BOLETIN LATINOAMERICANO Y DEL CARIBE DE PLANTAS MEDICINALES Y AROMÁTICAS
© / ISSN 0717 7917 / www.blacpma.ms-editions.cl

Articulo Original / Original Article

# Effect of anisodamine on regional cerebral blood flow in patients with dizziness: A randomized single-blind controlled trial

[Efecto de la anisodamina en el flujo sanguíneo cerebral regional en pacientes con mareos: un ensayo controlado aleatorizado de un solo ciego]

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Received: 23 September 2023
Accepted: 5 January 2024
Accepted corrected: 31 March 2024
Published: 30 September 2024

**Citation:**
Chen L, Lei B, Li Z, Jiang J. Effect of anisodamine on regional cerebral blood flow in patients with dizziness: A randomized single-blind controlled trial
**Bol Latinoam Caribe Plant Med Aromat**
23 (5): 811 - 822 (2024)
**https://doi.org/10.37360/blacpma.24.23.5.52**

**Abstract:** This study aimed to evaluate the effect of anisodamine on regional cerebral blood flow (rCBF) and associated dizziness. 150 patients with dizziness induced by low rCBF were divided randomly into groups A (n = 60; anisodamine), P (n = 60; alprostadil), and C (n = 30; normal saline). rCBF and dizziness severity were evaluated. After treatment, rCBF values increased both in groups A and P. The subjective symptom of dizziness improved in 55 (91.7%) patients with the DHI score decreasing from 65.9 ± 5.4 to 23.1 ± 7.4 in group A, and the symptom improved in 37 (61.7%) patients with the DHI score decreasing from 66.8 ± 6.2 to 43.8 ± 8.6 in group P. The difference in DHI score and rCBF values in group A was more significant than that in group P. Anisodamine could increase rCBF and alleviate symptoms of dizziness more effectively than alprostadil.

**Keywords:** Regional cerebral blood flow; $^{99m}$Tc-ethyl cysteinate dimer; Single-photonemission computed tomography; Anisodamine; Dizziness

**Resumen:** Este estudio tuvo como objetivo evaluar el efecto de la anisodamina en el flujo sanguíneo cerebral regional (rCBF) y los mareos asociados. 150 pacientes con mareos inducidos por un bajo rCBF fueron divididos aleatoriamente en los grupos A (n = 60; anisodamina), P (n = 60; alprostadil) y C (n = 30; solución salina normal). Se evaluaron el rCBF y la gravedad de los mareos. Después del tratamiento, los valores de rCBF aumentaron tanto en los grupos A como en P. El síntoma subjetivo de mareo mejoró en 55 (91.7%) pacientes con una disminución de la puntuación DHI de 65.9 ± 5.4 a 23.1 ± 7.4 en el grupo A, y el síntoma mejoró en 37 (61.7%) pacientes con una disminución de la puntuación DHI de 66.8 ± 6.2 a 43.8 ± 8.6 en el grupo P. La diferencia en la puntuación DHI y los valores de rCBF en el grupo A fue más significativa que en el grupo P. La anisodamina podría aumentar el rCBF y aliviar los síntomas de mareo de manera más efectiva que el alprostadil.

**Palabras clave:** Flujo sanguíneo cerebral regional; $^{99m}$Tc-etil cisteinato dímero; Tomografía computarizada de emisión monofotónica; Anisodamina; Mareos

## INTRODUCTION

The term "dizziness" is subjective and nonspecific, but is customarily defined as vertigo, lightheadedness, presyncope, disequilibrium, or just not feeling well (Noij *et al*., 2021). Dizziness is a common complaint in clinical practice. The percentage of patients with dizziness is more than 3% of all emergency department visitors (Newman-Toker *et al*., 2008). Long-standing and short-duration mixed dizziness occurs more than once a month and affects primarily the functional aspects in patients with advanced age, especially in women (Rosa *et al*., 2016). Moreover, dizziness confers a huge burden on the medical care system. Troublesomely, the pathogenesis of dizziness is extensive and complicated, including the harmless and the life-threatening. A wide range of causes have been related to dizziness, such as vestibular, cardiovascular, respiratory, neurologic (including cerebrovascular), injury/poisoning, metabolic, psychiatric, digestive, genitourinary, and infectious conditions (Newman-Toker *et al*., 2008). In addition, many studies have demonstrated that dizziness is the most common symptom in patients with posterior circulation ischemia, and the low regional cerebral brain flow (rCBF) could be responsible for dizziness (Searls *et al*., 2012; Firwana *et al*., 2022). Hence, it is reasonable to hypothesize that the vasodilating drugs that can increase the rCBF might have a therapeutic effect on dizziness.

Anisodamine, extracted initially in 1965 from the Chinese medicinal herb *Scopolia tangutica Maxim* and synthesized in 1975, has a long history in clinical practice in China and shows extensive medical value by a large number of basic and clinical studies. Thus, it has been widely used in various diseases such as organophosphorus poisoning, gastric ulcers, gastrointestinal colic, eclampsia, migraine, respiratory diseases, rheumatoid arthritis, acute glomerular nephritis, obstructive jaundice, snake bite, and radiation damage (Yu *et al*., 2021b). In addition, the effect of anisodamine on improving microcirculation is attracting increasing attention. It is commonly used in the rescue of disseminated intravascular coagulation (DIC) and septic shock (Zhang *et al*., 1987; Zhang *et al*., 2015), which are closely related to microcirculatory disturbance. Further investigations showed that anisodamine also possessed salutary effects on brain microcirculation in rats (Varma & Yue, 1986). Hence, anisodamine may be the drug we need to increase rCBF and ameliorate low rCBF-associated dizziness.

The $^{99m}$Tc-ethyl cysteinate dimer (ECD) brain perfusion single-photon emission computed tomography (SPECT) is a noninvasive method to evaluate rCBF (Amen *et al*., 2017; Zheng *et al*., 2017; Huaijantug *et al*., 2020). By ECD SPECT, we can effectively determine whether there is a low rCBF in patients with dizziness. Thus, this study aimed to evaluate the role of anisodamine in increasing the rCBF determined by ECD SPECT and investigate the therapeutic effect of anisodamine compared with alprostadil (prostaglandin $E_1$, $PGE_1$) on low rCBF in patients with dizziness.

## PATIENTS AND METHODS

### *Patient information*

Patients complaining of dizziness, occasionally accompanying headache, were recruited in this study from January 2015 to October 2021. The inclusion criteria for this study included symptoms of dizziness and low rCBF in $^{99m}$Tc-ECD brain perfusion SPECT. The exclusion criteria were as follows: (1) carotid artery stenosis > 50%, (2) lethal diseases, such as cerebral hemorrhage, malignant tumor, acute cerebral infarction, and myocardial infarction, (3) age < 18 years, (4) severe insufficiency of the heart, liver, lung, or kidney, (5) epilepsy and cerebral trauma, (6) vestibular disease, (7) contraindication of drugs, including pregnancy, glaucoma, myasthenia gravis, prostatic hyperplasia, and obstructive gastrointestinal disorders, (8) patients who were unwilling to receive or could not tolerate the treatment of anisodamine or alprostadil. Ultimately, a total of 150 patients aged 66.4 ± 8.8 years (67 male, 83 female) were enrolled in the present study.

A complete and thorough description of the study was given to all subjects who gave written informed consent prior to the study according to the institutional guidelines and the Declaration of Helsinki. The study protocol was reviewed and approved by the ethics committee of Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine, China.

### *Study design*

This study used a prospective, single-blind, randomized, and controlled method. All patients enrolled were divided into three groups: group A (anisodamine group, n=60), received an intravenous administration of anisodamine (Hangzhou Minsheng Pharmaceutical Group Co., Ltd, China) at a dose of 0.5 mg/kg, diluted with 50 mL normal saline, which was carried out at a rate of 5 mL/h via a micro-infusion pump; group P (alprostadil group, n=60), received an intravenous drip of 20 μg of alprostadil

(Beijing Tide Pharmaceutical Co., Ltd, China), diluted with 50 mL normal saline, within 15 to 20 minutes; and group C (control group, n=30), received a placebo of 50 mL of normal saline only, administered at a rate of 5 mL/h via a micro-infusion pump. The treatment cycle in each group is 14 days. All patients had no knowledge of any details about the specific drugs they received until the end of this study. The CONSORT diagram for the study is presented in Figure No. 1.

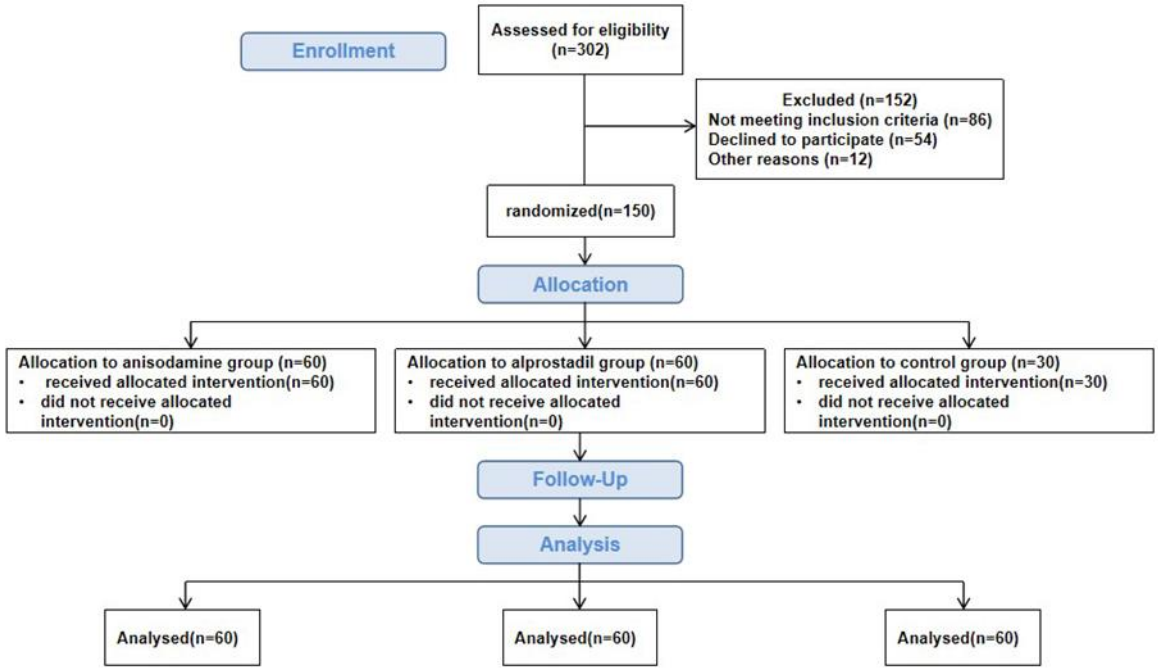



**Figure No. 1**

***$^{99m}$Tc-ECD brain perfusion SPECT***

$^{99m}$Tc-ECD brain perfusion SPECT was performed as previous literature in the patients with dizziness on admission and within 7 days after treatment, respectively, by using a Symbia T16 SPECT/CT (Siemens, Germany) (Lei *et al*., 2017). Before scanning, all patients were required to keep a supine position with eyes closed in a dark and quiet room for 30 minutes. SPECT/CT scans were performed 10 min after the intravenous injection of 1480 MBq of $^{99m}$Tc-ECD (Neurolite, Bristol-Myers Squibb, USA). The images were acquired in a matrix of 128 × 128 through a rotation of 360° at steps of 2.8° for 80,000 counts per view. Patients should keep still during this period. The SPECT images were reconstructed using filtered back-projection with ordered subset expectation materialization (OSEM) (Gorelick *et al*., 2011; Liang *et al*., 2016). Each brain perfusion SPECT/CT study was quantified and compared with an age- and sex-matched normal database using the NeuroGam software package (Segami Corporation, USA).

The interpretations of all images were carried out by 2 senior nuclear physicians in accordance with a uniform standard without knowing any information about the patients in advance. Data were analyzed using a revised 3-dimensional stereotaxic region of interest (ROI) template which was composed of 8 segments (1, frontal lobe; 2, parietal lobe; 3, temporal lobe; 4, occipital lobe; 5, basal ganglia; 6, thalamus; 7, hippocampus; 8, cerebellum) on each side (Takeuchi *et al*., 2002). Quantification of rCBF was evaluated according to the noninvasive Patlak plot method (Matsuda *et al*., 1995). Quantitative values of rCBF were expressed as mL/100g/min. Abnormal areas with perfusion defects were defined as those

with decreased uptake below two standard deviations of the normal mean.

***Symptom evaluation***

Dizziness Handicap Inventory (DHI), an internationally recognized method for evaluating the severity of vertigo, which contains 25 questions with a score ranging from 0 to 100, was recorded in this study to evaluate the severity of dizziness (van de Wyngaerde *et al*., 2019). This evaluation was carried out before and 4 weeks after the end of treatment, respectively.

***Statistical analysis***

Data management and statistical analyses were performed by using SAS 9.13 software (SAS Institute Inc., USA). Continuous variables were expressed as mean ± standard deviation (SD) and were compared using General linear model (GLM) test among the three groups. A Student's *t* test was used for the comparisons of continuous variables between pre-and post-intervention in each group. Categorical variables were expressed as numbers and percentages (%), which were compared using Cochran-Mantel-Haenszel Chi-square (CMH-$\chi^2$) test. A statistical significance was set at $p<0.05$.

***Ethics approval and consent to participate***

The study was approved by the Ethics Committee of Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine. Patients who participated in this research, signed the informed consent and had complete clinical data. Signed written informed consents were obtained from the patients and/or guardians.

**RESULTS**

***Clinical characteristics***

The demographic data and baseline characteristics of the patients with dizziness are shown in Table No. 1. There were no significant differences in gender, age, or concomitant disease (hypertension, diabetes mellitus, coronary artery disease, cerebral infarction, lacunar infarction, Parkinson's disease) among the three groups ($p>0.05$). No significant differences with respect to basic medications that patients needed for maintenance treatment, such as angiotensin-converting enzyme inhibitors (ACE-I), angiotensin receptor blockers (ARB), calcium channel blockers (CCB), β-blockers, statins, aspirin, and cilostazol, were found among the three groups ($p>0.05$).

***Changes in rCBF on $^{99m}$Tc-ECD SPECT***

The distributions of low rCBF before treatment among the three groups are listed in Table No. 2. The most common regions of low rCBF in the patients with dizziness included bilateral frontal and parietal lobes, and then temporal lobes and basal ganglia. There were no statistical differences in baseline distributions of low rCBF among the three groups ($p>0.05$).

The mean rCBF quantitative values in all ROIs on 99mTc-ECD SPECT before and after intervention are listed in Table No. 3. No statistical difference was observed in each brain region among the three groups before treatment ($p>0.05$). In group A, the post-intervention values in all regions were significantly higher than pre-intervention levels ($p<0.05$). Following the intervention in Group P, the rCBF values of the frontal lobe, parietal lobe, and temporal lobe exhibited an increase compared to their pre-intervention levels. However, no statistically significant alterations were observed in the occipital lobe, basal ganglia, thalamus, hippocampus, and cerebellum before and after the intervention. ($p>0.05$). In group C, few changes were found in rCBF after intervention ($p>0.05$).

Then, the quantitative values in those regions only with low rCBF were further compared in Table No. 4. Similarly, there were no statistical differences in all brain regions among the three groups before intervention ($p>0.05$). Except in group C, all rCBF values in group A and group P increased after medicine administrations. However, no statistical differences were observed in the right occipital lobes, right thalamus, left hippocampus, and right cerebellum in group P ($p>0.05$). Meanwhile, all of the post-treatment values in group A were significantly higher than those in group P ($p<0.05$). Figure No. 2 shows the changes in rCBF in one of the patients with dizziness who were treated with anisodamine.

***Symptom evaluation***

Four weeks after the end of 14-day anisodamine administration, in group A, the subjective symptom of dizziness improved in 55 (91.7%) patients, and the DHI score remarkably decreased from 65.9 ± 5.4 to 23.1 ± 7.4 ($p<0.01$). Then in group P, the symptoms improved in 37 (61.7%) patients and the DHI score decreased from 66.8 ± 6.2 to 43.8 ± 8.6 ($p<0.01$). No significant changes in subjective symptom or DHI score (from 63.7 ± 4.6 to 62.6 ± 5.8, $p>0.05$) were observed in group C (Figure No. 3).

**Table No. 1**
**Baseline characteristics of patients with dizziness**

| Variables | Group A (n = 60) | Group P (n = 60) | Group C (n = 30) | *p* |
|---|---|---|---|---|
| Male gender | 22 (36.7) | 27 (45.0) | 18 (60.0) | 0.110 |
| Age, years | 67.2 ± 9.1 | 66.1 ± 8.9 | 65.4 ± 8.0 | 0.701 |
| concomitant disease | | | | |
| Hypertension | 37 (61.7) | 31 (51.7) | 14 (46.7) | 0.336 |
| Diabetes mellitus | 14 (23.3) | 11 (18.3) | 8 (26.7) | 0.634 |
| Coronary artery disease | 7 (11.7) | 10 (16.7) | 6 (20.0) | 0.547 |
| Cerebral infarction | 11 (18.3) | 16 (26.7) | 4 (13.3) | 0.286 |
| Lacunar infarction | 14 (23.3) | 18 (30.0) | 6 (20.0) | 0.530 |
| Parkinson's disease | 6 (10.0) | 10 (16.7) | 2 (6.7) | 0.321 |
| Medications | | | | |
| ACE-I/ARB | 12 (20.0) | 16 (26.7) | 5 (16.7) | 0.497 |
| CCB | 10 (16.7) | 6 (10.0) | 4 (13.3) | 0.562 |
| β-blockers | 5 (8.3) | 2 (3.3) | 2 (6.7) | 0.507 |
| Statins | 17 (28.3) | 14 (23.3) | 5 (16.7) | 0.468 |
| Aspirin | 16 (26.7) | 17 (28.3) | 6 (20.0) | 0.689 |
| Cilostazol | 13 (21.7) | 11 (18.3) | 5 (16.7) | 0.825 |

**Data are expressed as mean ± SD or as numbers (%)**
**ACE-I, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CCB, calcium channel blockers**

**Table No. 2**
**Comparisons of baseline distributions of low rCBF among 3 groups**

| Region | Group A (n = 60) | Group P (n = 60) | Group C (n = 30) | *p* |
|---|---|---|---|---|
| L frontal | 37 (61.7) | 31 (51.7) | 18 (60.0) | 0.513 |
| R frontal | 34 (56.7) | 35 (58.3) | 14 (46.7) | 0.556 |
| L parietal | 36 (60.0) | 32 (53.3) | 16 (53.3) | 0.723 |
| R parietal | 32 (53.3) | 31 (51.7) | 14 (46.7) | 0.835 |
| L temporal | 19 (31.7) | 22 (36.7) | 13 (43.3) | 0.549 |
| R temporal | 14 (23.3) | 19 (31.7) | 8 (26.7) | 0.589 |
| L occipital | 7 (11.7) | 10 (16.7) | 2 (6.7) | 0.387 |
| R occipital | 5 (8.3) | 7 (11.7) | 4 (13.3) | 0.730 |
| L basal | 17 (28.3) | 13 (21.7) | 10 (33.3) | 0.464 |
| R basal | 19 (31.7) | 17 (28.3) | 10 (33.3) | 0.868 |
| L thalamus | 7 (11.7) | 10 (16.7) | 7 (23.3) | 0.357 |
| R thalamus | 7 (11.7) | 6 (10.0) | 6 (20.0) | 0.387 |
| L hippocampus | 2 (3.3) | 4 (6.7) | 2 (6.8) | 0.673 |
| R hippocampus | 5 (8.3) | 10 (16.7) | 4 (13.3) | 0.387 |
| L cerebellum | 5 (8.3) | 6 (10.0) | 1 (3.3) | 0.543 |
| R cerebellum | 2 (3.3) | 4 (6.7) | 2 (6.7) | 0.673 |

**Data are expressed as number (%).**
**L, left; R, right**

**Table No. 3**
**Comparisons of rCBF values in all regions between pre-and post-intervention**

| Region | Group A (n = 60) | | | Group P (n = 60) | | | Group C (n = 30) | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre | Post | *p* | Pre | Post | *p* | Pre | Post | *p* |
| L frontal | 48.1 ± 10.3 | 56.6 ± 9.3 | 0.003 | 50.5 ± 13.4 | 58.1 ± 12.8 | 0.047 | 49.5 ± 11.8 | 49.9 ± 11.7 | 0.933 |
| R frontal | 50.5 ± 12.4 | 58.2 ± 10.8 | 0.024 | 48.4 ± 12.9 | 55.7 ± 12.7 | 0.049 | 50.0 ± 13.2 | 49.8 ± 13.0 | 0.967 |
| L parietal | 46.9 ± 10.9 | 55.4 ± 9.5 | 0.005 | 47.7 ± 12.7 | 54.9 ± 11.5 | 0.041 | 48.6 ± 12.0 | 49.3 ± 12.4 | 0.876 |
| R parietal | 49.4 ± 11.8 | 58.3 ± 11.4 | 0.009 | 49.1 ± 11.9 | 56.3 ± 12.0 | 0.037 | 51.0 ± 12.9 | 51.5 ± 13.5 | 0.935 |
| L temporal | 53.9 ± 10.9 | 61.6 ± 10.9 | 0.015 | 51.9 ± 11.3 | 58.4 ± 11.0 | 0.044 | 51.3 ± 12.1 | 50.8 ± 11.4 | 0.921 |
| R temporal | 55.2 ± 10.1 | 63.0 ± 10.3 | 0.010 | 52.6 ± 11.8 | 59.4 ± 11.7 | 0.045 | 53.7 ± 12.0 | 53.8 ± 11.9 | 0.981 |
| L occipital | 59.5 ± 8.1 | 65.7 ± 6.2 | 0.004 | 61.1 ± 11.0 | 66.6 ± 10.7 | 0.080 | 61.4 ± 11.3 | 60.7 ± 11.2 | 0.877 |
| R occipital | 60.5 ± 8.3 | 66.8 ± 6.4 | 0.005 | 62.6 ± 10.1 | 66.9 ± 10.5 | 0.151 | 62.0 ± 11.2 | 61.0 ± 11.9 | 0.825 |
| L basal | 56.1 ± 11.9 | 63.6 ± 9.6 | 0.019 | 58.3 ± 12.1 | 63.9 ± 12.1 | 0.108 | 56.9 ± 12.0 | 57.4 ± 12.6 | 0.934 |
| R basal | 57.2 ± 13.7 | 64.9 ± 10.8 | 0.031 | 57.8 ± 12.8 | 63.0 ± 13.3 | 0.166 | 57.2 ± 14.0 | 57.7 ± 14.4 | 0.923 |
| L thalamus | 62.3 ± 10.3 | 69.4 ± 7.4 | 0.008 | 61.1 ± 11.2 | 66.8 ± 10.1 | 0.065 | 60.8 ± 10.6 | 61.3 ± 10.8 | 0.906 |
| R thalamus | 60.9 ± 9.8 | 68.5 ± 6.1 | 0.002 | 60.7 ± 9.7 | 65.8 ± 10.7 | 0.080 | 62.3 ± 8.4 | 63.0 ± 8.9 | 0.826 |
| L hippocampus | 64.7 ± 6.5 | 70.3 ± 6.2 | 0.003 | 63.1 ± 8.5 | 65.6 ± 8.9 | 0.313 | 62.0 ± 8.3 | 62.9 ± 8.8 | 0.793 |
| R hippocampus | 63.2 ± 8.0 | 68.9 ± 7.7 | 0.013 | 61.6 ± 10.9 | 64.9 ± 10.6 | 0.277 | 61.1 ± 11.5 | 62.0 ± 11.4 | 0.839 |
| L cerebellum | 65.3 ± 9.1 | 71.3 ± 6.8 | 0.010 | 64.1 ± 10.7 | 67.9 ± 9.6 | 0.193 | 65.4 ± 11.6 | 64.3 ± 11.9 | 0.813 |
| R cerebellum | 67.1 ± 6.9 | 72.1 ± 6.3 | 0.010 | 66.5 ± 7.1 | 69.5 ± 6.6 | 0.130 | 67.6 ± 9.0 | 66.6 ± 9.0 | 0.797 |

**Data are expressed as mean ± SD (mL/100g/min).**
**L, left; R, right; Pre, pre-intervention; Post, post-intervention**.

***Side effects***

The side effects detected during the course of intervention in group A and group P are listed in Table No. 5. Thirst (83.3%), blurred vision (20.0%), and dysuria (11.7%) were observed in group A but not found in group P. On the contrary, headache (1.7%), vascular pain (18.3%), and vasculitis (8.3%) were detected in group P but not found in group A. Meanwhile, 10 patients (16.7%) in group A and 1 patient (1.7%) in group P complained of symptomatic palpitation or tachycardia, 5 patients (8.3%) in group A and 2 patients (3.3%) in group P developed facial flushing. All side effects were slight and tolerable and spontaneously subsided within 2-3 h after the end of intravenous administration.

## DISCUSSION

Cerebral microangiopathy is usually characterized by the reduction of CBF and vasomotor reactivity (Thudium *et al*., 2023). The rCBF is a useful marker of neuronal activity and has been widely used in neurological studies. So far, low rCBF has been implicated in a variety of neurological diseases such as Alzheimer's disease (Yoshii *et al*., 2018), carbon monoxide poisoning (Chen *et al*., 2016), Machado–Joseph disease (Braga-Neto *et al*., 2016), and disorders of consciousness (Liu *et al*., 2016). Importantly, low CBF was linked to a higher risk of all-cause, cardiovascular, and non-cardiovascular mortality in older people regardless of clinical cardiovascular status (Sabayan *et al*., 2013).

Therefore, it has been an important method for the treatment of cerebral microvascular disease by increasing rCBF. The data obtained from our study suggested that anisodamine exhibited the potential to enhance rCBF in individuals experiencing dizziness. Notably, the observed enhancement of rCBF in specific brain regions, such as the occipital lobe, basal ganglia, thalamus, hippocampus, and cerebellum, surpassed that achieved by alprostadil. Furthermore, the subjective severity of dizziness in patients was found to be reduced by anisodamine, as evidenced by the DHI score.

**Table No. 4**
**Comparisons of quantitative values in regions with low rCBF between pre-and post-intervention**

| Region | Group A | | | Group P | | | Group C | | |
|---|---|---|---|---|---|---|---|---|---|
| | Pre | Post | *p* | Pre | Post | *p* | Pre | Post | *p* |
| L frontal | 38.7 ± 3.7 | 49.5 ± 5.3 | < 0.001 | 38.3 ± 2.9 | 44.5 ± 6.0 | 0.003 | 37.5 ± 2.2 | 38.2 ± 2.1 | 0.432 |
| R frontal | 40.1 ± 3.2 | 51.3 ± 6.3 | < 0.001 | 38.6 ± 3.1 | 45.0 ± 5.6 | < 0.001 | 38.5 ± 2.1 | 38.6 ± 2.3 | 0.912 |
| L parietal | 37.3 ± 3.4 | 48.9 ± 5.9 | < 0.001 | 37.0 ± 2.9 | 44.2 ± 5.0 | < 0.001 | 38.1 ± 2.2 | 38.6 ± 2.4 | 0.457 |
| R parietal | 39.5 ± 3.0 | 50.7 ± 6.2 | < 0.001 | 38.2 ± 2.4 | 45.6 ± 5.8 | < 0.001 | 38.1 ± 2.3 | 37.9 ± 2.1 | 0.822 |
| L temporal | 39.0 ± 3.2 | 49.8 ± 4.1 | < 0.001 | 38.3 ± 2.6 | 44.4 ± 4.3 | < 0.001 | 36.9 ± 2.0 | 37.5 ± 2.2 | 0.563 |
| R temporal | 40.2 ± 3.6 | 49.3 ± 3.9 | < 0.001 | 38.4 ± 2.4 | 45.0 ± 5.6 | 0.004 | 37.0 ± 1.4 | 36.9 ± 1.5 | 0.898 |
| L occipital | 38.3 ± 1.5 | 47.0 ± 3.3 | < 0.001 | 37.4 ± 1.5 | 42.8 ± 3.2 | 0.001 | 38.8 ± 1.2 | 38.9 ± 1.1 | 0.910 |
| R occipital | 39.6 ± 2.0 | 49.2 ± 2.5 | < 0.001 | 37.8 ± 2.2 | 41.4 ± 3.9 | 0.080 | 37.5 ± 1.4 | 36.3 ± 1.1 | 0.304 |
| L basal | 37.4 ± 2.9 | 46.8 ± 4.2 | < 0.001 | 37.6 ± 2.5 | 42.5 ± 3.8 | 0.004 | 37.4 ± 1.6 | 36.9 ± 1.5 | 0.542 |
| R basal | 37.9 ± 3.2 | 51.3 ± 6.6 | < 0.001 | 38.4 ± 2.4 | 43.1 ± 4.8 | 0.039 | 37.7 ± 1.7 | 37.7 ± 1.3 | 0.913 |
| L thalamus | 36.8 ± 1.6 | 46.7 ± 4.3 | < 0.001 | 37.4 ± 1.5 | 42.2 ± 3.2 | 0.002 | 39.2 ± 2.4 | 38.9 ± 2.1 | 0.820 |
| R thalamus | 35.9 ± 1.5 | 46.4 ± 3.8 | < 0.001 | 37.0 ± 1.3 | 39.6 ± 3.3 | 0.141 | 38.0 ± 2.2 | 37.8 ± 2.1 | 0.874 |
| L hippocampus | 40.1 ± 1.0 | 49.6 ± 1.6 | 0.018 | 39.2 ± 1.4 | 41.9 ± 4.2 | 0.358 | 37.0 ± 2.1 | 37.0 ± 1.6 | 0.981 |
| R hippocampus | 38.7 ± 1.9 | 45.8±2.6 | 0.001 | 38.0 ± 1.8 | 41.7 ± 2.9 | 0.008 | 37.0 ± 1.6 | 38.0 ± 1.7 | 0.491 |
| L cerebellum | 39.1 ± 1.6 | 49.8 ± 4.8 | 0.006 | 38.6 ± 1.4 | 43.0 ± 3.8 | 0.042 | 39.4 | 38.8 | — |
| R cerebellum | 39.6 ± 1.7 | 47.3 ± 1.1 | 0.033 | 38.8 ± 1.9 | 41.9 ± 4.2 | 0.316 | 38.5 ± 2.3 | 38.2 ± 1.3 | 0.868 |

**Data are expressed as mean ± SD (mL/100g/min).**
**L, left; R, right; Pre, pre-intervention; Post, post-intervention**

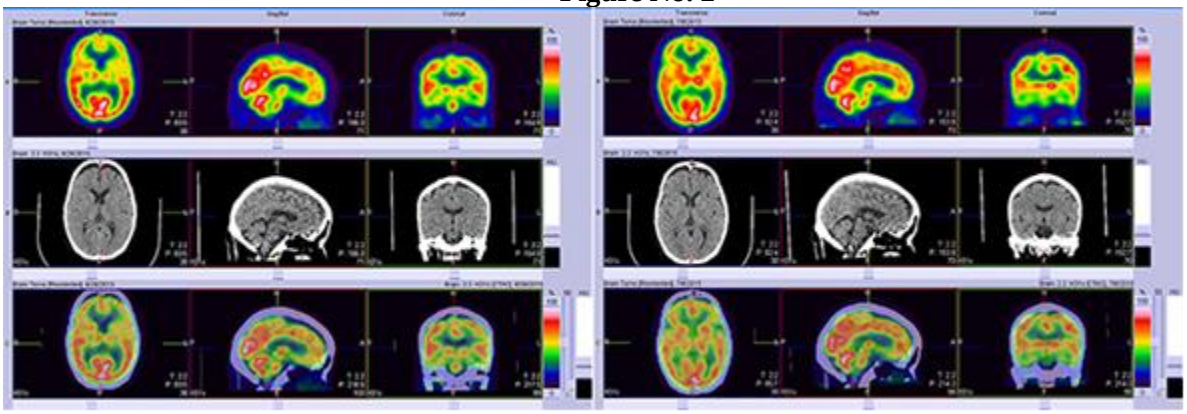
**Table No. 5**
**Side effects during the course of treatment**

| Variables | Group A (n = 60) | Group P (n = 60) |
|---|---|---|
| Thirst | 50 (83.3) | 0 (0) |
| Blurred vision | 12 (20.0) | 0 (0) |
| Palpitation/tachycardia | 10 (16.7) | 1 (1.7) |
| Dysuria | 7 (11.7) | 0 (0) |
| Flushing | 5 (8.3) | 2 (3.3) |
| Headache | 0 (0) | 1 (1.7) |
| Vascular pain | 0 (0) | 11 (18.3) |
| Vasculitis | 0 (0) | 5 (8.3) |

**Data are expressed as numbers (%).**

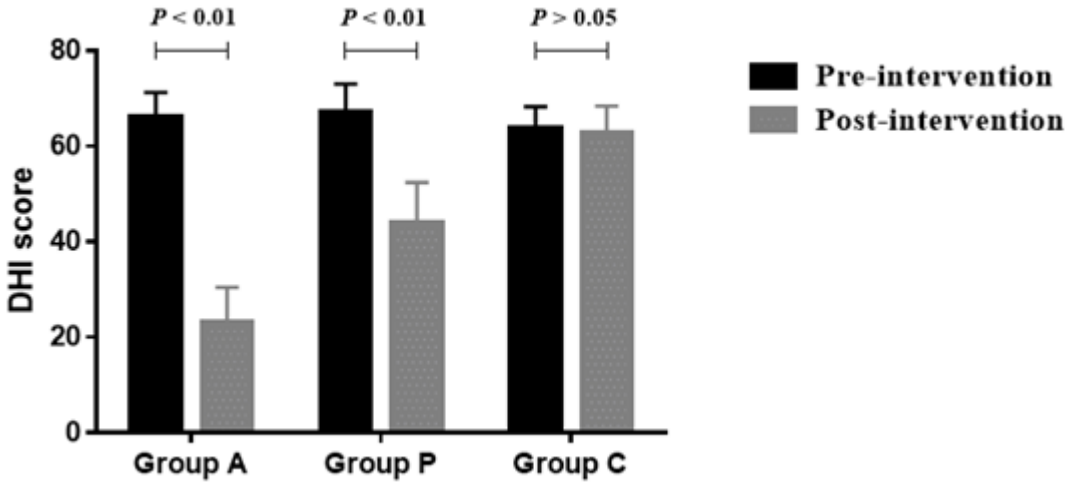
There are many causes of dizziness, and the disease factor is one of the most common cerebrovascular diseases (Pfieffer *et al*., 2019) with a higher incidence among the elderly (Maarsingh *et al*., 2010). Our research findings further corroborated this observation, as our study population exhibited an average age exceeding 65 years, and 54.67% (82/150) of individuals reporting dizziness also presented with hypertension. Prior investigations have demonstrated that hypertension can induce constriction of cerebral arterioles and luminal narrowing, consequently impairing collateral circulation functionality and blood supply, thereby precipitating dizziness in affected patients (Pires *et al*., 2013). In addition, other cardiovascular and cerebrovascular diseases, including coronary artery disease, cerebral infarction, and lacunar infarction, accounted for 15.33% (23/150), 20.67% (31/150), and 25.33% (38/150) of the total study subjects, respectively.

**Figure No. 2**



**Changes in rCBF in a patient with dizziness who was treated with anisodamine. Left, before treatment, focal decrease of radioactivity distribution was seen in bilateral frontal lobe, left basal ganglia and left thalamus. Right, after treatment, radioactivity distribution of the above segments increased significantly**.

**Figure No. 3**




**Comparisons of DHI scores between pre- and post-intervention among 3 groups**.

In the realm of clinical practice, scopolamine and anisodamine are both classified as anticholin ergic medications. Scopolamine primarily exerts its influence on the central nervous system, resulting in inhibitory effects, and is primarily employed in the treatment of vertigo stemming from vestibular dysfunction. On the other hand, anisodamine is predominantly utilized for its ability to relax smooth

muscles and alleviate vasospasm, making it particularly effective in combating shock. Numerous studies have substantiated a comprehensive comprehension of anisodamine's mechanism of action in counteracting shock, which notably enhances blood circulation within the microcirculatory system (Volkan-Salanci *et al*., 2012; Yu *et al*., 2021a). The utilization of $^{99m}$Tc-ECD SPECT brain perfusion imaging has been documented as a means to observe regional cerebral blood flow perfusion. For instance, Zhao *et al*. (2011), employed cerebral perfusion SPECT to examine regional cerebral blood flow in 40 patients diagnosed with ischemic moyamoya disease (Zhao *et al*., 2011). Patients experiencing cerebral ischemia accompanied by symptoms of dizziness exhibit enhanced disease management through medication, which concurrently elevates regional cerebral blood flow in the brain, thereby leading to an amelioration of dizziness symptoms (Inoue & Harada, 2008; Johkura *et al*., 2012; Inoue *et al*., 2014). Hence, the objective of this research is to examine the correlation between alterations in rCBF and the amelioration of dizziness symptoms in patients subjected to anisodamine treatment.

In the realm of dizziness treatment, contemporary medicine predominantly employs vasodilators to address both symptoms and underlying causes by expanding cerebral blood vessels and enhancing cerebral circulation. Furthermore, calcium antagonists are utilized to induce relaxation in vascular smooth muscle (No authors listed, 2021). Additionally, antiplatelet medications, including aspirin, are administered to avert vasoconstriction and ameliorate dizziness (Molnar & McGee, 2014). For instance, Johkura *et al*. (2012), investigated the efficacy of cilostazol versus aspirin for chronic dizziness following ischemic stroke (Johkura *et al*., 2012). After 6 months of antiplatelet therapy, 30 patients (83.3%) in the cilostazol group showed significant improvement in dizziness symptoms. However, the efficiency in the aspirin group was 39.0% (16 patients). Correspondingly, the rCBF increased only in the cilostazol group. These suggested that while cilostazol and aspirin exhibit similar antiplatelet properties, they have different effects in improving rCBF in dizziness patients. Intravenous administration of anisodamine was effective on variant angina and had a notable effect on coronary microvascular dysfunction in patients with obstructive epicardial coronary artery disease after percutaneous coronary intervention (Hou & Jiang, 2014; Chen *et al*., 2022), which further confirmed the salutary effect of anisodamine on coronary microcirculation. Our study assessed cerebral blood flow perfusion by dividing the anterior and posterior circulation systems of the brain into various regions of interest using a semi-quantitative rGBF method. To evaluate the efficacy of anisodamine in treating dizziness, we used PGE1 as a control due to its strong vasodilator activity. After a 4-week treatment period, anisodamine demonstrated a high improvement rate in dizziness and an increase in rCBF in specific brain regions, including the frontal, parietal, temporal, occipital, basal ganglia, thalamus, hippocampus, and cerebellum. The blood circulation of the brain is classified into two distinct systems: the anterior circulatory system and the posterior circulatory system. The anterior circulatory system, known as the internal carotid artery system, originates from both internal carotid arteries. Within the brain, the frontal, parietal, and temporal lobes are nourished by the middle carotid artery. On the other hand, the posterior circulation is facilitated by the subclavian artery. This circulation primarily provides blood supply to the occipital lobe, brainstem, thalamus, hippocampus, and cerebellum (Yu *et al*., 2021a). Then, the result that after treatment the rCBF values in each region with originally low CBF in group A were higher than those in group P further indicate that anisodamine may be superior to alprostadil in ameliorating low rCBF. What's more, throughout the whole course of treatment, the side effects of anisodamine were slight, transient, and tolerable. Accordingly, anisodamine has certain advantages in the treatment of dizziness by improving rCBF.

Despite the encouraging results, there are some limitations to this study. Firstly, this was a single-center study with a relatively small sample size. For some regions such as occipital lobe, thalamus, hippocampus, and cerebellum, the number of patients with low rCBF was too small to reach a definite conclusion with statistical significance. Further large-scale multicenter investigations are required to support our findings. Secondly, the ROI based on the structural information could not effectively reflect the functional brain information. The Statistical Parametric Mapping method based on the functional brain information should be applied in future studies. Thirdly, the four-week follow-up in this study might be too short to evaluate the long-term effect of anisodamine on such disease. It will be necessary to follow up for at least one year. Fourthly, the dose of anisodamine used in this study was according to the previous investigation on septic

shock and coronary microvascular disorders (Zhao *et al*., 2011; Zhang *et al*., 2015). Different dose groups should be established to determine the optimum dose of anisodamine in the treatment of dizziness in future studies. Finally, we are not sure whether prolonging or shortening the intervention period or converting to oral preparation of anisodamine may result in different effects, all of which require more investigations to elucidate.

## CONCLUSIONS

Anisodamine could increase rCBF, ameliorate cerebral ischemia, and alleviate symptoms of dizziness caused by low rCBF more effectively than alprostadil ($PGE_1$). The side effects of anisodamine were slight, transient, and tolerable. Therefore, intravenous anisodamine administration might be an appropriate choice for the treatment of dizziness associated with low rCBF. However, more studies are expected to verify the efficacy of anisodamine and further explore its therapeutic mechanism.

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