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| Journal:       | Canadian Journal of Physiology and Pharmacology |
|----------------|-----------------------------------------------|
| Manuscript ID  | cjp-2020-0277.R2                              |
| Manuscript Type| Article                                       |
| Date Submitted by the Author: | 28-Aug-2020                                    |
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| Is the invited manuscript for consideration in a Special Issue: | Not applicable (regular submission) |
| Keyword:       | hemorrhagic stroke, oxidative stress, hospital lethality, prognostic markers, cytoflavin |
EARLY PREDICTIVE BLOOD MARKERS OF HEMORRHAGIC STROKE –
INFLUENCE OF CYTOFLAVIN THERAPY

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Abstract

Examination of the patterns of free-radical processes (FRP) and changes of the early screening markers to predict the course of hemorrhagic stroke (HS) and applied pathophysiologically based therapy, can be of great practical importance. This study aimed to determine early changes in the parameters of oxidative stress and routine biochemistry blood tests in patients with HS and to assess their relationship with clinical outcome. The effects of early applied cytoflavin were also investigated. The prospective study included 151 patients with HS. 48% of patients in the standard conservative therapy was added cytoflavin antioxidant energy therapy from the first day of hospitalization. The neurological status, neuroimaging, biochemical blood tests and free radical processes were assessed on days 1, 5, 10, 20 of hospitalization. In patients with HS, an imbalance of all stages of FRP was detected proportionately to the severity of HS. The MDA concentration above 5.3 μmol/l, the number of leukocytes above 15.8 thousand, glucose above 11.9 mmol/l, lactate dehydrogenase above 574 IU/l, lactate above 2.5 mmol/l, detected on the 1st day, predetermined a high risk of death. Additional cytoflavin treatment allowed stabilizing the clinical-laboratory picture of HS, improved the treatment results and reduced hospital mortality rate.

Keywords: hemorrhagic stroke, oxidative stress, lethality, prognostic markers, cytoflavin
Introduction

The urgency of the hemorrhagic stroke (HS) problem is beyond doubt since HS is the leading cause of neurological mortality and disability. Despite the implementation of modern diagnostic techniques and treatment into clinical practice, the hospital mortality rate is still high and reaches 50% (Truelsent et al. 2015; Krishnamurthi et al. 2014). This determines the high relevance of the search for early prognostic criteria and new pathophysiological methods of rational therapy for HS based on the fundamental research data.

The main pathogenetic mechanisms of HS are the presence of blood in the brain material, the progression of secondary ischemia, which provokes secondary vascular spasm, and the increase of occlusive hydrocephalus with deepening of focal neurological disorders and stem syndrome with the exclusion of brain matter in the foramen magnum. The development of an ischemic cascade in HS is associated with a disturbance of oxidative phosphorylation and an active release of cytokines, leading to damage to lysosome membranes and the release of autolytic enzymes into the intercellular space of brain tissue (Xiao et al. 2017; Zygun et al. 2005). In recent years, much attention has been paid to the search for theories explaining the universal mechanisms of apoptosis and necrosis type cell death that occurs in the development of diseases associated with ischemia and hypoxia, including cerebral stroke. One of them is the theory of free-radical processes (FRP) and oxidative stress (Liguori et al. 2018; Yaribeygi et al. 2018; Lujan and Sayes 2017) associated with energy deficiency and mitochondrial dysfunction, whose role has been proven in a variety of pathologies, including stroke (İçme et al. 2015; Silina et al. 2017). Hyperglycemia is closely connected with oxidative stress, which during the first hours and days of stroke is an independent prognostic factor in worsening neurologic symptoms and adverse outcomes (Yaribeygi et al. 2017; Hirata and Okamura 2018; Stead et al. 2009). A further in-depth study
examining patterns of FRP and early screening markers for predicting the course of HS, as well as the searching for timely ways of correcting the revealed disorders, can be of great practical importance in the treatment of these patients.

Therefore, the present study aimed to estimate the role of oxidative stress and early prognostic laboratory markers in the course and outcome of HS to improve the therapy results through the involvement of pathogenetically substantiated treatment.

**Materials and Methods**

This multicenter study included 151 patients (82 men and 69 women) with HS verified by CT/MRI, which were performed in the first 2 hours of hospitalization. Patients entered the hospital within up to 72 hours from the onset of the disease and had moderate to severe stroke with more than 7 NIH scores. All hemorrhagic strokes were exclusively intracerebral hematomas. All patients received conservative treatment. Surgical treatment of hemorrhagic stroke was a criterion for exclusion or withdrawal from this study.

Research was conducted in accordance with the principles outlined in the Declaration of Helsinki and the principles of Good Clinical Practice (GCP). Written informed consent was obtained from all the participants, and the study protocol was approved by the Ethics Committee of the Clinical Centre of Russia, prior to the onset of the study.

During hospitalization, patients were randomized into two groups:

1. The control group included 79 patients with HS who received standard baseline conservative therapy that meets the standards of medical care for this category of patients in a hospital setting.

2. The treatment group (Cytoflavin group, Cyt) consisted of 72 patients, who in addition to standard therapy, received the energy corrector and antioxidant cytoflavin
(succinic acid+inosine (riboxin)+nicotinamide+riboflavin sodium phosphate (riboflavin)) from the first day of hospitalization in a daily dose of 20 ml (slow intravenous drip in dilution with NaCl physiological solution 400 ml, or with 5% or 10% glucose solution in a volume of 400 ml) daily for 10 days.

Patients of both groups were comparable by sex, age, hospitalization, and initiation of therapy, severity, background focal neurological symptoms, HS volume (Table 1).

All patients underwent comprehensive assessment in dynamics, including anamnesis, clinical examination, neuroimaging (MRI/CT scan of the brain); assessment of the dynamics of neurological status on the NIH scale (National Institutes of Health – National Institute of Neurological Disorders and Stroke), general and biochemical blood tests, as well as studies of FRP in blood plasma on days 1, 5, 10, 20. Some biochemical blood parameters (including glucose, lactate, lactate dehydrogenase) were additionally examined on days 3 and 7.

During the study of FRP, the following methods were used: sampling of heparinized blood, isolation of leukomain from whole blood, isolation of a numerical population of neutrophils from whole blood, staining and differential counting of leukocytes, preparation of a working mixture of zymosan and its opsonization, study of the actual indicators of FRP. In the morning fasting blood sample (10 mL) was taken from the patient's cubital vein into a test tube containing 1.5 ml of saline with a pH of 7.35 and 0.5 ml of heparin solution (5000 U/ml).

FRPs were studied in all patients for oxygen and peroxide-lipid indicators of oxidative stress. The first were the indices of reactive oxygen species generation by leukocytes. This is a basal indicator of chemiluminescence intensity (ICb) and an indicator of stimulated chemiluminescence intensity (ICs). The chemiluminescence intensity (ChL) was stimulated when using a solution of opsonized zymosan, so that 100 parts of zymosan would fall to 1 leukocyte. The indices of reactive oxygen species generation by leukocytes were calculated...
after measuring the basal and stimulated ChL leukocyte suspension according to the formula

\[= \text{maximum ChL} \times 10^6 / \text{the number of granulocytes and monocytes in the studied volume of leukomain. The result is expressed in mV/s} \times 10^6 \text{leukocytes} \times 10^6 \text{leukocytes}.\]

All oxygen indices of oxidative stress were studied on an adapted chemiluminometer Wallac LKB1251 (Sweden), treating ICb as an indicator characterizing spontaneous leukocyte chemiluminescence, reflecting the restructuring of oxidative metabolism of leukocytes, that is, the initial state of metabolic processes, and ICs as an integral indicator reflecting the presence of active oxygen species in the plasma.

The peroxide-lipid component of oxidative stress was evaluated with the help of indicators of antiperoxide activity of secondary plasma (APA) and malondialdehyde (MDA) (Bolevich 2006; Vladimirov and Proskurnina 2009). The APA investigation method was based on measuring and determining the ratio of the spontaneous chemiluminescence index of secondary plasma to its hydrogen peroxide-induced chemiluminescence. The MDA concentration in the plasma (products reacting with thiobarbituric acid) was determined by optical density on a spectrophotometer Jenway (Great Britain) at a wavelength of 532 nm, calculating the indicator by the formula: 

\[C = D \times 10^p / 1.56,\]

where D is the optical density, p is the dilution rate, 1.56 is the correction factor, expressing the final result in \(\mu\)mol per 1 liter of plasma. The norm of the FRP parameters was taken based on blood counts of 30 healthy people.

Statistical processing of data was carried out by SPSS 17.0 programs using standard parametric and nonparametric criteria for estimating statistical significance. Differences were considered significant at \(p < 0.05\). Descriptive statistics of quantitative continuous variables are presented as mean values (M) and standard deviations (±SD) for normally distributed data, and as medians (Me), upper (75%) and lower (25%) quartiles, and 95% confidence interval (95CI) for non-normally distributed data. The risk of in-hospital lethality by
laboratory markers was calculated from the analysis of 95CI estimates. The Mann-Whitney U test was used to compare two independent non-parametric samples. The Wilcoxon test was used to compare two dependent non-parametric samples. Qualitative parameters were compared using the $\chi^2$ test (analysis of contingency tables).

**Results**

**Characteristics of the study group**

The main characteristics of patient groups with hemorrhagic stroke are presented in Table 1. The mean age of patients was 60.9±13.6 years while there were 54.3% of men, (mean age 56.5±14.6 years) and 45.7% of women (mean age 66.3±10.4 years). The volume of the hematoma on average (median) was 23.6 cm$^3$, while in 24.5% of patients the volume of HS was less than 10 cm$^3$, and in 36.4% – more than 30 cm$^3$ (Table 1).

**Parameters of FRP**

The markers of the oxygen stages increased relative to the norm: the ICb increased by an average of 1.30 times ($p<0.01$), the ICs increased by 1.42 times ($p<0.01$). Simultaneously, an imbalance of peroxide-lipid markers of oxidative stress was revealed in the form of a significant increase in MDA by 1.38 times on average ($p<0.01$) and a decrease in APA by 1.2 times ($p<0.05$) (Table 2). Already on the first day of hospitalization, the upper limit of the norm was higher than that of ICb in 32% of patients, ICs in 41%, MDA in 23%, while APA was less than the lower normal limit in 21% of patients with HS (Table 2).

The imbalance of FRP was expressed in an increase in ICb by an average of 1.23 times ($p<0.05$), ICs by 1.15 times ($p<0.05$), MDA by 1.32 times, and decrease in APA by 1.15 times ($p<0.05$) compared to the norm. On the 1$^{\text{st}}$ day of patients hospitalization with an unfavorable outcome, the ICb increased by a factor of 1.57 ($p<0.05$), the ICs increased by
1.54 times (p<0.01), MDA by 1.44 times (p<0.01) and the APA decreased by 1.26 times (p<0.05). The MDA indicator revealed the intergroup difference (Table 2).

**Concentration of MDA**

Comparative analysis of MDA in patients with different volume of hemorrhagic stroke is presented in Figure 1. The level of MDA of blood plasma in 35% of patients with an unfavorable outcome of HS exceeded the upper limit of the norm; this is 3.5 times more than with a favorable outcome. The analysis of the 95% confidence interval (CI) of the MDA index made it possible to formulate the criteria for early prognosis in patients with HS. The concentration of MDA in blood plasma above 5.3 μmol/l predetermined a high risk of in-hospital mortality. Low risk of in-hospital mortality is established at an MDA concentration below 1.5 μmol/l.

**Clinical blood parameters**

The most informative prognostic markers of the clinical blood test were the increased number of leukocytes, stab and segmented neutrophils, with an unfavorable outcome, (averaged 12,600), 8% and 73%, respectively, which is significantly higher than in the patients discharged (p<0.05) and normal (p<0.05). At a normal level of leukocytes (≤9 thousand) lethality was 17.3%, and with leukocytosis >9 thousand – 2.7 times higher (46.3%, p<0.05). The decrease in the number of lymphocytes was 10% on average in the deceased and 15% in the discharged, which is less than the lower norm limit (p<0.05) (Table 3).

**Concentrations of glucose and activity of lactate dehydrogenase (LDH)**

Disorders of glycolysis were detected in the majority of patients with HS, but to the maximum extent, they were expressed in an unfavorable outcome, which was expressed by
an increase in the glucose concentration (above 6.4 mmol/l in 71.4% in the deceased and 44.2% in the discharged), lactate dehydrogenase (LDH) above 470 IU/l (69.6% of deaths and 41% of discharges) and venous blood lactate above 1.6 mmol/l (67.9% of deaths and 58.9% of discharges) accompanying energy deficiency in patients with HS (Figure 2).

*Early laboratory prognostic markers of blood plasma for HS*

Early prognostic markers of oxidative stress, energy synthesis, and other laboratory-related blood plasma parameters that are reliably correlated with HS outcome are shown in Table 4. Significant correlations of glucose and lactate level, as well as MDA concentration, have been shown.

*Dynamics of FRP (APA and MDA)*

Dynamics of FRP (APA and MDA) in patients with HS who received and did not receive antioxidant energy-correcting therapy (cytoflavin) as part of standard conservative therapy is presented in Figure 3. As can be seen in the figure, both FRP parameters had the same dynamics during the course of disease between the groups, with APA concentrations higher in the antioxidant group compared to the other group.

*Dynamics of blood glucose and lactate concentrations*

Dynamics of blood glucose and lactate concentrations in patients with HS who received and did not receive antioxidant energy-correcting therapy (cytoflavin) as part of standard conservative therapy is presented in Figure 4. Both glucose and lactate were lower during the course of disease in the antioxidant group compared to the other group.
Dynamics of neurologic failure assessed by the NIH scale

Dynamics of neurologic failure assessed by the NIH scale in patients with HS who received and did not receive antioxidant energy-correcting therapy as part of standard therapy is presents in Figure 5. Already on the 5th day in the antioxidant group, the NIS score was lower (10) than in the control group (12), and after 20 days the difference between the groups was 1.6 times (5 and 8 points, respectively, p <0.05).

Effect on in-hospital mortality

A total of 56 (37.1%) patients died in the hospital. In the standard therapy group, the mortality rate was 41.8% (n=33). Administration of antioxidant therapy resulted in a significant reduction in in-hospital mortality by 1.3 times (31.9%, p <0.05).

Discussion

The aim was to determine early changes in the parameters of oxidative stress and routine biochemistry blood tests in patients with HS and to assess their relationship with clinical outcome. The effects of early applied antioxidant energy-correcting therapy (cytoflavin) were also investigated.

During hospitalization, activation of FRP processes by oxygen markers was detected in patients with HS, which indicates an intensification of processes involving active oxygen forms, which are the catalysts of the peroxide-lipid phase. This was realized by increasing the level of peroxide-lipid markers detected along with a decrease in protective anti-peroxide activity.

Early prognostic clinical and laboratory markers of HS have been established. The role of disturbance of glycolysis and oxidative stress as a single mechanism of manifestation of disenergization, as well as true neutrophilic leukocytosis, in the development and outcome of
HS, has been shown. The impossibility of the full flow of energy synthesis stages naturally correlates with an increase in lethality against the background of progressive energy instability, leading to an increase in brain cell death. An important role in this is played by the accumulation of lactic acid as a result of anaerobic metabolism, which provokes the activation of glutamate release, as well as the intensification of cerebral edema. Hyperglycemia, hyperlactatemia, and oxidative stress activation significantly correlate with the volume of HS and clinical symptoms. The combination of the effects of these mutually potent factors leads to hospital lethality. The authors would like to emphasize that all these mechanisms are interrelated with oxidative stress.

In addition to a high dose of succinate (1000 mg in an ampoule of 10 ml), cytoflavin contains coenzymes nicotinamide, riboflavin and inosine (riboxin), stimulating glucose-pyruvate transformations in the Krebs cycle. The preparation of cytoflavin has an evidentiary base that objectifies its positive effect on the clinical course and on the volume of foci of ischemia (Rumyantseva et al. 2017; Odinak et al. 2010). This makes it expedient to use it in the early period of the HS.

During hospitalization, in patients with HS we have detected an imbalance of all stages of FRP. With HS, oxidative stress is characterized by hyperactivation of both oxygen and peroxide-lipid stages. This gives the right to assume that HS is an acute uncompensated critical condition, accompanied by a rapid violation of the blood-brain barrier and an increase in homeostatic dysregulation. Perhaps, that is why the severity of HS is more pronounced, and the lethality is much higher than with cerebral infarction. Markers of oxidative stress on the first day of hospitalization were more pronounced in case of lethal (unfavorable) HS outcome.

The greatest degree of oxidative stress in severe patients is confirmed by an analysis of oxidative stress indicators for different volumes of HS. The gradual aggravation of the FRP
imbalance severity is revealed with its shift towards peroxidation processes along with a decrease in the activity of antiradical systems as hemorrhage increases. With an HS volume of more than 30 cm³, the highest free radical imbalance is recorded, which leads to the progression of secondary ischemia, often determining the disease outcome. In line with our results, other studies have also shown strong prognostic values of oxidative stress parameters and degree of HS (Cherubini et al. 2005). Furthermore, some biomarkers have been proposed as reliable peripheral predictors of increased oxidative damages within the brain tissue during a stroke. One of them is certainly malondialdehyde whose concentration often correlates with the size of stroke and clinical outcome (Cherubini et al. 2005; Hu et al. 2016; Duan et al. 2016). A possible explanation for enhanced FRP and oxidative stress during and after ischemic and hemorrhagic stroke could be mitochondrial dysfunction, hemoglobin, and inflammatory cells (Hu et al. 2016).

On the other hand, the results regarding the most informative prognostic markers of the clinical blood indicate a decrease in protective mechanisms, inhibition of immune responses, regression of antibody formation. Leukocyte transformations, determined in the majority of patients with HS already on the first day, mainly in hospitalized patients, become a reflection of the systemic inflammatory reaction, which is confirmed by the growth of ESR. After the analysis of leukocyte values, it can be noticed that their rise on the first day of hospitalization predetermines a high risk of death in patients with HS.

The study of clinical blood counts on day 1 revealed an increase in the number of leukocytes with an increase in stab and segmented neutrophils and a decrease in lymphocytes against the background of an increase in the erythrocyte sedimentation rate (ESR) in the majority of patients with HS as compared to the norm. Thus, in the conditions of HS, neutrophilic leukocytosis develops. It is not redistributed (the transition of leukocytes from the parietal to the circulating pool with a normal leukocyte formula), developing in response
to hypoxia, hemorrhage, the action of endo- and neurotoxins that provide the output of neutrophils from bone marrow depot and their accelerated differentiation is proportional to the speed and severity of tissue decay. This is combined with morphological and functional changes in neutrophils, the main function of which is phagocytosis. Unlike changes in leukocyte count, the normal values of erythrocytes, hemoglobin, hematocrit, and color index, not distinguishable in deceased and discharged patients with HS, indicates the absence of gross changes in the transport of oxygen in the blood.

Other investigations have indicated that increased leukocyte count on admission can be a prognostic marker for reduced risk of hematoma expansion (Morotti et al. 2016). On the contrary, some authors suggested that increased white blood values in HS were associated with stroke severity, larger hematoma volume, and intraventricular extension (Yu et al. 2016). These fluctuations in leukocyte dynamics during HS can be a consequence of inflammatory response and therefore confirm the role of inflammation in pathophysiology of HS (Morotti et al. 2016; Yu et al. 2016). Moreover, some studies have found that mean platelet volume can be an independent risk factor for ischemic and hemorrhagic stroke, but without significant association with the prognosis of both strokes (Du et al. 2016).

Hyperglycemia, detected as early as on day 1 of HS, reflects the severity of the oxidative imbalance triggered by glycolysis disorders. The impossibility of a full course of the energy synthesis stages naturally correlates with an increase in lethality against the background of progressive energy instability leading to an increase in intracellular and tissue necrosis/apoptosis. An important role in this is played by the accumulation of lactic acid as a result of anaerobic metabolism, which provokes the activation of glutamate release, as well as the intensification of cerebral edema. Moreover, with an unfavorable outcome of HS, on the first day, an acid-reduction imbalance, a violation of glucose utilization, and therefore a violation of glycolysis and a disruption in the work of the Krebs cycle with the development
of energy deficiency are more pronounced. After the analyses of our results, we can notice that the glucose level above 11.9 mmol/l, LDH above 574 IU/l and/or lactate above 2.5 mmol/l, predetermines a high risk of death. Our findings are in line with the results of recent studies that pointed out that hyperglycemia is connected with poorer clinical outcome and a higher risk of in-hospital death in HS patients (Snarska et al. 2017; Mi et al. 2017). Even in non-diabetic hemorrhagic stroke patients hyperglycemia has an impact on the long-term prognosis of the disease (Yoon et al. 2016).

Hyperglycemia, hyperlactatemia, and oxidative stress lead to increased expression of proinflammatory genes, enhancement of the processes of polyol and hexosamine pathways, activation of protein kinase C, transforming growth factor-β, renin-angiotensin-aldosterone system, and enhancement of education final glycation products. The combination of the effects of these mutually potent factors leads to in-hospital lethality.

Reliable correlations of hyperglycemia, hyperlactatemia, and FRP (an increase of MDA and decrease in APA) confirm that energy deficiency and oxidative stress are interrelated. In addition, these processes are more pronounced in severe patients.

Administration of cytoflavin led to a positive dynamics of FRP, an increase in protective APA against the background of regression of the MDA destruction marker, as well as glucose and lactate levels. As a result, this positively affected the clinical picture of the disease. These results can be logical having in mind the antioxidant properties of cytoflavin, so this agent justified its usage.

Moreover, early supplementation of antioxidant therapy in the intensive treatment of patients with HS led to a more rapid regression of impaired consciousness at different localizations and HS volumes. During treatment, the patients of the main group showed a more pronounced positive dynamics of neurologic failure regression, estimated by the NIH stroke scale. Beginning from the 3rd day of treatment, a faster regression of focal neurologic
symptoms was noted with a significant improvement relative to the control group by the 20th day of the disease. The most significant reliable regression of focal neurological insufficiency was noted in groups of patients with a hematoma volume of up to 10 cm³ and more than 30 cm³, as well as in lobar, mixed, and medial hematomas. In addition, the use of cytoflavin in the complex treatment of patients with HS led to a reduction in disability by 17% by the 20th day from the onset of the stroke, with an improvement in its structure towards a decrease in severe disability and an increase in the proportion of good functional recovery. Similar results have been shown in a very recent study where a strongly reduced NIHSS score on the 10th day of treatment with cytoflavin and a more noticeable improvement in the Rankin scale and Barthel index were noted (Sazonov et al. 2018). Besides with hemorrhagic stroke, cytoflavin also showed promising effects in acute ischemic insult (Sazonov et al. 2016; Sazonov et al. 2017).

Finally, it is important to emphasize that the most positive dynamics of regression of neurological failure and the best functional outcome were revealed within up to 24 hours from the onset of the disease, with early antioxidant therapy. It was in this early period that the pathogenetically grounded antioxidant therapy could be used to inhibit the vicious cycle of mutually potent reactions of oxidative stress and energy deficiency, as a result of which the size of the zone of secondary ischemia surrounding the HS focus area was reduced.

Conclusions

The results of present study showed that severity of HS was associated with an imbalance of all stages of FRP. The MDA concentration above 5.3 μmol/l, the number of leukocytes above 15.8 thousand, glucose above 11.9 mmol/l, lactate dehydrogenase above 574 IU/l, lactate above 2.5 mmol/l, detected on the 1st day, predetermined a high risk of
death. The obtained data also indicate potential usefulness of early administration of pathophysiologically based antioxidant energy-correcting therapy in HS. Cytoflavin treatment allowed stabilizing the clinical-laboratory picture of HS, improved the treatment results and reduced hospital mortality rate.

Conflict of Interest

The authors declare no conflict of interest.

Acknowledgments

This work was supported by Russian Academic Excellence Project 5-100.

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Table 1 The characteristics of patient groups with hemorrhagic stroke.

| Characteristics                          | Control group (n=79) | Cytoflavin group (n=72) | Total (n=151) | p    |
|------------------------------------------|---------------------|-------------------------|---------------|------|
| Mean age                                 | 59.8±13.5           | 61.2±13.7               | 60.9±13.6     | >0.05|
| sex: men                                 | 44 (55.7%)          | 38 (52.7%)              | 82 (54.3%)    | >0.05|
| women                                    | 35 (44.3%)          | 34 (47.2%)              | 69 (45.7%)    | >0.05|
| NIH M±m                                  | 13.7±5.4            | 13.8±5.6                | 13.7±5.3      | >0.05|
| Me                                       | 14                  | 14                      | 14            |      |
| Volume of HS: Me, cm³                    | 27.5                | 21.2                    | 23.6          | >0.05|
| n, % <10 cm³                             | 15 (19.0%)          | 22 (30.6%)              | 37 (24.5%)    |      |
| 10-30 cm³                                | 31 (39.2%)          | 28 (38.9%)              | 59 (39.1%)    |      |
| >30 cm³                                  | 33 (41.8%)          | 22 (30.6%)              | 55 (36.4%)    |      |
| Duration of hospitalization from the onset of the disease: |                     |                         |               |      |
| <24h                                     | 47 (59.5%)          | 44 (61.1%)              | 91 (60.3%)    | >0.05|
| 24-48h                                   | 22 (27.8%)          | 17 (23.6%)              | 39 (25.8%)    |      |
| >48h                                     | 10 (12.7%)          | 11 (15.3%)              | 21 (13.9%)    |      |
Table 2 Parameters of FRP in patients with a different outcome of HS upon admission to hospital compared to the norm.

| Parameters | ICb \((\text{mV/sec} \times 10^6 \text{leucocytes})\) | ICs \((\text{mV/sec} \times 10^6 \text{leucocytes})\) | APA \((\text{μmol/L})\) | MDA \((\text{μmol/L})\) |
|------------|---------------------------------|-----------------|----------------|------------------|
| HS         | 81.45                           | 667.20          | 3.04           | 3.73             |
|            | 49.99/160.58 \((p=0.001)\)      | 404.35/1028.50  | 2.6/4.1        | 2.86/4.54        |
|            | *(p=0.002)                       | *(p=0.014)      | *(p=0.004)     |                  |
| Discharged | 76.90                           | 541.35          | 3.13           | 3.56             |
|            | 52.48/138.10 \((p=0.018)\)      | 401.50/909.00   | 2.52/4.33      | 2.52/4.28        |
|            | *(p=0.017)                       | *(p=0.030)      | *(p=0.045)     |                  |
| Deceased   | 97.91                           | 722.70          | 2.86           | 3.89             |
|            | 47.64 / 229.60 \((p=0.011)\)    | 411.95/1186.40  | 2.31/3.82      | 2.94/6.61        |
|            | *(p=0.003)                       | *(p=0.021)      | *(p=0.001)     |                  |
| p (outcome)| 0.423                           | 0.232           | 0.109          | 0.043 \#         |

Note: statistical results are presented in the form of the following data: the first line is the median (me), the second line is the lower and upper quartiles (quartile 25%; quartile 75%), the third line – comparison with the norm (*– the difference between the indicator and the norm for \(p<0.05\); Mann-Whitney test). \# – \(p<0.05\) difference in the hs outcome (Mann-Whitney test).
Table 3 Clinical blood parameters in patients with a different outcome of hemorrhagic stroke, examined on day 1 of hospitalization.

| Parameters (norm)          | Deceased          | Discharged        | p         |
|----------------------------|-------------------|-------------------|-----------|
| Rbcs (3.8-5.1 x 10^{12}/l) | 4,5               | 4,6               | p> 0.05   |
|                            | 4,0/5,1 (3,2; 5,6)| 4,2/5,0 (3,6; 5,4)|           |
| Hematoglobulin (120-160 g/l) | 144               | 141               | p> 0.05   |
|                            | 134/154 (103; 175)| 130/151 (103; 167)|           |
| Haematocrit (35-49%)       | 40,4              | 41,5              | p> 0.05   |
|                            | 36,7/45,2 (29,2; 49,2) | 39,0/45,2 (31,8; 48,4) |           |
| CP (0.85-1.05)             | 0,93              | 0,91              | p> 0.05   |
|                            | 0,89/1,01 (0,85; 1,06) | 0,88/0,97 (0,77; 1,05) |           |
| Thrombocyte 180-320 thousand | 218               | 209               | p> 0.05   |
|                            | 202/276 (138; 435)| 180/259 (144; 406)|           |
| Leukocyte (4-9 x 10^9/l)   | 12,6 *            | 9,2               | #p<0.05   |
|                            | 9,7/17,3 (5,6; 21,2) | 7,2/11,7 (5,7; 15,8) |           |
| Stab neutrophils (1-6%)    | 8 *               | 7 *               | p=0.05    |
|                            | 5/12 (1; 27)      | 6/9 (2; 13)       |           |
| Segmented neutrophils (47-72%) | 73 *              | 70                | # p <0.05 |
|                            | 66/79 (52; 86)   | 64/76 (50; 82)    |           |
| Lymphocyte (19-37%)        | 10 *              | 15 *              | # p <0.05 |
|                            | 8/16 (3; 27)     | 9/20 (5; 34)      |           |
| Eosinophil (0-5%)          | 0                 | 0                 | p> 0.05   |
|                            | 0/0 (0; 2)       | 0/0 (0; 3)        |           |
| Monocyte (3-11%)           | 4                 | 5                 | p> 0.05   |
|                            | 4/5 (1; 9)       | 3/6 (1; 11)       |           |
| Parameters                  | Low risk   | Average risk | High risk |
|-----------------------------|------------|--------------|-----------|
| MDA (μmol/l)                | 1.01-1.53  | 1.54-5.32    | >5.32     |
| Glucose (mmol/l)            | 3-5        | 5-11.9       | >11.9     |
| Lactate dehydrogenase (IU/l)| < 309      | 309-574      | >574      |
| Lactate (mmol/l)            | < 1        | 1-2.5        | >2.5      |
| AST (U/l)                   | < 18       | 18-50        | >50       |
| Leukocyte, 10⁹/l            | < 5.7      | 5.7-15.8     | >15.8     |
| Stab neutrophils (%)        | < 2        | 2-13         | >13       |
| Segmented neutrophils (%)   | < 52       | 52-82        | >82       |
| Lymphocyte (%)              | > 27       | 5-27         | <5        |
| ESR (mm/hr)                 | < 3        | 3-39         | >39       |
Figure captions

Figure 1. Comparative analysis of MDA in patients with different volume of the hemorrhagic stroke (differences from the norm statistically significant at $*p < 0.05$).

Figure 2. Level of glucose and lactate dehydrogenase (LDH) on the day 1 of hospitalization and patients with a favorable and unfavorable outcome of the hemorrhagic stroke (differences from the norm statistically significant at $*p < 0.05$).

Figure 3. Dynamics of FRP (APA and MDA) in patients with HS who received and did not receive antioxidant energy-correcting therapy (cytoflavin) as part of standard conservative therapy (median indicators are indicated).

Figure 4. Dynamics of glucose and lactate in patients with HS who received and did not receive antioxidant energy-conserving therapy as part of standard conservative therapy (median indicators are indicated).

Figure 5. Dynamics of neurologic failure assessed by the NIH scale in patients with HS who received and did not receive antioxidant energy-correcting therapy as part of standard therapy (* – the difference between groups at $p <0.05$; Mann-Whitney test).
Figure 1

This box plot illustrates the distribution of MDA (μmol/l) across different stroke volume categories: Healthy (Norm), < 10 cm³, 10-30 cm³, and > 30 cm³.
Figure 3

**APA**

- **Norm**
- **Standard therapy**
- **Standard therapy + Cytoflavin**

**MDA (μmol/L)**

- **Norm**
- **Standard therapy**
- **Standard therapy + Cytoflavin**
Figure 4

**Glucose (mmol/l)**

- Day 1: 6.0
- Day 3: 6.8
- Day 5: 7.3
- Day 7: 6.3

**Lactate (mmol/l)**

- Day 1: 2.1
- Day 3: 2.1
- Day 5: 2.2
- Day 7: 1.8

- Standard therapy
- Standard therapy + Cytoflavin
Figure 5

![Chart showing NIH score over days for different treatment groups.](chart)