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Реферати

СОСТОЯНИЕ АГРЕГАЦИИ ТРОМБОЦИТОВ И ДЕЙСТВИЕ ИНТЕРЛЕЙКИНОВ 4 И 6 ПРИ ЭКСПЕРИМЕНТАЛЬНОМ АЛЬВЕОЛИТЕ

Черемисина В. Ф., Березнякова А. И.

В работе представлены результаты по выявлению взаимосвязей между содержанием цитокинов и функциональной активностью тромбоцитов у крыс с нарушением обмена костной ткани пародонта при альвеолите. При этом заболевании повышается уровень ИЛ-4, сокращается время достижения максимальной скорости агрегации при концентрации АДФ 2,5 мкмоль/л, а также имеется взаимосвязь между степенью агрегации тромбоцитов и уровнем ИЛ-6 при концентрации АДФ 10,0 мкмоль/л.

Ключевые слова: агрегация тромбоцитов, интерлейкины, костная ткань, альвеолит.

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STATE OF PLATELET'S AGGREGATION AND THE EFFECT OF INTERLEUKIN 4 AND 6 AT EXPERIMENTAL ALVEOLITIS

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The paper presents the results of identifying the relationship between the content of cytokines and the functional activity of platelets in rats with disturbance of the bone marrow periodontal metabolism with alveolitis. At this disease, the level of IL-4 increases, the time reaches the maximum aggregation rate at an ADP concentration of 2.5 micromol/L, and also the relationship between the degree of aggregation of platelets and the level of IL-6 at an ADP concentration of 10.0 μmol/L.

Key words: platelet's aggregation, interleukins, bone tissue, alveolitis.

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INFLUENCE OF HAES-LX-5% INFUSION SOLUTION ON THE DNA CONTENT OF ENDOCRINE GLANDS CELLS AGAINST THE BACKGROUND OF THERMAL BURN OF SKIN IN RATS

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The results of the experimental study of the DNA content by the method of duct DNA cytometry in adenohypophysis, thymus and adrenal glands cells on the background of thermal burn of the skin and correction of the HAES-LX-5% infusion solution in comparison with a similar burn on the background of application of 0.9% solution are given in the article. NaCl. The use of the HAES-LX-5% drug causes a positive polyfactorial effect on the DNA content in adenohypophysis, thymus and adrenal cells. Its effect has specific manifestations in each of the cell groups and provides a balance recovery between the processes of DNA synthesis and apoptosis. So the use of this infusion solution softens the negative impact of the adverse effects of skin burn in adenohypophysis cells, mainly affecting synthetic processes, which is especially manifested in the delay in the development of burn disease. In adrenal cells, the HAES-LX-5% solution more definitely reduces the symptoms of apoptosis from day 7 of the experiment, rather than affecting synthetic processes. The effect of this solution on the content of thymus DNA cells consists in the reducing the parameters of the interval SUB-G0G1 practically in all terms of the experimental study with simultaneous insignificant increase of synthetic processes.

Key words: DNA-cytometry, thermal damage to the skin, rats, solution of HAES-LX-5%, adenohypophysis, adrenal glands, thymus.

The development of new therapies for burn disease is one of the topical issues of modern medicine, which is due to the significant increase in this damage in many countries of the world and, in particular, in Ukraine, especially the thermal nature, which remains extremely difficult during the course and prognosis as a type of burn injury [3, 6, 7, 12]. The search for new treatments for burn disease is also due to the inadequate effectiveness of existing drugs that have their contraindications and complications that may affect the outcome of therapy. One of the main areas of medical therapy for burn inflammation

is infusion therapy with various solutions, which has a polyfactor effect on the pathogenetic factors of burn disease - 0.9% NaCl solution, lactoprotein with sorbitol, albumin, other plasma substitutes preparations [25, 27]. However, their application is not always effective, that in the background of significant thermal burn injuries of the skin leads to the development of various complications and even to lethal leakage [21]. That is why the development of new drugs aimed at the comprehensive impact on the main factors of burn disease remains the focus of attention of domestic and foreign researchers. One of the new solutions that potentially can be effective in the treatment of burn disease is the domestic hyperosmolar solution HAES-LX-5%, which in numerous studies has shown its effectiveness against the background of thermal damage to the skin [5, 11, 14].

One of the main pathogenetic factors of the burn disease is systemic damage to the endocrine system, organs and their cells, which creates preconditions for the development of numerous complications and a cascade of acute and distant manifestations of this pathology. Histological, immunological and biochemical manifestations of adenohypophysis [2], adrenal glands [10, 18] and thymus [13, 28] damages have been established at different times in the course of burn disease, which lead to severe organ damage [23, 22]. However, the molecular mechanisms of these disorders remain poorly understood, which makes it difficult to develop pathogenetic treatments for burn disease. Particularly this issue seems relevant given the direct impact of burning disease endotoxins on the DNA of cells of all organs and systems. Today, one of the standard methods of DNA damage is the method of cytometric flow DNA, which is particularly precise in determining the intracellular signs of apoptosis, which in turn is a generally recognized trigger of injury in a burn disease [1, 4, 15]. There are data [8] about intracellular mechanisms action of infusion drugs on cell cycle performance and DNA fragmentation of tissues of various organs in the treatment of burn disease. Accordingly, it is important to determine the effect of both the pathology itself and the therapy on the content of DNA of the cells of the endocrine system at various times after the thermal damage.

Research purpose – to analyze the peculiarities of the effect of the HAES-LX-5% solution on the content and fragmentation of the DNA of adenohypophysis, adrenal glands and thymus cells in the context of a burn disease.

Material and methods. Experimental studies on 108 white male rats weighing 160-180 g obtained from the vivarium of the Institute of Pharmacology and Toxicology of the National Academy of Medical Sciences of Ukraine were conducted on the basis of the research laboratory of functional morphology and genetics of the research center of the National Pirogov Memorial Medical University, Vinnitsa (VNMU n.a. M. I. Pirogov), which is certified by the Ministry of Health of Ukraine (certificate number 003/10 dated January 11, 2010). Rats were in the conditions of the scientific and experimental clinic of VNMU n.a. M. I. Pirogov on a standard water and food ration with free access to water and food in the form of balanced feed in accordance with established norms. The temperature in the room where the animals were kept was at a level of 24-25 °C, humidity of air - within 40-60%. Animal retention and manipulation were conducted in accordance with the "General ethical principles of animal experiments" adopted by the First National Congress on Bioethics (Kyiv, 2001), and also guided by the recommendations of the "European convention for the protection of vertebrate animals used for experimental and other scientific purposes" (Strasbourg, 1985) and the provisions of the "Rules for preclinical safety assessment of pharmacological agents (GLR)". During the work with laboratory animals, we adhered to: rules of humane attitude towards of experimentation animals and approved by the Bioethics Committee of the VNMU n.a. M. I. Pirogov (minutes № 1 dated January 14, 2010); International requirements for the humane treatment of animals, following the rules of the "European convention for the protection of vertebrate animals used for experimental and other scientific purposes" (1984); methodical recommendations of the State Pharmacological Center MoH Ukraine on pre-clinical research of medicinal products [24]. Before modeling skin burns, all the animals shaved lateral surfaces of the body with a mechanical typewriter and a safe razor. The trauma was caused by applying to the lateral surfaces of the body of the animals four copper plates for 10 seconds (two plates on each side, the surface area of each plate was 13.86 cm2) which were pre-held for 6 minutes in water at a constant temperature of 100 ºC [9, 20]. To calculate the surface area of the skin of the rat, the formula M. O. Lee [16] was used. Accordingly to masses, the average area of the body surface of the rats was 240±26 cm2, and consequently, the burn from the exposure of the four heated plates with a total area (S = 55.44 cm2) corresponded to 21-23% of the body surface of the animal. The depth of burns was set according to the four-level classification adopted in Ukraine. According to it, 1% of 1-2 degree burns are taken for 1 unit of injury severity index; 1% burn of 3A degree - for 2 units of severity index damage; 1% burn 3B degree - for 3 units of severity index damage; 1% burns 4 degrees - for 4 units of severity index damage. Having

established the found value, determined the degree of severity of burn shock based on the depth of the damage. It should be noted that the value of the index of severity of damage in the range up to 30 units determined a burn shock of a mild degree; the value of the index of the severity of damage in the range from 31 to 60 units - a burn shock of moderate severity; the value of the index of the severity of damage in the range from 61 to 90 units - severe burn shock; with an index of severity of damage of more than 90 units - an extremely severe burn shock. In the studies conducted, the magnitude of the index of gravity of the damage ranged from 52 to 56 units, which corresponds to a burn injury of moderate severity.

An infusion of 0.9% solution of NaCl or HAES-LX-5% in a volume of 10 ml/kg body weight of the animal was carried out in the lower vena cava after its catheterization in aseptic conditions through the femoral vein. The catheter was applied under the skin, and its clearance throughout the length was filled with titrated heparin solution (0.1 ml of heparin per 10 ml of 0.9% NaCl solution) after each substance administration. Infusions were performed once a day during the first 7 days. Shaving of rats, burns, catheterization of major vessels and decapitation (after 1, 3, 7, 14, 21 and 30 days) were carried out under conditions of propofol anesthesia (60 mg/kg mass i/v). The content of DNA in the nuclei of adenohypophysis, adrenal glands and thymus cells of rats was determined by flow cytometry. In animals, after decapitation, glands were removed, deprived of the capsules (if necessary), and from all their contents, the nucleic suspensions for flow cytometry were prepared. Cell suspensions from these cell cultures were prepared using a CyStain DNA nuclear DNA sample from Partec, Germany, according to the manufacturer's protocol. This solution allows rapid extraction of nuclei and the labeling of nuclear DNA by diaminophenylindole (DAPI), which is part of its composition. CellTrics 50 μm disposable filters (Partec, Germany) were used in the production of nucleic suspensions. The flow analysis was performed on a multi-functional flow-through cytometer "Partec PAS" manufactured by Partec, Germany, at the Research Center of the VNMU named after. M. I. Pirogov. UV radiation was used to stimulate DAPI fluorescence. From each sample of the nucleic suspension of the analysis, 10 thousand events were subject to. The cell cycle analysis was performed by FloMax software (Partec, Germany) in full numeric matching according to the mathematical model, which determined: G0G1 - percentage ratio of cells of the G0G1 phase to all cells of the cell cycle (DNA content = 2 c); S phase - is the percentage of the phase of DNA synthesis to all cells of the cell cycle (DNA content > 2c and < 4c.). The determination of DNA fragmentation (apoptosis) was accomplished by isolating the SUB-G0G1 site on the RN1 DNA histograms before the peak G0G1, which points to nuclei of cells containing DNA < 2c.

The statistical processing of the obtained results was carried out in the license package "STATISTICA 6.1" with the use of nonparametric methods for evaluating the obtained results. Evaluated the correctness of the distribution of characteristics for each of the variation series received, the mean values of each studied feature and the standard quadratic deviation. The reliability of the difference between independent quantitative values was determined using the Mann-Whitney U Test.

Results and its discission. The results obtained by us (Table 1, 2) showed the existence of a complex DNA damage on the background of a burn skin injury with a predominant lesion in DNA synthesis and activation of apoptosis in endocrine glands in rats using 0.9% NaCl solution and HAES-LX- 5%. However, against the background of infusion of 0.9% NaCl solution in the cells of the investigated organs, more distinct negative changes are set.

Table 1

Dynamics of S-phase indices (%) of adenohypophysis, adrenal and thymus cells in rats on the background of skin burn injury and correction with 0.9% NaCl solution and HAES-LX-5%, (M±σ)

Day of research	Adenohypophysis		Adrenal		Thymus	
	0.9% solution NaCl + burn	HAES-LX-5%, + burn	0.9% solution NaCl + burn	HAES-LX-5%, + burn	0.9% solution NaCl + burn	HAES-LX-5%, + burn
1	0,110±0,016	0,312±0,030**	0,662±0,197	0,464±0,137	4,275±1,846	5,365±1,680
3	0,220±0,021	0,376±0,056	1,202±0,439	0,566±0,141**	12,54±3,48	8,987±3,171
7	0,374±0,030	0,472±0,110	0,658±0,162	0,358±0,034**	11,16±2,94	8,170±2,488
14	1,186±0,215	0,750±0,150	0,498±0,099	0,310±0,065	6,317±2,977	8,840±2,550
21	1,734±0,399	0,892±0,086	0,298±0,141	0,238±0,058	6,662±2,086	9,097±2,150
30	1,036±0,093	0,706±0,089	0,246±0,188	0,232±0,041	6,642±2,195	8,195±1,453

Notes: here and in the following table * - a significant (p <0,05) difference with the parameters of the group of 0.9% solution NaCl + burn; ** - a significant (p <0,01) difference with the parameters of the group of 0.9% NaCl solution + burn.

The S-phase and SUB-G0G interval data in adenohypophysis cells under the conditions of HAES-LX-5% solution after burn skin injury were similar to the group burn+0.9% NaCl solution dynamics. However, the amplitude of these changes throughout the experiment was significantly lower (Table 1, 2). The use of HAES-LX-5% infusion solution during thermal burning of the skin significantly

reduces the elevated levels of the sub-G0G1 and S-phase of the adrenal glands during the whole experiment (see Table 1, 2). It is important to note that starting from the 14th day, these data are not reliable, or trends differ from the burns groups+0.9% NaCl solution (Table 1, 2).

Table 2

Dynamics of sub-G0G1 interval (%) of adenohypophysis, adrenal and thymus cells in rats on the background of skin burn injury and correction with 0.9% NaCl solution and HAES-LX-5% solution, (M±σ)

Day of research	Adenohypophysis		Adrenal		Thymus	
	0.9% solution NaCl + burn	HAES-LX-5%, + burn	0.9% solution NaCl + burn	HAES-LX-5%, + burn	0.9% solution NaCl + burn	HAES-LX-5%, + burn
1	0,594±0,047	0,574±0,044	3,362±0,237	2,682±0,454*	11,90±4,46	7,588±1,156*
3	0,740±0,042	0,624±0,054	5,480±0,851	3,432±0,720**	12,03±3,20	6,110±1,565*
7	0,918±0,167	0,712±0,103	4,120±0,571	2,578±0,338**	5,515±0,780	4,378±0,434
14	1,114±0,199	0,768±0,152**	3,248±0,866	2,338±0,939	3,672±0,928	3,013±1,178
21	0,976±0,193	0,554±0,053	2,332±0,251	2,048±0,182	3,233±0,998	2,458±0,726
30	0,792±0,169	0,512±0,064	2,344±0,236	1,880±0,408	2,428±0,736	2,520±0,684

The application of the HAES-LX-5% product positively affects the broken cell cycle in the thymus 1 day after burn injury and prevents DNA fragmentation (see Table 1, 2). 3 days after burning the skin, HAES-LX-5% using was followed by a significant decrease in cells that were in the range of SUB-G0G1. Within 7 days of burning in the burn group+HAES-LX-5%, a slight decrease in the number of cells that were in the range of SUB-G0G1 is maintained. However, 14 days after burning the skin, differences in the burns of the group+0.9% NaCl solution with HAES-LX-5% were practically not found (Table 1, 2). 21 days after skin burns, the tendency to increase the number of cells in the S phase in the burn + HAES-LX-5% group, as compared to the burns + 0.9% NaCl solution (see Table 1, 2), is drawn attention. Thus, we have found that a thermal burn of the skin against the background of the application of 0.9% NaCl solution negatively affects the DNA of the cells of the endocrine glands. Attention is drawn to unidirectional changes in DNA content in the cells of the investigated organs, which indicate a significant increase in apoptosis in adenohypophysis, thymus and adrenal cells from day 1 of study and reduction of synthetic processes in the form of a significant decrease in the S-phase. The obtained data indicate a special role of the balance between apoptosis and DNA synthesis in endocrine glands, which may play a protective role from further damage. Recent studies [8, 19] confirm the dualistic mechanism of apoptosis in damaging cells of various genes, including those with burns. After all, the activation of apoptosis against the background of the influence of endotoxins is not only a result of the negative effects of pathology, but also an internal mechanism of protection and renewal of the cell population. The S-phase and the SUB-G0G1 interval data, in our opinion, may be markers of intracellular DNA damage on the background of thermal burns of the skin. A deep imbalance between the above-mentioned indicators, recorded by us with the use of 0.9% NaCl solution, indicates an insufficient protective effect of this preparation. The use of the HAES-LX-5% solution positively affects the S-phase and SUB-G0G1 interval in the adenohypophysis, adrenal glands and thymus, and has its own characteristics for each investigational organ. So in adenohypophysis cells the drug mitigates the negative effects of burn disease, mainly affecting synthetic processes, which is especially manifested in the delay in the development of burn disease. At the same time, but not so definitely, the fragmentation of DNA decreases. In our opinion, this is a particularly significant positive effect of the HAES-LX-5% solution, since it has been proven [10] that clinical manifestations of adenohypophysis damage in the context of a burn disease develop in the long-term of pathology. In adrenal cells this drug more clearly reduces the symptoms of apoptosis from day 7 of the experiment, rather than affecting synthetic processes. In our opinion, this is a sign of the projective effect of the study drug on this cell group, since it has been established [2] that the increased activity of apoptosis can lead to clinical manifestations of adrenal insufficiency. Also, indirectly, this is confirmed by the effectiveness of adrenal hormones in different periods of burn disease [18, 26]. Unlike the previous two groups of DNA cells, cells of the thymus against the background of skin burn and application of 0.9% NaCl solution are damaged early in the pathology and are restored very quickly. The influence of the HAES-LX-5% solution on the content of thymus cells DNA consists in reducing the parameters of the SUB-G0G1 interval practically in all terms of the experimental study with simultaneous insignificant increase of synthetic processes. In our opinion the findings reveal a predominantly anti-apoptotic effect of the drug on thymus cells on the background of thermal damage to the skin. The realization of this effect over a long period of development of burn disease potentially must reduce the clinical manifestations of damage to this organ, which were documented in numerical experimental studies [17, 22, 23] in the early and delayed periods of this pathology. The use of HAES-LX-5% produces a positive polyfactor effect on the DNA content in adenohypophysis,

thymus and adrenal cells. Its effect has specific manifestations in each of the cell groups and provides a balance recovery between the processes of DNA synthesis and apoptosis.

Conclusion

1. Obtained results at a burn disease on the background of the use of 0.9% NaCl solution indicate the existence of complex intracellular damage to the DNA of adenohypophysis, thymus and adrenal cells, indicating an imbalance between synthetic processes and apoptosis. For cells of each investigated organ, there are specific peculiarities of DNA damage.
2. The use of an infusion solution HAES-LX-5% polyfactorically reduces the negative effects of burn disease in cells of adenohypophysis, thymus and adrenal glands as a reduction in apoptosis and an increase in the synthesis of DNA. The effect of HAES-LX-5% has its peculiarities in each of the cell populations, indicating its complex protective properties.

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Реферати

ВПЛИВ ІНФУЗІЙНОГО РОЗЧИНУ HAES-LX-5% НА ВМІСТ ДНК КЛІТИН ЕНДОКРИННИХ ЗАЛОЗ НА ФОНІ ТЕРМІЧНОГО ОПІКУ ШКІРИ У ЩУРІВ

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В статті наведені результати експериментального дослідження змісту ДНК методом проточної ДНК-цитометрії в клітинах аденогіпофіза, тимуса і надниркових залоз на тлі термічного опіку шкіри і корекції інфузійним розчином HAES-LX-5% у порівнянні з аналогічним опіком на тлі застосування 0,9% розчину NaCl. Використання препарату HAES-LX-5% викликає позитивний поліфакторний ефект на вміст ДНК в клітинах аденогіпофіза, тимуса і надниркових залоз. Його ефект має специфічні прояви в кожній з клітинних груп і забезпечує відновлення балансу між процесами синтезу ДНК і апоптозом. Таким чином, використання цього інфузійного розчину пом'якшує негативний ефект несприятливого впливу опіку шкіри на клітини аденогіпофіза, в основному впливаючи на синтетичні процеси, що особливо проявляється в затримці розвитку опікової хвороби. У клітинах надниркових залоз розчин HAES-LX-5% більш виразно зменшує симптоми апоптозу з 7-го дня експерименту і не впливає на синтетичні процеси. Ефект цього розчину на вміст ДНК в клітинах тимуса полягає в зниженні параметрів інтервалу SUB-G0G1 практично на всіх термінах експериментального дослідження з одночасним незначним збільшенням синтетичних процесів.

Ключові слова: ДНК-цитометрия, термічне пошкодження шкіри, щури, розчин HAES-LX-5%, аденогипофиз, наднирники, тимус.

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ВЛИЯНИЕ ИНФУЗИОННОГО РАСТВОРА HAES-LX-5% НА СОДЕРЖАНИЕ ДНК КЛЕТОК ЭНДОКРИННЫХ ЖЕЛЕЗ НА ФОНЕ ТЕРМИЧЕСКОГО ОЖОГА КОЖИ У КРЫС

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В статье приведены результаты экспериментального исследования содержания ДНК методом проточной ДНК-цитометрии в клетках аденогипофиза, тимуса и надпочечников на фоне термического ожога кожи и коррекции инфузионным раствором HAES-LX-5% по сравнению с аналогичный ожогом на фоне применения 0,9% раствора NaCl. Использование препарата HAES-LX-5% вызывает положительный полифакторный эффект на содержание ДНК в клетках аденогипофиза, тимуса и надпочечников. Его эффект имеет специфические проявления в каждой из клеточных групп и обеспечивает восстановление баланса между процессами синтеза ДНК и апоптозом. Таким образом, использование этого инфузионного раствора смягчает негативный эффект неблагоприятного воздействия ожога кожи на клетки аденогипофиза, в основном влияя на синтетические процессы, что особенно проявляется в задержке развития ожоговой болезни. В клетках надпочечников раствор HAES-LX-5% более определенно уменьшает симптомы апоптоза с 7-го дня эксперимента и не влияет на синтетические процессы. Эффект этого раствора на содержание ДНК в клетках тимуса заключается в снижении параметров интервала SUB-G0G1 практически на всех сроках экспериментального исследования с одновременным незначительным увеличением синтетических процессов.

Ключевые слова: ДНК-цитометрия, термическое повреждение кожи, крысы, раствор HAES-LX-5%, аденогипофиз, надпочечники, тимус.

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ЕКСПРЕСІЯ В-ТУБУЛІНУ В СЕНСОМОТОРНІЙ КОРІ ВЕЛИКИХ ПІВКУЛЬ ПРИ МОДЕЛЮВАННІ ТРАНЗИТОРНОЇ ІШЕМІЇ НА ТЛІ ПОПЕРЕДНЬОЇ СЕНСИБІЛІЗАЦІЇ МОЗКОВИМ АНТИГЕНОМ ТА ІМУНОКОРЕКЦІЯ ВИНИКЛИХ ЗМІН

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З метою аналізу динаміки експресії β-тубуліну в сенсомоторній корі при моделюванні транзиторної ішемії на тлі попередньої сенсибілізації мозковим антигеном та імунокорекції їх наслідків був проведений експеримент на 185 білих статевозрілих щурах-самцях масою 260 – 290 г. Були застосовані гістологічні, імуногістохімічний, денсіометричний та статистичний методи дослідження. Встановлено, що сенсибілізація мозковим антигеном призводить до дифузних дегенеративних змін у корі головного мозку, які супроводжуються зниженням експресії β-тубуліну. Попередня сенсибілізація мозковим антигеном призводить до посилення виразності ураження мозку та зниження експресії β-тубуліну при гострому порушенні кровообігу. Застосування імунофану забезпечує зменшення змін експресії β-тубуліну в сенсомоторній корі, викликаних як сенсибілізацією мозковим антигеном, так і при її комбінації з транзиторним порушенням мозкового кровотоку.

Ключові слова: головний мозок, сенсибілізація мозковим антигеном, ішемія мозку, β-тубулін, імунофан.

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Мозковий інсульт є актуальною проблемо не тільки в Україні, а й в усьому світі. Це пов'язано з тим, що дане захворювання займає одне з перших місць в структурі захворюваності та