Am J Transl Res 2024;16(7):3005-3013
www.ajtr.org /ISSN:1943-8141/AJTR0152379

Original Article

The effects of dexmedetomidine on postoperative cognitive dysfunction in rats with bone fractures undergoing open reduction

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Received July 23, 2023; Accepted October 8, 2023; Epub July 15, 2024; Published July 30, 2024

Abstract: Objective: To investigate the effects of dexmedetomidine on the cognitive dysfunction of aged rats after open tibia fracture surgery and the expression of inflammatory cytokines in the hippocampus. Methods: A total of 45 aged healthy male Sprague Dawley rats were divided into control group, sham group, and dexmedetomidine group. The open tibia fracture surgery rat model was established, and dexmedetomidine was intraperitoneally injected before operation. The cognitive function of aged rats was examined by Morris Water-Maze Test, open field experiment, and passive avoidance memory test. The expression levels of IL-6, IL-1β, and TNF-α in the hippocampus were examined by enzyme-linked immunosorbent assay (ELISA). Results: The escape latency over 5 continuous days in the dexmedetomidine group was significantly shorter than that in the control group (all $P<0.05$). The number of swimming times and the percentage of swimming time in the dexmedetomidine group were significantly higher and longer than those in the control group (all $P<0.05$). Moreover, rats in the dexmedetomidine group exhibited shorter time of stay at the central square and higher number of standing times in comparison with the control group (all $P<0.05$). Compared with the control group, dexmedetomidine intraperitoneally injected before surgery significantly inhibited the expression levels of IL-6, IL-1β, and TNF-α in the hippocampus (all $P<0.05$). Conclusion: Dexmedetomidine could significantly relieve the postoperative cognitive dysfunction in aged rats. The mechanism may be associated with the decreased inflammatory cytokines in the hippocampus.

Keywords: Dexmedetomidine, postoperative cognitive dysfunction, inflammatory cytokine, mechanism, open tibia fracture surgery

Introduction

Postoperative cognitive dysfunction has been considered as a degenerative neurological disorder, which usually occurs in elderly people. It is characterized by progressive deterioration of cognitive function and reduced self-care ability, with symptoms such as personality changes, mental disorder, memory impairment, and attention loss [1]. It was reported that among elderly patients over 60 years old, the incidence rate of postoperative cognitive dysfunction after operation with anesthesia could reach 25% [2]. In recent years, with the increase of the elderly population, postoperative cognitive dysfunction has become a major problem. Some studies showed that the mechanism of postoperative cognitive dysfunction involved various factors, such as dysfunction of the central cholinergic system, inflammation, and apoptosis of nerve cells [3], but the exact mechanism remains unknown. Other studies revealed that the inflammatory response played an important role in the pathogenesis of postoperative cognitive dysfunction [4]. The incidence of hippocampal inflammation could lead to Alzheimer's disease and cognitive decline after surgery [5]. Some studies revealed that galantamine therapy improved the neuroinflammation through inhibiting the inflammatory signal-

https://doi.org/10.62347/QQKB3082

ing pathway and cytokines, such as IL-1β, TNF-α, and IL-6, in the hippocampus of lipopolysaccharide-induced mice [6]. Other studies found that Sirtuin 3 had a protective effect against postoperative cognitive dysfunction via inhibiting hippocampal neuroinflammation cytokine levels, including IL-1β, TNF-α, and IL-6 [7]. Therefore, it is necessary to further explore promising prevention and treatment strategies for postoperative cognitive dysfunction.

Dexmedetomidine, as an intravenous central sympatholytic drug, is a highly selective α-2 adrenergic receptor agonist. It is widely applied in intensive care units and surgical rooms. Dexmedetomidine could be used for analgesia, sedation, inhibition of the sympathetic activity, and anti-anxiety. Numerous studies showed that dexmedetomidine could reduce delirium in patients [8]. Some studies suggested that dexmedetomidine relieved postoperative cognitive dysfunction via protecting the function of nerve cells [9]. Another study reported that dexmedetomidine showed no effect on postoperative cognition in patients over 70-years old receiving elective operations [10]. Thus, further studies are required for evaluating the effects of dexmedetomidine on postoperative cognitive dysfunction and investigate the involved mechanisms.

In the current study, a model of tibia fracture surgery in aged rats was established to simulate the cognitive dysfunction after operation. The effects of dexmedetomidine pretreatment on the postoperative cognitive dysfunction in aged rats were examined. Additionally, the influence of dexmedetomidine on the levels of IL-6, TNF-α, and IL-1β in the hippocampus was evaluated to investigate whether dexmedetomidine relieved the inflammation in central nervous system. The findings of this study would provide a theoretical basis for clinical practice.

Material and methods

Animal model

This study was approved by the animal ethics Committee of Affiliated Hospital of Weifang Medical University (Approval No. 2022-211) and was performed according to the guidelines issued by the Chinese Association for Laboratory Animal Sciences. A total of 45 male specific-pathogen free Sprague-Dawley (SD) aged rats, aged 16 months, weighing 800-1000 g, were purchased from Animal Centre of Weifang Medical University. These experiment animals were kept at a room temperature 22±1°C, a relative humidity of 45-75%, and a 12 h light-dark cycle. The SD rats had free access to food and water.

The postoperative cognitive dysfunction mice model was established according to the description in a previous study [11]. Before operations, SD rats were fasted for 12 h, and isoflurane anesthesia was performed. The procedures of open tibia fracture surgery in rats were as follows. First, the hair on left lower limbs were removed, and the surgical incision area (left tibia) was disinfected with iodophors. Next, the incision away from the bone on the lateral side of the tibia was performed, and a bone marrow internal fixation pin (internal diameter = 0.38 mm) was inserted into the bone marrow cavity at the tibial tubercle. Then, the soft tissue at the 2/3 lower part of the tibia was separated, and the periosteum was removed for 10 mm. Finally, a scissors were used for osteotomy at the junction of the middle and distal 1/3 of the tibia under direct vision. During the whole operation, a warm pad was applied to keep a rectal temperature at 37±0.5°C. To relieve pain related with the skin incision, 2% lidocaine solution was employed locally before the incision, and after the operation, 1% tetracaine hydrochloride mucilage was used for the wound twice daily for 3 days. The vital signs of the mice, such as heart rate, pulse oxygen saturation, mean arterial pressure and body temperature (between 36°C and 37°C) during anesthesia and operation were measured using MouseOX® Small Animal Vital Signs Monitor (Shanghai Yuyan Instruments Co., Ltd.). All the vital signs were observed to be normal, and there were no differences in these parameters among the groups. SD rats were sent back to the animal room for subsequent research after awakening.

The 45 male SD rats were assigned into a sham surgery group, a control group, and a dexmedetomidine group. Rats in the dexmedetomidine group received the tibia fracture surgery, and dexmedetomidine (20 μg/kg) was intraperitoneally injected half an hour before operation. Rats in the sham surgery group received operation without bone fracture, and

normal saline was intraperitoneally injected half an hour before operation. Rats in the control group underwent tibia fracture operation, and the same amount of normal saline was intraperitoneally injected half an hour before operation.

The rotarod test

In order to exclude the possibility of motor coordination-caused postoperative cognitive dysfunction, the rotarod test was conducted. A DIGBehv-RRTG system was applied for this examination. This equipment included a smooth rod with a diameter of 6.7 cm, separated in five compartments with a width of 5 cm, which located at the height of 30 cm above five planks. For the first time, SD rats were required to get adapted to this equipment for two minutes with a low rotation at a speed of 4 rpm and 30 s with no rotation. SD rats were excluded if they could not stay on this rod for two minutes. SD rats from the three groups were examined at 5 min, 15 min, and 25 min after the operation. The parameters were performed with a start speed of 4 rpm, an acceleration speed of 3 rpm/10 s, and a maximal speed of 40 rpm. The rod velocity (rpm) and time (second) were recorded.

Morris water-maze test

Before Morris water maze test, the rats were wide-awake, and the swim speed was between 30 cm/s and 35 cm/s. According to a previous study [12], the 2-day spatial navigation training (Day 1 and Day 2) and 1-day probe test (Day 3) were performed in Morris water maze test. For acquisition training, the rats were subjected to eight consecutive trials. The sequential position for Day 1 was south (S)-west (W)-southeast (SE)-northwest (NW)-southeast (SE)-northwest (NW)-S-SE, and for Day 2 was SE-NW-W-S-W-SE-S-NW. The time limit to locate the platform was 120 s, and the inter-trial interval was 15 s. At 24 h after Day 2 training (Day 3), a single probe test was provided. The platform was removed from the pool, and the rats were let to swim freely for 60 s. The place navigation test and spatial probe test were performed in rats from all the groups [13]. The maze included a circular pool and a clear round platform. The pool was separated into four quadrants. The platform was placed in one quadrant below the water surface. Five days was a training cycle. The rats from three groups were trained four times every day to observe the average daily escape latency. The interval time of each train was 120 s. Rats were released at different quadrants in the pool, facing toward the wall of the pool. The time for reaching the platform was recorded. If a rat did not arrive the platform within 60 s, it was guided onto the platform and let stay for 10 s on the platform, and the escape latency wase recorded as 60 s. After place navigation test, the platform was removed. The rats were tested one time each day for two days by placing them at the same point of entry in the pool, and facing toward the wall of the pool. The number of swimming times crossing the original platform within 60 s was observed. At the same time, the percentage of swimming time in the targeted quadrant in which the original platform located was recorded.

Open field experiment

The behavioral tests were performed 7 days after the operation. All behavioral experiments were performed between 8:00 am and 5:00 pm in the light phase. The related data were collected by an investigator who was blinded to the animal grouping. Open field experiment was performed according to a previous study [14]. Before experiment, 75% alcohol was used to clean the feces and urine of rats. The whole experiment time was 5 min. The light source was kept at the side of the box. Rats from three groups were placed in the open field test box, and their activities were observed. Each instance where the forelegs were lifted off the ground was recorded as one positive activity.

Passive avoidance memory test

According to a previous study [15], the shuttle box test was used to evaluate the passive avoidance memory test. The shuttle box was made of light and dark compartments. Each rat was kept in the light compartment with unconditioned stimulus for 5 s. The initiative avoiding latency was defined as the entering delay of each rat in the dark chamber. After 10 min, the conditioned stimulus was conducted. Passive avoiding latency was considered as the delay of fleeing to safety. The times of avoidance were examined under the conditioned and unconditioned stimulus. The results of avoiding latency

at 7th day were examined after training for six days.

Determination of inflammatory factors

The hippocampal tissue was separated and freshly collected 24 h after the tests. Frozen hippocampal samples from three groups were obtained and were completely homogenized in Phosphate Buffer Saline. The total protein was quantified by BCA (bicinchoninic acid) analysis according to the instructions in the kits (Beyotime, Shanghai, China). Then, the mixture was centrifuged at 8000×g for 15 min at 4°C. The hippocampus homogenates supernatant was obtained and Enzyme-linked immunosorbent assay (ELISA) was employed for examining the expression levels of IL-6 (Catalogue numbers: PI328; Beyotime, Shanghai, China), IL-1β (Catalogue numbers: PI301; Beyotime, Shanghai, China), and TNF-α (Catalogue numbers: PT516; Beyotime, Shanghai, China) in the supernatant. The experimental procedures strictly followed the manufacturer's protocols.

Statistical analysis

All data included in this study were processed using SPSS 22.0. The measurement data were expressed by Mean ± Standard Deviation (Mean ± SD), and one-way ANOVA followed by post hoc Bonferroni analysis was performed for comparison among three groups. For multi-time point data, repeated measures ANOVA followed by post hoc Bonferroni test was used. The enumeration data was presented as percentage or rate. Chi square test was applied for their comparison between two groups, and partitioned ki squared test was used for the comparison among three groups. P<0.05 indicated statistically significant differences.

Results

Comparison of rotarod test results

As shown in **Figure 1A** and **1B**, the repeated measures ANOVA followed by post hoc Bonferroni test showed there were no statistical differences in rod velocity and time to fall among the three groups. Similar motor coordination was observed among the dexmedetomidine group, sham group, and control group at all three time points.

Comparison of Morris water maze test results

The Morris Water-Maze Test results in three groups were shown in **Figure 1C**. The repeated measures ANOVA followed by post hoc Bonferroni test showed that there were significant differences in the escape latency among different time points in each group or among three groups. As seen in **Table 1**, in the place navigation test, there were statistically significant differences in escape latency over 5 continuous days between the control group and the sham group (all P<0.05). The dexmedetomidine group exhibited significantly shorter escape latency over 5 continuous days than the control group, while obviously longer escape latency when comparing to the sham group (all P<0.05).

As shown in **Table 2**, in spatial probe test, there were significantly statistical differences in the swimming times and the percentage of swimming time between the control group and the sham group (P<0.05). The number of swimming times and the percentage of swimming time in the dexmedetomidine group were obviously more than those in the control group and less than those in the sham group (all P<0.05).

Comparison of open field test results

As shown in **Figure 2**, rats from the sham group showed a short time of stay at the central square and higher number of standing times in comparison with the control group (all P<0.05). In additional, intraperitoneal injection of dexmedetomidine significantly decreased the time of stay at the central square and increased the number of standing times comparing with the control group (all P<0.05).

Comparison of shuttle box test results

The rats in the control group demonstrated increased latency of the initiative avoiding (7.1±2.4 s vs. 4.8±1.2 s, P<0.05) and latency of the passive avoiding (11.4±1.7 s vs. 9.3±1.4 s, P<0.05), as well as reduced times of avoiding (5.6±1.3 s vs. 10.6±1.7 s, P<0.05) in comparison with the sham group. Moreover, rats in dexmedetomidine group showed decreased latency of the initiative avoiding (5.4±1.3 vs. 7.1±2.4 s, P<0.05) and latency of the passive avoiding (10.1±1.1 s vs. 11.4±1.7 s, P<0.05), as well as increased times of avoiding (8.3±1.5

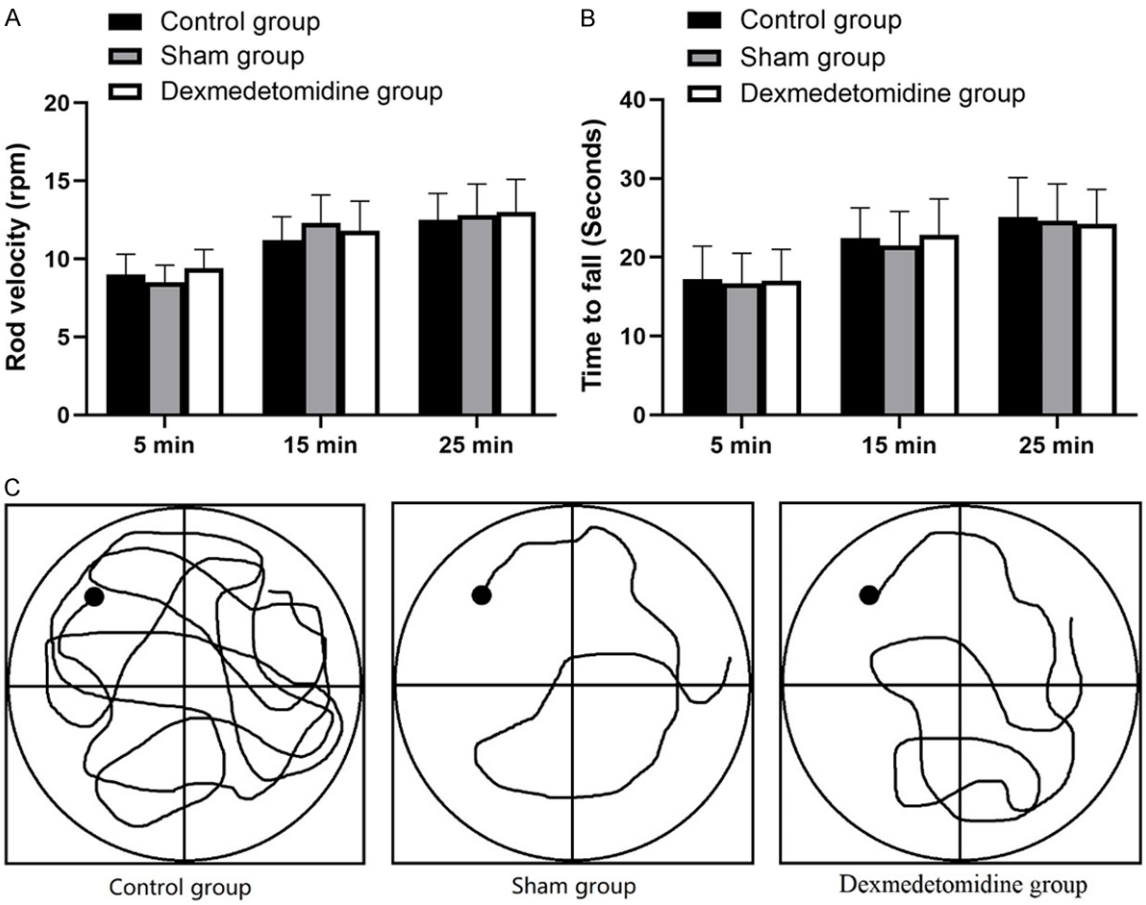

Figure 1. Results of the rotarod test and Morris water maze test. A: The rod velocity in the Rotarod Test. B: The time to fall in the Rotarod Test. C: The movement route in the Morris Water Maze Test. The swimming speed of rats from the control group, the sham group and the dexmedetomidine group were 32 cm/s, 30 cm/s, and 31 cm/s, respectively.

Table 1. Comparison of escape latency at different time points among the three groups (Seconds)

Groups	1 d after surgery	2 d after surgery	3 d after surgery	4 d after surgery	5 d after surgery
Control group	59.6±2.4	50.9±2.1	45.7±1.8	34.8±1.6	30.9±1.4
Sham group	53.2±1.6*	35.7±1.3*	22.9±0.7*	14.9±0.5*	10.7±0.6*
Dexmedetomidine group	57.1±1.9*,#	41.6±2.6*,#	28.7±1.6*,#	23.9±1.2*,#	18.6±0.8*,#

Note: Compared with the control group, *P<0.05, Compared with the sham group or the control group, #P<0.05.

Table 2. Comparison of swimming times and percentage of swimming time among the three groups

Groups	Number of swimming times (times/min)	Percentage of swimming time (%)
Control group	1.2±0.5	20.9±0.8
Sham group	3.4±0.7*	35.7±1.1*
Dexmedetomidine group	2.6±0.9*,#	31.2±0.6*,#

Note: Compared with the control group, *P<0.05, Compared with the sham group or the control group, #P<0.05.

vs. 5.6±1.3, P<0.05) comparing with the control group. See **Figure 3**.

Comparison of the expression levels of inflammatory factors

As shown in **Figure 4**, the dexmedetomidine group exhibited significantly higher expression levels of IL-6, IL-1β, and TNF-α than the sham group (all P<0.05), while significantly lower levels of IL-6, IL-1β, and

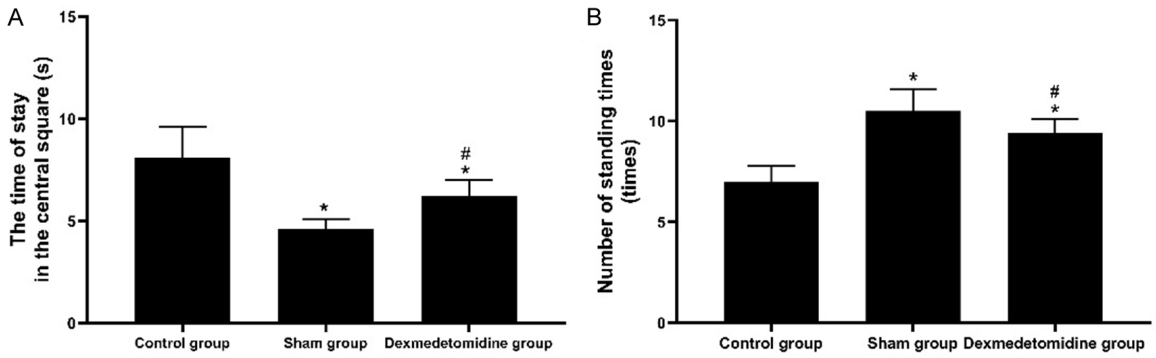

Figure 2. Comparison of the open field test results among three groups. A: The time of stay at the central square; B: The number of standing times. Note: Compared with the control group, *P<0.05, Compared with the control group or the sham group, #P<0.05.

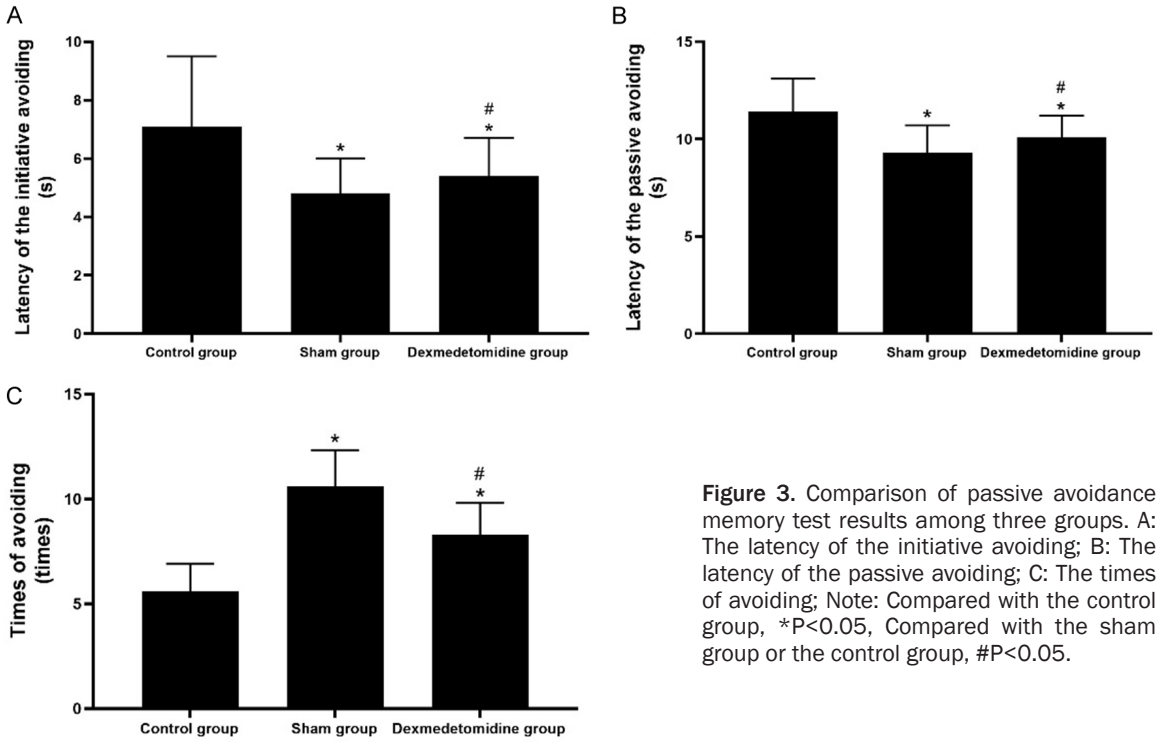

Figure 3. Comparison of passive avoidance memory test results among three groups. A: The latency of the initiative avoiding; B: The latency of the passive avoiding; C: The times of avoiding; Note: Compared with the control group, *P<0.05, Compared with the sham group or the control group, #P<0.05.

TNF-α in contrast to the control group (all P<0.05). In additional, the differences in the levels of inflammatory cytokines were also significant between the control group and the sham group (all P<0.05).

Discussion

Postoperative cognitive dysfunction is defined when there was no mental disorder in patients before operation, and impairments of orientation, memory, and concentration appear in patients after operation. Previous studies showed that the incidence of postoperative cognitive dysfunction was 25.8% at one week after major non-cardiac surgery in patients aged over 60 years old. At present, there is no effective treatment for postoperative cognitive dysfunction. Studies showed that the reductions of neuron count, cognitive related neurotransmitters and corresponding receptors could cause the decline of cognitive function [16]. Other studies showed that surgical trauma was a high risk factor for the cognitive dysfunction [17]. This is because surgical trau-

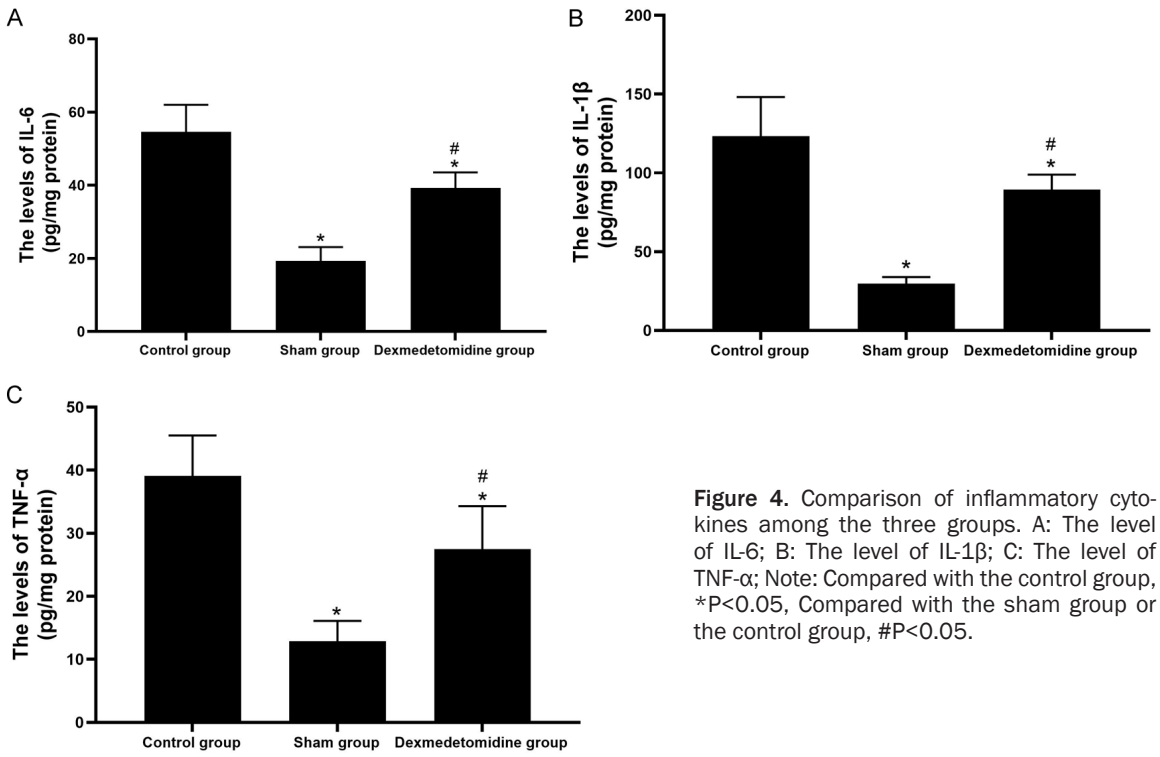

Figure 4. Comparison of inflammatory cytokines among the three groups. A: The level of IL-6; B: The level of IL-1β; C: The level of TNF-α; Note: Compared with the control group, *P<0.05, Compared with the sham group or the control group, #P<0.05.

ma can cause the release of inflammatory cytokines, which play an important role in the development of cognitive dysfunction [18]. To investigate whether surgical trauma could affect the cognitive function in rats, in this study, SD rats, aged 16 months, underwent open tibia fracture surgery to simulate the clinical conditions of postoperative cognitive dysfunction. The results of Morris water-maze test, shuttle box test, and open field test revealed that compared with the sham group, the control group exhibited increased escape latency over 5 continuous days, longer time of stay at the central square, elevated latency of the initiative avoiding, and increased latency of the passive avoiding, while fewer swimming times, lower percentage of swimming time, lower number of standing times, and fewer times of avoiding. It was indicated that the adaptability, memory, learning, and cognitive abilities were damaged in the rats undergoing open tibia fracture surgery. Therefore, the animal model of cognitive dysfunction was established successfully in the control group. In addition, the results of this study also showed that in contrast to the control group, the escape latency over 5 continuous days, the time of stay at the central square, the latency of the initiative avoiding, and the latency of the passive avoiding decreased, while the swimming times, the percentage of swimming time, the number of standing times, the times of avoiding increased in the dexmedetomidine group. These results indicate that dexmedetomidine can relieve the cognitive dysfunction after surgery in aged rats. The results of this study are similar to those of a previous study [19].

In the context of postoperative cognitive dysfunction, numerous immune cells and inflammatory cytokines from the peripheral blood infiltrate the brain, affecting the central nervous system. It was reported that peripheral inflammatory mediators could activate the microglial cells, leading to the production of various inflammatory factors [20]. Various inflammatory mediators, such as TNF-α, IL-1β, and IL-6, in turn, could lead to a cascade of amplified inflammatory responses [21]. It was confirmed that excessive inflammation could irreversibly or reversibly damage the brain tissues and result in the impairment of cognitive function via different mechanisms, such as necrosis and degeneration [22]. Hippocampual tissue in the brain is sensitive to increased inflammatory factors because of widely expressed receptors of inflammatory cytokines. Hence, the hippocampus is also one of the

most widely studied areas [23]. TNF-α, IL-1β, and IL-6, as a class of inflammatory factors, have a wide range of biological activities. Previous studies reported that these inflammatory mediators could lead to edema of nerve cells and dysfunction of synaptic connections, resulting in cognitive dysfunction. It was reported that the elevated levels of IL-1β in the hippocampus tissue could cause the impairment on learning and memory functions [24]. Some studies reported that TNF-α and IL-1β could stimulate actin and play an important role in the process of neurodegenerative diseases [25]. Hudetz et al. reported that high IL-6 level was correlated with short-term and middle-term memory after coronary artery bypass surgery [26]. Cibelli et al. reported that IL-6 could enhance the effects of IL-1β regulating the inflammatory response, and cause impaired hippocampus-dependent memory function [27]. In this study, IL-6, Il-1β, and TNF-α expression levels in the hippocampi tissue of rats were examined by ELISA. The results showed that these inflammatory factors were increased after the surgery, in accordance with previous studies. Moreover, this study revealed that dexmedetomidine could obviously decrease the expression levels of IL-6, Il-1β, and TNF-α, indicating that inhibiting the expression levels of inflammatory factors in the brain may serve a role in improving postoperative cognitive function. Chen et al. reported that dexmedetomidine effectively improved the postoperative cognitive function in rats through inhibiting hippocampal inflammation induced by surgical trauma [28], which supported this hypothesis.

There are some limitations in the present study. First, a single dose of dexmedetomidine was investigated in this study, so it is unknown whether the effects of dexmedetomidine on cognitive dysfunction are concentration-dependent. Second, the effects of dexmedetomidine on a group of male rats were determined, so it is unclear whether the same effect can be found in females. Finally, this study utilized observation and simple detection methods, so further research is necessary to delve into the precise mechanism through which dexmedetomidine improves postoperative cognitive dysfunction and inhibits inflammation response.

In summary, this study found that intraperitoneal administration of dexmedetomidine could significantly improve the cognitive dysfunction in aged rats after open tibia fracture surgery and effectively decrease the expression levels of IL-6, IL-1β, and TNF-α in the hippocampus. Thus, this research provides a potential clinical strategy for the therapy of postoperative cognitive dysfunction in elderly patients undergoing open bone fracture surgery.

Disclosure of conflict of interest

None.

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