Amelioration of Cerebral Vasospasm and Secondary Injury by Vigabatrin After Experimental Subarachnoid Hemorrhage in the Rabbit

Ramazan Fesli[1], Pınar Kuru Bektaşoğlu[2,3], Bora Gürer[2], Ata Türker Arıkök[4], Özden Çağlar Öztürk[2], Hüseyin Bozkurt[5], Hayri Kertmen[1]

BACKGROUND: **Vigabatrin, an antiepileptic drug, increases the level of gamma aminobutyric acid in the brain by inhibiting its catabolism. Because gamma aminobutyric acid has been proved to have vasodilatory effects, in the present study, we investigated the effect of vigabatrin to treat experimental subarachnoid hemorrhage (SAH)-induced vasospasm.**

METHODS: **A total of 30 New Zealand white rabbits were divided into 3 groups of 10 each: the control group, SAH group, and vigabatrin group. Experimental SAH was established by injection of autologous arterial blood into the cisterna magna. In the vigabatrin group, the rabbits were administered vigabatrin for 3 days after induction of the SAH. The first dose of vigabatrin was given 2 hours after SAH induction. A daily dose of 500 mg/kg vigabatrin was administered intraperitoneally. After 3 days, the rabbits were sacrificed, and the brains were removed, together with the cerebellum and brainstem. The basilar artery wall thickness and lumen areas were measured. The neuronal degeneration in the hippocampus (CA1, CA3, and dentate gyrus) was also evaluated.**

RESULTS: **The arterial wall thickness of the vigabatrin group was less than that in the SAH group ($P < 0.001$), and the mean luminal area of the vigabatrin group was greater than that in the SAH group ($P < 0.001$). Additionally, the hippocampal neuronal degeneration score of the vigabatrin group was lower than that of the SAH group ($P < 0.001$).**

CONCLUSION: **These findings have indicated that vigabatrin has a vasodilatory effect in an experimental SAH model in the rabbit. Moreover, it showed a neuroprotective effect in the hippocampal neurons against secondary injury induced by SAH.**

INTRODUCTION

Cerebral vasospasm is a delayed, but reversible, contraction of the cerebral arteries after subarachnoid hemorrhage (SAH).[1,2] The occurrence of cerebral vasospasm and accompanying ischemia are the most important causes of mortality and morbidity after SAH.[1,3,4] Generally, a decrease occurs in the perfusion of the distal affected artery and, radiologically, intracranial arteries will show a narrowing of the lumen.[5] Cerebral vasospasm should be examined using 2 methods: clinically for symptomatic vasospasm and radiologically for angiographic vasospasm.[5] Radiological vasospasm will occur several days after SAH and will peak in severity ~1 week later.[5] Form contraction and contrast filling can be present on digital subtraction angiography, occurring in 50%–90% of cases.[5] Clinical vasospasm will develop in only 30%–40%, occurring 3–12 days after SAH with a late focal or diffuse ischemic neurological disorder and decreasing in severity within 2–4 weeks.[6]

One of the main factors involved in cerebral vasospasm is the numerous spasmogens that occur as a result of the destruction of erythrocytes and platelets in the blood.[6] Histamine, serotonin, catecholamines, prostaglandins, angiotensin, and oxyhemoglobin are some of these spasmogens.[7] Neuroinflammation, oxidative stress, and related apoptosis are the main pathophysiological

Key words
- Subarachnoid hemorrhage
- Vasospasm
- Vigabatrin

Abbreviations and Acronyms
GABA: Gamma aminobutyric acid
GABA-T: Gamma aminobutyric acid transaminase
SAH: Subarachnoid hemorrhage

From the [1]Department of Neurosurgery, University of Health Sciences, Dışkapı Education and Research Hospital, Ankara; [2]Department of Neurosurgery, University of Health Sciences, Fatih Sultan Mehmet Education and Research Hospital, Istanbul; [3]Department of Physiology, Marmara University School of Medicine, Istanbul; [4]Department of Pathology, University of Health Sciences, Dışkapı Education and Research Hospital, Ankara; and [5]Department of Neurosurgery, Cumhuriyet University School of Medicine, Sivas, Turkey

To whom correspondence should be addressed: Bora Gürer, M.D. [E-mail: boragurer@gmail.com]

Citation: World Neurosurg. (2020) 141:e559-e565. https://doi.org/10.1016/j.wneu.2020.05.230

Journal homepage: www.journals.elsevier.com/world-neurosurgery

Available online: www.sciencedirect.com

mechanisms responsible for the development of the early brain injury occurring with SAH-induced vasospasm and can cause cerebral edema and cell death.[8-10] The exact underlying mechanisms of cerebral vasospasm have remained unclear. An imbalance between vasoconstrictors and vasodilators, neuronal mechanisms that regulate vascular tone, and endothelial proliferation are some of the other factors contributing to the pathology.[11]

Drugs such as thiocolchicoside, which act on the gamma aminobutyric acid (GABA) system, have also been used experimentally in the treatment of cerebral vasospasm.[7] Vigabatrin (γ-vinyl GABA) is a new-generation antiepileptic drug that is a structural analogue of GABA.[12] It is an antiepileptic drug that acts by blocking the GABA transaminase (GABA-T) enzyme and activates the GABA system, resulting in a GABAergic effect.[13,14] Vigabatrin has been used in particular for patients with infantile spasm associated with tuberous sclerosis and for patients with refractory partial epilepsy.[15] The GABAergic system has been found to induce vasodilation of cerebral arteries.[16-18] It has also been reported that GABA has a dose-dependent cerebral vasodilatory effect.[16,17,19] However, to the best of our knowledge, the effects of vigabatrin on SAH-induced vasospasm have not been investigated.

In the present study, the effects of vigabatrin, an antiepileptic drug, on vasospasm in the rabbit basilar artery was investigated in an experimental SAH model. In addition, the neuroprotective effect of hippocampal CA1, CA3, and dentate gyrus on the neuronal damage caused by the vasospasm was evaluated.

METHODS

The local ethics committee of the Ankara Training and Research Hospital, Ministry of Health, Republic of Turkey, approved the present study (approval date August 10, 2013; approval no. 2013-0015-231). In our study, 30 New Zealand white rabbits weighing 2500–3850 g were used. During the experiment, all the rabbits were kept under constant and standard environmental conditions, fed with standard animal feed, and provided free access to water. For the experiment, the rabbits were divided into 3 groups of 10 each:

1. Control group: only sham surgery was performed, with SAH not induced and no medication given
2. SAH group: SAH was induced as described but no medication was given
3. Vigabatrin group: SAH was induced as described and intraperitoneal vigabatrin was administered at a dose of 500 mg/kg for 3 days

Vigabatrin was administered at a dose of 250, 500, and 1000 mg/kg intraperitoneally as previously reported in experimental animal studies in which vigabatrin was found in the brain parenchyma via microdialysis methods.[20]

Surgical Treatment

Anesthesia. Preoperatively, the rabbits were given an intramuscular injection of 70 mg/kg of ketamine hydrochloride (Ketalar [Parke Davis, Eczacıbaşı, Turkey]) and 5 mg/kg of xylazine (Rompun [Bayer, Leverkusen, Germany]) for general anesthesia, and spontaneous breathing was protected.

Cisterna Magna Puncture and SAH. The SAH and the vigabatrin groups were shaved from the inion to the lower cervical area after the induction of general anesthesia. After the necessary cleaning with polyvinylpyrrolidone iodine, the head was flexed, and a 25-guage cannula was entered into the cisterna of the atlanto-occipital region, and puncture was performed. After 1 mL/kg of cerebrospinal fluid discharge, an equal amount of blood was taken from the ear artery and injected into the cisterna magna for 2 minutes without heparinization. After the injection, the rabbits were kept in a 45° Trendelenburg position for 15 minutes to distribute the blood to the basal cisterns.[21-23]

Drug Application to the Treatment Group. In our study, we mechanically homogenized vigabatrin at a dose of 500 mg/kg with 0.9% physiological saline solution. The rabbits in group 3 (vigabatrin group) were administered vigabatrin intraperitoneally for 3 days, with the first dose given 2 hours after SAH induction.

Perfusion, Fixation, and Tissue Sampling. All the rabbits were sacrificed by perfusion and fixation after 72 hours. Thoracotomy was performed after the induction of general anesthesia. A cannula was placed in the left ventricle. The right atrium was opened wide, and the thoracic aorta was clamped. After perfusion with 300 mL of physiological saline solution, fixation with 200 mL of 10% formaldehyde was achieved.

During the fixation procedure, formaldehyde was administered 100 cm above the rabbit's chest. Next, the scalp was opened, and the calvarium was exposed with a large craniectomy to remove the brain and brain stem as a whole. The removed brain tissues were fixed in 10% formaldehyde solution at 4°C for 24 hours.

Histopathological Evaluation and Morphometric Measurements of Basilar Artery

A total of 3 sections of tissue were taken from the brainstem and basilar artery tissues and sectioned at 2-mm intervals. The tissue sections were taken from each block and embedded in 5-μm-thick paraffin blocks. These sections were stained with hematoxylin and eosin and prepared for examination. The morphometric measurements of all 3 segments of the basilar artery were performed using the imaging and analysis system BS 200 ProP (BAB Imaging System, Ankara, Turkey). The limits of the internal elastic lamina were measured in the luminal space. The wall thickness of each basilar artery was measured from 4 quadrants to the external muscle layer. Each of these measurements was repeated 3 times by 2 pathologists who were unaware of the study groups, and the mean value was computed.

Histological Evaluation of the Hippocampus

Neuronal swelling, hyperchromasia, and nuclear pyknosis with morphological findings of neuronal degeneration were evaluated using a light microscope. The presence and level of neuronal degeneration were scored semiquantitatively in the dentate gyrus, CA1, and CA3 regions.[7] Using this scoring method, a normal appearance was given 1 point; degenerated neurons found between normal neurons, 2 points; few normal neurons scattered among many degenerated neurons, 3 points; and

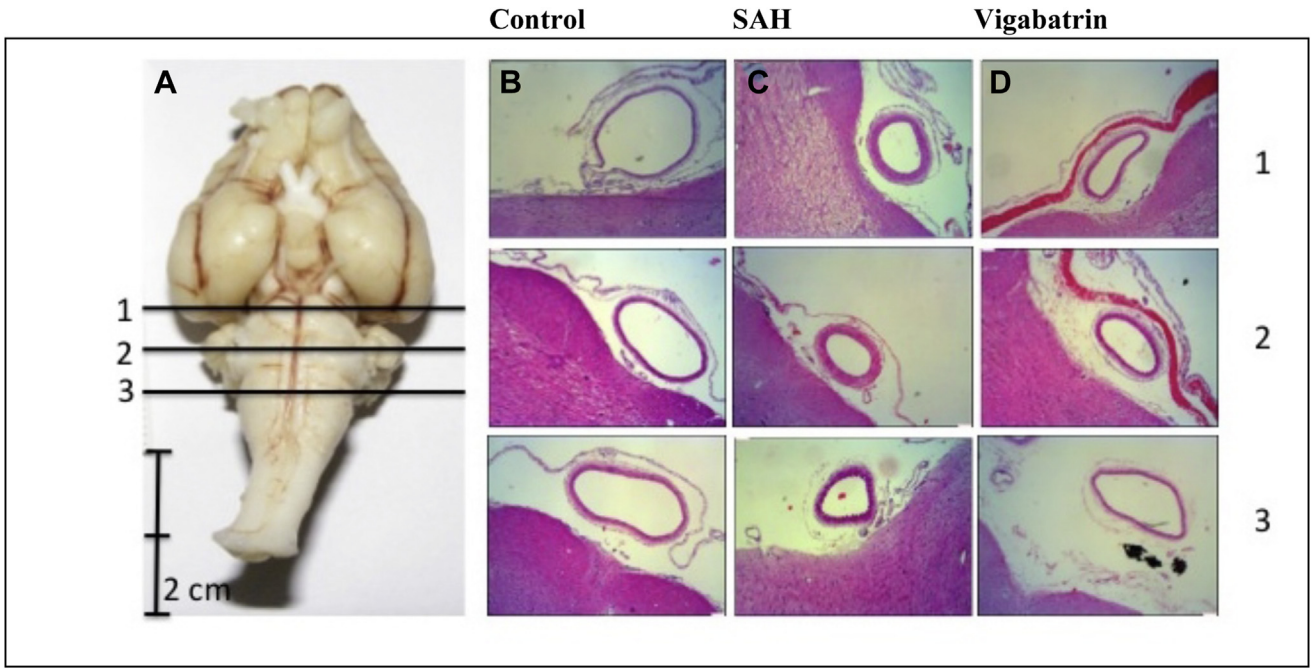

Figure 1. (**A**) Photograph of cross-sectional areas of the basilar artery taken from the brain stem. Histologic slides of basilar artery view for the (**B**) control group, (**C**) subarachnoid hemorrhage group, and (**D**) vigabatrin group (hematoxylin and eosin stain, original magnification ×200).

totally degenerated neurons with no normal neurons, 4 points. Scoring was performed for all 3 regions from the hippocampus. The sum of these scores was considered the degeneration score, and the average of these scores was used in the statistical analysis.

Statistical Analysis

Statistical analyses were performed using SPSS for Windows, version 11.5 (IBM Corp., Armonk, New York, USA). The mean ± standard deviation and minimum and maximum values were used to summarize the numerical parameters, and statistical significance was determined as $P < 0.05$. The Shapiro-Wilk test was used to determine the distribution of continuous variables, and the Levene test was used to evaluate the homogeneity of the variables. The data are presented as the median and interquartile range or median and range. The median differences for the groups were analyzed using the Kruskal-Wallis test. $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Macroscopically, in the SAH and vigabatrin groups, diffuse SAH on the ventral surface of the brain was observed. The basilar artery luminal area and arterial wall thickness were examined microscopically (Figure 1). In the SAH group, the mean vessel luminal diameter (153,618.3 ± 17,356.9) had decreased compared with that of the control group (289,993.2 ± 88,628.6; $P < 0.001$). In the vigabatrin group, the vessel luminal diameter (277,297.1 ± 6,7683.0) was significantly increased compared with that of the SAH group. The mean vessel luminal area of the control group was significantly greater than those of the other 2 groups ($P < 0.001$). The mean vessel luminal areas of the groups are listed in Table 1.

The mean arterial wall thickness was significantly increased in the SAH group (46.3 ± 1.4) compared with that in the control group (26.0 ± 4.2; $P < 0.001$). In the vigabatrin group, the mean vessel wall thickness (27.4 ± 1.7) was significantly decreased compared with that in the SAH group ($P < 0.001$). The mean vessel wall thickness of the control group was significantly lower statistically than that in the other 2 groups ($P < 0.001$). The mean vessel wall thickness of the 3 groups are given in Table 2.

Table 1. Area Comparison Among the Groups

Group	Area
Control	289,993.2 ± 88,628.6*
SAH	153,618.3 ± 17,356.9*†
Vigabatrin	277,297.1 ± 67,683.0†
P value‡	<0.001

Data presented as mean ± standard deviation.
SAH, subarachnoid hemorrhage.
*Control versus SAH group ($P < 0.001$).
†SAH versus vigabatrin group ($P < 0.001$).
‡Kruskal-Wallis test.

Neuronal swelling, hyperchromasia, and nuclear pyknosis with morphological findings of neuronal degeneration were investigated using light microscopy in the dentate gyrus, CA1, and CA3 regions of the hippocampus (Figures 2–4). The mean degeneration scores are listed in Table 3. The dentate gyrus degeneration score in the SAH group (median, 4; range, 3–4) was significantly greater than that in the control group (median, 1; range, 1–2; $P < 0.001$). Dentate gyrus degeneration was significantly less in the vigabatrin group (median, 2; range, 1–2) than that in the SAH group ($P < 0.001$). The CA1 degeneration score was significantly greater in the SAH group (median, 4; range, 3–4) compared with that in the control group (median, 1; range, 1–2; $P < 0.001$). In the vigabatrin group, CA1 degeneration was significantly less than that in the SAH group (median, 1; range, 1–2; $P < 0.001$). The hippocampal CA3 degeneration score in the SAH group (median, 4; range, 3–4) was significantly greater than that in the control group (median, 1; range, 1–2; $P < 0.001$). In the vigabatrin group, the CA3 degeneration score (median, 2; range, 1–3) was significantly less than that in the SAH group ($P < 0.001$). Overall, the mean degeneration score in the SAH group (median 11.5, range, 9–12) was significantly greater than that in the control group (median, 4; range, 3–5; $P < 0.001$), and the mean degeneration score in the vigabatrin group (median, 4.5; range, 3–7) was lower than that in the SAH group ($P < 0.001$).

DISCUSSION

Cerebral vasospasm is the most important cause of cerebral ischemia. Angiographically, it occurs 3–4 days after bleeding and reaches its maximum level by day 7.[24] The development of ischemia and neurological deficits will mostly occur during this period.[24] In experimental rabbit SAH models, cerebral vasospasm reaches its maximum by the third day.[25] Therefore, in our study, the most severe day of vasospasm was considered the third day after the experimental SAH had formed.

GABA, a neurotransmitter, is present in the central nervous system at ~30%, and the effect of GABA is generally inhibitory.[26] The presence of GABA receptors in the cerebrovascular system and the vasodilatory effect of GABA on cerebral arteries has been demonstrated by multiple studies.[16,18,19] In experimental studies, glutamic acid decarboxylase and nerve fibers with intense GABA-T activity were detected in the anterior circulation of the cerebral circulation.[18] It was observed that these fibers, which were detected in the neighborhood of the smooth muscle layer of the cerebral arteries, actively performed GABA synthesis.[18] Experimental studies have shown that the GABAergic system causes vasodilatation by acting as an agonistic effect on GABA type A receptors in the cerebrovascular

Table 2. Arterial Wall Thickness Comparison Among the Groups

Group	Arterial Wall Thickness
Control	26.0 ± 4.2*
SAH	46.3 ± 1.4*†
Vigabatrin	27.4 ± 1.7†
P value‡	<0.001

Data presented as mean ± standard deviation.
SAH, subarachnoid hemorrhage.
*Control versus SAH group ($P < 0.001$).
†SAH versus vigabatrin group ($P < 0.001$).
‡Kruskal-Wallis test.

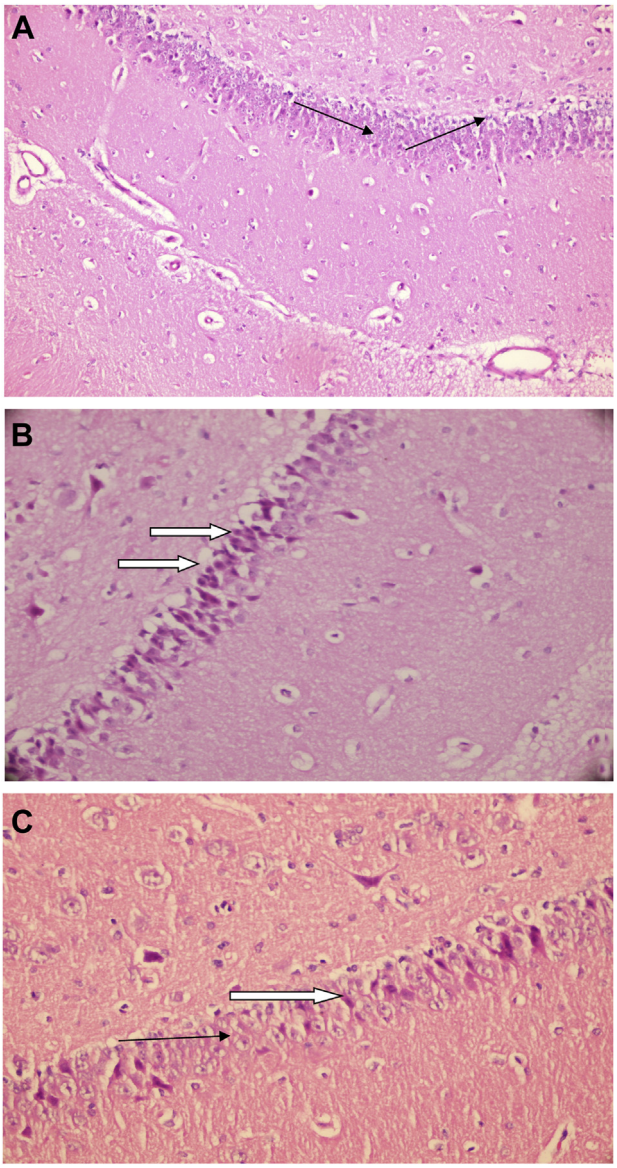

Figure 2. Histologic slides of the hippocampus dentate gyrus region for the (**A**) control group showing totally normal neurons (*black arrows*), (**B**) subarachnoid hemorrhage group showing almost completely degenerated neurons (*white arrows*), and (**C**) vigabatrin group showing occasional degenerated neurons (*white arrow*) between normal neurons (*black arrow*; hematoxylin and eosin stain, original magnification ×200).

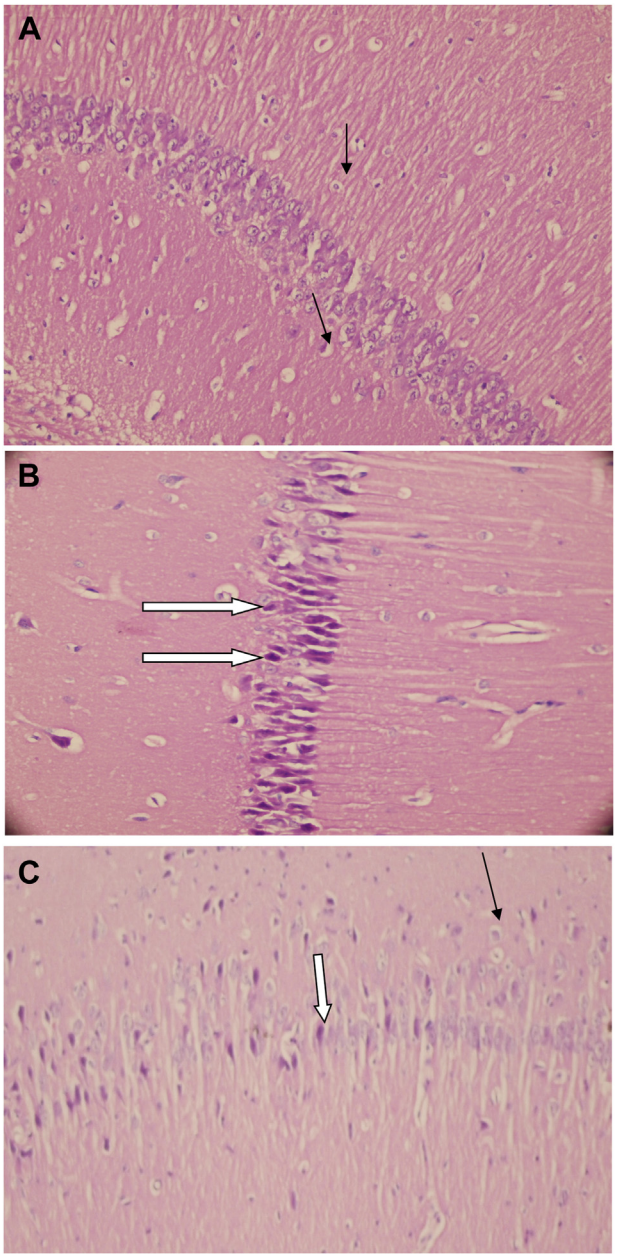

Figure 3. Histologic slides of the hippocampus CA1 region for the (**A**) control group showing totally normal neurons (*black arrows*), (**B**) subarachnoid hemorrhage group showing degenerated neurons (*white arrows*), and (**C**) vigabatrin group showing occasional degenerated neurons (*white arrow*) between normal neurons (*black arrow*; hematoxylin and eosin stain, original magnification ×200).

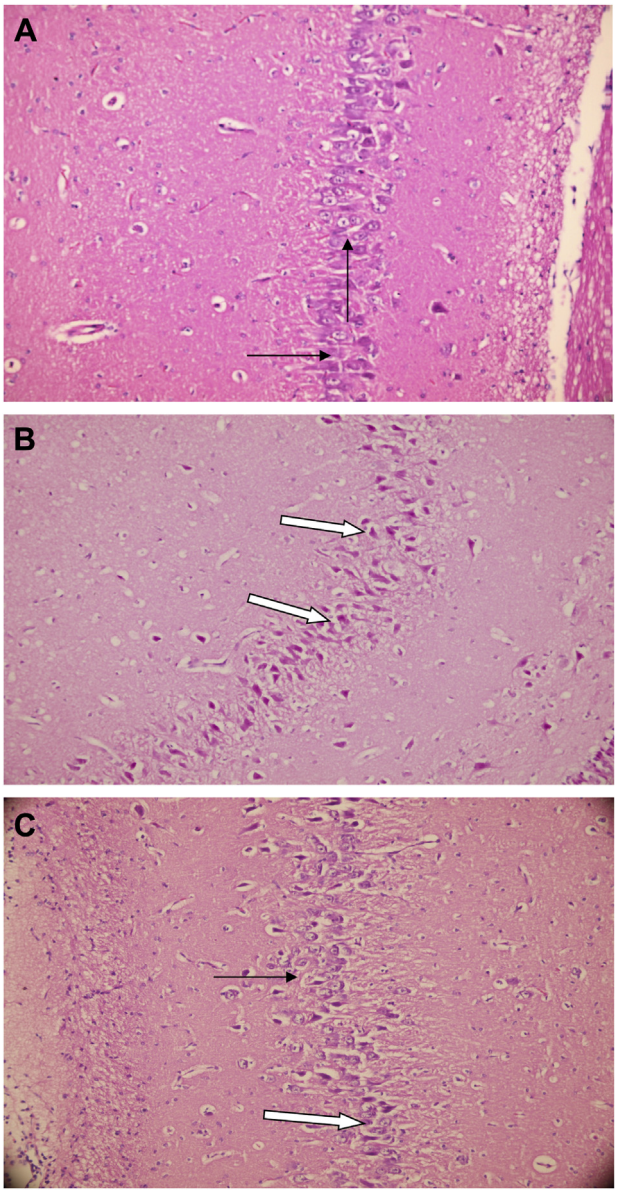

Figure 4. Histologic slides of the hippocampus CA3 region for the (**A**) control group showing totally normal neurons (*black arrow*) with no degenerative neurons in the region, (**B**) subarachnoid hemorrhage group showing almost completely degenerate neurons (*white arrows*), and (**C**) vigabatrin group showing degenerated neurons (*white arrow*) somewhere between normal neuron cells (*black arrow*; hematoxylin and eosin stain, original magnification ×200).

system.[24] In addition, the study by Cetas et al.[27] showed that the rostral ventromedial medulla will be activated despite antagonism of the GABAergic system and increases cerebral blood flow by 20%–30% by vasodilatation. In the thiocolchicoside study by Kertmen et al.,[7] the vasodilatory effect of the GABAergic system has been shown to be both an agonist and an antagonist effect. In summary, previous studies have shown that both the agonistic and the antagonistic effects of the GABAergic system have vasodilatory effects.

Vigabatrin is a new-generation antiepileptic drug that is a structural analogue of GABA.[28] The blood concentration of vigabatrin is dose dependent and can be detected in the brain parenchyma 15 minutes after administration.[29] It inhibits this

Table 3. Comparison of Hippocampal Neuronal Degeneration Score Among the Groups

Variable	Control	SAH	Vigabatrin	*P* Value*
Dentate gyrus	1 (1–2)†	4 (3–4)†‡	2 (1–2)‡	<0.001
CA1	1 (1–2)†	4 (3–4)†‡	1 (1–2)‡	<0.001
CA3	1 (1–2)†	4 (3–4)†‡	2 (1–3)‡	<0.001
Degeneration score	4 (3–5)†	11.5 (9–12)†‡	4.5 (3–7)‡	<0.001

Data presented as median (range).
SAH, subarachnoid hemorrhage.
*Kruskal-Wallis test.
†Control versus SAH group ($P < 0.001$).
‡SAH versus vigabatrin group ($P < 0.001$).

enzyme by binding covalently and irreversibly to the GABA-T enzyme.[13,14] This inhibition results in increased GABA in the synaptic range and stimulates the GABAergic system. The GABAergic activity of vigabatrin results in vasodilatory activity against SAH-induced vasospasm.

Cerebral ischemia after vasospasm is associated with glutamate excitotoxicity.[30] Glutamate activates the N-methyl-D-aspartate receptor and results in an influx of sodium and calcium into neurons.[31] This mechanism is expected to cause neuronal cell death.[32] Neuronal apoptosis in the cortex and hippocampus has been shown in humans and animals after SAH.[33,34] Because GABA is the principal inhibitory neurotransmitter, the balance of glutamatergic and the GABAergic system is crucial for healthy neurological function.[35] It was hypothesized that vigabatrin, as a structural analogue, would ameliorate the glutamate excitotoxicity and would exert neuroprotective actions on the hippocampal regions. In previous studies, other drugs such as statins were also tried in experimental SAH models.[36,37] The mostly anti-inflammatory actions of statins have been reported to be related to their vasodilatory action.

In the present study, we hypothesized that vigabatrin can be used as a part of the treatment of vasospasm after SAH. The findings from the present study have shown that the largest vessel lumen area in the rabbit basilar artery examined after experimental SAH was in the control group. In contrast, in the SAH group, the vessel lumen area had decreased significantly and was compatible with the occurrence of vasospasm. In addition, in the control group, the mean arterial wall thickness was the thinnest. In the SAH group, the mean arterial wall thickness had increased significantly. In contrast, the vessel lumen area and arterial wall thickness in the vigabatrin group were significantly different statistically from the values for the control and SAH groups both. Therefore, vigabatrin, a GABA-T enzyme inhibitor, had a reducing effect on vasospasm.

In terms of the preservation of nerve tissue, the differences in the neurodegeneration scores between the SAH and vigabatrin groups in the dentate gyrus, CA1, and CA3 regions was statistically significant. The CA1 region is the most sensitive region in the hippocampus to hypoxia.[4] Therefore, the CA1 region can be affected by the occurrence of vasospasm. A statistically significant increase in the neurodegeneration score in the vigabatrin group compared with the SAH group suggested neuroprotective activity by vigabatrin owing to its GABAergic effects. However, the efficacy of vigabatrin at different doses to determine its effects on vasospasm and neuronal damage requires further investigation.

CONCLUSION

In the present study, vigabatrin, an antiepileptic drug, was investigated to determine its effects on vasospasm and neurodegeneration in an experimental SAH model. GABAergic activity plays an important role in the etiopathogenesis of vasospasm after SAH. Vigabatrin, which inhibits the GABA-T enzyme, has been shown to cause vasodilatation by activating the GABAergic system, and this effect is thought to reduce vasospasm. In the present study, we have shown, to the best of our knowledge, for the first time, that vigabatrin has preventative effects on SAH-induced vasospasm and vasospasm-induced ischemic neuronal damage. We also discussed the possible underlying mechanisms of the neuroprotective and vasodilatory effects of vigabatrin. However, further studies are needed to determine whether vigabatrin could play a role in the treatment of SAH-induced vasospasm.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Ramazan Fesli: Conceptualization, Data curation, Formal analysis, Funding acquisition, Project administration, Resources, Writing - original draft. **Pınar Kuru Bektaşoğlu:** Validation, Visualization, Writing - original draft, Writing - review & editing. **Bora Gürer:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - original draft, Writing - review & editing. **Ata Türker Arıkök:** Data curation, Methodology. **Özden Çağlar Öztürk:** Data curation, Funding acquisition. **Hüseyin Bozkurt:** Funding acquisition. **Hayri Kertmen:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing - review & editing.

REFERENCES

1. Barker FG II, Heros RC. Clinical aspects of vasospasm. *Neurosurg Clin N Am*. 1990;1:277-288.
2. Liu-Deryke X, Rhoney DH. Cerebral vasospasm after aneurysmal subarachnoid hemorrhage: an overview of pharmacologic management. *Pharmacotherapy*. 2006;26:182-203.
3. French JA, Mosier M, Walker S, Sommerville K, Susman N, Vigabatrin Protocol 024 Investigate Cohort. A double-blind, placebo-controlled study of vigabatrin 3 g/day in patient with uncontrolled complex partial seizures. *Neurology*. 1996;46:54-61.
4. Şirvancı S, Midillioğlu Ş, Meshul C, Onat F, Şan T. Dendritic spines in the hippocampus of genetic absence epilepsy rats (GAERS): an ultrastructural quantitative analysis. *Marmara Med J*. 2016;16:195-200.
5. Daou BJ, Koduri S, Thompson BG, Chaudhary N, Pandey AS. Clinical and experimental aspects of aneurysmal subarachnoid hemorrhage. *CNS Neurosci Ther*. 2019;25:1096-1112.
6. Pluta RM, Afshar JK, Boock RJ, Oldfield EH. Temporal change in perivascular concentrations

of oxyhemoglobin, deoxyhemoglobin, and methemoglobin after subarachnoid hemorrhage. *J Neurosurg*. 1998;88:557-561.

7. Kertmen H, Gürer B, Yılmaz ER, et al. The effect of thiocolchicoside on cerebral vasospasm following experimental subarachnoid hemorrhage in the rabbit. *Acta Neurochir*. 2012;154:1431-1436.

8. Miller BA, Turan N, Chau M, Pradilla G. Inflammation, vasospasm, and brain injury after subarachnoid hemorrhage. *Biomed Res Int*. 2014;2014:384342.

9. Ayer RE, Zhang JH. Oxidative stress in subarachnoid haemorrhage: significance in acute brain injury and vasospasm. *Acta Neurochir Suppl*. 2008;104:33-41.

10. Yuksel S, Tosun YB, Cahill J, Solaroglu I. Early brain injury following aneurysmal subarachnoid hemorrhage: emphasis on cellular apoptosis. *Turk Neurosurg*. 2012;22:529-533.

11. Kolias AG, Sen J, Belli A. Pathogenesis of cerebral vasospasm following aneurysmal subarachnoid hemorrhage: putative mechanisms and novel approaches. *J Neurosci Res*. 2009;87:1-11.

12. Ben-Menachem E. Mechanism of action of vigabatrin: correcting misperceptions. *Acta Neurol Scand Suppl*. 2011;192:5-15.

13. Petroff OAC, Rothman DL, Behar KL, Collins TL, Mattson RH. Human brain GABA levels rise rapidly after initiation of vigabatrin therapy. *Neurology*. 1996;47:1567-1571.

14. Sills GJ, Butler E, Thompson GG, Brodie MJ. Vigabatrin and tiagabine are pharmacologically different drugs: a pre-clinical study. *Seizure*. 1999;8:404-411.

15. Willmore LJ, Abelson MB, Ben-Menachem E, Pellock JM, Shields WD. Vigabatrin: 2008 update. *Epilepsia*. 2009;50:163-173.

16. Alborch E, Torregrosa G, Terasa JC, Estrada C. GABA receptors mediate cerebral vasodilation in the unanesthetized goat. *Brain Res*. 1984;321:103-110.

17. Edvinsson L, Krause DN. Pharmacological characterization of GABA receptors mediating vasodilation of vertebral arteries in vitro. *Brain Res*. 1979;173:89-97.

18. Imai H, Okuno T, Wu JY, Lee TJ. GABAergic innervation in cerebral blood vessels: an immunohistochemical demonstration of L-glutamic acid decarboxylase and GABA transaminase. *J Cereb Blood Flow Metab*. 1991;11:129-134.

19. Fujiwara M, Muramatsu I. Gamma-aminobutyric acid receptor on vascular smooth muscle of dog cerebral arteries. *Br J Pharmacol*. 1975;55:561-562.

20. Sills GJ, Butler E, Forrest G, Ratnaraj N, Patsalos PN, Brodie MJ. Vigabatrin, but not gabapentin or topiramate, produces concentration-related effects on enzymes and intermediates of the GABA shunt in rat brain and retina. *Epilepsia*. 2003;44:886-892.

21. Gürer B, Kertmen H, Kuru Bektaşoğlu P, et al. The effects of cinnamaldehyde on early brain injury and cerebral vasospasm following experimental subarachnoid hemorrhage in rabbits. *Metab Brain Dis*. 2019;34:1737-1746.

22. Gürer B, Turkoglu E, Kertmen H, Karavelioglu E, Arikok AT, Sekerci Z. Attenuation of cerebral vasospasm and secondary injury by testosterone following experimental subarachnoid hemorrhage in rabbit. *Acta Neurochir (Wien)*. 2014;156:2111-2120 [discussion: 2120].

23. Kertmen H, Gürer B, Yilmaz ER, et al. The comparative effects of recombinant human erythropoietin and darbepoetin-alpha on cerebral vasospasm following experimental subarachnoid hemorrhage in the rabbit. *Acta Neurochir (Wien)*. 2014;156:951-962.

24. Findlay J, Nisar J, D'Assaut T. Cerebral vasospasm: a review. *Can J Neurol Sci*. 2016;43:15-32.

25. Vorkapic P, Bevan JA, Bevan RD. Two indices of functional damage of the artery wall parallel the time course of irreversible narrowing in experimental vasospasm in the rabbit. *Blood Vessel*. 1991;28:179-182.

26. Wang P, Eshaq RS, Meshul CK, Moore C, Hood RL, Leidenheimer NJ. Neuronal gamma-aminobutyric acid (GABA) type A receptors undergo cognate ligand chaperoning in the endoplasmic reticulum by endogenous GABA. *Front Cell Neurosci*. 2015;9:188.

27. Cetas JS, Lee DR, Alkayed NJ, Wang R, Iliff JJ, Heinricher MM. Brainstem control of cerebral blood flow and application to acute vasospasm following experimental subarachnoid hemorrhage. *Neuroscience*. 2009;163:719-729.

28. Ben-Menachem E. Mechanism of action of vigabatrin: correcting misperceptions. *Acta Neurol Scand Suppl*. 2011;192:5-15.

29. Tong X, Ratnaraj N, Patsalos PN. Vigabatrin extracellular pharmacokinetics and concurrent gamma-aminobutyric acid neurotransmitter effects in rat frontal cortex and hippocampus using microdialysis. *Epilepsia*. 2009;50:174-183.

30. Sabri M, Lass E, Macdonald RL. Early brain injury: a common mechanism in subarachnoid hemorrhage and global cerebral ischemia. *Stroke Res Treat*. 2013;2013:394036.

31. Choi DW. Excitotoxic cell death. *J Neurobiol*. 1992;23:1261-1276.

32. Dhawan J, Benveniste H, Luo Z, Nawrocky M, Smith SD, Biegon A. A new look at glutamate and ischemia: NMDA agonist improves long-term functional outcome in a rat model of stroke. *Future Neurol*. 2011;6:823-834.

33. Nau R, Haase S, Bunkowski S, Brück W. Neuronal apoptosis in the denate gyrus in humans with subarachnoid hemorrage and cerebral hypoxia. *Brain Pathol*. 2002;12:329-336.

34. Prunell GF, Svendgaard NA, Alkass K, Mathiesen T. Delayed cell death related to acute cerebral blood flow changes following subarachnoid hemorrhage in the rat brain. *J Neurosurg*. 2005;102:1046-1054.

35. Guerriero RM, Giza CC, Rotenberg A. Glutamate and GABA imbalance following traumatic brain injury. *Curr Neurol Neurosci Rep*. 2015;15:27.

36. Shen J, Shen J, Zhu K, Zhou H, Tian H, Yu G. Efficacy of statins in cerebral vasospasm, mortality, and delayed cerebral ischemia in patients with aneurysmal subarachnoid hemorrhage: a systematic review and meta-analysis of randomized controlled trials. *World Neurosurg*. 2019;131:e65-e73.

37. Merlo L, Cimino F, Scibilia A, et al. Simvastatin administration ameliorates neurobehavioral consequences of subarachnoid hemorrhage in the rat. *J Neurotrauma*. 2011;28:2493-2501.

Conflict of interest statement: The authors declare that the article content was composed in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

The present study was presented as a poster at the World Federation of Neurosurgical Societies International Meeting, March 21—24, 2019, Belgrade, Serbia.

Received 6 March 2020; accepted 25 May 2020

Citation: World Neurosurg. (2020) 141:e559-e565.
https://doi.org/10.1016/j.wneu.2020.05.230

Journal homepage: ***www.journals.elsevier.com/world-neurosurgery***

Available online: ***www.sciencedirect.com***

1878-8750/$ - see front matter