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Original Article

Trigeminal neuralgia increases cerebral blood flow in a focal cerebral ischemic model in rats

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Abstract: Objective: To investigate the influences of trigeminal neuropathic pain on the cerebral blood flow in a ET-1 focal cerebral ischemia model. Methods: Male Sprague-Dawley (SD) rats (220-260 g) were randomly divided into a model group (trigeminal neuralgia, TN group) and a sham operation group (sham group). The TN group received bilateral infraorbital nerve chronic constriction surgery, and the sham group only underwent exposure of the infraorbital nerve. The mechanical pain threshold of the rats was continuously monitored for 30 days post surgery. On postoperative day 30, the animals were anesthetized, and 3 μL (120 pM/μL) ET-1 was injected into the surroundings of the middle cerebral artery (MCA) to establish a cerebral focal ischemia-reperfusion injury model in rats. The changes in cerebral blood flow of these two groups were monitored 30 min after the injection of ET-1. Results: The mechanic pain threshold values between rats in the two groups were not significantly different ($P>0.05$). The threshold value in the TN group on postoperative day 9 significantly decreased compared with that before surgery ($P<0.01$). Between postoperative days 9 and 30, the pain threshold values in the TN group were significantly lower than those in the sham group ($P<0.01$). From postoperative day 10, the mean arterial pressure in the TN group significantly increased compared with that before surgery ($P<0.05$), and the blood pressure (BP) in the TN group was higher than that in the sham group between postoperative days 10 and 30 ($P<0.05$). After 75 min of ET-1 microinjection, the cerebral blood flow in the rat frontal cortex exhibited reperfusion, and the cerebral blood flow in the TN group was significantly higher than that in the sham group ($P<0.05$). In addition, the content of calcitonin gene-related peptide (CGRP) in the blood of rats in the TN group was significantly higher than that in the sham group ($P<0.05$). Conclusions: Trigeminal neuropathic pain may increase the mean arterial pressure and the content of CGRP in the plasma of rats, thus increasing the cerebral blood flow in the frontal cortex of the ET-1 ischemia-reperfusion model.

Keywords: Trigeminal neuralgia, cerebral ischemia, ET-1, cerebral blood flow

Introduction

Trigeminal neuralgia (TN) is a recurrent paroxysmal severe pain located in the distribution region of trigeminal nerves. The major clinical feature is lightning, stabbing, burning, and unbearable severe pain; which can be induced by talking, washing the face, brushing the teeth, and feeling a gentle breeze [1]. Previous studies have revealed that the incidence of TN is 4-27/100,000 people/year [2]. The main TN disease group is composed of middle-aged and elderly people [3]. Ischemic cerebrovascular disease is a clinical disease with high mortality and morbidity, which endangers human health and has a higher incidence in the middle-aged and elderly people. Current clinical studies on pain and stroke primarily focus on whether migraine is a risk factor for stroke. Several meta-analyses of migraine and stroke have shown that the migraine attack, especially migraine with aura, may increase the risk of stroke [4-6]. The study of Eikermann-Haerter et al [7] on a murine model of familial hemiplegic migraine (FHM) revealed that FHM may increase stroke vulnerability by facilitating ischemic depolarizations.

However, current studies on the relationship between neuropathic pains, especially trigemi-

nal neuropathic pains, and cardiovascular diseases and stroke are very limited. There is only one clinical epidemiological study showing that TN might be a risk factor for stroke. Patients with TN have increased risks of stroke; however, the increased risks of stroke are concentrated in the group that is 60-65 years of age. This increase in risks might be associated with age-related vascular changes [8]. However, the mechanism underlying the influences of TN on stroke has not been reported.

Calcitonin gene-related peptide (CGRP) is a neuropeptide, extensively distributed in the central nervous system. CGRP participates in many physiological and pathological processes in the body, and approximately 50% of trigeminal-nerve-related neurons express CGRP [9]. CGRP is a neurotransmitter regulating nociceptive stimuli in the nervous system, which is particularly prominent in the trigeminal nerve system [10]. The CGRP immunopositive rate in trigeminal sensory fibers is higher than that in other extracranial sensory fibers [11]. The CGRP receptors are also located in the cell body of trigeminal ganglion cells [10, 12]. In addition, CGRP has a very strong vasodilation function and has been used as a cardioprotective agent to reduce reperfusion injury in cardiac muscles. Its effect on the dilation of intracranial blood vessels is stronger than that of cardiac blood vessels [13, 14]. Furthermore, CGRP also plays diversified functions. However, it is still not clear whether TN can influence cerebral blood flow and the occurrence of cerebrovascular events by affecting CGRP release.

In this study, we observed changes in relevant cardiovascular parameters in TN rats, measured the plasma content of CGRP, and monitored the changes in cerebral blood flow in rats before and after establishing the middle cerebral artery occlusion (MCAO) model to investigate the influences of TN on the local cerebral ischemic stroke model and the underlying potential mechanisms.

Materials and methods

Materials and reagents

ET-1 was purchased from Meilun Biology Technology(Shanghai,China).Triphenyltetrazolium chloride (TTC) was from Sigma (USA). Von-Frey filaments were purchased from Stoelting (USA). The ALC-NIBP rat tail artery pressure-measuring instrument was purchased from Alcott Biotech (Shanghai, China). The Doppler ultrasound cerebral blood flow meter was purchased from AD instruments (Australia).

Experimental animals and grouping

Sixty-five male Sprague-Dawley (SD) rats with a body weight of 220-260 g were purchased from the Experimental Animal Center of The Second Military Medical University. Three days before the experiments, the rats were placed singly in special brown and non-transparent cages. The rats were calmed for 20 min before measurement. Von-Frey filaments were used to stimulate the rats' whisker pads for five times on each side to allow the rats to adapt to the stimulation of Von-Frey filaments. The basal mechanical pain threshold values were recorded, and rats that were very sensitive to the Von-Frey filaments were excluded. After the training was completed, rats that were adapted to the training were randomly divided into the model group (TN group, 35 animals) and the sham group (30 animals). Initially, there were 35 rats in the TN group; the model was successfully established in 32 rats and failed in three animals. Rats in the TN group received infraorbital nerve cerclage of the bilateral trigeminal nerves; the sham group only received infraorbital nerve separation and did not receive cerclage. Thirty days after cerclage, ET-1 was injected into the surroundings of the MCA.

Surgical method

The model was established using the chronic constriction cerclage of the infraorbital nerve, branch of the trigeminal nerves in rats. Rats were anesthetized by intraperitoneal injection of 10% chloral hydrate (0.35 mL/100 g). A 1-cm incision was made at approximately 0.5 cm below the zygomatic bone in the rats' cheeks. The subcutaneous tissues, muscle, and surrounding fascia were blunt separated to expose the infraorbital foramen. The infraorbital nerve traveled from the infraorbital foramen was observed in a fan-shape distribution. A glass-dissecting needle was used to free the infraorbital nerve from the proximal end for approximately 4 mm. The infraorbital nerve was ligated using two pieces of absorbable thread (4-0 chromic catgut suture) under a microscope; the spacing was approximately 2 mm with proper

strength to mainly form a constriction ring. The incision was sutured. The animals were normally fed. The infraorbital nerve of the sham group was exposed using the same method but was not ligated.

On postoperative day 30, rats in the TN group and the sham group all received ET-1 to establish the local cerebral ischemia MCAO model. The specific surgical method is described as below. Rats were anesthetized by isoflurane and immobilized in the supine position on a stereotaxic instrument. Furs at the median of two ears were shaved, and a 1.5-cm incision was made along the parietal midline to expose the cranial bone until the bregma could be clearly observed. The bregma point was used as a marker, and the incision was moved forward by 0.9 mm, to the left side by 5.2 mm, and then downward by 8.7 mm. Three microliters of ET-1 at 120 pmol/μl was injected by a microinjector into the surroundings of the MCA at 0.6 μL/min; the needle was retained for 10 min.

Measurement of the mechanic pain threshold

Changes in the behavioral reaction of the animals were observed on preoperative day 3 and postoperative per 5 days, and the testing was performed using the Von-Frey filaments. The stimulation strengths from low to high were 0.07, 0.16, 0.4, 0.6, 1.0, 1.4, 2.0, 4.0, 6.0, 8.0, 10.0, 15.0, and 26.0 g. Each stimulation strength was tested five times on the bilateral whisker pads of the rats. The mechanical pain threshold value was the corresponding stimulation strength of one or more items presented by the rats, as follows: (1) Dodge actions such as backward movement, turning around, or shaking the head: to avoid the stimuli, the rats would curl their body, move closer to the cage walls, or hide their face and head under their body. (2) Scratching their face: the presentation was scratching the stimulated region on the face more than three times. (3) Aggressive behaviors: the rats grasped and bit the stimulating device and exhibited attack actions.

Measurement of blood pressure (BP) and heart rate (HR)

Non-invasive measurement of the rat tail arterial pressure: The rat tail arterial pressure measuring instrument was turned on, and the temperature was set at 37°C to pre-heat for 10 min. The calibration was performed in real-time according the pressure signals. The fixed box was adjusted according to the rats' body size. The rats were gently placed in the box, and flipping the rats in the box was avoided if possible. A pressurizing sleeve was placed on the tail root of the rats, and the temperature probe was inserted into the fixed box to observe the temperature changes at any time, to ensure the stability of the rat body temperature. The BP was measured when the rat pulses were stabilized. During the measurement, pressure was applied using the pressurizing sleeve to a value above the systolic BP to block the blood flow in the tail artery, and the pulse gradually disappeared. When the externally applied pressure decreased to the systolic pressure, the pulse reappeared, thereby signifying the systolic pressure. With a continuous decrease in the externally applied pressure, the wave amplitude of the pulse continuously increased. When the applied pressure decreased to the diastolic pressure, the pressure on the trail artery applied by the pressurizing sleeve disappeared, and the wave amplitude of the pulse reached the maximum value, which was the diastolic BP. Based on the BP curve, the values including the systolic pressure, diastolic pressure, and HR were fitted using the pressure measurement software. Each rat was measured 10 times with an interval of 2 min. The average value was used as the final BP value.

Measurement of the femoral artery BP: Rats were anesthetized by intraperitoneal injection of 3% sodium pentobarbital (0.2 mL/100 g). After being anesthetized, the rats were placed on the operation table in the supine position, and four limbs were immobilized. After skin preparation, the skin in the middle of the neck was cut open, and the tissues were blunt separated to expose the trachea. An incision was made at the trachea, and a sterilized tracheal catheter was inserted into the trachea; the tracheal catheter was fixed at a depth of approximately 2 cm from the upper incisor tooth. At the right groin, skin was prepared, disinfected, and cut open to separate the femoral artery and vein. A sterilized arterial catheter was filled with heparinized 0.9% normal saline. Blood vessels were cut open using ophthalmic microsurgical forceps, and the arterial catheter was inserted into the femoral artery along the blood vessel incision; the insertion depth was 1-2 cm. The PowerLab/8SP and the corresponding com-

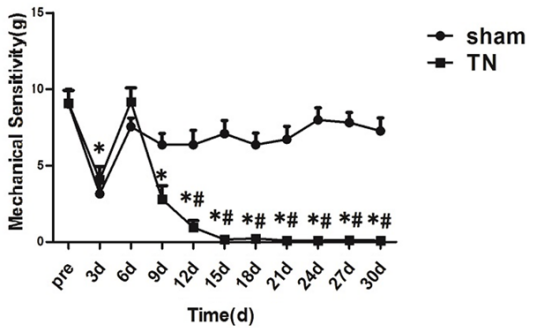

Figure 1. Changes in the mechanic pain threshold in rats before and after constriction cerclage of the infraorbital nerve (n=8) (*P<0.05 post-operation vs pre-operation, #P<0.05 sham vs TN).

puter software were turned on, and the arterial catheter was connected to a transducer to record the changes in BP and HR.

Measurement of cerebral blood flow using Doppler ultrasound

Rats were anesthetized using isoflurane gas, disinfected, and immobilized on a stereotaxic instrument in the supine position to expose the bregma point. The bregma point was used as the coordinate origin; a bone window was drilled 2 cm to the back and 1 cm to the left to expose the cortical leptomeninges. The probe of the laser Doppler flowmeter was placed on the leptomeninges. To prevent probe movement during recording, the probe was fixed onto a probe rack. The 75-min blood flow volume and blood flow velocity curve were continuously recorded. During data analysis, one segment of relative stable blood flow volume was selected every 15 min to obtain the mean blood flow during this period using software analysis.

Measurement of CGRP in the plasma

The neck skin of the rats was cut open and disinfected. The right internal carotid vein was identified, and the proximal end was closed using a hemostatic clamp. A 2.5-mL heparinized empty syringe was inserted along the external carotid vein toward the head end to draw 1.3 mL of venous blood. The blood sample was placed in a 2-mL centrifuge tube, and 20 μL EDTA and 25 μL aprotinin were added immediately. After gentle mixing, the blood sample was centrifuged in a 4°C centrifuge (4000 rpm/min for 10 min). The CGRP measurement was performed using a CGRP radioimmunoassay reagent kit according to the instruction manual.

TTC staining

Twenty-four hours after surgery, the animals were deeply anesthetized by 3% pentobarbital and decapitated to collect brain samples. The brain tissues were stored in a -20°C freezer for 30 min. Coronal sections were conducted from the anterior pole backward for every 2 mm. Sections were placed in 1% TTC phosphate buffer and incubated at 37°C in the dark for 30 min. The normal tissues showed red staining, and the infarcted tissues exhibited white staining. After being stained, the sections were fixed in 4% paraformaldehyde solution for 24 hours. The results were photographed using a digital camera and analyzed using the ImageJ software to calculate the percentage of the infarcted area.

Statistical analysis

All experimental data are presented as the mean ± standard deviation. The mechanical pain threshold measurement, tail arterial pressure measurement, and cerebral blood flow volumes were analyzed using the repeated-measure analysis of variance (ANOVA). Other data were analyzed using the t test or ANOVA. Statistical analysis was performed using SPSS15.0.

Results

Changes in the mechanic pain threshold in rats before and after INOX surgery

Before and after infraorbital nerve constriction surgery, behavioral changes in the rats were observed every 3 days. The changes in the mechanic pain threshold were recorded using a Von-Frey pain measurement pen. The results are presented in **Figure 1**. The pain threshold values in the sham group between before surgery and 6 days after surgery did not exhibit a significant change ($P>0.05$), and the fluctuation was approximately 8 g. However, the pain threshold values in the two groups on postoperative day 3 exhibited temporary reductions (TN group: 4.08±0.85 g, n=10; sham group: 3.15±0.82 g, n=10), which were lower than the preoperative levels ($P<0.01$).On postoperative day 6, the pain threshold values of the two

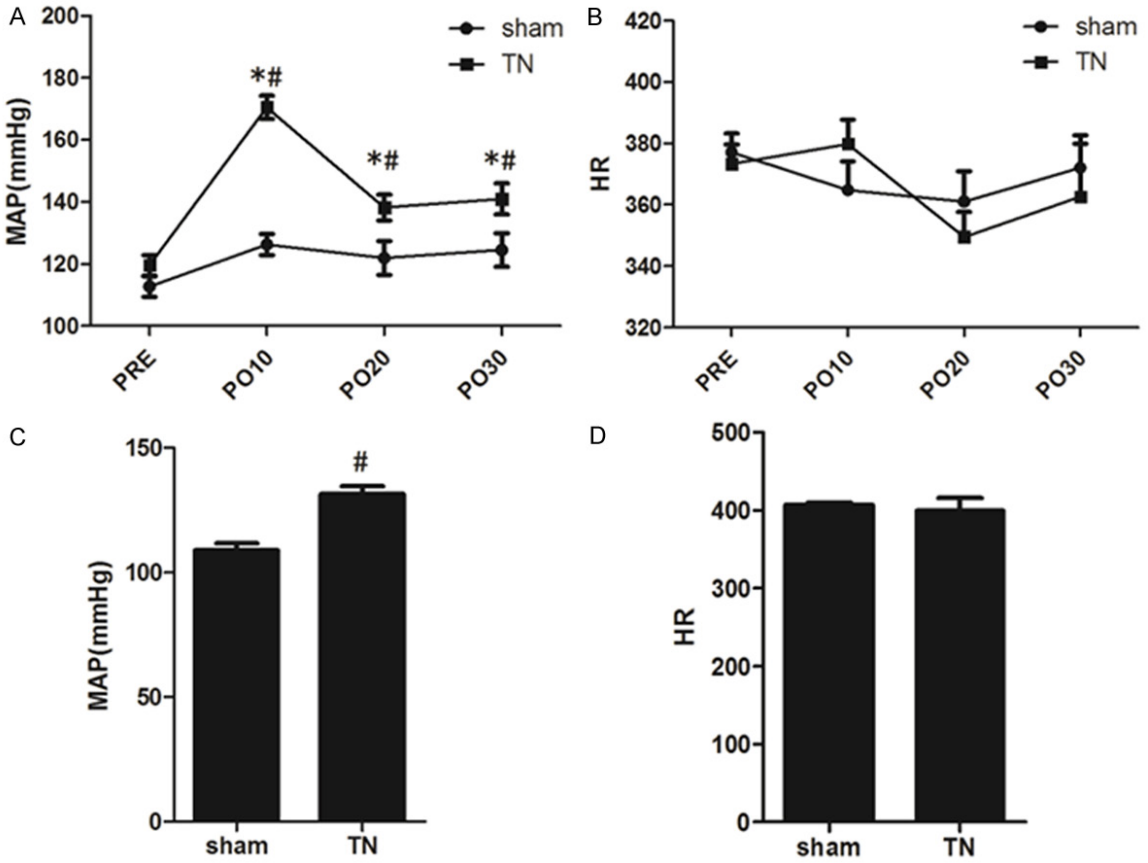

Figure 2. The influences of TN on BP and HR. The mean value of the preoperation data of the BP and HR were continuously measured using the non-invasive tail artery pressure measuring for a week. The sham group (n=6) only received infraorbital nerve separation but did not receive cerclage. Rats in the TN group (n=6) received infraorbital nerve cerclage of the bilateral trigeminal nerves. A. The difference of tail mean arterial pressure (MAP) between preoperation and postoperation were analyzed using the repeated-measure ANOVA. The MAP in the TN group began to increase and reach the peak on postoperative day 10, then decreased from postoperative day 10 to postoperative day 30, but the value was still significantly higher than that before surgery and in the sham group. The mean arterial pressure values before and after surgery in the sham group did not exhibit significant changes. B. The HR in the TN group reached the peak point on postoperative day 10, and then came down. The HR before and after surgery in the sham group did not significantly changes, and the changes at all timepoints between these two groups were not significantly different. C. The mean arterial pressure values between postoperative days 10 and 30 were all significantly higher than those before surgery and in the sham group. D. The changes in HR between these two groups deeply anesthetized were not significantly different (*P<0.05 postoperation vs preoperation, #P<0.05 sham vs TN).

groups recovered to the preoperative levels. In the TN group, the pain threshold value significantly decreased on postoperative day 9 (2.81±0.78 g) and decreased to the lowest level on postoperative day 15. The reaction sensitivity to pain induced by mechanic stimuli significantly increased (P<0.01), indicating that rats in the TN group were sensitive to pain. The data revealed that the pain threshold values between the two groups before surgery did exhibit a significant difference and that the pain threshold value in the TN group after surgery was significantly lower than that in the sham group (P<0.01).

Influences of TN on BP and HR

Before and after the infraorbital nerve constriction surgery, the BP and HR of the rats were continuously measured using the non-invasive tail artery pressure measuring method every 10 days (**Figure 2A** and **2B**). On postoperative day 30, a catheter was placed into the femoral artery of the rats to measure the BP and HR under anesthesia (**Figure 2C** and **2D**). The mean arterial pressure values before and after surgery in the sham group did not exhibit significant changes (P>0.05). The mean arterial pressure in the TN group began to increase on post-

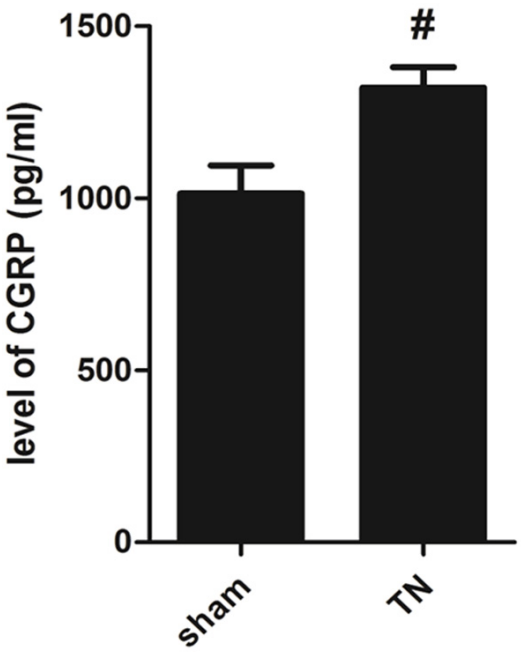

Figure 3. The effects of TN on the plasma CGRP content. Thirty days after the infraorbital constriction surgery, blood samples were collected from the right internal carotid vein of the rats to measure the plasma CGRP content, the CGRP content in the TN group (n=5) was significantly higher than that in the sham group (n=5) (#*P*<0.05 sham vs TN).

operative day 10, and the value was significantly higher than that before surgery and in the sham group (*P*<0.05). The mean arterial pressure values between postoperative days 10 and 30 were all significantly higher than those before surgery and in the sham group (*P*<0.05). However, the changes in HR at all time points between these two groups were not significantly different (*P*>0.05).

Influences of TN on the plasma CGRP content

Thirty days after the infraorbital constriction surgery, blood samples were collected from the right internal carotid vein of the rats to measure the plasma CGRP content. As shown in **Figure 3**, the CGRP content in the TN group (1321.64± 101.78 pg/mL) was significantly higher than that in the sham group (1031.70±147.75 pg/mL) (*P*<0.05).

Changes in the amount of cerebral blood flow

The surroundings of the rat MCAs were microinjected with ET-1, and 30 min later (marked as point 0), the changes in the cerebral blood flow of the brain surface blood vessels were measured continuously (**Figure 4**). The basal value at the beginning of the measurement was (461.93±56.19 PU/s). The blood flow after 45min significantly increased, and the blood flow in the TN group (1174.69±81.01 PU/s) was significantly higher than that in the sham group (667.20±36.15 PU/s).

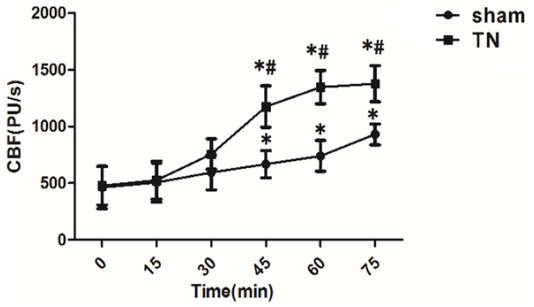

Figure 4. The influences of TN on the amount of cerebral blood flow in the ET-1 focal ischemic stroke model. The surroundings of the rat MCAs were microinjected with ET-1, and 30 min later, the changes in the cerebral blood flow of the brain surface blood vessels were measured continuously. During data analysis, stable blood flow volume was selected every 15 min to obtain the mean value. The blood flow after 45 min (microinjected with ET-1 after 75 min) significantly increased, and the blood flow in the TN group (n=6) was significantly higher than that in the sham group (n=8) (**P*<0.05 postoperation vs. preoperation, #*P*<0.05 sham vs TN).

Influences of TN on the percentage of the cerebral infarction area in the focal ischemic stroke model

The surroundings of the rat MCAs were microinjected with ET-1, and the rats were sacrificed by decapitation after 24 hours. The cerebral infarction area of the rats was measured using the TTC staining method, and its percentage in the cerebral hemisphere was calculated (**Figure 5**). **Figure 5A** and **5B** present the TCC staining results of brain sections in the sham and TN groups, and **Figure 5C** shows the statistical results regarding the percentage of cerebral infarction. The percentage of cerebral infarction in the hemisphere was 10.48±3.7% in the sham group and 4.7±1.64% in the TN group. The percentage of infarction area in the sham group was larger than that in the TN group (*P*>0.05).

Discussion

TN is a recurrent refractory pain. Its presence severely influences the quality of life of patients.

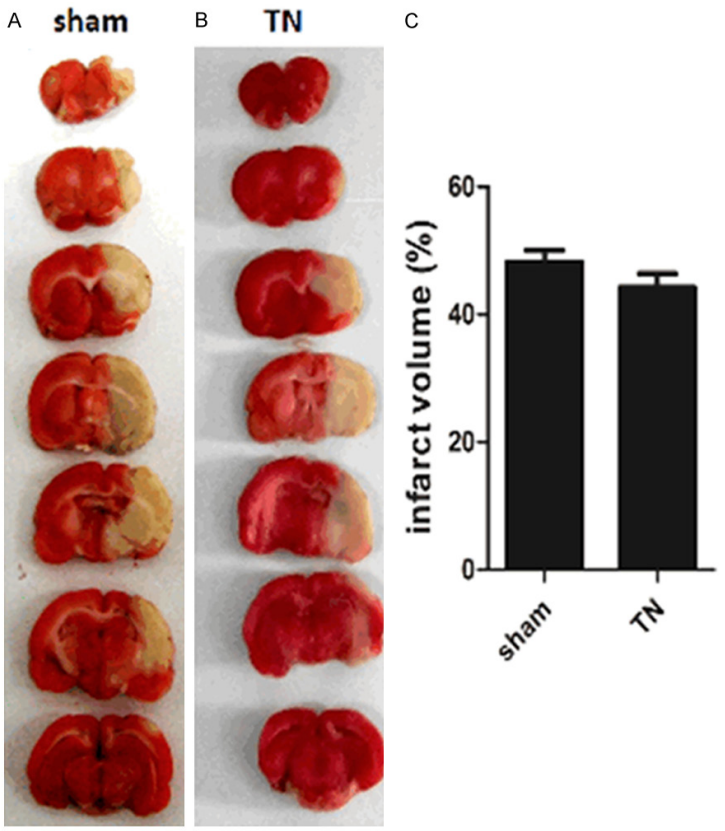

Figure 5. Influences of TN on the percentage of the cerebral infarction area in the focal ischemic stroke model. The surroundings of the rat MCAs were microinjected with ET-1, and the rats were sacrificed by decapitation after 24 hours. The cerebral infarction area of the rats was measured using the TTC staining method, and its percentage in the cerebral hemisphere was calculated. A. TCC staining results of brain sections in the sham groups. B. TCC staining results of brain sections in the TN groups. C. The percentage of cerebral infarction in the hemisphere in the sham group (n=8) and in the TN group (n=10). The percentage of infarction area in the sham group was larger than that in the TN group ($P>0.05$).

A face-to-face survey conducted in Germany revealed that the current incidence of TN is approximately 0.3% [15]. Studies have shown that 95% of patients are affected by compression of the blood vessels at the trigeminal nerve roots [16]. Therefore, in the present study, we selected suborbital nerve constriction surgery to constrict the nerve and cause vascular compression to simulate the TN commonly observed in clinical practice. This study had the following major findings: (1) after suborbital nerve constriction, the mechanical pain threshold in the rats significantly decreased, indicating that the model was established successfully. The pain stimulation existed, and this nociceptive stimulus could last for 30 days (**Figure 1**). (2) We monitored changes in the cardiovascular indicators (BP and HR) of rats during the experimental process. The results showed that the mean arterial pressure of rats in the TN group was significantly higher than that in the sham group, which lasted for 30 days post surgery. However, the changes in HR between these two groups did not significantly differ (**Figure 2**). (3) This study used the Doppler ultrasound method to monitor changes in the cerebral blood flow in the frontal cortex after 30 min of ischemia-reperfusion injury in the focal ischemic stroke model. The results revealed that the cerebral blood flow in the TN group was significantly higher than that in the sham group (**Figure 4**). (4) To identify the reason for the increase in cerebral blood flow in the TN group, the concentration of the plasma CGRP was further detected. The results revealed that the serum CGRP concentration in the TN group was higher than that in the sham group. This difference was statistically significant (**Figure 3**). (5) To clarify the influences of TN on the prognosis of the focal cerebral ischemia-reperfusion model, the cerebral infarction areas in these two groups were measured. The result revealed that the cerebral infarction area in the TN group was smaller than that in the sham group.

Pain is a complex physiological and psychological activity, which usually yields an unpleasant experience caused by nociceptive stimuli. Certain pains (such as migraine, TN, and cancer pain) even cause unbearable torture to the body. From in-depth studies in recent years, some scholars have found that pain not only causes serious problems for patients but also associates with diseases such as hypertension, diabetes mellitus, and stroke. The study of Eikermann-Haerter et al [7] demonstrated that migraine associated with a gene mutation can aggravate stroke by promoting ischemic depolarization. The study of Kang et al [17]

showed that neuralgia after a varicella zoster attack is also a risk factor for stroke; however, the neuralgia mayalso be associated with the destruction of blood vessel structures by the varicella zoster infection and with the virus infection-related inflammation. The clinical survey of Pan et al [8] demonstrated that TN might be a risk factor for stroke; however, the mechanism underlying the association between TN and stroke is still not clear. Our present study revealed that in the focal ischemia-reperfusion model, TN increased the cerebral blood flow in the frontal cortex; however, the difference in the cerebral infarction areas measured 24 hours after ischemia-reperfusion was not significant.

Our study results regarding cerebral blood flow were similar to the conclusions reached by several scholars in clinical studies. Their studies showed that acute pain is associated with the co-activation of many brain regions including the thalamus, somatosensory center, insula, and cingulate cortex. During acute pain, cerebral blood flow in these regions increases[18, 19]. Although the influence of chronic neuropathic pain on cerebral blood flow has a certain difference from that of acute pain, clinical studies have demonstrated that, during TN, the cerebral blood flow in higher centers such as the frontal cortex, precuneus, and anterior cingulate increases [20]. On one hand, it is possible that the frontal cortex brain area is always in an activated state during trigeminal neuropathic pain; therefore, blood vessels in this area are dilated and establish an abundant collateral circulation, thereby increasing cerebral blood flow. On the other hand, CGRP has a strong vasodilatory function, and the CGRP receptors extensively distribute throughout the vascular system in the brain. The binding between CGRP and its receptors can exert a strong intracranial vasodilatory effect. Studies have also confirmed that during a headache attack in migraine patients, CGRP can induce dilation of the MCA and the middle meningeal artery. The vasodilatory function of CGRP might be associated with its induction of substance P release. Substance P affects mast cells and can induce increased histamine release, thus causing a series of inflammatory responses. The HR between these two groups was not significant different, and the BP of rats in the TN group was always higher than that in the sham group, indicating that the increased BP was mainly associated with the factors of peripheral vascular resistance and blood flow. The long-term high-BP status would cause increased cerebral blood flow.

CGRP is a strong vasodilator substance. However, in this study, TN induced the BP increase because the mechanism of BP regulation is complex, being mainly the combined function of baroreceptors, chemoreceptors, and renal body fluid regulation. The major function is exerted by the sympathetic nervous system. Pain will induce increased sympathetic excitability. The effect of the increase in BP caused by the increase in sympathetic excitability is larger than the vasodilatory function of CGRP; therefore, the BP increases. In addition, this study also measured the areas of cerebral infarction after 24 hours of ischemia-reperfusion in these two groups; however, the difference between these two groups was not statistically significant. On one hand, the pathophysiological process of stroke is more complex and includes hemorrhagic stroke and ischemic stroke. The increased BP and increased cerebral blood flow in this study might influence the prognosis of hemorrhagic stroke and have protective effects on ischemic stroke; however, this influence still awaits further studies for confirmation. On the other hand, the clinical pathogenesis of ischemic stroke is also highly complex. Its prognosis is a result of the combined action of various pathophysiological processes, including energy metabolism disorders, amino acid toxic excitability, inflammatory responses, and cell apoptosis. The influences of trigeminal neuropathic pain on ischemic stroke might be associated with the aforementioned mechanisms; however, the underlying mechanisms still require further in-depth studies.

Disclosure of conflict of interest

None.

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