The Effect Of Resveratrol On Vasospasm In Experimental Triple Subarachnoid Hemorrhage Model

Fuat TORUN [1], Hakan TUNA [2], Tanzer SANCAK [3], Emine DEMIREL [4] , Celal BAGDATOGLU [5], Nihat EGEMEN [2]

[1]Harran University, Faculty of Medicine, Department of Neurosurgery, Sanliurfa, Turkey
[2]Ankara University, Faculty of Medicine, Department of Neurosurgery, Ankara, Turkey
[3]Ankara University, Faculty of Medicine, Department of Radiology, Ankara, Turkey
[4]Ankara University, Faculty of Medicine, Department of Pharmacology, Ankara, Turkey
[5]Mersin University, Faculty of Medicine, Department of Neurosurgery, Mersin, Turkey

ABSTRACT

Backgraund

Cerebral vasospasm which follows aneurysmal subarachnoid hemorrhage has an important impact on mortality and morbidity. Despite many studies, the exact etiology and pathogenesis of cerebral vasospasm have yet to be fully understood and an appropriate treatment method has not yet been identified. In this study, the effects of resveratrol on acute phase of vasospasm, which was developed in the basilar artery by a triple subarachnoid hemorrhage (SAH) model, were examined angiographically in rabbits.

Methods

In this study, the effects of resveratrol and its solvent dimethyl sulfoxide (DMSO) on the basilar arterial vasospasm were evaluated by angiography in an experimental triple subarachnoid hemorrhage model which was performed on 6 groups of New Zealand rabbits. Each group consisting of 8 rabbits and forty-eight rabbits were studied totally.

Results

Statistical analysis to compare measurements before and after resveratrol in SAH (-) rabbits (Group 3) revealed no difference ($p>0.05$). In the SAH (+) group in which resveratrol was used for treatment (Group 6), comparison of the basilar artery diameter obtained at the 15th minute and 72nd hour of SAH showed significant improvement ($p<0.05$).

Conclusions

Our results suggest that resveratrol may be an appropriate therapeutic agent for the prevention of acute vasospasm that develops after SAH and it may be potentially therapeutic in previously developed vasospasm.

Key Words: Resveratrol, cerebral vasospasm, angiography, basilar artery, rabbit.

Deneysel Üçlü Subaraknoid Kanama Modelinde Resveratrolün Vazospazm Üzerine Etkisi

ÖZET

Amaç

Anevrizmal subaraknoid kanamayı takiben gelişen serebral vazospazmın mortalite ve morbidite üzerinde önemli etkileri vardır. Yapılmış olan pek çok çalışmaya rağmen serebral vazospazmın kesin nedeni ve etiyolojisi bilinmemektedir ve uygun bir tedavi yöntemi de henüz belirlenmemiştir. Bu çalışmada resveratrolün üçlü subaraknoid kanama (SAK) modeli ile tavşan baziler arterinde oluşturulan akut serebral vazospazm üzerine etkisi anjiyografik olarak incelenmiştir

Gereç ve yöntem

Bu çalşımada 6 grup Yeni Zelanda tavşanında deneysel olarak oluşturulan üçlü subaraknoid kanama modelinde resveratrol ve çözücüsü dimetil sülfoksitin baziler arterdeki vazospazm üzerine etkisi anjiyografi ile değerlendirilmiştir. Her grupta 8 tavşan bulunuyordu ve toplam 48 tavşan çalışmaya dahil edildi.

Bulgular

SAK (-) tavşanlarda (3. Grup) resveratrol öncesi ve sonrası ölçümler arasında istatistiksel olarak bir fark yoktu ($p>0.05$). tedavi için resveratrolün kullanıldığı SAK (+) grupta (6. Grup) 15. Dakika ve 72. Saatte elde edilen baziler arter çapları karşılaştırıldığında anlamlı bir düzelme olduğu görüldü ($p<0.05$).

Sonuç

Elde ettiğimiz bu sonuçlar resveratrolün SAkK sonrası gelişen akut vazospazmın önlenmesinde uygun bir tedaviedici ajan olabileceğini ve önceden gelişmiş olan bir vazospazmda da potansiyel bir tedavi edici ajan olabileceğini desteklemektedir.

Anahtar kelimeler: Resveratrol, serebral vasospasm, anjiyografi, basiller arter, tavşan

INTRODUCTION

Cerebral vasospasm which follows aneurysmal subarachnoid hemorrhage has an important impact on mortality and morbidity (1). Vasospasm affects 20-40% of the patients who develop SAH (1,2,3,4). In two-thirds of the patients who develop vasospasm, permanent neurological deficit or death has been observed (3, 4). Despite many studies, the exact etiology and pathogenesis of cerebral vasospasm have yet to be fully understood and an appropriate treatment method has not yet been identified. To date, various effects of resveratrol have been observed on different tissues. Its anti-oxidant, anti-

thrombocyte, anti-inflammatory and anti-carcinogenic effects are known (5,6,7,8,9,10). In this study, the effects of resveratrol on vasospasm were evaluated with digital subtraction angiography (DSA) imaging in an SAH-based vasospasm model.

MATERIALS and METHODS

This study was conducted in the microsurgery laboratory of the Department of Neurosurgery and Pharmacology, Faculty of Medicine, Ankara University. Dimethyl sulfoxide, which binds to resveratrol, was used in combination in order to prevent the settling of resveratrol in the artery.

In this study, 48 white New Zealand male rabbits aged three months and each weighing 3-3.5 kg were used. Rabbits were divided into six groups of eight rabbits each. All procedures were well tolerated and a standard diet and water program were applied. Comparison of the psychological parameters among the groups revealed no significant difference ($p>0.05$).

Group-1: SAH was not performed. Angiographies were performed at the beginning and at the 72nd hour [SAH(-)].

Group-2: SAH was not performed. After basal angiographic evaluation, intravenous DMSO was administered via ear vein at the 24th, 36th, and 48th hours. Angiographies were performed at the 72nd hour [SAH(-)+DMSO].

Group-3: SAH was not performed. After basal angiography, intravenous resveratrol was administered via ear vein at the 24th, 36th, and 48th hours. The angiographies were performed at the 72nd hour [SAH(-)+Resveratrol].

Group-4: Experimental SAH was performed. Basal imaging of the basilar artery was performed before SAH and the angiography was repeated 15 minutes and 72 hours after SAH [SAH(+)].

Group-5: Experimental SAH was performed. Basal imaging of the basilar artery was performed before SAH and the angiography was repeated 15 minutes after SAH. Intravenous DMSO via ear vein was administered at the 24th, 36th, and 48th hours of SAH. The control angiographies were performed at the 72nd hour [SAH(+)+DMSO].

Group-6: Experimental SAH was performed. Basal imaging of the basilar artery was performed before SAH and the angiography was repeated 15 minutes after SAH. Intravenous resveratrol via ear vein was injected at the 24th, 36th, and 48th hours of SAH. The control angiographies were performed at the 72nd hour [SAH(+)+Resveratrol].

Anesthesia:

Anesthesia was induced with intramuscular ketamine hydrochloride (10 mg/kg) (Ketolar®, Pfizer**,** Luleburgaz, Turkey) and xylazine hydrochloride (0.5 mg/kg) (Rompun®, Bayer, Istanbul, Turkey). When maintenance of anesthesia became necessary, additional intramuscular ketamine hydrochloride (0.5 mg/kg) was administered.

Experimental Subarachnoid Hemorrhage:

Autologous blood of the subjects, which is essential for performing SAH, was obtained from each ear artery. The subjects that underwent SAH were positioned in lateral decubitis and a 20 gauge butterfly needle was introduced into the occipito-atlantal distance in order to reach the subarachnoid space via the cisterna magna. 3 mL of cerebrospinal fluid is punctioned and the autologous blood (3 ml) obtained from the subject was injected into the subarachnoid space. This procedure was repeated at the 24th and 48th hours to maintain the vasospasm.

Angiography:

In all rabbits, cerebral angiography was performed by catheterizing the right femoral vein. 0.3 g/kg of iomeprol (Iomeron®, 400 mg/mL, Santa Farma, Turkey), a contrast agent which was kept at 37°C, was injected intravenously with a pressure of 2 mL/s (70 psi). Maximum dose was 4 mL. After a delay of only 1 second, DSA imaging (Multistar Plus/T.O.P., Siemens AG, Forchheim, Germany) was obtained in submento-occipital position and the basilar arterial diameters were recorded. Ideal opacification of the basilar artery was obtained 5-7 seconds after injection. After calibration according to the measurement scale, the arterial diameters were measured 0.5-0.7 cm above the bifurcation of the basilar artery. Following the basal angiographies, the subjects in the SAH (+) groups were positioned in ventral recumbency for at least 15 minutes to allow blood to clot**.** In order to measure and show differences in the diameter of the basilar artery after SAH, the same procedure was repeated at the 15th minute. The angiographies were repeated at the 72nd hour with the same method in each group. In the SAH (-) groups, basal and 72nd hour angiographies were performed, but not the 15th minute angiography. The angiographic procedure used in this study was performed according to the in vivo rabbit models of SAH that exist in the literature (11).

Resveratrol and DMSO:

Resveratrol was injected in the artery together with an agent called DMSO to prevent its settling. Following the basal angiography, DMSO (1500 mg/kg) was injected alone to the 2nd and 5th

groups at the 24th, 36th and 48th hours. In the 3rd and 6th groups, only one dose of resveratrol (Sigma, St. Louis, MO, 10 mg/kg, with its solvent DMSO, iv) was injected following the basilar angiography at the 24th, 36th and 48th hours. The infusion doses of resveratrol were adjusted according to the doses used in brain ischemia models in the literature (12,13).

Statistical Analysis:

Basal and 72nd hour angiographies were performed to determine the basilar artery diameter measurements of each of the groups. The statistical analysis of SAH(-), SAH(-)+DMSO, and SAH(-)+Resveratol groups was carried out using Wilcoxon matched-pairs signed-ranks test, and the difference was considered significant at $p<0.05$. In the SAH(+), SAH(+)+DMSO, and SAH(+)+Resveratrol groups, the basilar arterial diameters measured after SAH at the 15th minute and 72nd hour were analyzed using multiple-comparison test and the results were considered significant at $p<0.05$.

When the basal and 72nd hour basilar artery diameters of each rabbit were compared in the Figure 1 shows the 95% confidence intervals of basilar artery diameters over time.

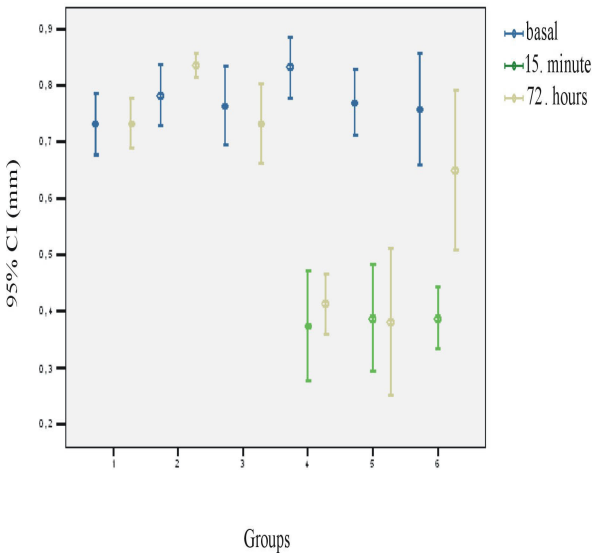

Figure 1: The 95% confidence intervals of vascular diameters of the rabbits.

RESULTS

There was a uniformly wide basilar artery diameter in the groups subjected to subarachnoid hemorrhage. The continuity of vasospasm was obtained in the rabbits subjected to experimental triple subarachnoid hemorrhage model (Figure 2).

SAH(-), SAH(-)+DMSO, and SAH(-)+Resveratrol groups, no significant difference was obtained ($p>0.05$). When the basal and the 15th minute basilar artery diameters of each rabbit were compared in the SAH(+), SAH(+)+DMSO, and SAH(+)+Resveratrol groups, the difference was significant ($p<0.01$).

Angiographic evaluation revealed significant difference between SAH(+) and SAH(+)+DMSO groups for basilar artery dimensions when basal and 72nd hour results were compared ($p<0.05$). Angiographic basilar artery diameters at the 15th minute and 72nd hour in subjects in the SAH(+) and SAH(+)+DMSO groups were compared with their own counterparts in the same group, and the results were not significant ($p>0.05$).

Comparison of the basal and 72nd hour angiographies of the SAH(+)+Resveratrol group revealed no significance ($p>0.05$). Comparison of the 15th minute and 72nd hour angiographies of the SAH(+)+Resveratrol showed a significant difference ($p<0.05$).

DMSO, used to prevent the settling of resveratrol in the artery, showed no angiographic effect on either the intact or the vasospastic basilar artery. Resveratrol, which was administered intravenously, showed no angiographic effect on the intact basilar artery (Figure 3). Resveratrol improved the radiological vasospasm which followed the SAH (Figure 4).

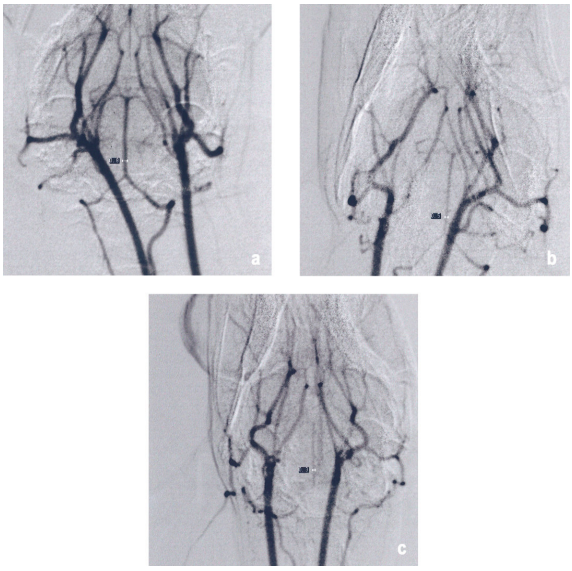

Figure 2: a) Basilar arterial diameter is 0.8 mm on the angiography before SAH. b) Angiography

15 minutes after SAH shows vasospasm of the basilar artery. c) Angiography at the 72nd hour shows the persisting vasospasm of the basilar artery in triple SAH model (0.3 mm).

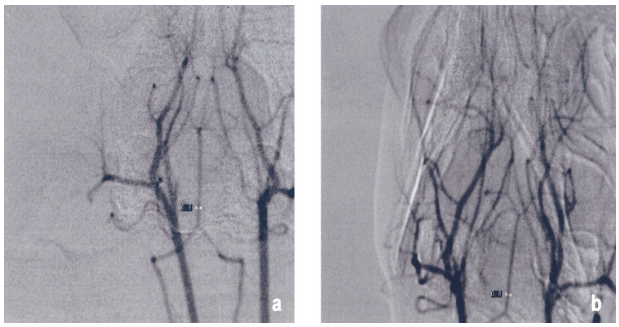

Figure 3: a) The basilar arterial diameter is 0.8 mm on the pre-SAH angiography.
b) 72nd hour angiography of the SAH (-) subjects after resveratrol shows no difference in the basilar arterial diameter compared with the first angiography.

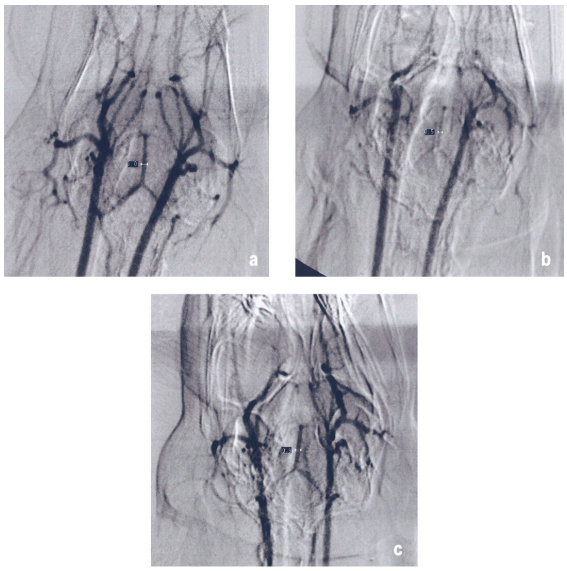

Figure 4: a) Basilar arterial diameter is 1.0 mm on the pre-SAH angiography.
b) Angiography at the 15th minute of the SAH shows the basilar arterial vasospasm (0.5 mm). c) 72nd hour angiography of the subjects that received resveratrol injections at the 24th, 36th and 48th hour of the SAH shows improvement in basilar arterial vasospasm.

DISCUSSION

To the best of our knowledge, this is the first study to show the preventive effect of systemically applied resveratrol on acute vasospasm created in rabbits following an experimental subarachnoid hemorrhage.

Since the first definition of angiographic vasospasm in 1951, the etiology of vasospasm remains unsolved. Experimental and clinical studies conducted with various pharmacological agents have demonstrated variable effects.

Currently, the most widely used treatment protocol is the hypertensive, hypervolemic, hemodilution (triple H) model (14,15). Furthermore, calcium channel blocking agents (16,17), arterial papaverine infusion or angioplasty (4,18,19,20), nitric oxide (NO) donors (21,22), endothelin converting enzyme inhibitors (23), potassium channel activators (24), intrathecal sodium nitroprusside (25), high-dose corticosteroids (26), trapidil (27), prostacyclin analogue iloprost (28,29) and dipyrone (30) have been shown to be effective in the treatment of vasospasm. Despite the intensive studies to date, no curable agent has been found to improve arterial vasospasm.

Resveratrol is a polyphenolic, antifungal natural phytoalexin that can be found in various food products, with particularly high levels in grape skin and red wine. It has been shown to have anti-inflammatory, anti-carcinogenic and anti-oxidant properties (6). Several studies have reported different effects of resveratrol in the circulatory system which inhibit vasoconstriction (31, 32).

In a study conducted on human umbilical cord endothelial cells, the effects of resveratrol on calcium-activated potassium channels were evaluated using the "whole cell patch clamp" technique, and it was shown that resveratrol contributed to the endothelium-derived vasodilation by activating potassium flux (31).

In one study conducted with an ischemia–reperfusion injured rat heart, resveratrol significantly decreased the levels of malondialdehyde, which is a lipid peroxidation marker (32). In the same study, resveratrol showed a dilatory effect in the endothelium-intact aorta but no effect in the endothelium-defective aorta, in a phenylephrine- and KCl-derived vasospasm model (32).

Olas et al. showed that resveratrol significantly inhibits thrombin and ADP- derived aggregation of platelets (33). In the aggregation process, intracellular free calcium influx through calcium channels provided by extracellular calcium and resveratrol has been shown to significantly decrease intracellular calcium (33).

In coronary heart disease, endogen mediators like endothelin-1 (ET-1) are known to be increased (34). ET-1 is the most potent vasoconstrictor known in the vascular system and this effect is modulated by activating the mitogen activated protein kinases (MAPK); resveratrol is shown to inhibit the phosphorylation of the MAPK (35).

In a study conducted with uterine and mesenteric arteries, investigators attempted to shed light on the mechanism of the vasodilatory action of resveratrol in the context of its relationship with NO and prostanoids (36,37). In both of the arteries, resveratrol showed an inhibition on the vasospasm induced with noradrenaline and KCl in a dose-dependent manner, and this effect is shown to be reversed by L-NAME (N (omega)-nitro-L-arginine-methyl esther), which is a nitric oxide synthase (NOS) inhibitor (36,37). In conclusion, this study showed that resveratrol reverses both receptor (noradrenaline)- and depolarization (KCI)-dependent vasoconstriction.

Cerebral blood flow auto-regulation is an important case in patients with SAH (38,39). In 60 minutes following SAH, the more than 40% decrease in the cerebral blood flow compared to the basal conditions has an important impact on 24-hour mortality in patients (40). NO is able to decrease the mortality in the early period of SAH. NO has been shown to repair the ischemic injury in the early periods of ischemia by increasing cerebral blood flow (41,42). In another study, decreased expression of eNOS mRNA was shown on the 7^{th} day following SAH, which meant that endothelium-derived vasodilation was impaired and vasospasm occurred (43). All of these findings suggest the protective effect of NO on autoregulation of cerebral blood flow in the early periods of SAH (44).

Resveratrol inhibits vasoconstriction via different mechanisms as shown in several studies conducted with various biochemical and histological parameters. In our study, we showed the reversal effect of resveratrol on vasospasm following SAH angiographically. In the light of these studies, although resveratrol may have a potential role in vasospasm, further studies are needed.

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Correspondence address:
Fuat TORUN (MD)
Harran University, Faculty of Medicine
Department of Neurosurgery, 63100
Sanliurfa/TURKEY
Tel : 90 414 3167464
Fax : 90 414 3139615
e-mail : fuatorun@hotmail.com