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Cerebral Hemodynamic Changes During Migraine Attacks and After Triptan Treatments

Migren Atağında ve Triptan Tedavisi Sonrasında Serebral Hemodinamik Değişiklikler

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ABSTRACT

Introduction: Migraine has been known for many years, but its mechanism remains unclear. Different cerebral hemodynamic changes have been observed at different stages of a migraine attack. Published results on cerebral hemodynamics are contradictory. For this reason, we aimed to investigate cerebral hemodynamic changes during attacks as well as the effects of frovatriptan and rizatriptan.

Methods: Forty migraine patients with aura using rizatriptan (n=20) and frovatriptan (n=20) and 20 healthy individuals were included in our study. Cerebral blood flow velocities and breath-holding indices were recorded bilaterally from middle and posterior cerebral arteries. All procedures were repeated one hour after treatments and one week after attacks.

Results: We observed similar values of cerebral blood flow velocities and breath holding indices in all patients with migraine during the attack-free period compared to the control group. All cerebral vascular structures in migraine patients had significantly lower cerebral blood flow velocities and higher values in breath-holding indices during attacks. After taking rizatriptan and frovatriptan for an attack, the changes in hemodynamics disappeared.

Conclusion: During attacks of migraineurs with aura, vasodilatation develops. In addition, higher vasomotor reactivity during attacks supports hypersensitivity in migraine pathophysiology. Triptans, acting as vasoconstrictor agents, were able to stop over-vasodilatation during attacks. In other words, it is possible that triptans show their effects by eliminating vascular hypersensitivity during acute attacks.

Keywords: Migraine, hemodynamics, rizatriptan, frovatriptan

ÖZ

Giriş: Migren uzun yıllardan beri bilinen ama sebebi ve mekanizması halen tam olarak açıklanamayan kompleks bir hastalıktır. Migren atağının farklı dönemlerinde farklı hemodinamik değişiklikler gözlenmektedir. Serebral hemodinami üzerine yapılan çalışma sonuçları karışıktır. Bu sebepten, frovatriptan ve rizatriptanın migren atağında serebral hemodinami üzerine etkilerini araştırmak istedik.

Yöntem: Çalışmaya frovatriptan (n=20) ve rizatriptan (n=20) kullanan 40 auralı migren hastası ve sağlıklı 20 birey alındı. Bilateral Orta serebral arter ve arka serebral arter kayıtları ve nefes tutma indeksleri hesaplandı. Tedaviden bir saat ve ataktan bir hafta sonra işlemler tekrarlandı.

Bulgular: Çalışma sonucunda migrenli hastaların tamamında ataksız dönemde kontrol grubu ile benzer serebral kan akım hızları ve nefes tutma indeksleri saptadık. Atak esnasında migrenli hastalarda incelenen bütün serebral vasküler yapılarda serebral kan akım hızları anlamlı derecede düşük, nefes tutma indeksleri ise anlamlı derecede artmış olarak saptandı. Kullanılan frovatriptan ve rizatriptan sonrasında atak esnasında saptanan bu değişikliğin ortadan kaybolduğu saptandı.

Sonuç: Auralı migrenlilerde atak esnasında vazodilatasyon gelişmektedir. Ayrıca atak esnasında vazomotor reaktivitenin sağlıklı bireylere göre daha yüksek saptanması da migrenlilerde bir hipersensitiviteyi desteklemektedir. Vazokonstriktör etki gösteren triptanların atak esnasında ortaya çıkan aşırı vazodilatasyonu yok ettikleri gösterildi. Bir başka deyişle, triptanların etkilerini akut atak esnasında vasküler etkilenme ile gelişen hipersensitiviteyi ortadan kaldırarak gösterdiğini söylemek mümkündür.

Anahtar Kelimeler: Migren, hemodinami, rizatriptan, frovatriptan

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INTRODUCTION

Migraine is mainly a neuron-related process. The hyperexcitable cerebral cortex probably plays an important role in migraine pathophysiology. The wave of excitation and cortical spreading depression (CSD) are responsible for the activation of the trigeminovascular system. CSD induces Pannexin1 channel opening and caspase-1 activation and this may activate trigeminal afferents via inflammatory cascades (1). CSD results from the spreading of neuronal depolarization caused by any internal or external factor (2).

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The main pathophysiological mechanism of migraine aura or prodrome period is intracranial vasoconstriction, the cause of which is still unclear. Migraine aura is associated with oligemia starting in the occipital cortex and spreading forward about 2–3 mm per minute. Oligemia may expand and affect the entire hemisphere. The spreading of oligemia is not related to vascular supply zones and vasoconstriction (3). The velocity of spreading cortical depression waves and scotoma during aura are similar, suggesting that these phenomena might be related.

Inflammatory molecules can mediate vasodilation of nearby vessels and cause nociceptor activation. Vessels can activate trigeminal neurons mechanically or by release of inflammatory mediators due to increased vascular permeability (4).

Transcranial Doppler (TCD) is a simple and non-invasive method for assessing cerebral blood flow velocity and cerebral vasomotor reactivity (VMR). Cerebral autoregulation helps cerebral blood flow (CBF) at regular intervals despite fluctuations, particularly in the cerebral perfusion (5).

Vasomotor reactivity can be detected by TCD as the blood flow rate changes via acetazolamide injection, hyperventilation, or carbon dioxide inhalation. Carbon dioxide inhalation is the preferred method because of low risk, strong effect, and more accurate results (6). Studies of cerebral blood flow and vasomotor reactivity in migraineurs with aura using TCD have contradictory results. Some report increases in basal cerebral blood flow (7, 8) while others show no difference (9, 10). Some studies showed a decrease in vasomotor reactivity due to CO_2 in the interictal period (11) while other studies showed an increase (11–15).

This study's aim was investigate vasomotor reactivity and cerebral blood flow responses to frovatriptan and rizatriptan treatments as well as cerebral hemodynamic changes during spontaneous migraine attacks.

METHODS

This study was conducted with patients with acute migraine attacks and healthy volunteers. Participants were informed about the study and consented to it, which was approved by GATA local ethic committee (Approval number 1491–1508–11/1539). The physical examination of healthy individuals and migraine with aura patients was made and inclusion and exclusion criteria for the study were evaluated. All individuals were given a code to make recordings. The study included a total of 40 migraine patients (20 using frovatriptan and 20 using rizatriptan) and 20 healthy volunteers matched by age and sex.

Patients included were those with no migraine attacks in the last 15 days, those not taking prophylactic treatment, and those admitted within two hours of the beginning of the aura or prodromal symptoms. Patients excluded were those with carotid artery disease, connective tissue disease, amyloidosis, liver-kidney or thyroid disorders, malignancies, and those with a history of alcohol abuse or other neurological or cardiac disease.

For all participants, TCD applications were made with the DWL Multi-Dop X4 device in a quiet room. Through the temporal bone window, first the middle cerebral artery and then posterior cerebral arteries were evaluated separately with 2 MHz probe. After resting for about ten minutes, a five-minute recording was made to evaluate basal cerebral blood flow. The average of these recordings was set as the baseline blood flow velocity (BFV). The same protocol was applied separately for Middle cerebral artery (MCA) and posterior cerebral artery (PCA). The same procedure was applied to patients with migraine attacks and then triptan was given to the patient. The procedures were repeated after one hour and after one week, to examine the basal cerebral hemodynamics of patients.

For statistical analysis, SPSS 15.0 was used. Frequency tables for categorical variables, descriptive statistics for quantitative variables (mean, standard deviation, median, minimum, maximum) were made. Between group comparisons chi-square, Kruskal-Wallis, and Mann-Whitney U tests were used. Values of $p<0.05$ were considered statistically significant. Groups 1 and 2 are patients treated with frovatriptan and rizatriptan, respectively.

RESULTS

Of the 60 patients in the study, 65% were female (n=39) and 35% were male (n=21). The averages age of the control group, group 1, and group 2 were 29.3±6, 28.05±5, and 28.4±5, respectively. There was no significant difference in ages between groups (p=0.790). There were no significant differences in basal BFV values for bilateral MCA and PCA between groups (Table 1). Significant changes were observed in MCA and PCA BFV values between interictal, ictal, and postictal periods (p<0.001) (Figure 1). There were no significant differences in bilateral MCA and PCA VMR values between groups (Table 2). Significant changes were observed in

Table 1. Basal BFV values

	Control Group	Group 1 Frovatriptan	Group 2 Rizatriptan
Interictal left MCA basal	56.95±6.67	57.05±6.60	57.18±4.70
Ictal left MCA basal	-	55.38±5.71	54.86±3.44
Postictal left MCA basal	-	56.78±6.26	56.81±4.26
Interictal right MCA basal	56.72±8.01	56.78±6.90	56.61±4.59
Ictal right MCA basal	-	55.51±6.47	54.60±4.17
Postictal right MCA basal	-	56.56±6.65	56.63±4.94
Interictal left PCA basal	25.48±2.89	25.98±2.69	26.13±2.54
Ictal left PCA basal	-	24.93±2.53	24.52±1.93
Postictal left PCA basal	-	25.95±2.55	25.90±2.35
Interictal right PCA basal	25.31±3.49	26.09±2.90	26.03±2.59
Ictal right PCA basal	-	25.45±2.96	24.45±1.85
Postictal right PCA basal	-	26.07±2.69	25.81±2.43

Table 2. VMR values

	Control Group	Group 1 Frovatriptan	Group 2 Rizatriptan
Interictal left MCA-VMR	1.41±0.15	1.42±0.06	1.42±0.05
Ictal left MCA-VMR	-	1.48±0.06	1.50±0.13
Postictal left MCA-VMR	-	1.43±0.08	1.42±0.03
Interictal right MCA-VMR	1.43±0.18	1.42±0.08	1.43±0.05
Ictal right MCA-VMR	-	1.47±0.07	1.50±0.12
Postictal right MCA-VMR	-	1.42±0.07	1.42±0.03
Interictal left PCA-VMR	1.46±0.09	1.46±0.10	1.47±0.09
Ictal left PCA-VMR	-	1.52±0.06	1.54±0.05
Postictal left PCA-VMR	-	1.46±0.06	1.47±0.08
Interictal right PCA-VMR	1.46±0.09	1.47±0.05	1.46±0.07
Ictal right PCA-VMR	-	1.52±0.05	1.54±0.05
Postictal right PCA-VMR	-	1.48±0.10	1.46±0.05

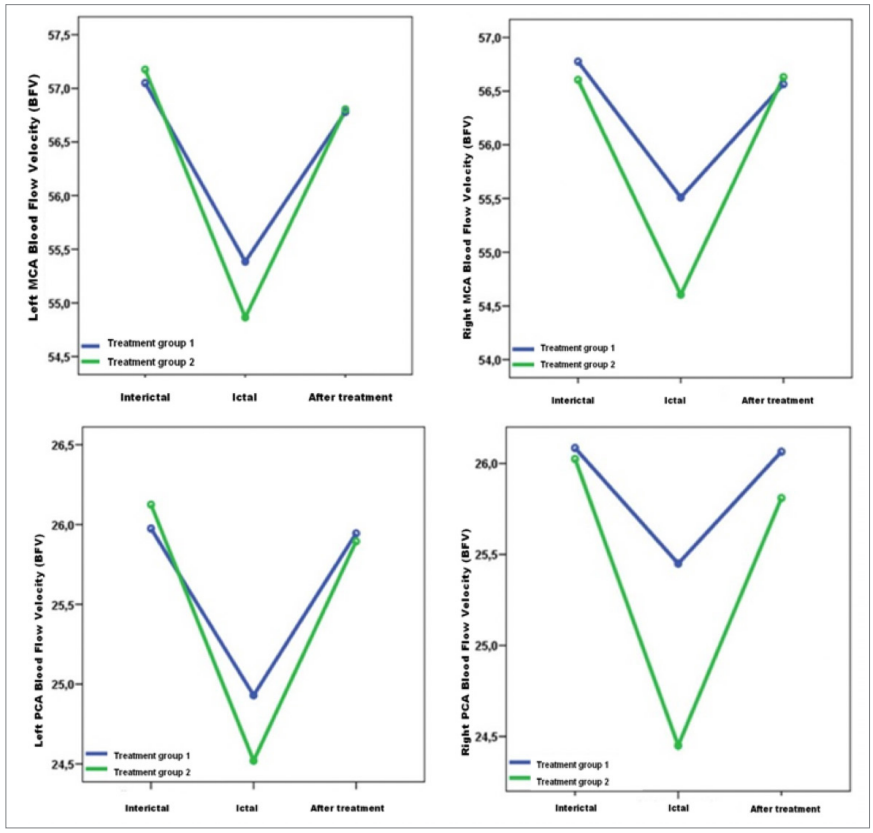

Figure 1. Bilateral MCA and PCA BFV changes in treatment groups.
Significant changes were observed in MCA and PCA VMR values between interictal, ictal, and postictal periods (p<0.001)

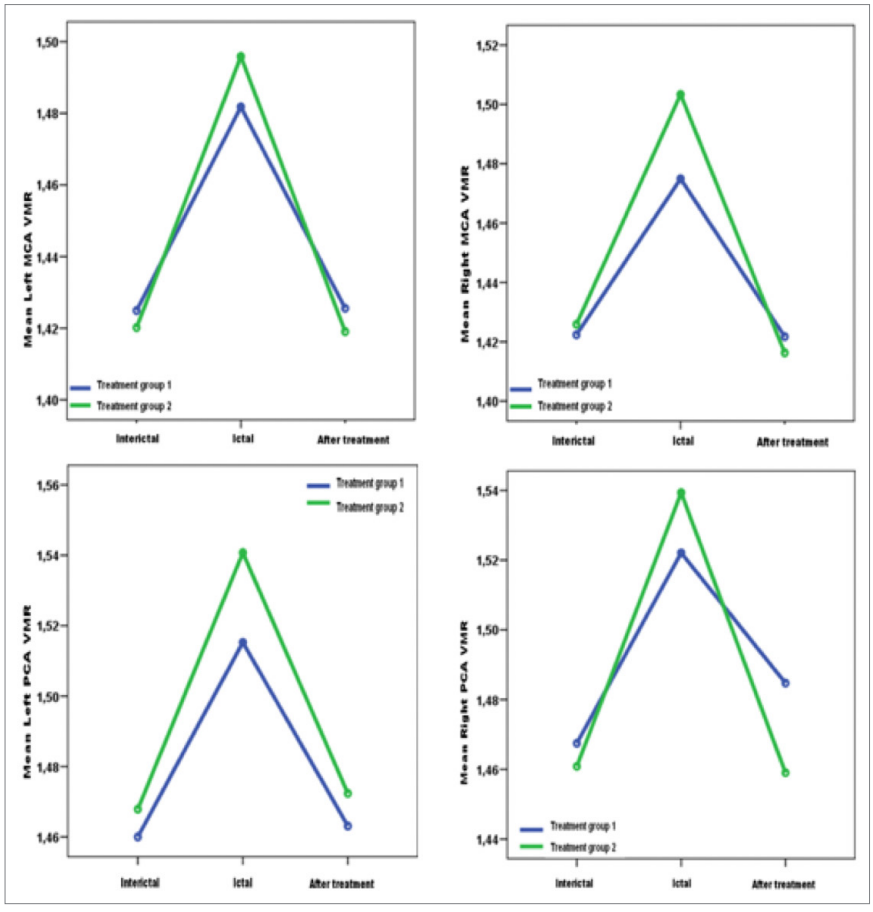

Figure 2. Bilateral MCA and PCA VMR changes in treatment groups.
There was no difference between the two treatment groups (p=0.687, p=0.440, p=0.761, p=0.162)

MCA and PCA VMR values between interictal, ictal, and postictal periods (p<0.001) (Figure 1). There was no difference between the two treatment groups (p=0.687, p=0.440, p=0.761, p=0.162) (Figure 2).

BFV and VMR values after treatment were similar to those from the pain-free period. But during attacks, these values were statistically and significantly different from values during the both pain-free period and after treatment (Table 3). In other words we observed a conspicuous increase in BFV and decrease in VMR values during spontaneous migraine attack. After triptan treatments these changes had been disappeared.

Table 3. P value comparisons between three periods

	Interictal-attack	Interictal-after treatment	Attack-after treatment
Left MCA BFV	<0.001	0.155	<0.001
Right MCA BFV	<0.001	0.683	<0.001
Left PCA BFV	<0.001	0.071	<0.001
Right PCA BFV	<0.001	0.130	<0.001
Left MCA-VMR	<0.001	0.982	<0.001
Right MCA-VMR	<0.001	0.663	<0.001
Left PCA-VMR	<0.001	0.778	<0.001
Right PCA-VMR	<0.001	0.405	<0.001

DISCUSSION

In this study, we investigated cerebral hemodynamics changes with TCD during spontaneous attacks and after treatments for attacks in migraineurs with aura and compared basal values with healthy subjects. Statistically significant changes in BFV and VMR values recorded from bilaterally MCA and PCA were observed during attacks as compared to the attack-free period and after taking triptan. Decreases in BFV from PCA in the rizatriptan group were more significant than in the frovatriptan group. Although migraine patients often complain of unilateral headache, we did not notice any significant difference in terms of right and left hemodynamic changes in our study.

Some studies have investigated the effects of triptans on cerebral hemodynamics during migraine attacks. Thie et al. (14) examined 100 migraine patients with

and without aura during the pain-free period and observed higher blood flow velocities in all intracranial arteries for migraine patients than control subjects. In addition, posterior cerebral artery vascular reactivity, a response to eye closure, was significantly higher in migraineurs. Rieke et al. (16) studied migraineurs during attacks and interictal period via functional TCD and magneto-ensefalography. Mean BFVs in MCA ipsilateral to pain were higher during the resting period in the migraine group than the control group whereas VMR values were lower on the same side. Similar to this study, Fiermonte et al. (12) evaluated migraineurs with or without aura during the interictal period via cerebrovascular CO_2 reactivity with TCD and found increased reactivity in migraineurs with aura. Harer et al. (13) showed a decrease in vasoreactivity after CO_2 inhalation in migraineurs.

Uzuner et al. (17) designed their study differently. They evaluated BFVs on TCD using simple and complex visual stimuli. In migraineurs with aura BFVs were higher bilaterally than in the control groups and migraine patients without aura. The increase was statistically significant on the aura-developing side. These results have been interpreted as cortical hyperexcitability in patients with migraine with aura. Uzuner et al. (18) studied vasoneuronal coupling in migraineurs during attacks. Silvestrini et al. (19) assessed BFVs after hypercapnia and mental and motor activity on MCA, ACA, and PCA in migraineurs during attack-free periods. Similar vascular responses were shown between groups.

Totaro et al. (20) showed a lower vasodilator response resulting in hypercapnia in migraineurs without aura than controls and migraineurs with aura; this has been linked to arteriolar basal dilatation.

Heckmann (11) used ergometer stress tests to assess vascular reactivity. Resistance indices were lower in migraine patients with aura than the control group and migraine patients without aura. He concluded that impairment in myogenic cerebrovascular autoregulation may exist in migraineurs with aura.

Dora and Balkan compared migraineurs without aura to the control group. BHIs were significantly higher in migraineurs (21). They evaluated 20 migraineurs' BHIs pre-and post-treatment with flunarizine. Pre-treatment values were significantly higher than in control groups. After a three-month treatment this difference disappeared (22). Fiermonte's study on migraineurs showed higher BFVs in all groups and increased VMR only in patients with aura before treatment (23). After two-month flunarizine treatments no changes in BFVs were seen while VMRs became normal.

In a study designed to evaluate the effects of triptans on cerebral hemodynamics in 45 healthy subjects and 15 migraineurs without aura, Thomaides used BFV and the pulcatility index before and after zolmitriptan and sumatriptan administration during attacks induced with nitroglycerin (24). There was a significant decrease in BFVs during attacks and normalized values one hour after treatment.

In another study, Silvestrini et al. evaluated cerebrovascular reactivity in bilateral MCA and basilar artery in 30 migraineurs (n=15 migraine with aura, n=15 migraine without aura) and 15 patients in the control group (25). Reactivity in MCAs were similar to controls whereas VMR in basilar arteries were lower in migraineurs than controls.

Schoonman et al. designed a 3T-MRA study on the existence of vasodilatation, which plays an important role in the migraine mechanism (26). Cerebral blood vessel diameters and blood flow velocities were assessed and compared with control subjects. External carotid artery, MCA, basilar artery, internal carotid artery, and the middle meningeal artery were used to measure vessel diameters. BFVs were recorded from PCA and basilar artery. Recordings were made in attack-free periods, during placebo, or induced by nitroglycerin, if an attack occurred within six hours of induction. Vasodilatation was not demonstrated. There are many limitations to this study. Extracranial vascular hemodynamics, the intracranial part of the middle meningeal artery, and the extracranial part of external carotid artery were not assessed. Migraine attacks were triggered by nitroglycerin, which may not be the same spontaneous attacks (27).

Nagata assessed meningeal arteries during spontaneous attacks (28). He did not determine vasodilatation in arteries, however, did report vasoconstriction, which developed after subcutaneous sumatriptan injection.

Migraine attacks decrease blood flow velocities in intra-and extracranial arteries whereas blood flow velocities increased due to vasoconstriction antimigraine drug injection (29, 30).

Rizatriptan's effect on cerebral hemodynamics was first investigated by Gori (31). He investigated the effect of rizatriptan on cerebral blood flow velocity in migraineurs without aura during spontaneous attacks. Cerebral hemodynamics were measured during attacks and after rizatriptan administration, four times at 30-minute intervals. Recording was repeated in the pain-free period for 30 minutes. No significant differences were shown between attack, pain-free, pre-, and post-treatment periods. However, this study was designed only with MCA and only BFVs were assessed.

All vascular agents playing role during migraine attack with a vasodilatation do not produce a migraine headache. For example Vasoactive Intestinal Peptide (VIP) induces only a mild headache (32). Calcitonin Gene Related Peptide (CGRP) is one of the most potent vasodilator peptide released during migraine attack. CGRP cause vasodilatation both in meningeal and cerebral arteries. CGRP infusion results in migraine patients in migraine-like headache (33).

In our study we observed a decrease in cerebral BFVs and an increase in VMR during spontaneous migraine attacks. This is considered to be an indirect indicator of vasodilation although an MRA study did not show vasodilatation. MRA studies provide us anatomical information. In addition, measurements made during angiographic studies are made momentarily. In our study, we recorded the blood flow velocities for 5 minutes and evaluated it on the average. So we did not miss any hemodynamic changes during attack. If we had a longer record, we would have had to give triptan more lately. This could change the effectiveness of the treatment.

Higher vasomotor reactivity during attacks than in healthy individuals supports vascular hypersensitivity in migraineurs. Vasoconstrictor effect of triptans was shown with the normalization of BFVs and VMRs. In other words, triptans have hemodynamic effects during acute attacks by normalizing hemodynamic dysregulation. VMR is considered as an indicator of the capacity to adapt to changes in brain hemodynamics. In our study, we showed that there was an increase in the blood flow velocity in the spontaneous migraine attack, whereas the vasomotor reactivity decreased. Here we can draw the following conclusion; vasodilatation develops in migraine attacks and cerebral hemodynamic autoregulation occurs. This vasodilatation is terminated by triptan treatment and vasomotor reactivity is normalized. Although there are few studies in the literature on the effect of triptans on BFV, there is no detailed study of its effect on VMR.

Ethics Committee Approval: The study was approved by the GATA local ethics committee (approval certificate 1491-15089111/1539).

Informed Consent: The participants were informed about the study by the GATA local ethics committee.

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Author Contributions: Concept - BÖ; Design - BÖ; Supervision - ÖK; Resource - BÖ; Materials - ÖK; Data Collection and/ or Processing - BÖ; Analysis and/or Interpretation - ÖK; Literature Search - BÖ; Writing - BÖ; Critical Reviews - ÖK.

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