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Review article

Potential role of statins in the intracerebral hemorrhage and subarachnoid hemorrhage

Dariusz Kotlęga [a,*], *Monika Gołąb-Janowska* [a], *Marta Masztalewicz* [a], *Sylwester Ciećwież* [b], *Przemysław Nowacki* [a]

[a] *Department of Neurology, Pomeranian Medical University, Szczecin, Poland*
[b] *Department of Gynaecology and Urogynaecology, Pomeranian Medical University, Police, Poland*

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ABSTRACT

Statins are used in primary and secondary prevention of cardiovascular episodes. Most of recent studies regard ischemic stroke. There are more emerging results of studies suggesting usefulness of these drugs in the other types of stroke e.g. intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Searching for new methods of treatment is important, because both ICH and SAH lead to poor prognosis and severe psychomotor disability.

The unquestionable role of inflammatory factors in the pathogenesis of these disorders justifies considering statin treatment. Previous results are contradictory, thus in present study we review results of studies and try to explain the potential pathomechanism of statin use in hemorrhagic strokes.

1. Introduction

Statins are used in primary and secondary prevention of cardiovascular episodes. Among neurological disorders they play a key role in ischemic stroke, but there are reports of possible beneficial effect of statins in dementia and multiple sclerosis [1–3].

Most of recent studies regard ischemic stroke. There are more emerging results of studies suggesting usefulness of this drugs in other types of stroke e.g. intracerebral hemorrhage (ICH) and subarachnoid hemorrhage (SAH). Searching for new methods of treatment is important, because both ICH and SAH lead to poor prognosis and severe psychomotor disability.

In a present study we review results of studies and try to explain the potential pathomechanism of statin use in hemorrhagic strokes.

2. Intracerebral hemorrhage

Intracerebral hemorrhage constitutes about 10% of strokes, leads to severe neurological deficit and mortality remains as high as 30–50% [4]. In everyday practice there is such a common notion that statins increase the ICH risk, which was justified by the results of some studies [5,6]. It is likely that such an opinion was unearthed by the results that showed connection between higher risk of ICH and low cholesterol level, but not between statins. These results were included in

* *Corresponding author at*: Department of Neurology, Pomeranian Medical University, Szczecin, ul. Unii Lubelskiej 1, 71-252 Szczecin, Poland. Tel.: +48 914253251; fax: +48 914253260.
E-mail address: dkotlega@poczta.onet.pl (D. Kotlęga).
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the stroke treatment guidelines in the year 2011 [7]. In the meta-analysis published in 2011 it was unequivocally presented that statins do not increase the ICH risk [8]. Similar conclusions were enclosed in the later meta-analysis in 2012 [9]. Moreover, post-ICH statin use is not associated with an increased risk of ICH recurrence [10].

Unfavorable effects of ICH are connected with initial mechanical injury produced by the hematoma and further damage that is believed to occur after the bleeding stops and called as the perihematomal edema (PE). Hematoma enlargement was seen for up to 2 days and almost always occurs within the first few hours. Clinical deterioration in subacute period is provoked by the progression of PE, increase of intracranial pressure and the risk of herniation. The late edema progression occurs in the second and third week after ICH. PE is responsible for about 75% of mass effect [11]. Significant midline shift (>3 mm) was reported in 62% of patients [12].

The formation of edema after ICH follows three distinct temporal phases: in the first hours after ICH, retraction of the clot begins. As the coagulation cascade becomes activated over the following 24–48 h, thrombin becomes activated and promotes edema formation and further disruption of the integrity of the blood–brain barrier (BBB). The third phase of edema formation starts when red blood cells in the hematoma begin to lyse, and hemoglobin with its degradation products are deposited into the brain parenchyma, thus initiating a potent inflammatory reaction. One presumed function of hemoglobin degradation products is the generation of reactive oxygen (ROS) and nitrogen species that would lead to lipid peroxidation, carboxylation, and tyrosine nitrosylation of proteins as well as eventual uncoupling of mitochondria.

An additional contributor to neuronal death is the increased presence of cytokines. Elevated levels of interleukin-6 (Il-6) and Il-10 have been associated with ICH and edema formation. Components of the complement (C) system have also been found in the perihematomal area. The presence of C3d and C9 have been documented in the parenchyma [12].

Mechanisms that trigger pathophysiological changes in and around the hematoma are linked to the role of thrombin and iron, released upon red blood cell (RBC) lysis, as 2 major factors causing brain injury after ICH. Thrombin causes brain damage at high concentrations and induces neuroprotection at low concentrations. Thrombin-induced brain injury may be mediated by the complement cascade. Thrombin activates matrix metalloproteinase-2 (MMP-2) in endothelial cells and tumor necrosis factor-α (TNF-α), which is one of the major proinflammatory cytokines. Matrix metalloproteinases are members of a family of zinc-dependent proteases that can degrade extracellular matrix and cause blood–brain barrier disruption [13]. Among 23 types of MMP's several of them were proved to play a role in the pathogenesis of ICH (MMP-2, 3, 9, 12). Increased level of MMP-3 is associated with mortality, both MMP-9 and 3 are related to residual cavity volume [14]. Increased level of TNF-α, Il-6 and MMP-9 in the first day after ICH is associated with the size of PE and subsequent enlargement of the hematoma [15].

Development of inflammatory process is connected with microglia activation and presence of leukocytes and macrophages. Neutrophils infiltration in and around hematoma takes place after 4 h, with the peak at day 2–3, remitting within 7 days after ICH. Neutrophils may disrupt neurons directly by the ROS or indirectly, by proinflammatory proteases activation. Microglial cells monitor the well-being of their environment, being able to respond to signs of homeostatic disturbance with a program of supportive and protective activities, to safeguard innate defense mechanisms, or to assist in specific immune reactions. There are many molecules involved in the inflammatory reactions in the central nervous system: TNF-α, the interferons (IFN), Il-1, -2, -3, -4, -6, -10, -12, -15, -18, transforming growth factor β (TGF-β), colony-stimulating factors (CSF), platelet-derived growth factor (PDGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), insulin-like growth factors (IGF), and neurotrophic factors such as nerve growth factor (NGF), neurotrophins (NT-3 and -4), or brain-derived neurotrophic factor (BDNF). The principal sources of cytokines in the brain are activated microglia/macrophages. Cytokines can be also released by many cell types, including microglia, astrocytes, neurons and endothelial cells. Nevertheless, evidence also supports the involvement of peripherally derived cytokines in brain inflammation. After ICH in humans, the blood–brain barrier permeability increases. Therefore, peripherally derived mononuclear phagocytes, T-lymphocytes, natural killer cells, and polymorphonuclear neutrophilic leukocytes, which produce and secrete cytokines, can all cross the BBB and contribute to brain inflammation [16,17].

In ICH and ischemic stroke patients levels of inflammatory cytokines change in the course of the disease. The serum level of Il-6 was most markedly elevated in the patients with acute stroke and tended to decrease thereafter. However, its level remained significantly elevated even at day 7. The level of TGF-β was significantly decreased at day 1 and day 3 and tended to return toward the control value thereafter. Il-6 has both proinflammatory and immunomodulatory actions. TGF-β plays mainly an immunomodulatory role in pathological conditions with a significant antagonistic effect against proinflammatory cytokine TNF-α [18]. Increased levels of Il-6 and Il-10 on the second day after ICH are associated with consciousness disturbances severity [19].

ROS are generated as by-products of cellular metabolism primarily in mitochondria, by neutrophils, endothelium and activated microglia. They are produced while electrons are leaking the respiratory chain and thus the amount of ROS formed, has been reported to be proportional to partial pressure of oxygen in the tissue. In addition to the mitochondrial electron transport chain, there are other ROS producing mechanisms, e.g. system of cytochrome P-450, oxidative enzymes, such as endothelial xanthine oxidase, nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, myeloperoxidases (MPO) of phagocytic cells, and arachidonate oxygenases. ROS have cytotoxic effects leading to cell destruction and degradation. They act both in ischemic and hemorrhagic damage to the brain [20].

The aim of ICH treatment should be the decrease in secondary ischemia, edema and intracranial pressure, as well as providing oxygen supply and optimizing cerebral metabolism. The treatment of ICH is still unsatisfactory, beside many conducted trials. Thus, new mechanisms of existing drugs should be considered and the use of new drugs should be tested.