

## The Effect of Sneezing on the Reduction of Infarct Volume and the Improvement of Neurological Deficits in Male Rats

### Abstract

**Background:** Sneezing transiently elevates cerebral blood flow. We speculated that induced sneezing, following embolism would restore arterial flow, thereby diminishing infarct volume and improving neurological deficits. **Materials and Methods:** Male rats were subjected to middle cerebral artery occlusion (MCAO) using prepared clots (embolization) and randomized into four equal groups as follows: (1) pre-MCAO-induced sneezing (PRMIS), (2) post-MCAO-induced sneezing (POMIS), and (3) pre- and POMIS (PRPOMIS) and the control group (eight rats per group). In the treatment groups, rats' sneezing episodes were induced before MCAO in PRMIS group or before regaining consciousness from surgical anesthesia in other treatment groups by cutting their whiskers during their anesthesia and subsequently inserted them into the rats' nostrils. Infarct volume was evaluated by 2, 3, 5-triphenyl tetrazolium chloride staining, and neurological deficits and brain edema were assessed by Bederson scale deficit scores 24-h post-MCAO. **Results:** The infarct volume and brain edema reduced and neurological deficits improved in the induced sneezing groups as compared with the MCAO control group. Compared to the control group, the highest improvements in the infarct volume and neurological deficits were seen in the PRPOMIS group, and POMIS group showed the most significant differences concerning the results of both ischemic and nonischemic brain edema. The highest protective effect was observed in the central region of the MCA territory. **Conclusions:** The reduction in ischemia-induced brain injury, brain edema, and neurological deficits by sneezing suggest that brief episodes of acute hypertension after stroke can increase blood flow to the ischemic area and improve recovery.

**Keywords:** Animals, brain edema, infarction, middle cerebral artery, rats

### Introduction

Stroke is defined as acute focal damage to the central nervous system, divided into three categories of cerebral infarction, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage. Stroke is one of the remarkable causes of disability and death in the world. The WHO definition of stroke in the 1970s has been globally accepted. The clinical symptoms are rapidly developing signs of focal or universal disturbances in the function of the brain that last longer than 24 h or even lead to death, and do not have other apparent causes other than that of vascular origin. Cerebral infarction is known to occur as focal ischemia within the perfusion territory of specified arteries due to a clot or stenosis. On the other hand, ICH can be defined as the blood accumulation in the cerebral parenchyma or the ventricles that

is not caused by traumatic accidents. The ICH has a lower prevalence of embolism but higher morbidity and mortality.<sup>[1]</sup>

The mechanism involved in sneezing reflex is similar to the Valsalva maneuver, in which venous return to the heart is reduced, and the autonomic system is involved by changing the tone of the vessels.<sup>[2-4]</sup>

The response of the cardiovascular system to Valsalva maneuver is divided into several phases. The first phase is the start of the strain, and during this phase, we could see the increased intrathoracic pressure, compressed significant vessels and subsequently increased the pressure of the aorta. Changes in cardiac output in this phase are insignificant. In the second phase, an increase in intrathoracic pressure causes compression of the veins at the thoracic inlet and disrupts the venous return. The blood volume of the heart decreases by

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25%–30%, resulting in a decrease in the preload of the heart and ultimately lowers the stroke volume. Then, arterial pressure and subsequently, pulse pressure are reduced. These changes cause sympathetic stimulation and vasoconstriction. As mean aorta pressure and pulse pressure are reduced, the carotid sinus baroreceptors are stimulated and this stimulation results in the sympathetic activation, heart rate elevation, and increased resistance of the arteries and veins outside the thorax. As a result, cardiac output and blood pressure (BP) are raised, and the sudden and the short-term occurrence of these processes cause the excessive increase in arterial pressure.<sup>[3,5]</sup>

Stroke is a significant cause of long-term disability due to neurological impairment,<sup>[6]</sup> and there are no broadly effective therapies to rescue neurological deficits. Sneezing increases intrathoracic and intraabdominal pressure, resulting in acute hypertension and transiently elevated cerebral blood flow.<sup>[7]</sup> Induced sneezing in the early period, following the stroke, may be a feasible method to restore cerebral blood flow because it can be evoked reliably even in unconscious subjects.

Induced sneezing and concomitant acute hypertension during the 1<sup>st</sup> h of recovery after ischemic stroke can improve recovery, presumably because the cerebral BP elevation causes recanalization of blocked vessels<sup>[8]</sup> and early vascular reperfusion is strongly related to clinical outcomes.<sup>[9]</sup> Furthermore, the rise in BP increases blood flow to ischemic regions.<sup>[10]</sup> Some studies have stated that Valsalva maneuver may increase the risk of ICH, and a few case report studies demonstrated that some individuals had blown O-ring in their heads while lifting weights, presumably under Valsalva maneuver. It is stated that sneezing could result in increased intrathoracic pressure and BP and intracranial pressure (ICP) and therefore, sneezing may predispose ICH. Hence, sneezing could be useful in the embolic stroke but is a risk factor for hemorrhagic stroke.<sup>[11-14]</sup>

Of the numerous animal stroke models, the embolic stroke model induced by natural clots is most relevant to the pathophysiological situation in patients with ischemic stroke.<sup>[15]</sup> Thus, we tested whether induced sneezing in rats could decrease infarct volume and improve neurological deficits, following clot occlusion of the middle cerebral artery (MCA).

## Materials and Methods

Animals were handled following the standards and procedures of the American Council on Animal Care.

The Committee for Animal Ethics of Isfahan Medical College approved all experimental protocols. A total of 67 male Wistar rats weighing 250–300 g (Pastor Institute, Tehran, Iran) were maintained on a 12-h light-dark cycle with food and water available *ad libitum*. The rats were housed in standard cages at room temperature (22°C–24°C).

Of 67 rats subjected to MCA occlusion (MCAO) surgery (described below), three died because of excessive bleeding. Therefore, 64 rats were equally randomized to the control MCAO group and three-induced sneezing groups, post-MCAO-induced sneezing (POMIS) group, pre-MCAO-induced sneezing (PRMIS) group, and pre-and POMIS (PRPOMIS) group (in this group sneezing was induced before and after MCAO). Eight rats from each group, i.e. 32 of 64 rats were induced with MCAO and were evaluated only for brain edema, whereas in the remaining 32 rats, MCAO was induced to evaluate the other parameters. All animals in the induced sneezing group survived until the end of the experiments. We determined the rate of arterial occlusion in different mice using laser Doppler flowmetry (Moor Instrument, England) which was borrowed from Rafsanjan University of Medical Sciences, Rafsanjan, Kerman, Iran. Previous studies have approved the Doppler laser method and explained its proficiency in determining the occlusions in the vessels.<sup>[16,17]</sup> Blood was directly transferred from the femoral artery of a catheterized rat into a 20 cm length of Polyethylene-50 (PE-50) tubing and was maintained at room temperature for 1 h. We inserted a 20G cannula into the right internal carotid artery in each rat to obtain blood samples for arterial blood gas (ABG) and blood sugar analysis. We used a glucose meter to interpret blood glucose levels and evaluated ABG samples using an analyzer device borrowed from Shahid Beheshti University, Iran. The clot was then refrigerated for 22 h at 4°C before use. A 20-mm portion of the clot was cut and transferred into another section of PE-50 tubing modified to have an outer diameter of 0.3 mm, which was employed to inject the clot into the MCA.<sup>[15]</sup> The embolic stroke model was established by directly injecting the clot into MCA. In brief, rats were anesthetized with 1.5% halothane in a 21% O<sub>2</sub> and 79% N<sub>2</sub> mixture. A linear incision was made in the midline of the ventral cervical skin. The right common carotid artery, external carotid artery, and internal carotid artery were exposed. The distal section of the external carotid artery was closed and cut. The modified PE-50 (Stoelting, USA) tubing containing the clot was connected to a 50- $\mu$ l Hamilton lock syringe and advanced 17 – 19 mm into the internal carotid artery until the tip was inside MCA. The clot was then injected and the tubing removed. The wound was closed, and the animal was returned to its cage.<sup>[16]</sup> Body temperature was maintained during the experiment at 37°C  $\pm$  2°C using a rectal thermometer and a heating lamp. ABG was measured in 0.2 ml of arterial blood samples taken 10 min before and after MCAO. At 24 h after MCA occlusion, animals were decapitated and brains removed. Six 2-mm thick coronal sections spanning the MCA territory were collected from each rat. The sections were incubated with 2% 2, 3, 5-triphenyl tetrazolium chloride (TTC, Merck, Germany) solution for 30 min at 37°C, followed by immersion in 10% formalin. Normal tissue is stained red by TTC, while the infarcted tissue remains unstained (white). The

infarct region in each section was defined in images, and the area was quantified by ImageJ (National Institutes of Health Image, version 1.63). Total infarct volume was calculated by adding the areas and multiplying by section thickness (2 mm).<sup>[18]</sup> Neurological deficits were assessed prior to animal sacrifice (24 h after MCAO) using the corrected 6-point scoring system of Bederson and coworkers: 0, no observable deficit; 1, forelimb flexion; 2, forelimb flexion plus decreased resistance to lateral push; 3, unidirectional circling; 4, unidirectional circling plus decreased level of consciousness; and 5, death.<sup>[19]</sup> Cerebral edema was evaluated by determining the brain water content (BWC).<sup>[20]</sup> At 24 h after MCAO, all rats were killed and their brains removed. These brains were divided into the right and left hemispheres comprising equal brain matrix. These hemispheres were weighted to obtain wet weight (WW) and then dried at 110°C for 24 h to determine dry weight (DW). BWC was calculated using the following formula:  $(WW - DW)/WW \times 100$ . Sneezing was induced immediately after the MCAO surgery and before the rat regained consciousness. In this study, we induced the sneeze reflex in the rats by cutting their whiskers during their anesthesia and subsequently inserted them into the rats' nostrils. This method for inducing the sneeze in mice has been reported to be successful in previous studies.<sup>[21,22]</sup> Each rat was closely observed and had between 15 and 20 sneezes, so the overall sneezing time lasted for 5 min. For inducing sneezing before MCAO, the rats were maintained for 1 week before MCAO in a separate chamber. In the PRMIS group, if sneezing continued until MCAO, the rats were excluded from the protocol, whereas if the number of sneezes was above 15, the rats were included in the sneezing therapy group.

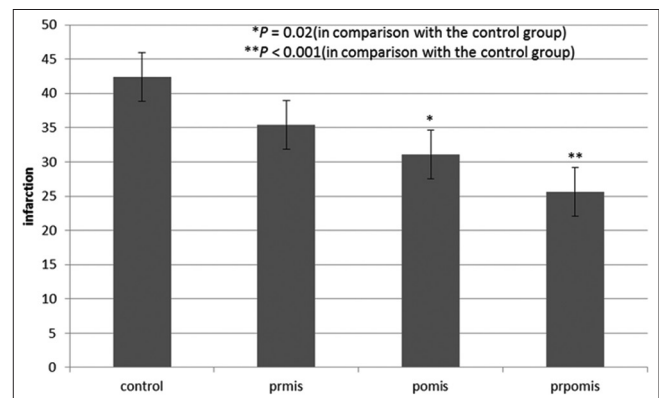
### Statistical analysis

Data are expressed as the mean  $\pm$  standard error of the mean. Infarct volumes and brain edema were compared between groups by one-way analysis of variance test. Neurological scores were reported as the mean and standard

deviation (SD) and were compared by the nonparametric K independent test. A value of  $P < 0.05$  was considered statistically significant.

### Results

Physiological data are presented in Table 1. There were no significant changes in any of the parameters between control and induced sneezing groups ( $n = 8$  rats per group). Furthermore, all groups revealed no significant differences before and after MCAO. Embolization of the right MCAO by injecting a premade blood clot led to infarction in the ipsilateral hemisphere, mainly in the MCA territory. The mean infarct volume was significantly lower in POMIS and PRPOMIS groups compared to the control group as measured by TTC staining of serial coronal sections (compared to the control group  $(42.41\% \pm 7.59\%)$ , the infarct volume reduced by %16.6 in PRMIS group  $(35.38\% \pm 6.62\%)$  ( $P > 0.05$ ), reduced by %26.8 in POMIS group  $(31.05\% \pm 6.75\%)$  ( $P < 0.05$ ), and reduced by %39.60 in PRPOMIS group  $(25.59\% \pm 5.68\%)$  ( $P < 0.001$ ) [Figure 1]. The infarct volumes in the cortex and striatum were also lower in the POMIS and PRPOMIS groups compared to the control



**Figure 1: Effect of sneezing therapy on infarct volume of ipsilateral hemisphere in comparison with the control group after ischemic brain injury. Induced sneezing decreased cerebral infarct volume at 24 h compared to the control group as measured by triphenyl tetrazolium chloride staining. Data are presented as mean  $\pm$  standard deviation**

**Table 1: Summary of physiological values at 5 min before and after middle cerebral artery occlusion in control, premiddle cerebral artery occlusion-induced sneezing, postmiddle cerebral artery occlusion-induced sneezing and pre- and post-middle cerebral artery occlusion-induced sneezing groups**

Study groups	Variables			
	pH	Glucose (Mmol/l)	PaCO <sub>2</sub> (mm Hg)	PaO <sub>2</sub> (mm Hg)
Control group (Before MCA occlusion)	7.39±0.03	14.87±0.54	37.2±1.2	76±6
Control group (After MCA occlusion)	7.38±0.05	14.47±0.61	36.49±1.51	81.3±6.3
PRMIS (Before MCA occlusion)	7.40±0.01	14.45±0.36	38.11±1.44	74.5±7.2
PRMIS (After MCA occlusion)	7.38±0.04	14.22±0.57	36.7±1.17	78.3±8.6
POMIS (Before MCA occlusion)	7.39±0.02	14.18±0.82	36.94±1.52	81±6.9
POMIS (After MCA occlusion)	7.38±0.05	14.06±0.76	35.75±1.3	86±8.4
PRPOMIS (Before MCA occlusion)	7.39±0.04	14.61±0.44	36.63±1.21	77.2±9.1
PRPOMIS (After MCA occlusion)	7.38±0.01	14.39±0.74	36.2±1.48	81±7.7

MCAO: Middle cerebral artery occlusion, PRMIS: Pre-MCAO-induced sneezing, POMIS: Post-MCAO-induced sneezing, PRPOMIS: Pre- and post-MCAO-induced sneezing

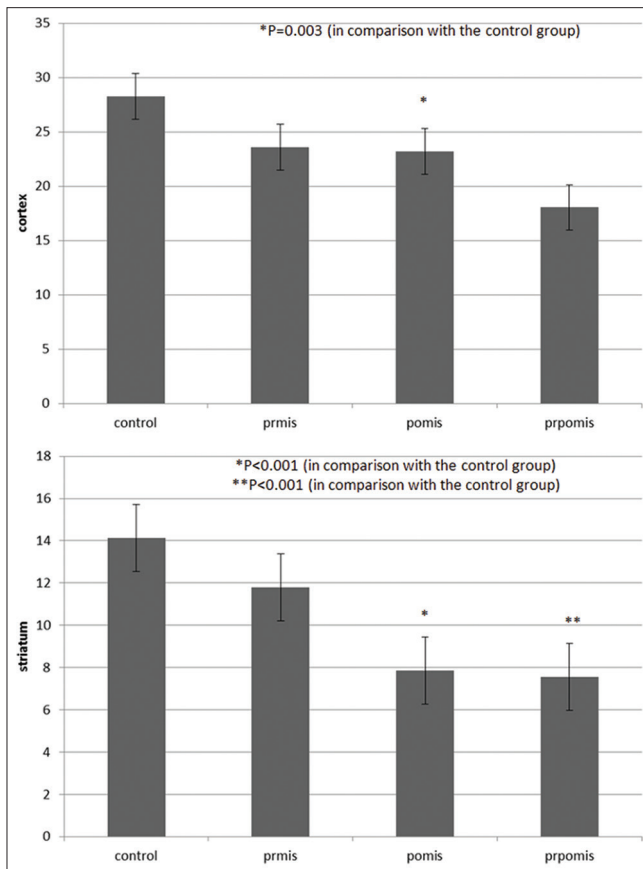
group. Findings of the infarct volume in cortex displayed significant difference between POMIS group (23.20% ± 5.37%) and the control group (28.27% ± 5.71%) ( $P < 0.05$ ) but PRMIS group (23.58% ± 4.96%) and PRPOMIS group (18.04% ± 3.22%) did not have significant differences with the control group ( $P > 0.05$ ). After evaluating the infarct volume in striatum, compared to the control group (14.13% ± 2.86%), both PRPOMIS (7.55% ± 1.82%) group and POMIS group (7.85% ± 1.96%) had significant differences ( $P < 0.001$  and  $P < 0.05$ , respectively), but PRMIS group (11.78% ± 2.4%) displayed no significant difference ( $P > 0.05$ ) [Figure 2]. Bederson neurological deficit scores were measured 24 h after stroke by observers blinded to the treatment history. Mean and SD findings were significantly lower in PRPOMIS sneezing group compared to the control group [Table 2]. Brain edema was evaluated separately for the right (ischemic) and left (nonischemic) hemispheres. Compared to the control group (83.68% ± 0.62%) ischemic brain edema results revealed significant results in the PRMIS group (82.26% ± 0.27%,  $P < 0.05$ ) and the POMIS group (82% ± 0,  $P < 0.001$ ) and

PRPOMIS group did not have significant difference (81.31% ± 0.28%,  $P > 0.05$ ). Compared to the control group (77.35% ± 0.8%), nonischemic brain edema results did not reveal significant results in PRMIS group (76.9% ± 0.55%,  $P > 0.05$ ) and the PRPOMIS group (PRPOMIS: 75.72% ± 0.34%,  $P > 0.05$ ), whereas POMIS group displayed significant difference (76.55% ± 0.39%,  $P < 0.001$ ) [Figure 3]. The

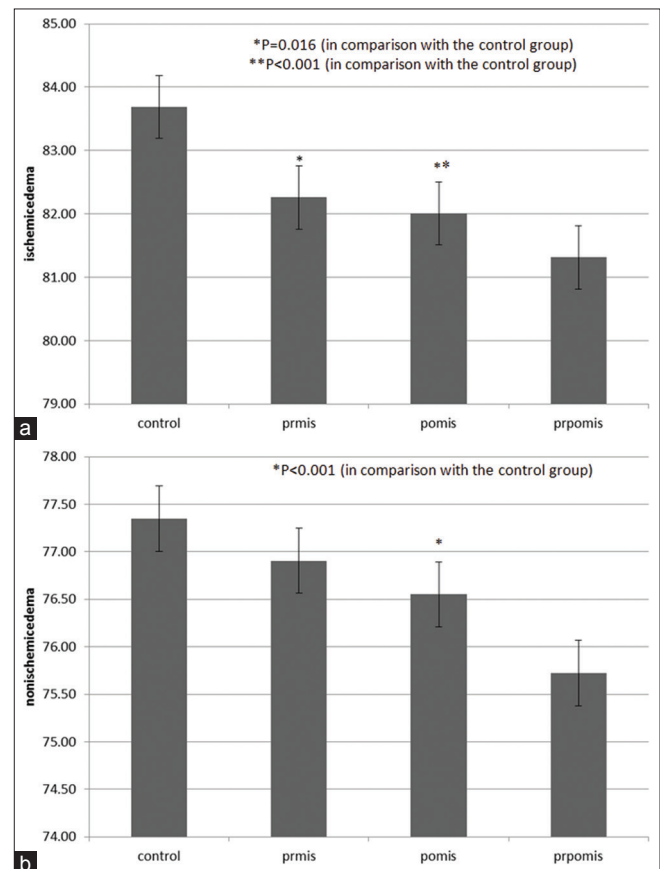
**Table 2: Neurological score 24 h after the stroke**

Groups	Control	PRMIS	POMIS	PRPOMIS
24 h	3.25±0.25	3.13±0.29	2.25±0.31	2±0.26*
Range	2-4	2-4	1-4	1-3

Neurological deficits were measured using a five-score scale at 24 h following the onset of embolic cerebral ischemia. The data are presented as the mean and SD. ANOVA test showed a significant difference between the control and induced sneezing groups 24 h after embolic stroke ( $*P=0.007$ ). MCAO: Middle cerebral artery occlusion, PRMIS: Pre-MCAO-induced sneezing, POMIS: Post-MCAO-induced sneezing, PRPOMIS: Pre- and post-MCAO-induced sneezing, SD: Standard deviation, SEM: Standard error of mean, ANOVA (Analysis of variance)



**Figure 2:** Cortical and striatal infarct volume in rats which received sneezing therapy in comparison with the control group. Values are presented as means ± standard deviation for each group (Comparison of post-middle cerebral artery occlusion-induced sneezing and pre-middle cerebral artery occlusion-induced sneezing:  $P=0.019$ , comparison of pre- and post-middle cerebral artery occlusion-induced sneezing and pre-middle cerebral artery occlusion-induced sneezing:  $P=0.01$ )



**Figure 3:** Brain water content in the ischemic hemisphere (a) and nonischemic hemisphere (b) in the induced sneezing groups versus the control group (Comparison of post-middle cerebral artery occlusion-induced sneezing and pre- and post-middle cerebral artery occlusion-induced sneezing:  $P=0.048$ , comparison of pre- and post-middle cerebral artery occlusion-induced sneezing and pre-middle cerebral artery occlusion-induced sneezing:  $P=0.003$ )

reduction in infarct area was greatest in coronal sections 3 and 4 ( $P < 0.001$ ), the central area of the MCA territory [Figure 4].

## Discussion

Induced sneezing immediately after embolic MCAO significantly improved neurological deficits and markedly reduced infarct volume in the central cortical MCAO territory and brain edema. During a sneeze, elevated intraabdominal, and intrathoracic pressure increases venous pressure in these regions, resulting in increased epidural venous and ICP. Arterial pressure rises with the rise in respiratory tract pressure.<sup>[23]</sup> Besides, both diastolic and systolic arterial pressures are elevated during the Valsalva maneuver.<sup>[24,25]</sup> Therefore, frequent sneezing will induce acute hypertension. We speculated that this would increase intra-arterial pressure and blood flow to the ischemic area, causing recanalization of MCA, resulting in reperfusion of hypoxic tissue.<sup>[7,26,27]</sup> Cerebral blood flow and BP are reduced in ischemic areas after vessel occlusion, and there is a direct correlation between the reduction in mean arterial BP and extent of ischemic brain injury.<sup>[28-31]</sup> Dysfunctional cerebral autoregulation occurs after ischemic stroke.<sup>[32,33]</sup> With impairment of cerebral autoregulation, cerebral blood flow is passively dependent on the mean arterial pressure;<sup>[34]</sup> therefore, changes in systemic BP may affect cerebral perfusion, particularly in the penumbral tissues, and may affect the infarction volume and neurological deficits. However, BP acutely elevates during the stroke.<sup>[35]</sup> Thus, elevated BP within a critical time window poststroke will increase cerebral blood flow to the ischemic area and rescue salvageable tissue. Several studies reported a temporary enhancement of BP in some cases with cerebral ischemic stroke.<sup>[36-38]</sup> Oliveira-Filho *et al.*<sup>[39]</sup> have shown that patients with good outcome had higher admission mean BP than those with poor outcome. Semplicini *et al.*<sup>[40]</sup> had found that the patients with the best neurological outcome had the highest

BP during the first 24 h, and the neurological outcome was dependent on the higher admission BP and better initial neurological condition. A correlation between severe stroke and high poststroke BP has been documented;<sup>[41]</sup> however, others reported that this increased BP resulted in poorer clinical outcomes<sup>[42]</sup> or had no significant effects.<sup>[43]</sup> Some studies have identified a U-shaped correlation between BP and outcome, with poor outcome at either end of the BP spectrum.<sup>[37,44]</sup> Cerebral blood flow in the penumbra depends on the systemic BP until the occluded artery is recanalized. There is a direct correlation between BP and recanalization, and timely recanalization improves neurological deficits.<sup>[45]</sup> One study reported a significant reduction in BP, following successful recanalization,<sup>[8]</sup> suggesting that poststroke BP elevation is a compensatory mechanism to accelerate recanalization.

However, our study has some limitations. We did not record cerebrovascular BP during sneezing. Nonetheless, there is sufficient evidence for an increase in ICP during sneezing, and there are few other explanations for the reduced infarct volume other than the promotion of reperfusion. Additional studies are required to confirm these conclusions.

## Conclusion

The present study suggests that induced sneezing can reduce ischemic brain damage. Elevated cerebrovascular BP can improve outcomes if applied early after ischemia. Therefore, sneezing is an easily induced response that could be used for protection against brain injury by increasing blood flow to the ischemic area.

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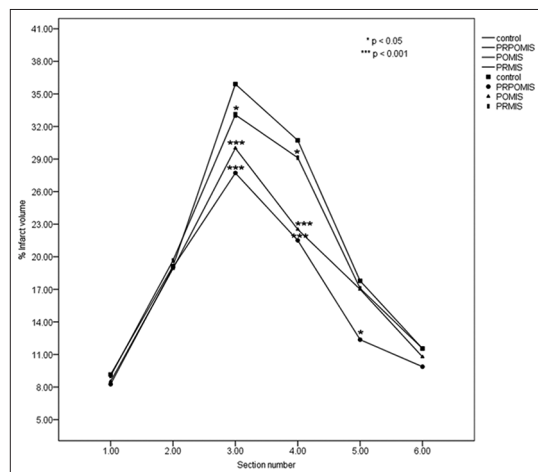
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## Conflicts of interest

There are no conflicts of interest.

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**Figure 4:** Infarct areas in each of the six coronal sections from anterior to posterior. Reductions in infarct area were most extensive in the central cortical region of the middle cerebral artery territory

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