EXPERIMENTAL STUDY

Ameliorating the effects of Adalimumab on rabbits with experimental cerebral vasospasm after subarachnoid hemorrhage

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ABSTRACT

BACKGROUND: Adalimumab (ADA), which is a new-generation recombinant human monoclonal antibody for tumor necrosis factor α (TNFα), has strong anti-inflammatory effects. The role of enhanced inflammation is well established for the development and progression of cerebral vasospasm. Investigated in the present study is the probable ameliorating and neuroprotective effects of ADA in rabbits using a cerebral vasospasm model with biochemical and histopathological methods.

METHODS: Thirty male New-Zealand white rabbits were randomly divided into control, subarachnoid hemorrhage (SAH) only and SAH plus ADA treatment groups. SAH was established as a single cisterna magna autologous arterial blood injection. ADA treatment was started just after intracisternal blood injection and continued for 72 hours once a day. The animals were sacrificed 72 hours after the induction of SAH, serum and brainstem tissue obtained for investigations.

RESULTS: Brainstem tissue and plasma levels of tumor necrosis factor-alpha and Interleukin-1β, brainstem tissue Matrix metalloproteinase-9 levels increased after SAH and partly decreased after treatment. Plasma levels of brain-derived neurotrophic factor decreased after SAH and partly restored after treatment. ADA treatment significantly increased the mean cross-sectional area of the vasospastic basilar arteries, reduced the basilar artery wall thickness and also ameliorates enhanced endothelial apoptosis.

CONCLUSION: Findings obtained in this study suggest that ADA is an effective neuroprotective agent for ameliorating cerebral vasospasm in experimental rabbit vasospasm.

Keywords: Adalimumab; cerebral vasospasm; cytokine; inflammation; neuroprotection; rabbit; subarachnoid hemorrhage.

INTRODUCTION

Cerebral vasospasm is an important complication of subarachnoid hemorhage (SAH), which leads to enhanced mortality and morbidity. Despite intensive studies, its multifactorial pathogenesis is not elucidated yet.[1] Enhanced inflammation has been postulated as an important cause of vasospasm in both experimental[2] and clinical[3] studies. Increased levels of adhesion molecules have been found in both cerebrospinal fluid (CSF) and serum of SAH patients, which may lead to the accumulation of leukocytes in inflamed tissue.[4] Enhanced cytokines[3] and activated complement system play important roles in[4] initiation of the multifaceted cascade of vasospasm after SAH. Tumor necrosis factor-alpha (TNFα) is an important proinflammatory cytokine that regulates systemic inflammation. Adalimumab (ADA) is a recombinant human IgG1 monoclonal antibody for TNFα, which binds TNFα by antigen-antibody interaction and inhibits its binding to its re-

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ceptor.[5] In this study, we aimed to investigate the effects of ADA on experimentally induced cerebral vasospasm by its strong anti-inflammatory properties.

MATERIALS AND METHODS

The experimental protocol was approved by the local Animal Ethics Committee (2016-042). All animals breathed spontaneously throughout the procedures. Arterial blood samples were taken from each animal from the catheterized ear arteries for blood gas analysis during the procedures. Heart rate and systemic blood pressure were measured with the use of an ear artery catheter. Core body temperature was monitored rectally and maintained at 37°±0.5°C with a heater. Mean physiological parameter values were not statistically significant between the groups ($p>0.05$).

Cerebral vasospasm was obtained by a single fresh nonheparininized autologous arterial blood injection to the cisterna magna of the rabbit.[1] Briefly, the head of the rabbit was extended in the prone position. With the use of aseptic techniques, a midline nuchal incision was made, the atlanto-occipital membrane was exposed and cisterna magna was punctured by a 25 gauge needle. 1.0 mL/kg of cerebrospinal fluid was withdrawn and an equal volume of blood injected into the cisterna magna within two minutes. Layers closed in anatomical planes after the needle were withdrawn. The animals were then placed in a head-down position for 15 minutes to facilitate blood settling around the basilar artery. After the recovery from anesthesia, and confirmation of vital signs, rabbits were left to their cages.

Groups

Thirty male New-Zealand white rabbits weighing 2000–3000 g were assigned randomly into three groups as follows: group 1: control group (n=10), group 2: SAH alone group (n=10), group 3: SAH + ADA treatment group.

Group I (control group, n=10) was a sham surgery group in which SAH was not induced. In this group, after induction of anesthesia, the atlanto-occipital membrane was exposed as described above and the cisterna magna was aseptically punctured by a 25-gauge needle, and 1 mL/kg of physiological saline (0.9% NaCl) was slowly injected into the cisterna magna after removal of the same amount of CSF.

In group II (SAH only group, n=10), the SAH protocol was used to induce cerebral vasospasm as described above.

In group III (SAH + ADA group, n=10), cerebral vasospasm was induced by SAH, as described above, and the rabbits received ADA (Humira, Abbott Laboratories, North Chicago, IL, USA) treatment. ADA 5 mg/kg/day was given intraperitoneally. The treatment was started just after intracisternal blood injection and continued for 72 hours once a day. This dosage and treatment regimen was decided according to the literature.[6] The animals tolerated this dosage well without any important side effects.

The animals were sacrificed under general anesthesia 72 hours after the induction of SAH. Before sacrification, 2cc fresh arterial blood was obtained from the ear artery of each rabbit. All rabbits were transcardiac perfused, as described. The thorax was opened and a cannula was placed in the aorta using the left ventricle. The right atrial appendage was opened, and the descending thoracic aorta clamped. The vascular system was perfused with 300 ml of physiological saline under a pressure of 120 cm H_2O.

After perfusion, the brain and brainstem were removed, and each brainstem cut coronally into two pieces as follows: the anterior part that contains basilar artery histopathological investigations and the dorsal part that contains brainstem tissue for biochemical investigations.

Biochemical Procedures

Brainstem tissues (dorsal part) of the rabbits were extracted after decapitation and rinsed with ice-cold PBS (phosphate-buffered saline) containing heparin and blood and clot remnants were removed. Subsequently, tissues were blotted on filter paper and stored in Eppendorf tubes at -80°C until biochemical analysis. Brain tissue samples were weighed and homogenized. Homogenates were centrifuged at +4C° and 10.000 g for 10 minutes.

Serum concentrations of the brain-derived neurotrophic factor (BDNF), TNFα, interleukin 1 beta (IL-1β) and brainstem tissue concentrations of the matrix metalloproteinase (MMP-9), TNFα and IL-1β were measured using the iMark™ Microplate Absorbance Reader, (Bio-rad Laboratories, CA, USA) using ELISA (enzyme-linked immunosorbent assay) analysis with rabbit BDNF, TNFα and IL-1β kits (Sunred Biological Technology Co., Ltd, Shanghai, China). Tissue protein levels were measured using the Thermo Scientific Pierce™ BCA Protein Assay Kit (Thermo Fisher Scientific, IL, USA).

Histopathological Procedures

In total, five artery sections were analysed per animal. The morphometric and immunohistological analyses were carried out in a blind fashion by one pathologist. Morphometric measurements on all five segments of the basilar artery were performed using an image analysis system (BAB image analysing systems, Ankara, Turkey). The luminal area was calculated from the perimeter of the luminal border and the area contained within the boundaries of the internal elastic lamina was neglected. The luminal area for each basilar artery was obtained by averaging these measurements. The mean± standard error of the mean (SEM) value obtained from each artery was used as the final value for a particular vessel.

For labeling apoptotic cells in samples by modifying DNA fragments utilizing terminal deoxynucleotidyl transferase for detection of apoptotic cells by specific staining the ApopTag® Plus Peroxidase In Situ Apoptosis Detection Kit (CHEMICON® International, Inc.) was used as described in user manual. An apoptotic index was calculated as the number of the immunoreactive nuclei per total number of endothelial cells and the result was expressed as a percentage.

Statistical Analysis

The SPSS (version 21.0, IBM SPSS Statistics, IL, USA) program was used to evaluate the findings of this study. The differences among groups were tested using the Kruskal-Wallis test. The Post-Hoc Bonferroni and Mann-Whitney U tests were used for the correction of groups in which diference were significant. A P-value less then 0.05 was accepted as significant ($p<0.05$).

RESULTS

All thirty animals survived to complete this study. The animals in the SAH only group was hypoactive and lethargic. Rabbits in the control group and ADA treated groups were as active as they were before.

Biochemical Results

Tissue levels of TNFα, IL-1β and MMP-9 elevated in the group 2 and they partly decreased in the group III. Plasma levels of TNFα and IL-1β also elevated in group II and partly decreased in the group III. In contrast, plasma levels of BDNF were higher in the group I, significantly reduced in group II and partly restored in group III. Findings are summarized in Table 1.

Histopathological Results

The mean cross-sectional area of the basilar artery significantly reduced after SAH when compared with group I. ADA treatment statistically significantly increased the mean cross-sectional area of the basilar artery when compared with group II. SAH-induced cerebral vasospasm significantly increased the wall thickness of the basilar artery, and ADA treatment statistically significantly reduced this increment. SAH statistically significantly increased the mean percentage of endothelial apoptotic cells when compared with group I. ADA treatment leads to a statistically significant reduction in the mean percentage of apoptotic endothelial cells when compared with group II. Morphometric and immunohistological results were presented in Table 2 and Figure 1 and Figure 2.

DISCUSSION

Cerebral vasospasm is an important complication of SAH, which leads to enhanced mortality and morbidity.[7] Despite extensive clinical and experimental studies, exact treatment of vasospasm is obscure. Multifactorial ethiopathogenesis of the vasospasm include lipid peroxide formation, an instability among endothelium-derived vasoconstrictor and vasodilator substances, nitric oxide toxicity, arachidonic acid metabolites, inflammatory cascades, a deterioration of neuronal mechanisms that regulate vascular tone, endothelial proliferation, and apoptosis.[8]

SAH triggers a systemic inflammatory cascade, which increases the level of circulating leukocytes and adhesion molecules, which cause accumulation of immunoreactive cells.[4] Progressing inflammatory response in the subarachnoid space is mediated by the release of various cytokines. Fassbender et

Table 1. Brainstem tissue and plasma levels of the biochemical parameters

	Tissue TNFα (pg/mg protein)	Tissue IL-1β (pg/mg protein)	Tissue MMP9 (ng/mg protein)	Plasma BDNF (pg/mL)	Plasma TNFα (pg/mL)	Plasma IL-1β (pg/mL)
Group I	1.16±0.16	1.90±0.16	0.61±0.06	661.60±56.68	18.26±7.36	25.64±1.08
Group II	3.39±1.52	5.71±3.72	1.29±0.20	293.80±29.32	44.86±2.58	55.00±3.92
Group III	1.40±0.14*	2.82±0.37*	0.85±0.09*	435.30±33.27*	23.23±1.29*	50.05±2.21*

*Statistically significantly difference when compared with group II ($p<0.05$). The presented values were given as the mean±SEM.

Table 2. Morphometric and immunohistological results

	Cross-sectional area (μm²)	Wall thickness (μm)	Apoptotic Index (%)
Group I	89202±3609	41.67±1.57	3.3±0.47
Group II	53231±1921	65.42±0.95	36.4±2.07
Group III	67687±1800*	51.07±1.23*	16.9±1.36*

*Statistically significantly difference when compared with group II ($p<0.05$). The presented values were given as the mean±SEM.

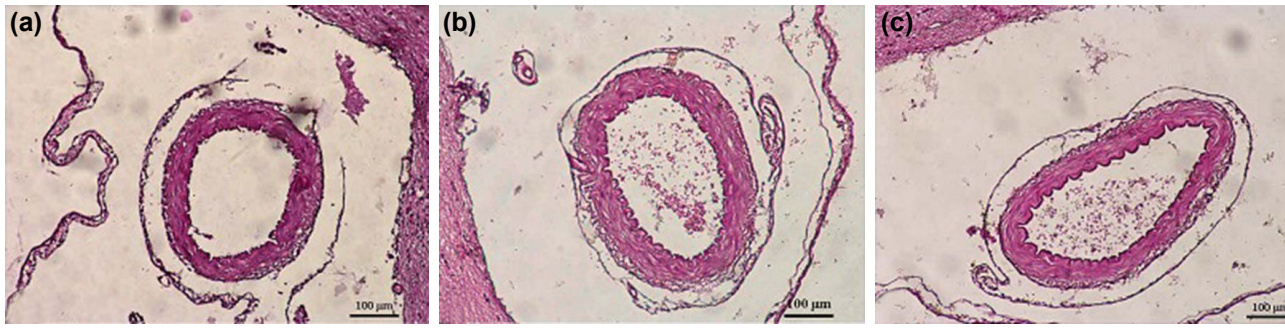

Figure 1. Representative hematoxylin–eosin (H&E)-stained basiller artery sections. **(a)** Group I, **(a)** Group II, **(a)** Group III (Bar=100 µm).

Figure 2. (a) Representative basiller artery sections stained in the TUNEL assay. **(a)** Group I, **(b)** Group II, **(c)** Group III. The black arrows indicate immunoreactive apoptotic endothelial cells (Bar=50 µm).

al.[3] and Takizawa et al.[9] reported an association between cytokines (powerful mediators and regulators of immune responses) in the CSF of patients with cerebral vasospasm after SAH. Takizawa et al.[9] concluded that regulation of cytokines might become a method to prevent complications following SAH. Bowman et al.[10,11] reported some therapeutic effects of cytokine-mediated treatments in the management of experimental cerebral vasospasm. A few cytokines, including TNFα, IL-1, IL-6, and IL-8, have been found to be upregulated in cerebral vasospasm.[12] Among these cytokines, TNFα takes particular interest in the development and progression of some central nervous diseases, including multiple sclerosis,[13] Alzheimer's disease[14] and autoimmune encephalomyelitis.[15,16]

ADA is a human monoclonal TNFα antibody drug that blocks the effects of TNFα. Adalimumab is used successfully for the treatment of disorders, such as Crohn's disease, ulcerative colitis, psoriasis, rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis.[5,17] To our knowledge, to date, there is no study in the literature concerning the beneficial effects of ADA on cerebral vasospasm.

Inflammatory cytokines, TNFα and IL-1β, have been shown to play a role in the development and progression of cerebral vasospasm and ischemia response after cerebral hemorrhage by accelerating the inflammatory response cascade.[18–20] In addition, TNFα and IL-1β play important roles in the activation of the apoptotic process.[21,22] Previous studies showed that the prevention of apoptosis ameliorates cerebral vasospasm.[8,23] MMP-9 is a collagen-degrading enzyme altering blood-brain barrier. Both have similar deleterious effects on the ischemic brain.[24] Recent clinical evidence verified the involvement of MMP-9 in the pathological process of hemorrhagic stroke and aggravation of the early brain injury and cerebral vasospasm after SAH.[25] TNFα induces MMP-9 expression by some signaling pathways that contribute to enhanced inflammation.[26] Inhibiting TNFα by ADA treatment ameliorates MMP-9 related joint inflammation in psoriasis patients.[27] In the present study, ADA treatment after experimental SAH ameliorates the emerging cerebral vasospasm by decreasing brainstem tissue TNFα, IL-1β, MMP-9 levels and plasma levels of TNFα and IL-1β.

BDNF have well-known neurotrophic actions and also maintains other neuroprotective effects, including anti-apoptosis, anti-oxidation, and suppression of autophagy. Various protective mechanisms of BDNF against mitochondrial dysfunction commonly associated with the pathogenesis of many chronic neurodegenerative disorders and the protective signaling pathways revealed by BDNF is under investigation for prevention from the progression of neurodegeneration.[28] In our study, plasma levels of BDNF as a marker of neuroprotection were also restored in the ADA treatment group.

Cerebral vasospasm affects all layers of the arterial wall with morphologic changes observed in the adventitia, media and intima. Cellular proliferation of cells in the arterial wall and apoptosis of endothelial cells leading to impairment of endothelium-dependent vasorelaxation promotes exposure of vascular smooth muscle cells to spasmogens and enhances vasospasm.[8] In this study, ADA treatment significantly in-

creased the mean cross-sectional area of the vasospastic basilar arteries, reduced the basilar artery wall thickness and also ameliorates enhanced endothelial apoptosis.

Conclusion

The findings obtained in this study suggest that ADA caused significant changes in cytokine activity, with positive effects on the amelioration of cerebral vasospasm. Beneficial anti-inflammatory, anti-apoptotic, neuroprotective effects of ADA worth further investigation for the implement this treatment option into the clinical practice.

Ethics Committee Approval: The Necmettin Erbakan University KONÜDAM Experimental Medicine Application and Research Center Directorate granted approval for this study (date: 29.07.2016, number: 2016-042).

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Conflict of Interest: None declared.

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DENEYSEL ÇALIŞMA - *ÖZET*

Adalimumab'ın tavşanlarda deneysel subaraknoid kanama sonrası oluşan serebral vazospasm üzerine iyileştirici etkileri

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AMAÇ: Tümör nekroz faktörü α (TNFα) için yeni nesil bir rekombinant insan monoklonal antikoru olan adalimumab (ADA), güçlü anti-enflamatuvar etkilere sahiptir. Serebral vazospazmın gelişimi ve ilerlemesi için artmış enflamasyonun rolü detaylı bir şekilde belirlenmiştir. Bu çalışmada, tavşanlarda deneysel olarak oluşturulan serebral vazospazm modelinde ADA'nın biyokimyasal ve histopatolojik yöntemlerle muhtemel hafifletici ve nöroprotektif etkileri araştırıldı.

GEREÇ VE YÖNTEM: Otuz adet erkek Yeni Zelanda beyaz tavşanı rastgele kontrol, sadece subaraknoid kanama (SAH) ve SAH artı ADA tedavi gruplarına ayrıldı. SAH, tek sisterna magna otolog arteriyel kan enjeksiyonu ile oluşturuldu. ADA tedavisine intrasisternal kan enjeksiyonundan hemen sonra başlandı ve günde 72 saat devam edildi. Araştırmalar için elde edilen SAH, serum ve beyin sapı dokusunun uyarılmasından 72 saat sonra hayvanlar öldürüldü. SAK oluşumundan 72 saat sonra araştırma için serum ve beyin sapı doku örnekleri alındıktan sonra hayvanlar sakrifiye edildi.

BULGULAR: Beyin sapı dokusu ve plazma TNFα ve interlökin-1β, beyin sapı dokusu matriks metaloproteinaz-9 seviyeleri SAH sonrasında arttı ve tedaviden sonra kısmen azaldı. Beyin kaynaklı nörotrofik faktörün plazma seviyeleri SAH sonrasında azaldı ve tedaviden sonra kısmen restore edildi. ADA tedavisi, vazospastik baziler arterlerin orta kesit alanını önemli ölçüde arttırdı, baziler arter duvarı kalınlığını düşürdü ve ayrıca endotelyal apoptozisi düzeltti.

TARTIŞMA: Sonuçlar ADA'nın deneysel tavşan vazospazmında, serebral vazospazmı iyileştirmede etkili bir nöroprotektif ajan olduğunu göstermektedir.

Anahtar sözcükler: Adalimumab; enflamasyon; nöroproteksiyon; serebral vazospasm; subaraknoid kanama; sitokin; tavşan.

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