Original article

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Clinical and neuroimaging predictors of the outcome of microsurgical intervention against the background of cerebral aneurysms rupture

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Objective: minimization of the risks of complications of microsurgical intervention (MI) for cerebral aneurysm (CA) rupture due to established clinical and neuroimaging predictors.

Material and methods. Evaluation of microsurgical treatment of 418 patients in the acute period of cerebral aneurysms (CA) rupture in the 2013-2018 period, that were operated at the Vascular Neurosurgery Center of the Dnipropetrovsk Regional Clinical Hospital named after I.I. Mechnikov, taking into account factors that may have an influence on favorable or unfavorable functional consequences. Age, gender, as well as clinical-neurological and neuroimaging assessment of the condition of patients according to the severity of aneurysmal subarachnoid hemorrhage (SAH) according to the Hunt-Hess classification, WFNS, level of consciousness impairment according to the Glasgow Coma Scale (GCS) were studied. The severity of aneurysmal subarachnoid hemorrhage was evaluated according to the Fisher prognostic scale according to the performed spiral computed tomography (SCT). Cerebral angiospasm (CAS) was evaluated according to cerebral angiography (CAG), and its severity according to transcranial dopplerography (TCD) on the day of hospitalization and surgery. The performed microsurgical intervention (MI) was evaluated according to the Glasgow Outcome Scale (GOS). The study was both retrospective and prospective.

Results. Among 77 (18.4%) patients with adverse consequences of MI according to 1-3 points of GOS, a dependence was reliably found on the level of consciousness disturbance according to GCS, the severity of meningeal and focal symptoms, the severity of parenchymal hemorrhage, CAS manifestations on the day of surgery according to TCD, the duration of surgery after the rupture of CA ($p<0.001$). There was no statistically significant relationship between age, sex, localization, form and side of CA rupture. Also, a strong inverse correlation was found between GCS and classification of SAH according to WFNS $r_s=-0.96$ (95% CI 0.96-0.97) and Hunt-Hess $r_s=-0.81$ (95% CI 0.77-0.84) during hospitalization.

Conclusions. The effectiveness of MI in the case of CA rupture depends on the severity of prognostic criteria of clinical and neurological examination - evaluation by the GCS, neurological disorders, severity of parenchymal hemorrhage, manifestations of CAS on the day of surgery for TCD, the duration of surgery after CA rupture. Revealed relationship between the score according to the GOS, classifications of SAH according to the WFNS and Hunt-Hess significantly simplifies diagnostic measures during the examination of patients in the acute period of CA rupture.

Keywords: *cerebral aneurysms; microsurgical intervention; clinical predictors of the outcome*

Introduction

The incidence of cerebral aneurysms (CA) among the adult population averages 3.2% (1.9–5.2%). CA rupture occurs in 6 out of 100,000 people in developed countries. It leads to the development of 5–7% of strokes annually with high mortality [1–4].

The subject of discussions is not only the method of CA exclusion, but also the timing of intervention. Determining clinical and neuroimaging predictors of complications will minimize risks and establish the optimal period for surgical intervention. This is especially relevant for microsurgical methods. To predict the consequences of aneurysmal subarachnoid hemorrhage (SAH), the clinical and neurological condition, type, distribution, and volume of intracranial hemorrhage detected during neuroimaging examination are traditionally used [5–8]. It has been established that the influence of such predictors is a mandatory link in the pathogenesis of aneurysmal SAH, determining the management strategy for patients [9–11].

Some authors suggest operating without considering the severity of predictors (severity and spread of cerebral angiospasm (CAS), initial manifestations of early cerebral edema according to neuroimaging data) at the time of hospitalization of patients using a timely and aggressive treatment strategy (early or ultra-early surgery). Most published series define "early surgical intervention" as performed within 48–72 h after CA rupture, in a small number of series defining it as performed within 24 h [12]. The disadvantage of this approach is the occurrence of complications during microsurgical intervention (MI), associated with concomitant cerebral edema and the risk of intraoperative rupture [13, 14]. First of all, this concerns cerebral ischemia, the main pathogenetic mechanism of which, according to many authors, is angiospasm of varying degrees of severity, which negatively affects the treatment outcome [15, 16].

Another traditional approach to patient management involves performing surgical intervention after the regression of unfavorable predictors (improvement of the level of consciousness and neurological deficit, regression of the development of CAS and secondary cerebral ischemia) mainly on the 10th-14th day after the rupture. However, a disadvantage of this approach and the associated technique is the threat of recurrent bleeding in the acute period of CA rupture, which is associated with high mortality rate [17].

Therefore, the choice of treatment strategy for the specified category of patients should be individual, taking into account many factors [18, 19].

Objective: to minimize the risk of complications of microsurgical intervention for cerebral aneurysms rupture using established clinical and neuroimaging predictors.

Materials and methods

Study design

A single-center retrospective and prospective controlled study was conducted. Case history data of 329 patients who underwent microsurgery between 2013 and 2017 were analyzed. The prospective cohort study was conducted in 2018.

Study participants

The outcomes of microsurgical treatment of 418 patients who underwent surgery in 2013–2018 at the Vascular Neurosurgery Center of the Dnipropetrovsk Regional Clinical Hospital named after I.I. Mechnikov in the acute period of CA rupture were evaluated, taking into account factors that may influence favorable or unfavorable functional consequences. The age of patients ranged from 18 to 76 years. Gender distribution was equal (209 females and 209 males).

Informed and voluntary written consent for participation in the study was obtained from all patients or their legal representatives.

The study was approved by the institutional review board of Dnipro State Medical University (Minutes No. 6 dated June 30, 2020)

Inclusion criteria

Patients in the acute period of CA rupture, verified by neuroimaging methods, aged over 18 years, who underwent MI, were included in the study.

Characteristics of groups

The distribution by age, clinical-neurological and neuroimaging assessment of patients' conditions according to the severity of aneurysmal SAH according to the Hunt–Hess and World Federation of Neurological Surgeons (WFNS) scales, and the level of impaired consciousness according to the Glasgow Coma Scale (GCS) were analyzed. The severity of aneurysmal SAH was assessed according to the Fisher prognostic scale based on the data of spiral computed tomography, CAS - based on the data of cerebral angiography (CAG), its severity – according to transcranial dopplerography (TCD) on the day of hospitalization and surgery. Evaluation of MI outcomes was carried out using the Glasgow Outcome Scale (GOS).

Statistical analysis

Statistical processing of the study materials was carried out using Kingsoft Office Software (WPS Office), Python v3.9.5 (https://www.python.org/downloads) and JupyterLab (https://jupyter.org/install) software packages. Comparison of independent groups by quantitative characteristics with normal distribution of values was performed using the Student's t-test (t), and for unconjugated samples with distribution that differed from normal or with inequality of variances, using Mann-Whitney (U) test. The statistical significance of differences in qualitative variables was assessed using Pearson's χ^2 test (with Yates' correction in particular) or Fisher's exact test. Spearman's rank correlation (r_s) method with p-values correction for multiple comparisons using Holm's method was used for the analysis. A value of p=0.05 was chosen as type one error. A value of p<0.05 (<5%) was considered critically significant for all types of analysis.

Results and discussion

The Glasgow outcome scale allowed for the assessment of favorable and unfavorable intervention outcomes ***(Table 1)***. Favorable outcomes (moderate functional disability and good recovery) were observed in the majority of patients (81.6%). The mortality rate was 9.8%. The difference in clipping outcomes according to the GOS was statistically significant (p<0.001).

The age of the patients ranged from 18 to 76 years, with the median age of 51.0 years. Younger age of patients was associated with better functional outcome.

Adverse consequences (1–3 points on the GOS) were more common in men (43 (55.84%)), but no statistically significant difference between men and women was found (p=0.813).

Correlation analysis revealed a non-significant inversely proportional relationship between age and male gender (r_s =–0.12, 95% confidence interval (CI) – 0.03–0.22, p=0.011). Adverse consequences and younger age were recorded more frequently in men, but no statistically significant difference by age and sex according to the GOS distribution was found.

At hospital admission, the patients' state of consciousness according to the GCS was on average (14.04±1.53) points (95% CI – 13.89–14.19), before MI – (14.34±1.36) points (95% DI – 14.21–14.48). In the case of adverse consequences of MI, the impairment of the level of consciousness according to the GCS was statistically significantly worse by 1-2 points compared to patients with favorable consequences and was 13.5 [12.0; 15.0] points. A statistically significant difference was established in terms of the level of consciousness disturbance according to the GCS during hospitalization and on the day of MI (p<0.001). Correlation analysis revealed a directly proportional relationship of average strength between the scores by GCS and GOS, both on the day of hospitalization (r_s =0.39, 95% CI – 0.3–0.47) and on the day of MI (r_s =0 .5, 95% CI – 0.42–0.51, p=0.001). It has been proven that a lower level of depression of the state of consciousness of patients with GCS in the acute period of CA rupture is associated with a more favorable MI outcome by GOS.

According to the Hunt–Hess scale, most patients corresponded to grade 1–3, but 15.2% of them had unfavorable outcomes. This was explained by the development of CAS and delayed cerebral ischemia (DCI) after clipping. The assessment of patients according to the Hunt–Hess scale, which corresponded to grade 4-5, was statistically significantly associated with adverse consequences in 62.1% of cases. A statistically significant relationship was found between the results of clipping according to GOS and Hunt–Hess scale score (p<0.001). More severe manifestations of SAH according to the Hunt–Hess scale correlated with worse MI outcomes ***(Table 2).***

Similar results were obtained when analyzing the condition of patients according to the WFNS SAH scale. Adverse outcomes were observed in 13.8% of patients with grade I-III SAH and 50.9% with grade IV-V SAH. Increasing WFNS severity, neurologic deficits that persisted or developed on the day of MI were statistically significantly (p<0.001) correlated with worse clipping outcomes ***(Table 3).***

Increasing SAH severity according to the Fisher scale, as expected, statistically significantly led to worsening outcomes of microsurgical intervention. More than 30% of patients with SAH severity grade 3 according to the Fisher scale and nearly 50% with SAH severity grade 4 experienced adverse outcomes ***(Table 4).***

The analysis of cerebral angiography (CAG) data, performed for all patients on admission to the hospital, revealed a statistically significant association between adverse outcomes according to the GOS and angiospasm development (p=0.036). Among patients with regional CAS, adverse outcomes were recorded in 11 cases (10.8%). The occurrence of widespread CAS led to adverse outcomes of MI (1-3 points) in 15 observations (21.2%), while diffuse CAS led to adverse outcomes in 10 cases (29.4%). Among 212 (100%) patients without angiographic signs of CAS, unsatisfactory outcomes were also observed in 41 cases (19.3%). In our opinion, in 21 cases (51.2%), this was associated with the early performance of neuroimaging, with CAS developing after MI, resulting in deterioration of the clinical condition due to symptomatic CAS and delayed cerebral ischemia (DCI). The mortality rate was 7 (6.9%) cases with regional CAS, 5 (7%) with widespread, and 6 (17.6%) with diffuse.

The surgical outcomes that depended on manifestations of CAS according to TCD performed before clipping were more evident and reliable ***(Table 5)***. Adverse outcomes were registered in 49 patients (63.6%) with detected CAS on TCD, with 44.4% experiencing moderate CAS. Critical nature of CAS led to severe functional impairment in one case. Adverse outcomes occurred even in the absence of CAS manifestations in 26.6% of patients (p<0.001). In our opinion, negative outcomes in these patients can be explained by the presence of other adverse factors.

The timing of the operation was of utmost importance: the median was 12.0 [7.0; 17.0] days. Among those operated on days 1 to 3, the highest number of fatal outcomes was recorded (22.4%), while among those operated on after the 14th day, the lowest (5.4%). An increase in the time of intervention after the cerebral aneurysm rupture statistically significantly improved its outcomes according to the GOS (p=0.008) ***(Table 6)***.

Table 1. Distribution of patients according to microsurgical intervention outcomes according to the Glasgow outcome scale (n=418)

Glasgow outcome scale	Number of patients	
	Abs.	%
Death (1 point)	41	9,8
Persistent vegetative state (2 points)	6	1,4
Severe functional impairment (3 points)	30	7,2
Moderate functional impairment (4 points)	69	16,5
Good recovery (5 points)	272	65,1

Table 2. Distribution of microsurgical intervention outcomes according to the Glasgow Outcome Scale score depending on the Hunt-Hess scale assessment (n=418)

Hunt–Hess scale	GOS, score					Total
	1	2	3	4	5	
1	4 (9,8%)	0	1 (3,3%)	7 (10,1%)	45 (16,5%)	57 (13,6%)
2	15 (36,6%)	2 (33,3%)	11 (36,7%)	24 (34,8%)	171 (62,9%)	223 (53,3%)
3	11 (26,8%)	3 (50,0%)	12 (40,0%)	30 (43,5%)	53 (19,5%)	109 (26,1%)
4	7 (17,1%)	1 (16,7%)	4 (13,3%)	7 (10,1%)	3 (1,1%)	22 (5,3%)
5	4 (9,8%)	0	2 (6,7%)	1 (1,4%)	0	7 (1,7%)
Total	41 (100,0%)	6 (100,0%)	30 (100,0%)	69 (100,0%)	272 (100,0%)	418 (100,0%)

Table 3. Distribution of microsurgical intervention outcomes according to the Glasgow outcome scale depending on the WFNS scale assessment (n=418)

WFNS	**GOS, score**					**Total**
	1	**2**	**3**	**4**	**5**	
I	15 (36,6%)	2 (33,3%)	12 (40,0%)	26 (37,7%)	192 (70,6%)	247 (59,1%)
II	10 (24,4%)	0	4 (13,3%)	13 (18,8%)	53 (19,5%)	80 (19,1%)
III	1 (2,4%)	1 (16,7%)	6 (20,0%)	17 (24,6%)	15 (5,5%)	40 (9,6%)
IV	13 (31,7%)	3 (50,0%)	8 (26,7%)	13 (18,8%)	12 (4,4%)	49 (11,7%)
V	2 (4,9%)	0	0	0	0	2 (0,5%)
Total	41 (100,0%)	6 (100,0%)	30 (100,0%)	69 (100,0%)	272 (100,0%)	418 (100,0%)

Table 4. Distribution of microsurgical intervention outcomes according to the Glasgow outcome scale score depending on the severity grade of subarachnoid hemorrhage according to the Fisher scale (n=418)

Fisher scale	**GOS, score**					**Total**
	1	**2**	**3**	**4**	**5**	
1	5 (12,2%)	0	1 (3,3%)	4 (5,8%)	38 (13,9%)	48 (11,5%)
2	1 (2,4%)	0	1 (3,3%)	6 (8,7%)	78 (28,7%)	86 (20,6%)
3	9 (22,0%)	2 (33,3%)	8 (26,7%)	11 (15,9%)	60 (22,1%)	90 (21,5%)
4	26 (63,4%)	4 (66,7%)	20 (66,7%)	48 (69,6%)	96 (35,3%)	194 (46,4%)
Total	41 (100,0%)	6 (100,0%)	30 (100,0%)	69 (100,0%)	272 (100,0%)	418 (100,0%)

Table 5. Distribution of microsurgical intervention outcomes according to Glasgow outcome scale score depending on the data of TCD (n=418)

TCD	**GOS, score**					**Total**
	1	**2**	**3**	**4**	**5**	
Not detected CAS	17 (41,5%)	2 (33,3%)	9 (30,0%)	19 (27,5%)	58 (21,3%)	105 (25,1%)
Mild	17 (41,5%)	1 (16,7%)	14 (46,7%)	37 (53,6%)	185 (68,0%)	254 (60,8%)
Moderate	5 (12,2%)	3 (50,0%)	4 (13,3%)	6 (8,7%)	9 (3,3%)	27 (6,5%)
Expressive	2 (4,9%)	0	2 (6,7%)	7 (10,1%)	20 (7,4%)	31 (7,4%)
Critical	0	0	1 (3,3%)	0	0	1 (0,2%)
Total	41 (100,0%)	6 (100,0%)	30 (100,0%)	69 (100,0%)	272 (100,0%)	418 (100,0%)

Table 6. Distribution of microsurgical intervention outcomes according to the Glasgow outcome scale depending on the timing (n=418)

GOS, score	**The timing of microsurgical intervention, days**				**Total**
	1–3	**4–8**	**9–14**	**≥14**	
4-5	38 (65,5%)	57 (79,2%)	120 (86,3%)	126 (84,6%)	341 (81,6%)
2-3	7 (12,1%)	6 (8,3%)	8 (5,8%)	15 (10%)	36 (8,6%)
1	13 (22,4%)	9 (12,5%)	11 (7,9%)	8 (5,4%)	41 (9,8%)
Total	58 (100,0%)	72 (100,0%)	139 (100,0%)	149 (100,0%)	418 (100,0%)

An important component in the treatment of CA is identifying factors that may cause complications during the intervention and their impact on postoperative outcomes. Clipping with intracerebral hematoma (ICH) removal was performed in 29 (6.9%) patients who required it considering the volume and localization of the hemorrhage. Adverse outcomes were reported in 12 (15.5%) of these patients. Rupture of blister-shaped CA was more often accompanied by the formation of ICH ($p<0.001$).

In the postoperative period, 15 (3.6%) patients required decompressive craniectomy due to the growth of CI and the development of dislocation symptoms. Adverse outcomes occurred in 13 (86.6%) patients.

Therefore, performing decompressive craniectomy on the background of delayed CI correlated with a worse outcome of MI according to GOS (p=0.001). The development of secondary brain ischemia leads to deterioration of patients' functional status and surgical outcomes. Decompressive craniectomy in these conditions saved patients' lives, but slightly improved the functional status.

Intraoperative rupture (IOR) during MI occurred in 23 (5.5%) patients mainly during clipping or isolation of the aneurysm artery carrier and only in 2 cases during opening of the dura mater. No statistically significant relationship between the results of GOS and IOR was revealed (p=0.364). The occurrence of IOR was more often registered in patients with giant CA (p=0.061), less often in the presence of diverticula (p=0.077).

In addition to early CAS, delayed CI developed on the background of CAS was observed. It persisted or occurred after MI in 62 (14.8%) patients. DCI led to adverse outcomes in 41.5% of patients with the specified complication. The development of DCI had a temporary character or entailed a moderate functional incapacity for GOS in 8.7% of patients. The development of DCI on the background of CAS led to a statistically significant (p<0.001) decrease in GOS score, preservation of neurological deficits, and sometimes to the development of dislocation symptoms and complications of MI.

The occurrence of recurrent hemorrhage (RH), which may be accompanied by high mortality, was found in 39 (9.3%) cases. In our study, adverse effects developed in 14 (18.1%) patients with RH and in 9 (23.1%) of them they led to a fatal outcome. Thus, RH significantly (p=0.003) worsened MI outcome according to the GOS, but had a weak direct proportional relationship with mortality (r_s =0.14, 95% CI – 0.03–0.25).

The total mortality among patients after MI was 9.8% (41 cases), among those operated on within the first 3 days after the rupture – 22.41% (13 cases) and was mainly caused by the severity of aneurysmal SAH, the presence of ICH with the development of dislocation symptoms in 6 (10.3%) observations. Among those operated on between days 4 and 14, it was associated with the development of DCI caused by an increase in CAS. Also, mortality was recorded in 9 cases that occurred on the background of RH (at the end of the 1st–on the 2nd week after rupture). In unfavorable cases, a delayed CI was registered due to the development of CAS. They were statistically significantly (p=0.001) correlated with fatal outcomes of MI.

It was found that the factors of adverse MI outcomes in 77 (18.4%) patients were impaired level of consciousness according to the GOS, severity of neurological deficit, severity of parenchymal hemorrhage. This is consistent with the data of other authors [1, 8–10, 20]. The findings obtained by us indicate negative effects of CAS manifestations on the day of surgery, according to both CAS and TCD, but some authors disagree with this [12, 21].

The timing of surgery after CA rupture has been statistically significantly proven to be important. Operations performed on the first day were associated with the highest mortality and number of severe adverse outcomes, whereas operations performed on days 10–14 had the best results. The majority of authors insist on the earliest possible surgical intervention to prevent RH in CA rupture [22, 23]. The data obtained by us indicate that RH, although it occurs, but the risk in the analyzed sample was 9.3% (n=39), which is significantly lower than the rates given in the literature [24]. Also, not every RH is fatal. According to our data, death due to RH was recorded in only 9 (2.1%) cases, which is lower than mortality after early surgery (13 (3.1%)).

Thus, the predictors of the adverse MI outcomes were impaired consciousness level according to the GCS, severity of neurological deficit, severity of parenchymal hemorrhage, manifestations of CAS on the day of surgery, duration of surgery after rupture of CA, development of RH and delayed CI (p<0.001). No statistically significant association between the consequences of MI and age, sex, localization, form and side of CA rupture was found. A strong inversely proportional relationship was found between the GCS score during hospitalization and SAH classification according to the WFNS scale (r_s =–0.96, 95% confidence interval– 0.96–0.97) and Hunt–Hess scale (r_s =–0,81, 95% confidence interval – 0.77–0.84).

Conclusions

1. Statistically significant predictors of the functional outcomes of MI in CA rupture were impaired level of consciousness of patients according to the GCS, severity of neurological deficit, severity of parenchymal hemorrhage, manifestations of CA on the day of surgery, timing of surgery after CA rupture.

2. It was found that increasing the timing of MI after the CA rupture statistically significantly (p=0.008) improved the intervention outcomes according to the GOS.

3. Delayed CI statistically significantly (p<0.001) led to deterioration of MI outcomes according to the GOS in the acute period of CA rupture.

4. It was revealed that increasing severity of SAH by Hunt–Hess and WFNS scales, decreasing level of consciousness according to the GCS, the severity of hemorrhage by Fisher scale, ICH formation and development of neurological deficit had a statistically significant (p<0.001) strong relationship with negative MI outcomes.

Disclosure

Conflict of interest

The authors declare no conflict of interest.

Ethical approval

All procedures performed on patients comply with the ethical standards of institutional and national ethics committees, the 1964 Declaration of Helsinki and its amendments or similar ethical standards.

Informed consent

Informed consent was obtained from each of the patients.

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