EFFECTS OF CEREBRAL VASOSPASM ON DISEASE OUTCOMES IN PATIENTS WITH SEVERE TRAUMATIC BRAIN INJURY

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ABSTRACT

Cerebral vasospasm (CV) is an urgent issue in the treatment of patients with severe traumatic brain injury (STBI).

OBJECTIVES

The aim of this study was to evaluate the effect of cerebral vasospasm on outcomes of STBI.

MATERIAL AND METHODS

The study included 43 patients with isolated and assocoated STBI. The depression of consciousness in patients upon admission was 8 or less according to the Glasgow Coma Scale (GCS).

RESULTS

Cerebral vasospasm was revealed in 33 (77%) patients. Groups were comparable according to age, type of TBI, GCS and average AP upon admission to hospital. The analysis of the disease outcomes according to GOS revealed significant between-group differences in the assessment of favorable outcomes (score 4–5, GOS), unfavorable outcomes (score 2–3, GOS) and deaths. In patients without CV and with moderate CV, the rate of cases with GOS 1 and GOS 2–3 was 30% (n=3) and 31% (n=5), respectively, and in patients with significant CV it was 82% (n=14).

CONCLUSION

The development of significant cerebral vasospasm in patients with severe traumatic brain injury results in increased mortality by 21% and recovery with adverse neurological outcomes by 31%. The post-traumatic CV may cause secondary ischemic brain damage, resulting in considerable disturbance of cerebral oxygenation.

Keywords: cerebral vasospasm, severe traumatic brain injury.

AD — arterial blood pressure
CA — cerebral angiospasm
CCA — common carotid artery
CCT — carotid compression tests
CFM — color flow mapping
CT — computed tomography
CV — cerebral vasospasm
GCS — Glasgow coma scale
GOS — Glasgow outcome scale
ICA — internal carotid artery
ICP — intracranial pressure
IL — индекс Линдегарда
KCA — constrictive stenosing arteriopathy
LVBF — linear velocity of blood flow
MCA — medial cerebral artery
OC — overshoot coefficient
PTA — posttraumatic angiospasm
PTV — posttraumatic vasospasm
SAH — subarachnoid hemorrhage
STBI — severe traumatic brain injury
TBI — traumatic brain injury
TCDS — transcranial duplex scan
TSAH — traumatic subarachnoid hemorrhage

Cerebral angiospasm (CA) is an urgent problem in the treatment of patients with severe traumatic brain injury (STBI). According to various authors, CA occurrence may increase the risk of death by 30% or more [1-5]. However, many researchers have noted that the assessment of the impact of CA on STBI outcomes is extremely problematic due to the heterogenity of the etiopathogenic factors comprising the clinical picture of the disease, and the need for life-time differential diagnosis of the causes for secondary brain damages [1, 3, 5].

The aim of this study was to evaluate the influence of CA on outcomes of STBI.

MATERIAL AND METHODS

Forty three patients with isolated and associated STBI were examined. The depression of consciousness in patients was 8 upon arrival according to Glasgow coma scale (GCS).

The average age of patients was 32.4±10.8 years, there were 36 men and 7 women. Twenty seven victims (63%) had an open injury, and 16 (27%) patients had closed STBI. The cause of traumatic brain injury (TBI) in 37 patients (86%) was a traffic accident, and falling from a height in the rest of cases. Severe brain contusion was diagnosed in all patients. Patients with multiple contusion foci of various localization prevailed. In 20 patients, intracranial hematomas were revealed and required neurosurgery. These patients underwent decompressive trepanation and removal of intracranial hematomas and contusion-crush foci of the brain. In 33 patients (77%), STBI was combined with fractures of the tubular bones of various localization and/or closed chest trauma. The severity of associated injuries was assessed according to *ISS*.

Diagnosis and monitoring of CA was performed by transcranial duplex scanning (TDS). Starting with day 2 after admission, all patients underwent duplex scanning of extracranial and intracranial arteries in color Doppler mode mapping (CFM). The study was performed by devices *Logiq Book XP (General Electric,* USA) with sensors of 2-5 MHz frequency and *Toshiba Viamo (Toshiba Medical Systems,* Japan) sensors with a frequency of 2.5 and 8 MHz. Insonation in M-mode of 1-2 segment of the middle cerebral artery (MCA) was performed from the front or middle temporal ultrasound windows. The study protocol included measurements of linear blood flow velocity (LBFV) in M-mode of 1-2 segments of MCA. We calculated systolic (V_s), average (V_m) and diastolic (V_d) LBFV, pulsatility index (P_i), Lindegard index (IL) and overshoot coefficient (OC). MCA was located on the screen vertically or at a slight angle (15-30 degrees) in the mode of power Doppler mapping, and its lumen stained red in the mode of CFM. For insonation of internal carotid artery (ICA), a sensor was located on the neck at a distance of 1-2 cm above the clavicle along the medial edge of the sternocleidomastoid muscle, directed at an angle of 45º and recorded Dopplerograms of starting parts of ICA. To assess cerebral autoregulation, CO was calculated using carotid compression tests (CCT). We calculated LBFV in MCA, then continuing location of MCA, we made finger clamping of the common carotid artery (CCA) on the neck to the same side for 5 cardiac cycles. Compression was stopped in diastole phase. After termination of CCA compression we continued CMA location to restore the original flow rate.

The diagnosis of cerebral angiospasm was established with increased linear systolic blood velocity in MCA on one side up to 120 cm/sec or more, and IL up to 3 or more. Cerebral angiospasm was ranked as mild (V_s 120-200 cm/sec) and significant (V_s more than 200 cm/sec) according to severity, and segmental (unilateral)/diffuse (bilateral) according to expansion [12].

All patients underwent a discrete definition of oxygen saturation of hemoglobin in the bulb of the jugular vein ($SvjO_2$) via retrogradely installed central venous catheter (distal end of the catheter was located at the mastoid process of the temporal bone in the projection of jugular bulb). The catheter was positioned on the side of the greatest damage to the brain according to computed tomography (CT). Measurement of $SvjO_2$ was performed at least twice a day with the gas analyzer *«ABL* 800 *FLEX» (Radiometer,* Denmark).

Computed tomography was performed with *«Toshiba»* (Japan) tomograph upon arrival and 12-24 hours after hospitalization. CT determined the anatomical shape of traumatic subarachnoid hemorrhage, the degree of lateral dislocation of median structures of the brain, the index of central departments of the lateral ventricles, the state of basal cisterns, the type of brain damage according *Marshall* classification.

In 19 patients, intracranial pressure (ICP) was measured using *Spiegelberg* Brain-Pressure Monitor (Germany). Parenchymal ICP sensor *(Intraparenchymal* Probe 3*PN,* Germany) was installed through the burr hole to a depth of 1-1.5 cm in the frontal lobe of the hemisphere, opposite the surgical access.

All patients underwent standard intensive therapy. Mechanical ventilation was carried out in the auxiliary mode with tidal volume of 8-10 ml per 1 kg of ideal body weight and a positive end-expiratory pressure of 6-8 cm of water column. To ensure a sufficient cerebral perfusion, the pressure of carbon dioxide in the arterial blood ($PaCO_2$) was sustained in the range of 30-35 mmHg. We tried to maintain normovolemia and average arterial blood pressure within 90-100 mmHg. If necessary, sympathomimetic therapy was performed. The volume of the infusion therapy was not less than 45 ml/kg/day for the first 3 days of the injury and at least 30-35 ml/kg/day for the entire observation period. The infusion therapy included balanced crystalloid solutions, gelatin and hydroxyethyl starch. Nutritional support was initiated on day 2-3 of the disease using enteral mixtures with a high content of omega-3 and 6 polyunsaturated fatty acids and caloric content of not less than 2000 kcal/day. If necessary, parenteral nutrition was added.

The study excluded patients older than 50 years with decompensated extracerebral disease and with a time gap from the moment of injury more than 6 hours.

Outcomes were assessed according to the Glasgow Outcome Scale (GOS) — death (GOS 1), vegetative state (GOS 2), rough neurological deficit (GOS 3), minimal neurological deficit (GOS 4) and the absence of neurological deficit (GOS 5).

Statistical processing of the data was performed using *STATISTICA* software package *6.0* (StatSoft, USA). The data is presented in the format $M\pm\sigma$ *(M* - arithmetic mean, σ - standard deviation) for normal distribution and the median format (25th and 75th percentiles) for abnormal distribution. Between-group comparisons were performed using Student's t test for normal and Mann-Whitney test for abnormal distribution. Correlation analysis of quality traits was performed using Spearman and Fisher criteria. Wilcoxon test was performed to evaluate intra-group

differences. Differences were considered statistically significant at a level of *p* less than 0.05.

RESULTS AND DISCUSSION

Depending on the outcome of the disease, all patients were divided into three groups: Group 1 — patients with a lethal outcome (GOS 1), Group 2 — patients with adverse outcomes — vegetative state (GOS 2) and rough neurological deficit (GOS 3), Group 3 — victims with a favorable outcome (recovery with minimal or no neurological deficit (GOS 4-5)). CA was detected in 33 victims (77%). There were no statistically significant age, type of TBI, GCS and ABP_{av} differences between groups upon admission to hospital (Table 1).

Table 1

General characteristics of examined patients

Parameters	Groups of patients		
	Patients with lethal outcomes GOS 1 (*n*=12)	Patients with unfavourable outcomes GOS *2-3* (n=9)	Patients with favorable outcomes GOS *4-5* (n=22)
Age, years	33.5±10.2	33.9±10.1	32.6±9.8
Male/female	10/2	6/3	20/2
GCS upon admission to hospital	5 (4, 8)	5 (5; 6)	6 (5; 8)
ABP_{av} upon admission, mmHg	70 (55; 76)	75 (60; 80)	76.5 (70; 83)
Operated patients	3	6	11
ISS upon admission	24 (18; 33)	22 (16; 29)	21 (16; 27)
Severity of *CV*, n (%)			
Without CA	2 (17%)	1 (11.3%)	7 (32%)
Moderate CA	3 (25%)	2 (22.3%)	11 (50%) * **
Significant CA	7 (58%)	6 (66.3%)	4 (18%) * **
Type of damage by *Marshall, n (%)*			
I	0	0	1 (4.5%)
II	0	1 (11%)	5 (23%)
III	4 (33.5%)	3 (33%)	1 (4.5%)
IV	1 (8.5%)	0	2 (9%)
V	0	5 (55%)	9 (41%)
VI	7 (58%)	0	4 (18%)
Anatomic type of SAH according to *S.M. Fisher, n (%)*			
I	4 (33%)	1 (11.3%)	8 (36%)
II	1 (8.5%)	0	7 (32%)
III	6 (50%)	6 (66.3%)	6 (27.5%) *, **
IV	1 (8.5%)	2 (22.3%)	1 (4.5%)

Note: * — *p* <0.02 compared with the group of patients with GOS 1, ** — *p* <0.05 compared with the group of patients with GOS 2-3. ABP — arterial blood pressure; CA — cerebral angiospasm; CV — cerebral vasospasm; GCS — Glasgow Coma Scale; GOS — Glasgow Outcome Scale; SAH — subarachnoid hemorrhage

The analysis of anatomical types of SAH according to *S.M. Fisher* showed significant differences in patients with different disease outcomes (see Table 1). Patients with a third form of hemorrhage dominated in groups of lethal and adverse outcomes according to GOS (1-3), and these patients had the significant CA more likely.

It should be noted that the development of CA had a significant impact on disease outcomes (Table 2). The development of significant CA was accompanied by increased frequency of adverse neurological outcomes (GOS 2-3) and deaths.

Comparing the dynamics of blood flow velocity, *IL,* and CO in victims with different outcomes according to GOS, we found patterns that influenced the course and outcome of the disease: the severity of CA, time of its manifestation, the rate of LBFV, the state of cerebral autoregulation.

Development of CA in patients with lethal outcome (GOS 1) was observed mainly on day 2-3 after injury. The maximum LBFV was noted on day 4-5 in 6 patients (60%), and on day 6-7 in 4 patients (40%) (Fig. 1). In 9 affected (90%), LBFV growth for any day of observation was 50 cm/sec and more, and we characterized this trend of CA development a "peak" one (Table 3). One patient in this group had unilateral CA.

Table 3

Characteristics of cerebral vasospasm in examined patients

Outcomes of TBI (GOS)	*n*	Features of CA				
		Time of CA initiation (days)			Type of CA course	
		2-3, *n* (%)	4-5 *n* (%)	6-7 *n* (%)	Progressive, n (%)	Peak, n (%)
1	10	7 (70%)	3 (30%)	-	1 (10%)	9 (90%)
2-3	8	6 (75%)	2 (25%)	-	0	8 (100%)
4-5	15	4 (27%) * **	10 (66%) * **	1 (7%)	11 (73%) * **	4 (27%) * **

Note: * — *p* <0.01 compared with the group of patients with GOS 1; ** — p<0.01 compared with the group of patients with GOS 2-3; *n* — number *of* patients. CA —

cerebral angiospasm; GOS — Glasgow Outcome Scale; TBI — traumatic brain injury

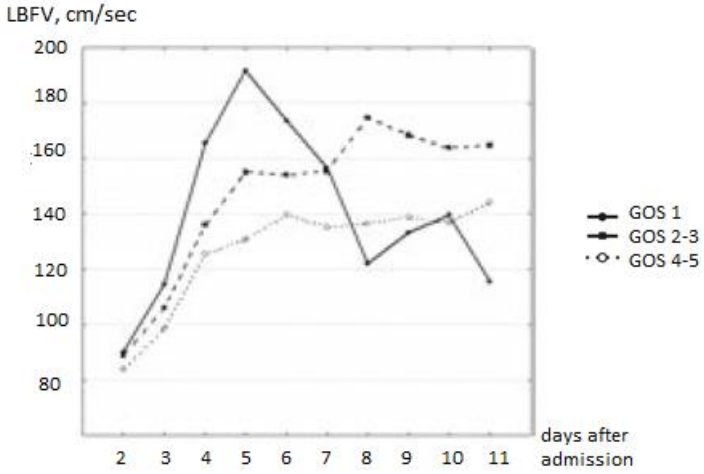

Fig. 1. Changes of linear blood flow velocity in patients with different outcomes of injury.
Note: GOS — Glasgow Outcome Scale; LBFV — linear blood flow velocity in the middle cerebral artery

It should be noted that victims with lethal and adverse outcomes (Group1 1 and Group 2) had similar beginning and development of CA. Thus, in patients with poor outcomes of the disease, who formed the Group 2, CA developed mainly on day 2-3 after injury in 6 cases (75%), on day 4-5 in 2 cases (25%) (see Table 3). The maximum LBFV was observed on day 4-5 in 2 patients (25%), on day 6-7 in 2 (25%) patients and on day 8-10 in 4 patients (50%). All the victims of the Group 2 had a "peak" type of CA course. Patients with favorable outcomes had CA mainly on day 4-5 from the moment of injury, with its peak development on day 4-5 in 3 cases (20%), on day 6-7 in 6 cases (40%), on day 8-9 in 4 cases (27%) and on day 10-11 in 2 cases (13%). The "progressive" CA course (V_s increase less than 50 cm/24h) was observed in 11 patients (73%), and the "peak" type was observed in 4 patients (27%). One patient in this group had unilateral CA.

Thus, early development of posttraumatic vasospasm (PTA) on day 2-3 after the injury and the "peak" increase of V_s (50 cm/sec per day) with a maximum growth by the 5th day of post-traumatic period were risk factor for adverse outcomes.

While calculating OC we revealed significant violations of cerebral autoregulation in all the affected. The values of OC in the range of 1.016-1.105 were observed in patients Group 1 and Group 2 (GOS 1-3), while in patients with GOS 4-5, OC did not fall below 1.1 during the entire period of observation (Fig. 2).

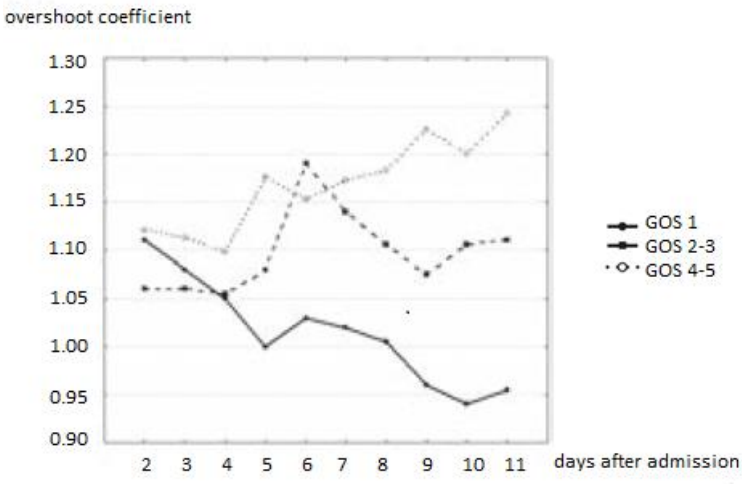

Fig. 2. Changes of overshoot coefficient in patients with different outcomes.
Note: GOS — Glasgow Outcome Scale

Development of CA in patients with GOS 1-3 was accompanied by a significant disturbance in cerebral oxygenation. In assessing the performance of global brain oxygenation — $SvjO_2$ we observed lower values in victims with lethal injuries and adverse outcomes (Fig. 3). The minimum $SvjO_2$ on day 4 after trauma corresponded to the peak of CA development in patients of the group with lethal outcomes.

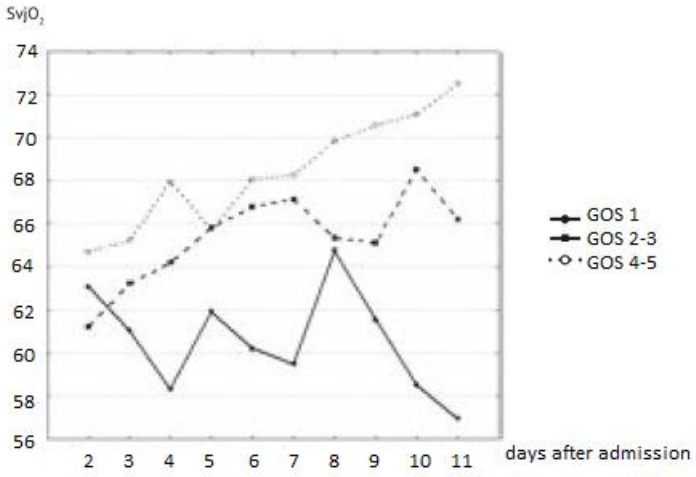

Fig. 3. Changes of $SvjO_2$ parameters in patients with different outcomes.
Note: GOS — Glasgow Outcome Scale

Posttraumatic vasospasm (PTV) was first described by F. Columnella et al. in 1963. In further studies, PTV rates ranged from 18.6 to 50% [3]. Thus, according to R.K. Kordestani et al. (1997), the cerebral vasospasm rate was 42.4% in a study involving patients with penetrating TBI [6]. A.S. Bolyuh et al. (2002) observed PTV in 28.2% of patients with traumatic brain injury [7]. B. Romner et al. (1996) found CV in 28% - 41% of patients with STBI. [8] M. Hadani et al. observed an increased incidence of PTV from 43 to 58% in patients with traumatic subarachnoid hemorrhage compared to patients with no signs of TSAH [2]. According to most researchers, PTV develops within 12 hours - 5 days after the injury and lasts from 12 hours to 30 days [1, 3-5, 9, 10]. Some authors think that generalized PTV develops within 12-48 hours after the injury, beginning with the posterior cerebral arteries system, reaches a peak on day 5-13 and lasts 2-3 weeks. [6] According to our study, the incidence of CA in patients with STBI was 77%. In 48% of patients, moderate CA developed, and in 52% of patients it was significant.

It should be noted that in the available literature there is practically no studies on the assessment of CA impact on the outcomes of STBI. Thus, Y.A. Zurynski et al. (1995) showed that PTA development was accompanied with increased frequency of adverse outcomes from 40 to 87% [9]. M. Hadani et al. (1997) found that in victims with TBI the increase of LBFV in the main artery to 90 cm/sec or more was accompanied by an increase in the probability of death up to 33%, and a vegetative state development — up to 42% compared to patients with LBFV increased to 75 cm/sec. [2]. J.F. Soustiel et al. (2002) found that in patients with TSAH and severe spasm of the basilar artery, the probability of persistent neurological deficits or death was 85.3% [11]. A.S. Bolyuh et al. (2002) noted an increase in the incidence of adverse outcomes of the disease with the development of CA by 34.1% [7]. A. Perrein et al. (2015) studied outcomes of the disease in patients with STBI complicated by the development of CA. The worst outcomes were observed in patients with the early development of CA (first 24 hours), and disease developed in patients with late development of CA (48 hours after trauma) more favorable. [5] According to D. Svistov et al. (2003), in patients with constrictive-stenotic arteriopathy (CSA), adverse outcomes of TBI were observed 3.8 times more often than in patients without CSA. [8] In studies of the National Institute of Health (USA) and the European Consortium for TBI it was noted that TSAH, defined by CT, is an independent predictor of poor outcome of the disease [13]. According to our data, the development of moderate CA did not have a significant effect on the outcome of the injury. However, the significant CA was accompanied by a high increase in mortality (21.5% in comparison to victims without CA) and recovery rate with adverse neurological outcome (25% compared to survivors without CA). The growth of adverse outcomes incidence was also observed in patients with III anatomic tupe of intracranial hemorrhage according to C.M. Fisher, with CA developed on day 2-3 of the post-traumatic period, with "peak" type of LBFV type and in patients with severe disturbances of cerebral autoregulation.

CONCLUSIONS

1. The development of significant cerebral vasospasm in patients with severe traumatic brain injury is accompanied by the increased mortality by 21.5% and a recovery rate with adverse neurological outcomes by 25%.

2. Risk factors for death, vegetative state and recovery with gross neurological deficits in patients with severe traumatic brain injury are: III anatomic type of intracranial hemorrhage according to C.M. Fisher, development of significant CA, development of CA on day 2-3 after the injury, "peak" type of LBFV growth with the maximum value to the 5^{th} day after injury and decrease in OC down to 1.1 or less.

3. Posttraumatic CA may result in secondary ischemic damage of the brain, causing considerable disturbances of cerebral oxygenation.

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Article received on July 28, 2016
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