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Impact of Comorbidity on Early Outcome of Patients with Subarachnoid Hemorrhage Caused by Cerebral Aneurysm Rupture

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ABSTRACT

Background: One of the complications aneurysms subarachnoid hemorrhage is the development of vasospasm, which is the leading cause of disability and death from ruptured cerebral aneurysm. **Aim:** To evaluate the significance of previous comorbidities on early outcome of patients with subarachnoid hemorrhage caused by rupture of a cerebral aneurysm in the prevention of vasospasm. **Patients and methods:** The study had prospective character in which included 50 patients, whose diagnosed with SAH caused by the rupture of a brain aneurysm in the period from 2011to 2013. Two groups of patients were formed. Group I: patients in addition to the standard initial treatment and "3H therapy" administered nimodipine at a dose of 15-30 mg / kg bw / h (3-10 ml) for the duration of the initial treatment. Group II: patients in addition to the standard initial treatment and "3H therapy" administered with MgSO4 at a dose of 12 grams in 500 ml of 0.9% NaCl / 24 h during the initial treatment. **Results:** Two-thirds of the patients (68%) from both groups had a good outcome measured with values according to GOS scales, GOS IV and V. The poorer outcome, GOS III had 20% patients, the GOS II was at 2% and GOS I within 10% of patients. If we analyze the impact of comorbidity on the outcome, it shows that there is a significant relationship between the presence of comorbidity and outcomes. The patients without comorbidity (83.30%) had a good outcome (GOS IV and V), the same outcome was observed (59.4%) with comorbidities, which has a statistically significant difference ($p = 0.04$). Patients without diabetes (32%) had a good outcome (GOS IV and V), while the percentage of patients with diabetes less frequent (2%) with a good outcome, a statistically significant difference ($p = 0.009$). **Conclusion:** The outcome of treatment 30 days after the subarachnoid hemorrhage analyzed values WFNS and GOS, is not dependent on the method of prevention and treatment of vasospasm. Most concomitant diseases in patients with SAH which, requiring additional treatment measures are arterial hypertension and diabetes mellitus. The best predictors in the initial treatment of patients with subarachnoid hemorrhage caused by rupture of a cerebral aneurysm has the presence of comorbidity, which has statistical significance.

Key words: subarachnoid hemorrhage, vasospasm, comorbidity.

1. INTRODUCTION

Fifty percent of survivors have neurological deficits. Re-rupture usually occurs within the first day and the risk is still very high for the first two weeks (about 25%), if left untreated (1,2). One of the complications aneurysm subarachnoid hemorrhage is the development of vasospasm, which is a leading cause of disability and death from ruptured cerebral aneurysm (3). Diseas-

es caused by rupture of intracranial aneurysms are complex and caused by genetic (4), and acquired risk factors (5), whose mechanisms in the formation, progress and rupture of aneurysms are poorly understood. Type 2 diabetes has a complex trait that affects the changes in the arterial wall through several different mechanisms (6). However, combining all studies, hypertension remains an important risk factor (7). Patients who used antihypertensive drugs may have a decreased risk for the formation and growth of the aneurysm (8). On the other hand, hypertension is associated with the development of subarachnoid hemorrhage is an important risk factor for poor treatment outcome (9). Nimodipine is indicated for the treatment of ischemic neurological deficits after subarachnoid hemorrhage caused by rupture of cerebral aneurysm (10). Clinical studies show that nimodipin reducing neurological deficit and prevents or reduces vasospazam (11, 12). In patients with stroke and SAH, magnesium is a convenient and secure (13, 14). The effectiveness of magnesium in SAH is reflected, in addition to its biochemical properties as a physiological antagonist of calcium, and ease of administration, low cost, able to measure and control the concentration in body fluids, as well as a favorable safety profile (15, 16).

2. PATIENTS AND METHODS

Study had prospective character in which included 50 patients. The subjects were patients admitted to the Intensive Case Unit (ICU) of the Clinic for Anesthesiology and Reanimatology, Neurology Clinic and Neurosurgery Clinic Center Tuzla diagnosed with SAH caused by the rupture of a cerebral aneurysm in the period from 2011 to 2013. Inclusion criteria are: patients with subarachnoid hemorrhage caused by rupture of cerebral aneurysm, patients older than 20 years and younger than 70 years, patients admitted within 72 hours after the occurrence of hemorrhage, patients who had initial measures and intensive care treatment up to 12 days after the occurrence of hemorrhage. Exclusion criteria are: patients underwent surgical treatment due to subarachnoid hemorrhage not originating from aneurysm, patients previously underwent surgical treatment due to cerebrovascular disease, patients who are already treated for cancer and other systemic diseases. Two groups of patients are formed: Group I: patients who in addition to the standard initial treatment and "3H therapy" also received nimodipine at a dose of 15-30 mg/kg bw/h (3-10 ml) for the duration of the initial treatment. Group II: patients who in addition to the standard initial treatment and "3H therapy" received Mg SO4 at a dose of 12 g in 500 ml of 0.9% NaCl/2 h during the initial treatment. All patients upon admission to the hospital underwent native brain CT which confirmed the existence of SAH, and after that CT angiography of blood vessels of the brain which revealed the existence, size, shape and localization of cerebral aneurysm. All patients are monitored by non-invasive monitoring of vital parameters: state of consciousness, blood pressure, heart rate, respiratory rate, body temperature, CVP, diuresis. State of consciousness was measured by the Glasgow Coma Scale–GCS. Measures of initial treatment were analyzed according to the values of World Federation of Neurosurgical Society scale–WFNS. Patients were analyzed also on the existence of underlying diseases prior to admission to hospital: hypertension, diabetes mellitus, cardiovascular diseases and previous neurological diseases. For testing statistical significance between groups were used parametric or non-parametric tests, χ2test and t-test. Statistical hypotheses were tested at the level of a = 0.05, or differences between samples were considered significant if $p < 0.05$. Regression analysis has determined the prognostic value of some potential predictors of treatment outcome after SAH (displayed as OR-odds ratio value).

3. RESULTS

Basic demographic and clinical characteristics were analyzed according to the age, gender, GCS, WFNS and pupil's examination at the hospital admission. The clinical characteristics were analyzed in form of existence of hypertension, diabetes, cardiomyopathy, or jointly observed as a comorbidity (Table 1).

Parameter	Nimodipin	MgSO4	p
Age (years)	56.93±8.94	55.8±9.20	0.667
Gender (% female)	15 (50 %)	15 (75 %)	0.077
Comorbidity			
Hypertension	17 (56.7 %)	13 (65.0 %)	0.556
Diabetes	3 (10 %)	3 (15 %)	0.594
Other	5 (16.7 %)	1 (5.0 %)	0.214
GCS			
<8	1 (3.3 %)	2 (10 %)	0.530
9-11	0	0	
12-13	5 (16.7 %)	2 (10.0 %)	
14-15	24 (80 .0%)	16 (80.0 %)	
WFNS			
I and II	28 (93.3 %)	18 (90 %)	0.456
III	1 (3.3 %)	0	
IV and V	1 (3.3 %)	2 (10. 0 %)	
Pupils			
Neat	29 (96.7 %)	18 (90 %)	0.846
Anisocoric	0	1 (5.0 %)	
Bilateral mydriasis	1 (3.3 %)	1 (5.0 %)	

Table 1. Age, gender, values of GCS, WFNS and pupil's findings at the hospital admission

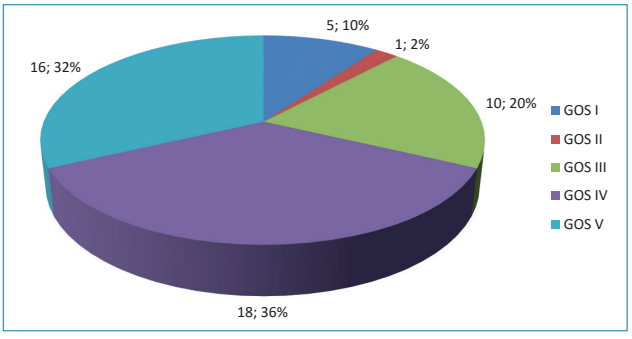

Figure 1. Recovery measured Glasgow Outcome Scale–GOS scale after one month

One month after admission, there was 16 (32%) patients with values of Glasgow Outcome Scale–GOS 5, GOS 4 had 18 patients (36%). GOS grade 3 had 10 patients (20%), GOS II had one patient (2%) and GOS I had 5 (10%) patients in both groups analyzed (Figure 1). This means that two-thirds of patients (68%) in both groups had a good outcome measured by GOS, GOS IV and V. The poorer outcome, GOS III had 20% of patients, GOS II was present at 2% and the GOS I was present 10 % of patients (Figure 1).

There were no significant differences between the groups in terms of recovery measured by GOS (Table 2).

GOS	Nimodipin	MgSO4	p
I	2 (10 %)	3 (10 %)	0,309
II	1 (5,0 %)	0 (0 %)	
III	3 (15 %)	7 (23,3 %)	
IV	5 (25 %)	13 (43,3 %)	
V	9 (45 %)	7 (23,3 %)	
Total	100 %	100 %	

Table 2. The difference in the recovery of the GOS scale between groups. $\chi 2=4.79$; df=4; p=0.309

Risk factors in the initial treatment

Also analyzed is the influence of comorbidity on treatment outcome, radiological findings, the influence of age and gender on the outcome of treatment, clinical parameters, the influence of the treatment and prevention of vasospasm during treatment of initial treatment outcome (Table 3).

Risk factors	OR	95 % CI	p
Comorbidities	3.7	0.00-9.43	0.016
Fisher	3.5	0.57-21.80	0.150
Age	2.2	0.63-7.48	0.208
WFNS	1.9	0.52-6.95	0.365
Gender	1.6	0.29-8.79	0.597
Type of treatment	1.6	0.29-8.79	0.597

Table 3. Values of risk factors in the initial treatment. OR (Odds ratio) value

The impact of comorbidity on the outcome of the situation

If we analyze the impact of comorbidity on the outcome it is obvious that there is a significant relationship between the presence of comorbidity and outcome. The patients without comorbidity (83.30%) had a good outcome (GOS IV and V), the same outcome was observed in 59.4% of patients with comorbidities, which has a statistically significant difference (p = 0.04). The poorer outcome, GOS III is present in higher percentage among patients with comorbidities (21.9%) than in patients without comorbidity (16.7%). Poor outcome (GOS I and II) was not present among patients without comorbidity, whereas in patients with comorbidity was present in 18.8% (Figure 2). If we separately analyze the impact of hypertension as the most common form of comorbidity in patients with SAH there is a noticeable higher frequency of negative outcomes in patients with hypertension, and this relationship is almost reaching statistical significance (p = 0.054) (Table 4). Also a diabetes is common comorbidity entity which have a significant impact on SAH treatment outcome. Patients without diabetes (32%) had a good outcome (GOS IV and V), while the patients with diabetes only in 2% had a good outcome, which represents a statistically significant difference (p = 0.009) (Table 5).

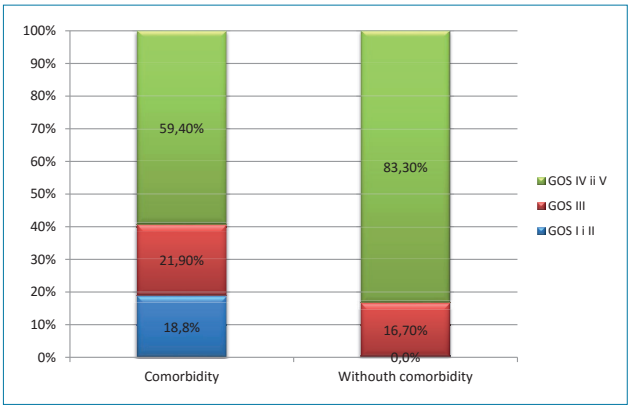

Figure 2. The effect of comorbidity on the SAH

GOS	GOS I and II	GOS III	GOS IV i V	p
Without hypertension	0 (0 %)	3 (15 %)	17 (85 %)	0.054
With hypertension	6 (20 %)	7 (23.3 %)	17 (56.7 %)	
Total	6 (12 %)	10 (20 %)	34 (68 %)	100 %

Table 4. The effect of hypertension on the outcome of SAH

4. DISCUSSION

Among the comorbidity registered in our sample hypertension is most common one (30 patients or 60%), followed by diabetes (6 patients or 12%). There were no significant differences in the presence of comorbidity between groups. If we analyze the impact of comorbidity on the outcome it can be seen that there is a significant relationship between the presence of comorbidity and the outcome. Results show that in case of hypertension as the most common form of comorbidity in patients with SAH there is a higher frequency of negative outcomes, and this relationship is almost reaching statistical significance (p=0.054). Also diabetes represents a common comorbidity entity and had a significant impact on SAH treatment outcome. Patients without diabetes (32%) had a good outcome (GOS IV and V), while the patients with diabetes were only in 2% had good outcome, which represents a statistically significant difference (p = 0.009). The patients without comorbidity (83.30%) had a good outcome (GOS IV and V), while the same outcome was observed (59.4%) with comorbidities, which has a statistically significant difference (p=0.04). The poorer outcome, GOS III in a higher percentage was present in patients with comorbidities (21.9%) than in patients without comorbidity (16.7%). Poor outcome (GOS I and II) was not present among patients without comorbidity, whereas in patients with comorbidity was present in 18.8%. In the study from 2010, Ingawa came to the conclusion that the hypertension was the most powerful risk factor for the aneurismal formation, regardless of age and sex, followed by hypercholesterolemia, heart disease, smoking, diabetes and that daily drinking was insignificant for aneurismal formation (17). Rasing and associates studied 2012 patients with SAH caused by rupture of cerebral aneurysms which as risk factors

GOS	GOS I and II	GOS III	GOS IV i V	p
Without diabetes	3 (6.8 %)	9 (20.5 %)	32 (72.7 %)	0.009
Diabetes	3 (50 %)	1 (16.7 %)	2 (33.3 %)	

Table 5. The effect of diabetes on the outcome of SAH

had hypertension and were smokers. The increase in RR (relative risk) for hypertension was found in women and in men, but an increase in RR for smoking was found only in women (18). Lindgren et al in 2013 published a study claiming that type 2 diabetes does not increase the risk of rupture of the aneurysm, but that his connection with the development of SAH, as the cause of ruptured aneurysms still remains unclear (19). In our study, is applied regression analysis, which is the model included all potential predictors of outcome. As potential predictors of outcome were considered: age, gender, presence of comorbidity, clinical condition at presentation, Fisher scale, and type of treatment (nimodipine or MgSO4). The best and one independent good predictor of outcome proved the presence of comorbidity, with OR value above 3.5. Unexpectedly, the clinical condition at presentation gradient WFNS scale has not proved to be a good predictor of outcome. Schmid-Elsaesser et al in 2006 examined one hundred and thirteen patients with aneurysmal SAH infection and were randomized to receive either magnesium sulfate (10 mg/kg followed by 30 mg/kg daily), or nimodipine (48 mg/d) injecting at least until the seventh postoperative day. There was no difference in the results between the groups. The effectiveness of magnesium in preventing delayed ischemic neurological deficit in patients with aneurysmal SAH seems to be comparable to that of nimodipine. The difference in their pharmacological properties seems to raise the possibility of their combination (20). However, Van den Bergh, 2005 proved that, MgSO4 infusion reduces ischemic neurologic deficit by 34% and fatalities by 23% (21). Mortality in patients with SAH is still very high, despite substantial qualitative progress in their treatment, the improvement of microsurgical and endovascular treatment method (the adoption of new insights into the etiology and pathophysiology of events after SAH and possibilities of medication complications) (22).

5. CONCLUSIONS

Patients who received MgSO4 had less neurological deficits, better functional recovery in the initial phase and a better outcome in the GOS-in, but without statistical significance. The outcome of treatment 30 days after the occurrence of SAH, analyzed values WFNS and GOS, is not dependent on the method of prevention and treatment of vasospasm. The most common comorbidities in patients with aneurysms SAH, requiring additional treatment measures are: arterial hypertension and diabetes mellitus. The biggest pro-activity in the initial treatment of patients with subarachnoid hemorrhage caused by rupture of cerebral aneurysms has the presence of comorbidity, which has statistical significance.

CONFLICT OF INTEREST: NONE DECLARED

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