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CHRONIC SUBDURAL HEMATOMA: CURRENT STATE OF THE ISSUE (LITERATURE REVIEW)

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Abstract
The presented literature review provides current data on chronic subdural hematomas. The importance of discussing this pathology is due to its increasing frequency at the present stage, increasing incidence in older age groups due to demographic changes in society. Aspects of etiology, epidemiology, pathogenesis, classification, and patient management tactics are considered. The development of ideas about the pathogenesis of chronic subdural hematomas in the historical aspect and the most significant modern data are given. In the tactics of patient management, attention is focused on the most significant clinical symptoms, features of neuroimaging data, and alternatives for choosing treatment are considered. The features of various options for neurosurgical interventions, their possible complications are presented, and the prospects for conservative treatment are discussed taking into account modern data on the pathogenesis of the pathology in question.
Key words: traumatic brain injury, chronic subdural hematoma, diagnostics, treatment

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Аннотация
В представленном обзоре литературы приведены актуальные данные в отношении хронических субдуральных гематом. Значимость обсуждения данной патологии обусловлена возрастающей на современном этапе её частотой, нарастающей встречаемостью у лиц более старших возрастных групп в связи с демографическими изменениями в обществе. Рассмотрены аспекты этиологии, эпидемиологии, патогенеза, классификации, тактики ведения пациентов. Приведено развитие представлений о патогенезе хронических субдуральных гематом в историческом аспекте и наиболее значимые современные данные. В тактике ведения пациентов акцентировано внимание на наиболее значимых клинических симптомах, особенностях нейровизуализационных данных, рассмотрены альтернативы выбора лечения. Представлены особенности различных вариантов нейрохирургических вмешательств, их возможные осложнения, обсуждены с учётом современных данных о патогенезе рассматриваемой патологии перспективы консервативного лечения.
Ключевые слова: черепно-мозговая травма, хроническая субдуральная гематома, диагностика, лечение

Annotatsiya
Taqdim etilgan adabiyotlarni ko'rib chiqish surunkali subdural gematomalar bo'yicha joriy ma'lumotlarni taqdim etadi. Ushbu patologiyani muhokama qilishning ahamiyati hozirgi bosqichda tez-tez o'sib borishi, jamiyatdagi demografik o'zgarishlar tufayli keksa yoshdagi guruhlarning ko'payishi bilan bog'liq. Etiologiyasi, epidemiologiyasi, patogenezi, tasnifi va

bemorni boshqarish taktikasi aspektlari ko'rib chiqiladi. Tarixiy jihatdan surunkali subdural gematomalarning patogenezi haqidagi g'oyalarni ishlab chiqish va eng muhim zamonaviy ma'lumotlar keltirilgan. Bemorni boshqarish taktikasida e'tibor eng muhim klinik belgilarga qaratiladi, neyroimaging ma'lumotlarining xususiyatlari va davolashni tanlashning muqobil variantlari ko'rib chiqiladi. Neyroxirurgik aralashuvlarning turli xil variantlari xususiyatlari, ularning yuzaga kelishi mumkin bo'lgan asoratlari va konservativ davolash istiqbollari ko'rib chiqilayotgan patologiyaning patogenezi bo'yicha zamonaviy ma'lumotlarni hisobga olgan holda muhokama qilinadi.
Kalit so'zlar: travmatik miya shikastlanishi, surunkali subdural gematoma, diagnostika, davolash

Introduction. Chronic subdural hematoma (CSH) is a polyetiological voluminous intracranial hemorrhage located under the dura mater, causing local and/or general compression of the brain and having (unlike acute and subacute subdural hematomas) a delimited capsule that determines all the features of cerebral pathophysiological reactions, clinical course and treatment tactics. Chronic subdural hematoma is one of the common neurosurgical pathologies [1, 2]. The study of chronic subdural hematomas dates back to 1656, when J.J. Wepfer gave their first description. Three centuries later, questions about the pathogenesis and treatment of this disease do not become fewer. This problem continues to be debatable in many of its aspects. It is worth noting that chronic subdural hematomas should be distinguished and differentiated from the terms "hygroma" or "hydroma" - these are formations that arise due to a violation of the circulation of cerebrospinal fluid of various origins. In computed tomography, the density of the hygroma never exceeds the density of the cerebrospinal fluid, which cannot be said about a chronic subdural hematoma. The density of the contents of a chronic subdural hematoma varies depending on the evolution of hemoglobin in it [3].

Epidemiology.

The prevalence of CSH in the general population is 1-5 per 100,000 per year, but the frequency increases significantly in older age groups. Thus, by the age of 65, the incidence rate increases to 7-13 per 100,000 per year, and in the age group over 70 years - to 17-58 cases per 100,000 per year [4]. In the gender aspect, men suffer more, the male/female ratio varies from 1.7 to 4.2:1 according to different sources, without significant differences in the gender coefficient in different age groups [5]. Given the demographic trends in the world and in the Russian Federation towards an increase in average life expectancy, which causes an increase in the proportion of the population in older age groups, an increase in the number of patients with the pathology in question is inevitable. According to some authors, the number of such patients may increase threefold by the 2030s, which defines the problem of chronic subdural hematomas as an important issue for the global medical community [6]. Mortality among patients with chronic subdural hematoma ranges from 1.5 to 25% [7]. Pathogenesis of chronic subdural hematomas. The initial source of bleeding, spontaneously or as a result of injury, are the intracranial vessels of the subdural space. However, for certain reasons, hematoma lysis does not occur, a capsule is formed. This fundamentally distinguishes CSDH from acute and subacute subdural hematomas. Understanding the mechanisms involved in the formation of CSDH developed from the concept of a hyperosmotic gradient, originally proposed by W.J. Gardner and later supported and developed by J. Suzuki et al. [8, 9]. This theory was opposed at the time by the studies of Weir et al. [10]. He continued the idea of the above-described authors: a decrease in pressure inside the hematoma (by evacuating the hematoma and draining the subdural space) should break the vicious circle and favor membrane fibrosis and fluid absorption. However, the percentage of relapses remained quite

high, which led to the idea of other mechanisms at work in the pathogenesis of CSDH. In parallel, studies were presented on the effect of erythrocyte lysis products inside the subdural space (as a consequence of rupture of some cortical bridging veins). Degradation products, according to them, induce a local inflammatory response and a bleeding-fibrinolysis cycle, where neoenzymes and neocapillaries are involved. The balance between repeated bleeding and the absorption process determines the volume of the hematoma and the tendency to increase or disappear [11, 12]. It was also found that the outer membrane of the hematoma contains plasma cells and macrophages, which lead to high concentrations of vascular endothelial growth factor and fibroblast growth factor, both of which are recognized as angiogenic factors, in the hematoma fluid [13, 14]. Thus, at present, CHS is considered an angiogenic disease in which fibrinolysis and inflammation processes play a predominant role. Neoangiogenesis is triggered by vascular endothelial growth factor and endothelial progenitor cells. Vascular endothelial growth factors/vascular endothelial growth factor (VEGF/VEGF) and its receptors play an important role in vasculogenesis and affect vascular permeability [15, 16]. According to studies, the level of VEGF is significantly increased in hematoma fluid, dura mater and in hematoma membranes [17, 18]. This high concentration of VEGF in hematoma fluid may have an important pathophysiological significance in the genesis and maintenance of hematoma volume [19]. Excessive concentration of VEGF promotes an increase in the number of blood vessels with high permeability of the vascular wall [20], as well as a qualitative change - immaturity and instability of vessels [21]. Bleeding from an immature vascular wall is complicated by the inflammation occurring in this area [22-24]. The imbalance between anti- and pro-inflammatory factors was confirmed by the study of the contents evacuated from the CSH, and this imbalance can affect the vascular permeability of the neomembrane and angiogenesis [23-25]. Features of the clinical picture of chronic subdural hematomas. The main criterion for the diagnosis of chronic subdural hematomas is the assessment of complaints, anamnesis, objective and neurological status, followed by verification of the diagnostic hypothesis using neuroimaging. Patients with a presumptive diagnosis of chronic subdural hematoma most often seek specialist consultation with complaints of headache, nausea, vomiting, changes in consciousness, and weakness of the limbs. During a neurological examination, changes in the level of consciousness, disorientation, speech and cognitive impairment, and hemiparesis are usually revealed. In a study by M. Gelabert-Gonzalez et al. in 2005 (Spain, 1000 patients), data are provided that in the group under 70 years of age, the most common symptom (131 cases – 13.1%) was headache, in the group over 70 years of age – behavioral/cognitive impairment (189 cases – 18.9%) [26].

According to the study by T. Santarius et al. [27], conducted on a group of 205 patients, the following symptoms were observed upon presentation:

1. gait disturbances – 116 (55.5%),
2. mental status changes – 71 (34.0%),
3. limb weakness – 71 (34.0%),
4. confusion – 67 (32.1%),
5. headache – 36 (17.2%),
6. drowsiness or coma – 20 (9.6%),
7. speech impairment – 12 (5.7%),
8. urinary incontinence – 1 (0.5%),
9. visual impairment – 1 (0.5%),
10. vomiting – 1 (0.5%). Assessment according to the Glasgow Coma Scale (hereinafter referred to as GCS; assessed in 202 patients in this study):

1. 13–15 – 163 (80.7%),
2. 9–12 – 25 (12.4%),
3. 3–8 – 14 (6.9%).

The McWald scale, first published in 1981 [28], is widely used to assess the severity of chronic subdural hematomas:

0 – asymptomatic, without neurological deficit; 1 – fully oriented, moderate headaches, mild neurological deficit (asymmetry of reflexes); 2 – disoriented, stupefied, neurological deficit (hemiparesis); 3 – coma, no response to external stimuli, decerebration/decortication. A clear correlation between the indicators of the above scales and the risks of death, the frequency of relapse in survivors has been repeatedly confirmed.

The method of choice in instrumental diagnostics is, of course, computed tomography of the brain. Usually, a chronic subdural hematoma is visualized as a hypodense zone (<30 Hounsfield units), but can have isodense density (30-60 Hounsfield units) and rarely be hyperdense (>60 Hounsfield units). Difficulties may arise in the diagnosis of isodense chronic subdural hematoma, especially if it is bilateral or does not cause displacement of midline structures [29]. Magnetic resonance imaging may also be necessary, especially in the case of an isodense hematoma structure [30].

Treatment of chronic subdural hematomas. According to the clinical guidelines of the Russian Association of Neurosurgeons for chronic subdural hematomas in 2015, all patients diagnosed with chronic subdural hematoma are subject to hospitalization in a neurosurgical hospital for observation, additional examination, and determination of treatment tactics. Surgical evacuation of chronic subdural hematoma to reduce brain compression is currently the gold standard of treatment [31], although the type of surgical intervention may vary. Over time, the treatment strategy has changed. In the era before computed tomography, craniotomy, despite its high surgical mortality, was the method of choice. This technique provided maximum visual control and the ability to excise the hematoma capsule, which were considered crucial for the success of surgical treatment until the 1970s. Craniotomy involves rotation of a larger (>30 mm) free bone flap, irrigation and evacuation of the CSH, and subsequent replacement of the flap. The accumulation of clinical experience, research materials, the introduction of neuroimaging, and the development of surgical techniques and instruments have led to a revision of previously relevant standards. Today, burr-hole and twist-drill craniostomy are used everywhere in clinics around the world, with clinics more often adhering to burr-hole craniostomy. The essence of burr-hole craniostomy is the imposition of burr holes (one or two) on the side of the hematoma, at points of maximum thickness. In the latter case, they are applied at a distance of about 5-8 cm from each other. A durotomy is performed, the hematoma is evacuated, and the cavity is irrigated with warm saline until the rinsing water is clear. Finally, a soft silicone catheter is inserted and connected to a closed external drainage system. The duration of drainage is about 48-72 hours [27, 29]. Twist-drill craniostomy involves creating a small craniostomy using a hand drill and drainage with a closed system as in burr-hole craniostomy. The advantage of the presented techniques is not only their low invasiveness. A milder anesthetic aid when using them (local anesthesia + intravenous sedation) is an important advantage, since, as already noted, CSH is a disease predominantly of older patients, often burdened with somatic pathology [32, 33]. Postoperative complications. Despite the simplicity of the interventions used, surgical treatment is associated with the risk of deterioration and death, especially in elderly patients with concomitant somatic pathology. The most common complication is recurrence of subdural hematoma. The recurrence rate of CSH ranges from 0 to 31.6% [26]. Other complications described include intraoperative penetration of the brain substance, pneumocephalus, and intracranial hemorrhage. It is also worth mentioning

purulent-septic complications, represented by subdural empyema and wound infection. Special attention is paid to extracranial complications. They are directly related to age and premorbid background. The most common, according to M. Gelabert-Gonzalez et al., was pneumonia. It occurred in 2.2% of those treated. Cardiovascular problems were observed in 1.1% of patients [26].

Conservative treatment. As mentioned above, surgical treatment of CSH is generally accepted. However, cases of spontaneous resolution have prompted the study of their conservative management. The development of conservative treatment is hampered by the lack of a rich statistical evidence base [34].

According to Delgado-López [14], drug therapy can be discussed as "reserve therapy" in the following cases:

1. asymptomatic course (0 according to McWalder),
2. low-symptom course (1–2 according to McWalder),
3. patients for whom surgical treatment is contraindicated.

As described above, the history of studying the pathogenesis of CSH began with the osmotic theory. In this regard, the first drugs described were hyperosmolar solutions, including mannitol. Currently, the greatest attention is paid to corticosteroids [14, 35] and statins [36, 37], and the literature also describes the use of angiotensin-converting enzyme inhibitors [38] and tranexamic acid [39]. The effect of corticosteroids is justified by inhibitory effects on vascular endothelial growth factor, tissue plasminogen activator, interleukin-6, interleukin-8 and platelet factor [40]. However, the scientific literature on this issue is still very limited [41]. With regard to statins, and atorvastatin in particular, the rationale for their use is based on a number of experimental studies describing the effect of these drugs on the pathogenetic links of CHS. Atorvastatin has been shown to improve angiogenesis and increase the level of circulating endothelial progenitor cells required for the formation of new blood vessels by activating endothelial nitric oxide synthase and endothelial protein kinase [36, 42, 43]. In addition, these drugs inhibit inflammatory processes [44, 45].

Every specialist may encounter a chronic subdural hematoma in their practice. Understanding the basic neurological symptoms in assessing the status, vigilance when collecting a traumatic and drug history; reasonable consultations with a neurologist and neurosurgeon, performing neuroimaging make it possible to timely verify the diagnosis and choose the optimal treatment tactics for the patient.

References:

1. Markwalder T.M. Chronic subdural hematomas: a review. J Neurosurg. 1981. № 54. P. 637-45.
2. Santarius T., Kirkpatrick P.J., Kolias A.G., Hutchinson P.J. Working toward rational and evidence-based treatment of chronic subdural hematoma. Clin Neurosurg. 2010. № 57. P. 112-22.
3. Лебедев В.В., Талыпов А.Э., Ховрин Д.В. Хронические посттравматические гематомы. Нейрохирургия. 2008. № 4. С. 13-20. Lebedev V.V., Talypov A.E., Xovrin D.V. Xronicheskie posttravmaticheskie gematomy. Nejroxirurgiya. 2008. № 4. S. 13-20.
4. Sambasivan M.: An overview of chronic subdural hematoma: experience with 2300 cases. Surg Neurol. 1997. № 47. P. 418-422.
5. Ohba S., Kinoshita Y., Nakagawa T., Murakami H. The risk factors for recurrence of chronic subdural hematoma. Neurosurg. Rev. 2013. № 36 (145-9). P. 149-50.
6. Kinsella K., Velkoff V.A.: US Census Bureau Series P95/01-1, 9. 2001. An aging world: 2001. 2001, Washington, DC: US Government Printing Office

7. Ueno K., Murata J., Sakuma S., Takano K., Lizuka T. Intraoperative lumbar injection of Ringer‘s solution for surgical treatment of chronic subdural haematomas. Neurol Surg. 1991. № 19. P. 511-6.
8. Gardner W.J.: Traumatic subdural hematoma with particular reference to the latent interval. Arch Neurol Psychiat. 1932. № 27. P. 847-858.
9. Suzuki J., Takaku A.: Nonsurgical treatment of chronic subdural hematoma. J Neurosurg. 1970. № 33. P. 548-553.
10. Weir B.: Oncotic pressure of subdural fluids. J Neurosurg. 1980. № 53. P. 512-515.
11. Ito H., Komai T., Yamamoto S.: Fibrinolytic enzyme in the lining walls of chronic subdural hematoma. J Neurosurg. 1978. № 48. P. 197-200.
12. Labadie E.L., Glover D.: Local alterations of hemostatic-fibrinolytic mechanisms in reforming subdural hematomas. Neurology. 1975. № 25. P. 669-675.
13. Santarius T., Hutchinson P.J.: Chronic subdural haematoma: time to rationalize treatment? Br J Neurosurg. 2004. № 18. P. 328-332.
14. Delgado-López P.D.; Martín-Velasco V.; Castilla-Díez J.M.; RodríguezSalazar A.; Galacho-Harriero A.M.; Fernández-Arconada O.: Dexamethasone treatment in chronic subdural haematoma. Neurocirugía. 2009. № 20. P. 346-359.
15. Ferrara N., Gerber H.P., Le Couter J. The biology of VEGF and its receptors. Nat Med. 2003. № 9. P. 669-76.
16. Takahashi H., Shibuya M. The vascular endothelial growth factor (VEGF)/ VEGF receptor system and its role under physiological and pathological conditions. Clin Sci (Lond). 2005. № 109. P. 227-41.
17. Hohenstein A., Erber R., Schilling L., Weigel R. Increased mRNA expression of VEGF within the hematoma and imbalance of angiopoietin-1 and -2 mRNA within the neomembranes of chronic subdural hematoma. J Neurotrauma. 2005. № 22. P. 518-28.
18. Saito A., Narisawa A., Takasawa H., Morita T., Sannohe S., Sasaki T., Kurotaki H., Nishijima M. Expression of the TGF-β-ALK-1 pathway in dura and the outer membrane of chronic subdural hematomas. Neurol Med Chir (Tokyo). 2014. № 54 P. 357-62.
19. Hua C., Zhao G., Feng Y., Yuan H., Song H., Bie L. Role of Matrix Metalloproteinase-2, Matrix Metalloproteinase-9, and Vascular Endothelial Growth Factor in the Development of Chronic Subdural Hematoma. J Neurotrauma. 2016. № 33. P. 65-70.
20. Tsigkos S., Koutsilieris M., Papapetropoulos A. Angiopoietins in angiogenesis and beyond. Expert Opin Investig Drugs. 2003. № 12. P. 933-41.
21. Yancopoulos G.D., Davis S., Gale N.W., Rudge J.S., Wiegand S.J., Holash J. Vascular-specific growth factors and blood vessel formation. Nature. 2000. № 407. P. 242-48.
22. Javadi A., Amirjamshidi A., Aran S., Hosseini S.H. A randomized controlled trial comparing the outcome of burr-hole irrigation with and without drainage in the treatment of chronic subdural hematoma: a preliminary report. World Neurosurg. 2011. № 75. P. 731-36.
23. Stanisic M., Lyngstadaas S.P., Pripp A.H., Aasen A.O., Lindegaard K.F. et al. Chemokines as markers of local inflammation and angiogenesis in patients with chronic subdural hematoma: a prospective study. Acta Neurochir (Wien). 2012. № 154. P. 113-20.
24. Stanisic M., Aasen A.O., Pripp A.H., Lindegaard K.F., Ramm-Pettersen J. et al. Local and systemic pro-inflammatory and anti-inflammatory cytokine patterns in patients with chronic subdural hematoma: a prospective study. Inflamm Res. 2012. № 61. P. 845-52.

25. Wang D., Li T., Wei H., Wang Y., Yang G., Tian Y., Zhao Z., Wang L., Yu S., Zhang Y., Chen J., Jiang R., Zhang J.N. Atorvastatin enhances angiogenesis to reduce subdural hematoma in a rat model. J Neurol Sci. 2016. № 362. P. 91-99.
26. Gelabert-Gonzalez M., Iglesias-Pais M., Garcia-Allut A., Martinez-Rumbo R.: Chronic subdural haematoma: surgical treatment and outcome in 1000 cases. Clin. Neurol.Neurosurg. 2005. vol. 107. P. 223-229.
27. Santarius T., Kirkpatrick P.J., Ganesan D. et al. Use of drains versus no drains after burr-hole evacuation of chronic subdural haematoma: a randomised controlled trial. Lancet. 2009. № 374. P. 1067-1073.
28. Markwalder T.M., Steinsiepe K.F., Rohner M., Reichenbach W., Markwalder H. The course of chronic subdural hematomas after burr-hole craniostomy and closedsystem drainage. J. Neurosurg. 1981. № 55. P. 390-396
29. Santarius, T., Kolias, A. G. & Hutchinson, P. J. in Schmidek and Sweet: Operative Neurosurgical Techniques: Indications, Methods and Results / ed. A. Quinones-Hinojosa. 2012. P. 1573–1578.
30. Hosoda K., Tamaki N., Masumura M., Matsumoto S., Maeda F., Magnetic resonance images of chronic subdural hematomas, J. Neurosurg. 1987. № 67 (5). P. 677-683.
31. Almenawer S.A., Farrokhyar F., Hong C., Alhazzani W., Manoranjan B., Yarascavitch B., Arjmand P., Baronia B., Reddy K., Murty N., Singh S.. Chronic subdural hematoma management: a systematic review and meta-analysis of 34,829 patients. Ann Surg. 2014. № 259. P. 449-57.
32. Lee J. Y. et al. Indications and surgical results of twist-drill craniostomy at the pre-coronal point for symptomatic chronic subdural hematoma patients. J. Korean Neurosurg. Soc. 2012. № 52. P. 133-137.
33. Gokmen M., Sucu H. K., Ergin A., Gokmen A., Bezircio Lu H. Randomized comparative study of burr-hole craniostomy versus twist drill craniostomy; surgical management of unilateral hemispheric chronic subdural hematomas. Zentralbl. Neurochir. 2008. № 69. P. 129-133.
34. Thotakura A.K., Marabathina N.R. Nonsurgical treatment of chronic subdural hematoma with steroids. World Neurosurg. 2015. № 84. P. 1968-72.
35. Berghauser Pont L.M., Dirven C.M., Dippel D.W., Verweij B.H., Dammers R. The role of corticosteroids in the management of chronic subdural hematoma: a systematic review. Eur. J. Neurol. 2012. № 19. P. 1397-1403.
36. Wang B., Sun L., Tian Y., Li Z., Wei H., Wang D. et al. Effects of atorvastatin in the regulation of circulating EPCs and angiogenesis in traumatic brain injury in rats. J Neurol Sci. 2012. № 319. P. 117-23.
37. Min X., Pin C., Xun Z., Cun-zu W., Xue-qiang S., Bo Y., Effects of atorvastatin on conservative and surgical treatments of chronic subdural hematoma in patients, World Neurosurgery 2016, doi:10.1016/j.wneu.2016.03.067.
38. Weigel R. et al. Angiotensin converting enzyme inhibition for arterial hypertension reduces the risk of recurrence in patients with chronic subdural hematoma possibly by an antiangiogenic mechanism. Neurosurgery. 2007. № 61 (4). P. 788-92. discussion 792–3.
39. Kageyama H., Toyooka T., Tsuzuki N., Oka K. Nonsurgical treatment of chronic subdural hematoma with tranexamic acid. J Neurosurg. 2013. № 119. P. 332-7.
40. Zarkou S., Aguilar M.I., Patel N.P., Wellik K.E., Wingerchuk D.M., Demaerschalk B.M.. The role of corticosteroids in the management of chronic subdural hematomas: a critically appraised topic. Neurologist. 2009. № 15. P. 299-302.

41. Berghauser Pont L.M.E., Dammers R., Schouten J.W., Lingsma H.F., Dirven C.M.F. Clinical factors associated with outcome in chronic subdural hematoma: a retrospective cohort study of patients on preoperative corticosteroid therapy. Neurosurgery. 2012. № 70. P. 873-80. discussion 880.
42. Kikuchi R., Takeshita K., Uchida Y., Kondo M., Cheng X.W. et al. Pitavastatininduced angiogenesis and arteriogenesis is mediated by Notch1 in a murine hindlimb ischemia model without induction of VEGF. Lab Invest. 2011. № 91. P. 691-703.
43. Matsumura M., Fukuda N., Kobayashi N., Umezawa H., Takasaka A. et al. Effects of atorvastatin on angiogenesis in hindlimb ischemia and endothelial progenitor cell formation in rats. J Atheroscler Thromb. 2009. № 16. P. 319-26.
44. Buttmann M., Lorenz A., Weishaupt A., Rieckmann P. Atorvastatin partially prevents an inflammatory barrier breakdown of cultured human brain endothelial cells at a pharmacologically relevant concentration. J Neurochem. 2007. № 102. P. 1001-8.
45. Jaiswal S.R., Sontakke S.D. Experimental evaluation of analgesic and antiinflammatory activity of simvastatin and atorvastatin. Indian J Pharmacol. 2012. № 44. P. 475-79.