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# Effects of intestinal flora on cerebral hemorrhage area and brain tissue inflammation in acute hemorrhagic stroke

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**Abstract**

To explore the impacts of intestinal flora on cerebral hemorrhage area and brain tissue inflammation in acute hemorrhagic stroke, seventy-two male C57BL/6 mice were randomly separated into 6 groups (n=12), the experimental group (EG, day 1, day 3 and day 7) and the control group (CG, day 1, day 3 and day 7). The mouse cerebral hemorrhage model was established by collagenase injection, and the EG received 0.4 mL fecal filtrate of healthy mice once a day, and the CG received the same amount of normal saline transplantation. The mNSS score, hematoma volume and cerebral edema content were used to evaluate nerve function injury and brain injury degree at each time point after operation. The expressions of inflammatory factors were detected by western blot. We found that at each time point after operation, compared with the CG, nerve function deficit scores of mice in the EG declined ($P<0.05$), the water content of mice brain tissue in the EG declined ($P<0.05$), and the protein expressions of inflammatory factors in the EG were decreased ($P<0.05$). Relative to the CG, the volume of hematoma in the EG declined on day 3 along with day 7 after operation ($P<0.05$). In conclusion, intestinal flora can reduce cerebral hemorrhage area and brain tissue inflammation, and then improve the performance of nerve function deficit in acute hemorrhagic stroke.

**Keywords:** Acute hemorrhagic stroke, Cerebral hemorrhage, Inflammation, Intestinal flora, Nerve function.

## 1. Introduction

Stroke belongs to an acute cerebrovascular disease which includes ischemic and hemorrhagic stroke. Stroke is caused by a sudden rupture or blockage of a blood vessel in the brain that inhibits blood flow to the brain, causing damage to brain tissue [1]. The survey shows that stroke has emerged to be the first cause of death in China, and is also the primary cause of disability for Chinese adults [2]. Stroke is characterized by high incidence, high mortality, and with high disability rate [3]. In spite of there have been numerous studies on hemorrhagic stroke, the study of hemorrhagic stroke lags significantly behind that of ischemic stroke [4].

Recent studies have revealed that alterations in the gut microbiota affect prognosis after stroke through a variety of factors, including local and systemic inflammation, intestinal leakage, endotoxemia, bacterial composition, metabolites, and the immune and nervous systems [5]. Therefore, in recent years, people have actively explored the pathogenic link between intestinal dysbiosis caused by stroke and adverse treatment outcomes, in order to find more effective treatment methods [6]. Stroke can cause intestinal motility disturbances, increase the permeability of the intestinal barrier, and allow microbes and microbe-derived products, such as lipopolysaccharide (LPS) and trimethylamino-n-oxide (TMAO), to transfer into the bloodstream, and these changes that accelerate systemic inflammation and worsening of symptoms, often leading to a poor prognosis [7]. It is worth noting that intestinal dysbiosis can produce chronic inflammatory responses both peripherally and centrally, thus accelerating the pathology of stroke [8]. Overall, dysregulation of the gut microbiome is considered to be a major risk factor positively associated with poor prognosis after stroke [9].

Over the past decade, fecal microbiota transplantation (FMT) has received obvious attention in terms of gut microbiota intervention in neurological injury prognosis [10]. However, no controlled clinical studies have evaluated the effect of FMT on the prognosis of human patients with neurological injury. Recent studies have demonstrated dysregulation of the gut microbiome after stroke and its relation with elevated inflammatory markers as well as several post-stroke sequelae, containing post-stroke cognitive impairment [11]. The modulation of immune cell function appears to exert a crucial role in the microbiome's modulation of stroke pathology [12]. More recently, a prospective

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case-control study showed higher disruption of gut microbiota during ischemic and hemorrhagic strokes compared to non-stroke-matched control subjects [13].

In this context, an animal model of acute hemorrhagic stroke was adopted to explore the effects of intestinal bacteria transplantation in healthy mice after stroke to explore the effects of intestinal flora on cerebral hemorrhage area and various indicators of brain tissue inflammatory factors in acute hemorrhagic stroke, and to study the neuroprotective effect of intestinal flora on ischemic stroke, providing a basis for clinical work.

## 2. Material and methods

### 2.1. Animals

A total of 72 male C57BL/6 mice aged 8 weeks and weighing 20-24 g were obtained from Shanghai JieSiJie Laboratory Animal Co., Ltd (Shanghai, China). The mice were housed in an environment free of specific pathogens (SPF) (temperature 22 ± 1°C, relative humidity 50±1%, normal day/night cycle 12/12 h). All animal experiments were conducted in line with the requirements of Animal Research Center of Hebei Medical University.

### 2.2. Modeling and treatment methods

The mice were separated into 6 groups (n=12) in random, the experimental group (EG, day 1, day 3 and day 7) and the control group (CG, day 1, day 3 and day 7). After 7 days of adaptive feeding, all the mice were deprived of water for 8 hours. 10% chloral hydrate 360 mg/kg was injected intraperitoneally. After the mice entered anesthesia, the head of the mice was skinned and fixed on a stereoscope in a prone position. The skin of the head was cut longitudinally along the median sagittal suture, the subcutaneous tissue was bluntly separated, and the periosteum was gently wiped off with cotton ball of hydrogen peroxide solution to fully expose the coronal suture and fontanel. The skull was drilled with a dental drill 3 mm to the right of the midline 1 mm before the coronal suture. Next, 0.03 U collagenase (Shanghai Yuanye Biotechnology Co., LTD, Shanghai, China) was injected into the caudate nucleus to establish a mouse cerebral hemorrhage model. After the operation, the EG received 0.4 mL fecal filtrate of healthy mice once a day, and the CG accepted the same amount of normal saline transplantation.

### 2.3. Observation indicators and detection methods

#### *2.3.1. Neurobehavioral score*

Modified Neurological Severity Score (mNSS) was used to assess the motor, sensory along with reflex functions of mice in each group at corresponding time points (1, 3, and 7 days after surgery). The score ranged from 0 to 14 points, and the score was positively related to the severity of ischemia-reperfusion injury (that is, the higher the score of mNSS, the more severe the ischemia-reperfusion injury, and vice versa).

#### *2.3.2. Cerebral hematoma volume*

The whole brain of the rat was removed after death, rinsed with normal saline, followed by fixing in 4% paraformaldehyde solution. Next, the brain tissue of the rat was fixed on a high-speed freezing micrograph, and continuous coronal sections were made with the injection channel of the syringe as the center, with layer thickness of 1 mm. The sections were embedded in paraffin and received staining with hematoxylin-eosin (HE). Observation and photography were performed under an optical microscope, and the volume of hematoma was calculated using an image analysis system. The volume of hematoma was equal to section thickness (mm) × section bleeding area ($mm^2$) × section number.

#### *2.3.3. Cerebral edema content*

Blot the surface moisture of the brain tissue with absorbent paper, and quickly put it into A small glass bottle with A lid that is weighed (A) in advance, and weigh (B) immediately to obtain wet weight; Dry for 24 h, take out the brain tissue to be tested and restore it to room temperature, then cover and weigh (C), C-A = dry weight, and repeatedly weigh to constant weight. Electronic balance was used for weighing, accuracy 0.1 mg. Formula: (wet weight - dry weight)/ wet weight ×100%, that is, (B-C)/ (B-A)×100%.

#### *2.3.4. Levels of inflammatory factors*

The brain tissue of mice in each group was split, and centrifuged for 15000 r/min for 5 min, supernatant could be collected, and total protein could be extracted by protein extraction kit (Thermo Scientific, USA). Followed by electrophoresis, the proteins were transferred from the gel to PVDF membranes. Followed by blocking in 5% bovine serum albumin for 2 h at room temperature, the membrane was cultivated with the following primary antibodies at 4 °C overnight: IL-1β, IL-6, IL-10, TNF-α as well as GAPDH. Followed by cultivating with specific horseradish peroxidase-conjugated secondary antibodies for 2 h at room temperature, the bands were visualized and detected with an enhanced chemiluminescence reagent kit (Thermo Scientific, USA).

### 2.4. Statistical analysis

SPSS 24.0 statistical software was adopted for data analysis. Measurement data were exhibited to be (x±s), and one-way ANOVA was adopted for comparison between groups at each time point, and least significant difference (LSD)-t test was adopted for pair comparison. P<0.05 meant statistical significance.

## 3. Results

### 3.1. mNSS scores in each group

The mice in the CG exhibited the symptoms of nerve defect on the first day after operation, and the symptoms of nerve defect on the third day were the most severe. In contrast to the CG, the nerve function score of mice in the EG presented reduction on day 1, day 3 as well as day 7 after operation (P<0.05, Fig. 1).

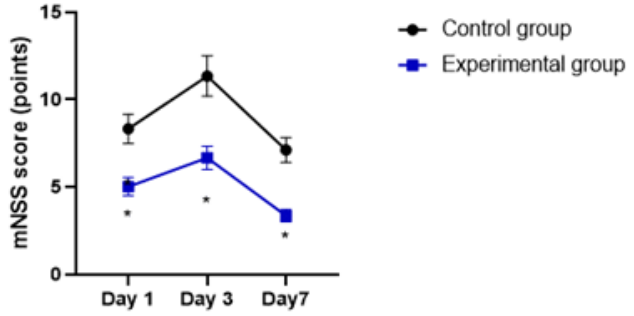


**Fig. 1.** mNSS scores in each group. * P<0.05.

### 3.2. Cerebral hematoma volume in each group

There was obvious hematoma in the CG, and the volume of hematoma was the largest 3 days after operation. In contrast to the CG, the volume of hematoma in the EG decreased on day 3 and day 7 after operation (P<0.05, Fig. 2).

### 3.3. Cerebral edema content in each group

Relative to the CG, the cerebral edema content in the EG exhibited reduction on day 1, day 3 as well as day 7 after operation (P<0.05, Fig. 3).

### 3.4. Levels of inflammatory factors in each group

Relative to the CG, the levels of IL-1β, IL-6, IL-10, along with TNF-α in the EG were decreased on day 1, day 3 as well as day 7 after operation (P<0.05, Fig. 4).

## 4. Discussion

The main causes of cerebral hemorrhagic stroke are hypertension, arteriosclerosis, etc., which mainly occurs in people over 40 years old, among which people over 50 years old are the highest incidence group [14]. However, recent studies have found that the incidence of cerebral hemorrhagic stroke tends to be younger [15]. The present treatment methods mainly contain drug therapy, surgical therapy as well as auxiliary therapy [16]. Although surgical treatment can remove the lesion in time, it cannot reverse the damaged nerve function, and the bleeding caused by surgery may also damage other brain tissues of patients [17]. Therefore, there is a lack of clear evidence of evidence-based medicine, and surgical treatment is still controversial. Adjuvant treatment includes lowering blood pressure, reducing intracranial pressure, maintaining water and salt balance, regulating body temperature, etc., which has no direct effect on the elimination of hematoma, but can only protect nerve function from further damage [18].

The inflammatory response after cerebral hemorrhage is a major factor leading to disease progression [19]. In this process, the recruitment of microglia and the release of pro-inflammatory cytokines have a key role [20]. In addition, peripheral inflammatory cells, such as white blood cells, can enter the central nervous system through the damaged blood-cerebrospinal fluid barrier, further amplifying inflammatory damage and worsening the condition [21]. Therefore, reducing the inflammatory infiltration and inhibiting the inflammatory cascade after cerebral hemorrhage may be a new strategy for treating cerebral hemorrhagic stroke, which has important clinical value and social significance [22].

Alterations in the microbiome have been shown to affect stroke outcomes [23]. The gut microbiome itself has a brain-protective effect in experimental stroke [24]. These are novel insights into the gut-brain axis in models of stroke and other acute brain injuries, which to date have specifically studied the effect of altered bacterial composition on disease outcomes [25]. Communication between the gastroenteric nervous system and the central nervous system is essential for keeping systemic environmental balance [26]. The gut's internal and external neural inputs modulate blood flow, peristalsis, hormone release, as well as immune function [27]. The health of the gut microbiome has a vital potential in modulating an individual's overall function together with well-being [28]. Microbes release short-chain fatty acids, modulate G-protein-coupled receptors, mediate release of hormone release and neurotransmitters, as well as modulate inflammation and mood. In addition, gas factors play an important role in modulating inflammation along with producing responses in injury [29]. Nerve injuries, including ischemic stroke, spinal cord injury, traumatic brain injury, as well as hemorrhagic cerebrovascular injury, can result in intestinal biological disorders [30]. In addition, adverse changes in the composition of the microbiota may be linked to an elevated risk of these nerve injuries because of elevated pro-inflammatory molecules as well as clotting factors [31]. Interventions containing probiotics, fecal microbiota transplantation as well as oral single-chain fatty acids have been displayed to stabilize and improve the composition of the microbiome [32]. Nevertheless, the impact of intestinal flora on hemorrhagic stroke is rarely reported, and its neuroprotective effect deserves further study.

In our study, the results suggested that relative to the CG, the nerve function score of mice in the EG presented reduction on day 1, day 3 as well as day 7 after operation, suggesting that intestinal flora could effectively reduce the nerve function score of mice with cerebral hemorrhage and improve the symptoms of nerve function deficit. Consistently, Chong-Su Kim et al. have proved that gut microbiota-produced indole-3-propionic acid can protect the microglia from inflammation, thus improving neuronal function [33].

The results of hematoma volume and cerebral water content revealed that relative to the CG, the volume of hematoma and cerebral water content in the EG was signifi-

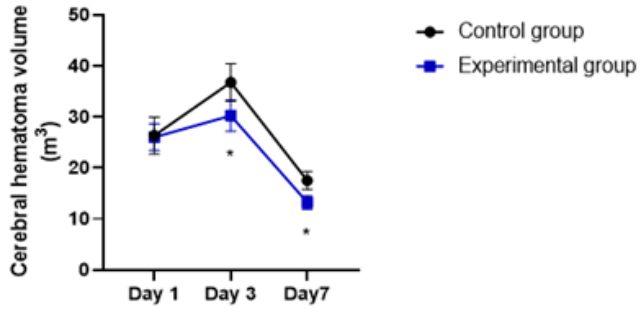


**Fig. 2.** Cerebral hematoma volume in each group. * P<0.05.

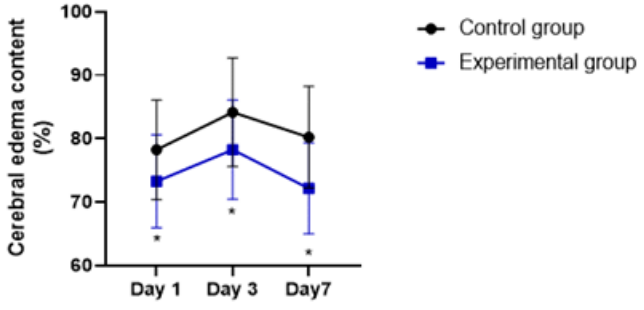


**Fig. 3.** Cerebral edema content in each group. * P<0.05.

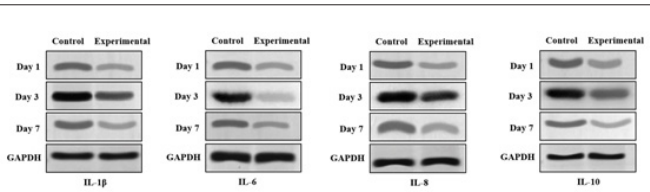


**Fig. 4.** Levels of inflammatory factors in each group.

cantly reduced, implying that intestinal flora could reduce the volume of hematoma, reduce the degree of local edema and relieve the pressure of hematoma on the surrounding tissue in mice with cerebral hemorrhage. In line with our findings, Li et al. have pointed out that gut microbiota can ameliorate white matter injury in mice after intracerebral hemorrhage [34].

In addition, our study revealed that relative to the CG, the levels of IL-1β, IL-6, IL-10, along with TNF-α in the EG presented reduction on day 1, day 3 and day 7 after operation, suggesting that intestinal flora could lessen the inflammatory response of mice with cerebral hemorrhage. Similarly, Liu et al. have indicated that gut microbiota can migrate neuroinflammation in mice after intracerebral hemorrhage [35].

## 5. Conclusion

In conclusion, intestinal flora can reduce cerebral hemorrhage area and brain tissue inflammation, and then improve the performance of nerve function deficit in acute hemorrhagic stroke.

## Conflict of interests

The authors declare no competing interests.

## Consent for publications

The author read and approved the final manuscript for publication.

## Ethics approval and consent to participate

We have received approval from the Experimental Animal Ethics Committee of First Hospital of Hebei Medical University.

## Informed consent

Not applicable.

## Availability of data and material

If you have any additional questions about the study's original contributions, please contact the corresponding author.

## Authors' contributions

YF and LJ contributed to the study conception and design. Experimental operation, data collection and analysis were performed by MX, ZJ, LH, LH, MZ and YF. The first draft of the manuscript was written by MX and ZJ. All authors commented on previous versions of the manuscript.

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