, as well as systolic and diastolic blood pressure), curtailing epinephrine, as well as norepinephrine and vasopressin release (13). However, this event was not observed in our study probably due to the low dose of magnesium sulfate (20 mg/kg) and modification of anesthetic drugs dosage (10% reduction).

Seyhan also confirmed that a bolus shot of magnesium sulfate, along with infusions, yielded a maximum effect on maintaining hemodynamic stability, as well as reducing the need for drug administration throughout surgery (11). The technique used in the mentioned study is similar to our method, except that we decided to maintain MAP in a range of 80-100 mmHg, with a 10% reduction in the maintenance dose of the anesthetic medications. Therefore, there was no significant difference in the hemodynamic status between the two groups.

In compliance with our findings, some

researchers reported that magnesium sulfate can play a preventive role in cases of vasospasm both during and following the surgery (14, 15). In contrast, Jeon presented a negligible effect of magnesium supplements in preventing vasospasm in patients diagnosed with subarachnoid hemorrhage owing to aneurysm (16).

Conclusion

In conclusion, though magnesium sulfate was ineffective in decreasing morbidity and mortality, it could prevent from vasospasm throughout coiling procedure for brain aneurysm when administered at a bolus dose of 20 mg/kg and infusion rate of 10 mg/kg/h. When this is coupled with a 10% reduction in the dose of induction medications, there will possibly be no adverse effect on the hemodynamic status of the patient.

Acknowledgments

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Conflict of Interest

The authors declare no conflict of interest.

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