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**Establishment and Assessments of a New Model for the
Postoperative Fatigue Syndrome by Major Small Intestinal
Resection in rats**

A New Model for the Postoperative Fatigue Syndrome

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Abstract

Objective: Postoperative Fatigue Syndrome (POFS) is a general and main complication after surgery. However, there is no stable and standardized animal model for POFS. The aim of the present study was to establish a rodent model of POFS by small intestinal resection, with POFS evaluated by acknowledged physical and ethological methods.

Material and Methods: Forty-two Sprague-Dawley rats were randomly divided into four groups according to the length of a “middle” small intestinal resection: 0% (sham group; i.e. laparotomy alone), 10%, 40%, 70% groups, with corresponding lengths of small intestinal resections. Following surgery, the general state of health was evaluated. Tail suspension test, open field test and Morris water maze test were used to evaluate the degree of POFS. Serum albumin, transferrin, prealbumin and fibronectin were measured to assess the nutritional status, and superoxide dismutase (SOD) and malondealdehyde (MDA) were also measured.

Results: As compared to the other 3 groups, the 70% small intestinal resection group showed the worst general state of health, decreased strength of the tail suspension test and the score of Morris water maze test ($P<0.05$) after operation. All rats suffering small intestinal resection demonstrated a certain degree of malnutrition and behaviour of depression, and the 70% resection group had the lowest levels of transferrin, prealbumin and fibronectin as compared to the other

groups ($P<0.05$), as well as decreased SOD and increased MDA in serum ($P<0.05$).

Conclusions: Resection of 70% of the small intestine resulted in typical characteristics of POFS. As this procedure is simple, stable and easily reproducible, it may serve as a model for research on POFS.

Key words: Animal Model; Postoperative Fatigue Syndrome; Small Intestinal Resection

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Introduction

The postoperative fatigue syndrome (POFS), well described more than 50 years ago, is characterized by a prolonged rehabilitation course after surgery, with a clinical syndrome including tiredness, muscular weakness, lethargy, concentration difficulties, and a reduction of activity levels [1-5]. Major surgeries evoke a physiological response, which may cause postoperative fatigue [6]. Multiple reports have demonstrated that POFS is a stress-endocrine hypermetabolic reaction following surgical interventions [7-9]. In addition, a specific brain-gut axis may be involved in the postoperative gastrointestinal tract function. Many factors, such as surgical trauma, declined nutritional state, and a stress-endocrine hypermetabolic reaction, have been considered to have a direct correlation with the development of POFS [5, 6, 10, 11]. As a common and main complication following surgery, POFS plays an important role for the prognosis, and directly influence on postoperative recovery.

An alternative suggestion is that psycho-social stress also participates in the development of POFS [12, 13], as previous studies showed that nutritional interventions were ineffective in improving recovery and that negative mood pre- or postoperatively is strongly related to increased fatigue [9, 14]. Behavioural and physiological evidence of POFS include impairment of muscle function, endurance depression, and immobilization. Therefore, the assessment of POFS severity became difficult and subjective when both factors were involved.

Generally, questionnaires have been shown to represent a convenient tool for measuring subjective feelings of fatigue, but there is though no “gold standard” for postoperative assessment [3, 15, 16]. As the underlying mechanism of POFS is not well-known, it has been difficult to find a valid and objective parameter that accurately reflected the severity of POFS [3, 4].

Until now, no established animal model of POFS has been reported. Determination of a POFS model and a reliable assessment system are thus relevant for concomitant studies on POFS, including improvement of therapeutic strategies, evaluation of curative effects of new drugs and etiological studies. Gastrointestinal surgery is one of the main causes of POFS [7, 17]. In addition, laparoscopic surgery has also been shown to be associated with less POFS, though less than following open surgery [10, 18]. These evidences suggest that a POFS model, induced by a sufficient amount of gastrointestinal surgery, could be suitable. We thus hypothesized that the key characteristics of POFS could be developed, given a sufficient magnitude of gastrointestinal surgical “trauma”. In this study, standard small intestinal resection was performed in rats in order to develop a POFS model. To reach a sufficient operative stress, different lengths of the small intestine were resected. The general state of health, tail suspension test, Morris water maze, open field test, and serum nutritional parameters were measured to evaluate the weakness, activity level and nutritional state of the POFS rats.

Materials and methods

Experimental animals

Forty-two male Sprague-Dawley (SD) rats (weighing from 225-255g; 8-9 weeks old) were supplied by the Experimental Animal Center of Wenzhou Medical College (Wenzhou, China). The rats were maintained under specific pathogen free conditions. The temperature was kept at 20-22°C in a 12h light-dark cycle, and all rats were fed with a standard rat chow and water, except for one day fasting before and after the operation. The protocol for the animal experiment was approved by the Institutional Animal Committee of Wenzhou Medical College. All animals received care in accordance with 'Guide for the Care and Use of Laboratory Animals'.

Animal model and design

The 42 male SD rats were randomized to four different groups according to the length of small intestinal resection: 0% (n=11, sham group), 10% group (n=10, 10% RG), 40% group (n=11, 40% RG), and the 70% group (n=10, 70% RG). All animals were fasted 24hrs before the operation, but had free access to water. Anesthesia was induced by the subcutaneous injection of 2% pentobarbital sodium (60mg/kg). The length of the small intestinal mesentery was measured and defined as the small intestinal length. 10cm below the ligament of Treitz', 10, 40 or 70% of the length of the small intestine was resected, followed by an end-to-end anastomosis by interrupted 6-0 sutures. Before closing the abdomen, the intestinal anastomosis was

inspected, as was the well-being and normal color of the intestine. The sham group went through the same procedure, though without any small intestinal resection. The rats were then maintained separately in cages after surgery. Within the first 24hrs postoperatively, animals had only access to water, after which standard chow was reintroduced. The general state of health, physical strength, endurance capacity, ability to learn and memorize, and exploratory behaviour were assessed at different time points.

General state of health

Mortality, body weight, the ability to clean themselves, piloerection, pelage color and luster, and defecation were observed and recorded daily.

Tail suspension test

The test was carried out at 24hrs and on the 7th day, respectively, after surgery. The rats were suspended for 6min by tails in the shielded box 30cm above the floor [19, 20]. The collection of data and analysis of the test were improved, as the mobile energy of rats responding to the inescapable stress was recorded as the form of electronic signal by multiplying a channel biological signal recorder (Medease Technology Company, NanJing, China). After filtering the threshold, the positive signals represented the objective mobile. The areas of signal wave above the threshold level were added up, which represents the total mobile strength. Prolonged single immobile time and total immobile time represents physical weakness and depressed

mood.

Morris Water Maze Test

The test was conducted according to a standardized protocol. All rats experienced 2 days of training that was conducted at 48hrs and on the 5th day after surgery, 60 seconds every time, and 4 times a day. An automatic recording and analytical system (JiLiang Software Technology Company, Shanghai, China) was used to record the time (Escape Latency, EL) and the pathway the rats needed to climb up the platform, to evaluate the ability of learning and spatial memory [13, 21, 22]. On the 6th day, the platform was removed, and the rats were allowed to swim in the water for 60s. The swimming time in the target quadrant and the frequency by which the rat passed through the hidden platform were recorded.

Open field test

The test was carried out at 24hrs and on the 7th postoperative day. The test is commonly used to assess locomotor and exploratory behaviour in the rats [23]. Briefly, the rats were moved to a specific box with camera lenses, and the journey, frequency of activities, time of rest and the rearing frequency were recorded and analyzed by specific software (OFT II).

Serum chemical detection

On the 8th day after operation, blood was drawn from the abdominal caval vein, and

serum was isolated by 3000r/min centrifugation for 15mins, and kept in -80°C. Albumin, malondealdehyde (MDA) and the activity of superoxide dismutase (SOD) were measured according to the manufacturer's protocol (Nanjing Jiancheng Biotech Co., Nanjing, China). Transferrin and fibronectin were analyzed by enzyme-linked immunosorbent assay (Groundwork Biotechnology Diagnosticate Ltd., San Diego, CA, USA) and prealbumin was detected by immunoprecipitation (Taiyang Biotech Co., Fujian, China).

Statistical analysis

Data were analyzed by SPSS software (11.0 version), and experimental data were all expressed as mean \pm standard deviation ($M\pm SD$). Statistical significance of differences among multiple groups was determined by one-way ANOVA (the variance was even) or rank-sum test (the variance was uneven). Differences between or among groups were considered statistically significant when *P*-values were less than 0.05.

Results

General state of health

After the small intestinal resection, only the 70% RG showed a significantly lower weight as compared to the sham group ($P<0.05$). As for the sham group, the weight of the 10% RG and 40% RG gradually increased during the study period, without any significant differences between the 3 groups ($P>0.05$). However, the 70% RG demonstrated a delay in weight increase ($P<0.01$) during the 7 days of the study period (Figure 1). In the study period, no mortality was encountered. The 70% RG appeared to present the most severe piloerection and lackluster hairs, lasting for the first three postoperative days. Diarrhea was not observed in any of the groups subjected to small intestinal resection.

The 70% RG rats could not keep themselves clean as bloodstain was observed on the abdominal fur, while excreta could be observed at eyes and nose until the 3rd day. In the other 3 groups, rats could keep themselves clean, while the piloerection and lackluster hair were only found the first day after resection.

Tail suspension test

At 24hrs and 7 days after surgery, the positive struggle signals of 70% RG showed discontinuous and lower waves as compared to the sham group, the 10% RG and the 40% RG. The value of accumulated areas above the threshold level was the lowest in the 70% RG (Figure 1). The value of the test was still significantly lower in the 70%

RG than the sham group at the 7th postoperative day.

The immobile time of the suspended period significantly increased in the 70% RG as compared to the other three groups, even at the 7th postoperative day. The longest mean single immobile time was seen in 70% RG rats (Figure 1).

Morris Water Maze Test

The time needed to learn was significantly prolonged in the 40% and 70% RG as compared to the sham group or the 10% RG ($P<0.05$), thus demonstrating that the higher the percentage of intestinal resection, the more recent memory traces were inhibited. Probe testing and frequency of passing through target platform locations significantly declined in the 70% RG ($P<0.05$) as compared to the other 3 groups (Figure 2).

Open field test

In the 70% RG, the time of resting significantly increased ($P<0.01$; Table 1). The rearing frequency, total travel distance and travel distance in center area significantly decreased as compared to the other 3 groups ($P<0.01$; Table 1, Figure 1).

Nutritional state and serum levels of SOD and MDA

Nutritional parameters in the 4 groups are illustrated in Tables 2, and the 3 resected groups demonstrated different degrees of decline in these parameters. Transferrin, prealbumin and fibronectin, representing nutritional state, were still decreased at the

8th postoperative day in the 70% RG ($P<0.05$). No significant difference was found in serum albumin levels between the different groups. A significant decrease of SOD and increase of MDA were seen in the 40 and 70% RG as compared to the sham group ($P<0.05$).

Discussion

The POFS is a common complaint after surgery. Generally, major abdominal and cardiac surgery represent the main types of interventions causing POFS. There is though no animal model established for POFS. In this study, we report a rodent model of POFS where the magnitude of the surgical challenge, based on the length of small intestinal resection, predicted POFS. A 70% small intestinal resection in rats thus demonstrated the worst general state of health, lowest muscle strength, longest resting time, declined ability of learning and worst endurance and nutritional state during the 8 days of study period. No signs of the short bowel syndrome were noted in the 70% RG, such as diarrhea and continuously decreasing nutritional status. Some psychological changes reflected by behaviour tests were also demonstrable, such as influence on learning, tolerance to inescapable stress and less exploratory behaviour. Thus, according to these physical and ethological changes, the 70% small intestinal resection represents a good model of experimental POFS.

The operative procedure is simple, standardized, easily mastered and reproducible (after 1 week's training the model can be finished within 45 minutes and no mortality was encountered, not shown data). The variable extent of small intestinal resection was introduced to vary the induced surgical trauma. Resection exceeding 75-85% of the small intestine has usually been reported to cause the short bowel syndrome [24], and resection less than 40% may not cause any significant physical postoperative response. Thus, the operation was standardized with identical lengths of the intestinal resection, achieved through measuring the length of the mesenterium. By this way,

the subjects suffered an equal surgical stress by the abdominal operation.

Previous studies have demonstrated that multiple factors participate in the development of POFS, mainly divided into physical and psychological causes [9, 11, 12]. Surgical trauma was first believed to represent the causal factor of POFS, and postoperative malnutrition, degeneration of cardiovascular and skeletal muscle function also were involved. Psychological factors were then also thought to be at least partly involved. In the clinical situation, there is no 'gold standard' for fatigue assessment. As to the animal model, the tail suspension test, Morris water maze and open field test could be used to evaluate postoperative fatigue. The presently reported rat model reflects the main characteristics described in clinical POFS. The model includes a development of "typical" physical weakness after surgery. Although the 40% RG demonstrated a slight fatigue, as evidenced by most parameters studied, the 70% RG showed a more severe fatigue, e.g. the change in body weight as the most simple and maybe most significant indicator of POFS evaluation. During the first day after the operation, the relative decline in body weight in the 70% RG implies that the rats consume body fat and muscular mass to maintain homeostasis, which indicates a phase of malnutrition and hypermetabolism [6, 7]. The distinct trend of the body weight change in the 70% RG demonstrated the significance of POFS. The condition was associated with low levels of transferrin, prealbumin and fibronectin. The proteins measured significantly correlated with a negative nitrogen metabolism and malnutrition. Serum albumin levels were lower, though not statistically significant, as compared to the sham group. In the present study, fibronectin was a good indicator,

well reflecting the severity of the model.

The tail suspension test showed a remarkable musculoskeletal weakness in the POFS model. Muscular strength is an objective assessment correlated with POFS, and also used in the clinical setting [7]. Reduction of muscle endurance in the model was substantially reflected by decreased struggle time and lower struggle strength. Morris water maze, a classical test to assess physical fatigue, suggested that learning and memory efficiency was impaired in the model of POFS [13]. Furthermore, reactive oxygen species were associated with different types of fatigue [25-29]. Surgical trauma caused major oxidative stress [30, 31], e.g. observed following colonic surgery [26]. Like the chronic fatigue syndrome, the significant changes in SOD and MDA levels in serum in the rat model points at an impairment of the oxygen free radical equilibrium.

Limited objective parameters were used to assess psychological factors, although questionnaires are well-established tools for measuring subjective feelings of fatigue [3]. Behavioural tests could partly reflect the psychological impact in rodents. The tail suspension test has been used to measure the degree of depression and negative mood [19, 32]. Prolonged immobility time in the rat model has been associated with negative mood. In addition, in the open field test, shorter travel distance and less center exploratory behaviour also correlated with a negative mood and psychological stress [29, 33].

Unfortunately, there are no satisfactory ways to predict, prophylaxis and cure the POFS. The rodent model will be helpful for us to explore the mechanisms of POFS in

humans, including peripheral (muscle, energy and nutrient state) and central mechanisms (brain and neurotransmitters). Moreover, the model can also be used as a good tool to study the efficiency of medicines. Based on the model, we plan to verify the beneficial effect of Chinese traditional herb, Panax ginseng to POFS.

To summarize, the data presented indicate that the 70% small intestinal resection represents a novel rodent model of POFS, demonstrating physical weakness and psychological stress. All parameters chosen to assess the model appear to mimic those seen in POFS in humans. Like the human situation, the rodent model demonstrates weight loss, muscular weakness, learning and memory impairment, malnutrition, oxidative stress and negative moods. However, application of the 70% small intestinal resection as a POFS model has to be further explored, also using e.g. rats data different ages and also larger animals like the canine. The present rat model, though, is easy, stable, standardized and reproducible. For these reasons, the model may represent a valuable and suitable tool for studying mechanisms and evaluating interventional strategies for the prevention or treatment of POFS.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Table 1. Results of open-field test

Groups	Total Journey (m)	Center Journey (m)	Resting Time (s)	Frequence of Rearing
70%RG	6.53±2.56#	2.48±0.82#	104.2±21.5#	11.43±2.78#
40%RG	9.45±3.21*	4.77±2.23	117.74±13.3#	18.64±4.71*
10%RG	14.35±2.74	5.19±2.29	76.67±13.7	22.01±3.71*
Sham Group	16.01±4.02	5.02±2.76	60.19±17.32	26.45±5.45

Compared with Sham Group * for $P<0.05$; # for $P<0.01$.

Table 2. Biochemical parameters in serum

Groups	Alb(g/L)	TF (mg/L)	Prealb (mg/L)	Fib (µg/ ml)	SOD (kU/L)	MDA (µmol/ L)
70%RG	24.6±2.7	311.76±156.46*	169.44±62.87#	154.3±58.8#	243.81±63.11*	11.12± 2.23*
40%RG	23.8±2.1	463.01±191.19	182.22±46.66*	180.0±63.4 *	230.87±71.03*	9.79 ± 1.54*
10%RG	26.4±2.9	446.09±133.75	190.13±53.87*	200.1±55.6	293.32±45.44	6.01 ± 0.77
Sham group	26.7±1.5	548.48±121.36	266.31±39.01	213.5±44.7	323.01±51.76	6.21 ± 0.21

Compared with Sham Group * for $P<0.05$; # for $P<0.01$.

Alb: Albumin;

TF: Transferrin;

Prealb: Prealbumin;

Fib: Fibronectin;

SOD: superoxide dismutase;

MDA: malondialdehyde

LEGENDS TO FIGURES

Fig. 1 The results of weight change, tail suspension test and open field test after surgery.

The 70% small intestinal resection group (RG) caused a significant weight loss (A). Tail suspension tests show that 70% RG had the lowest struggle strength and struggle time out of the 4 groups (B, C, and D). Less center exploratory behavior was found in the 70% RG (E). * for $P < 0.05$; # for $P < 0.01$.

Fig. 2 The results of Morris water maze test after surgery.

The 70% small intestinal resection group (RG) caused significant learning and memory changes as reflected by prolonged retention latencies, less time in target quadrant and less frequency in platform location. * for $P < 0.05$

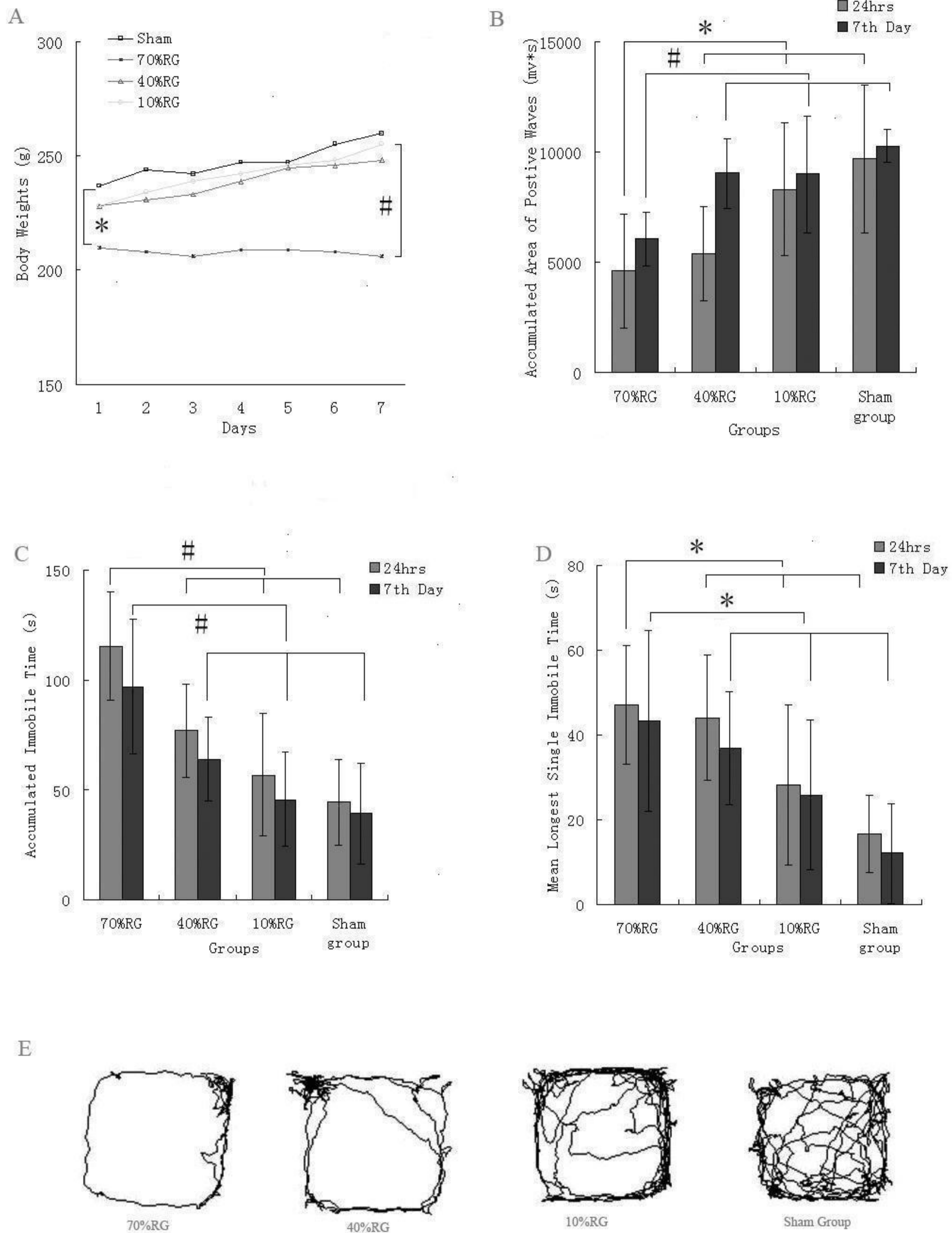


Figure 1.

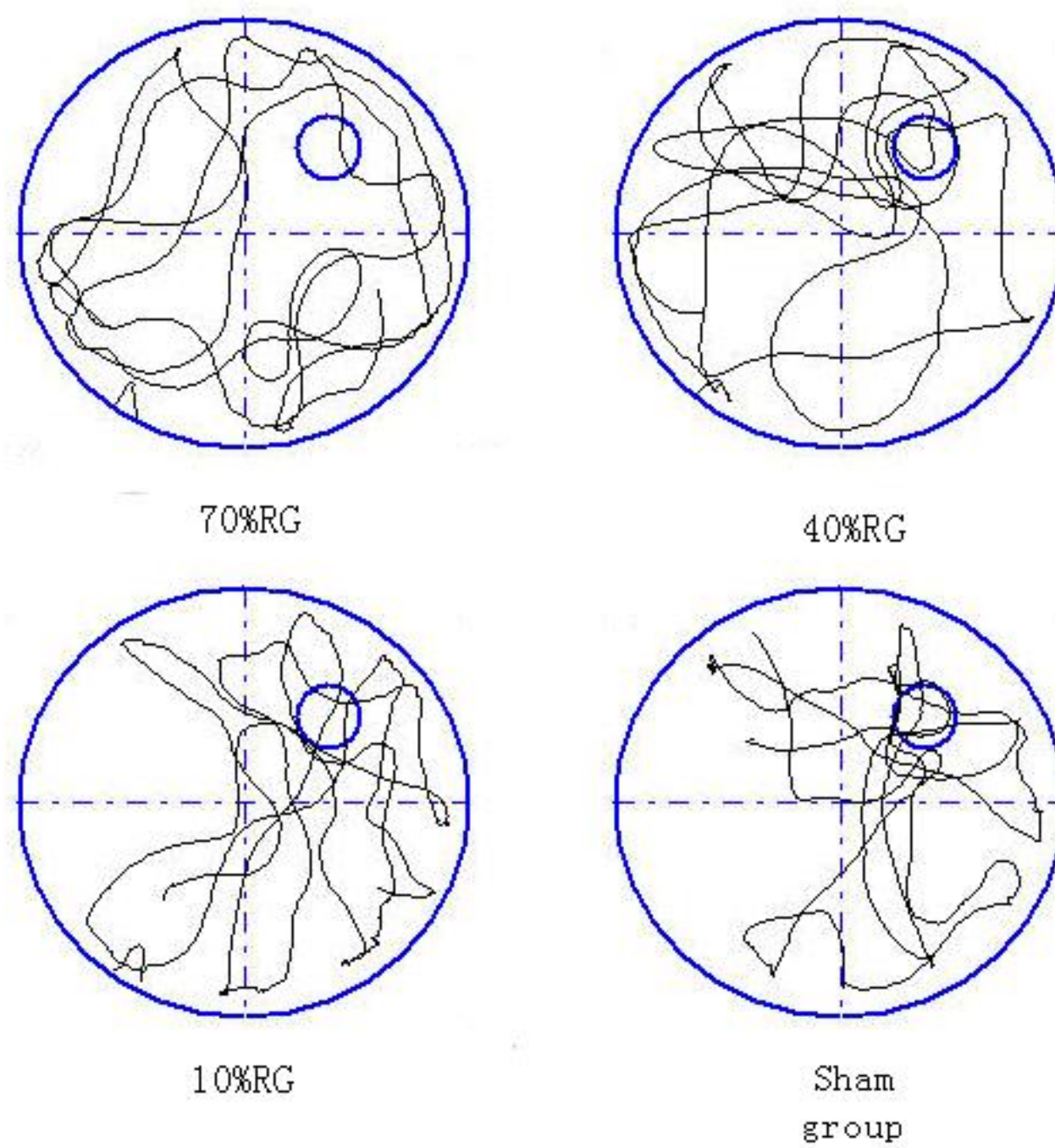
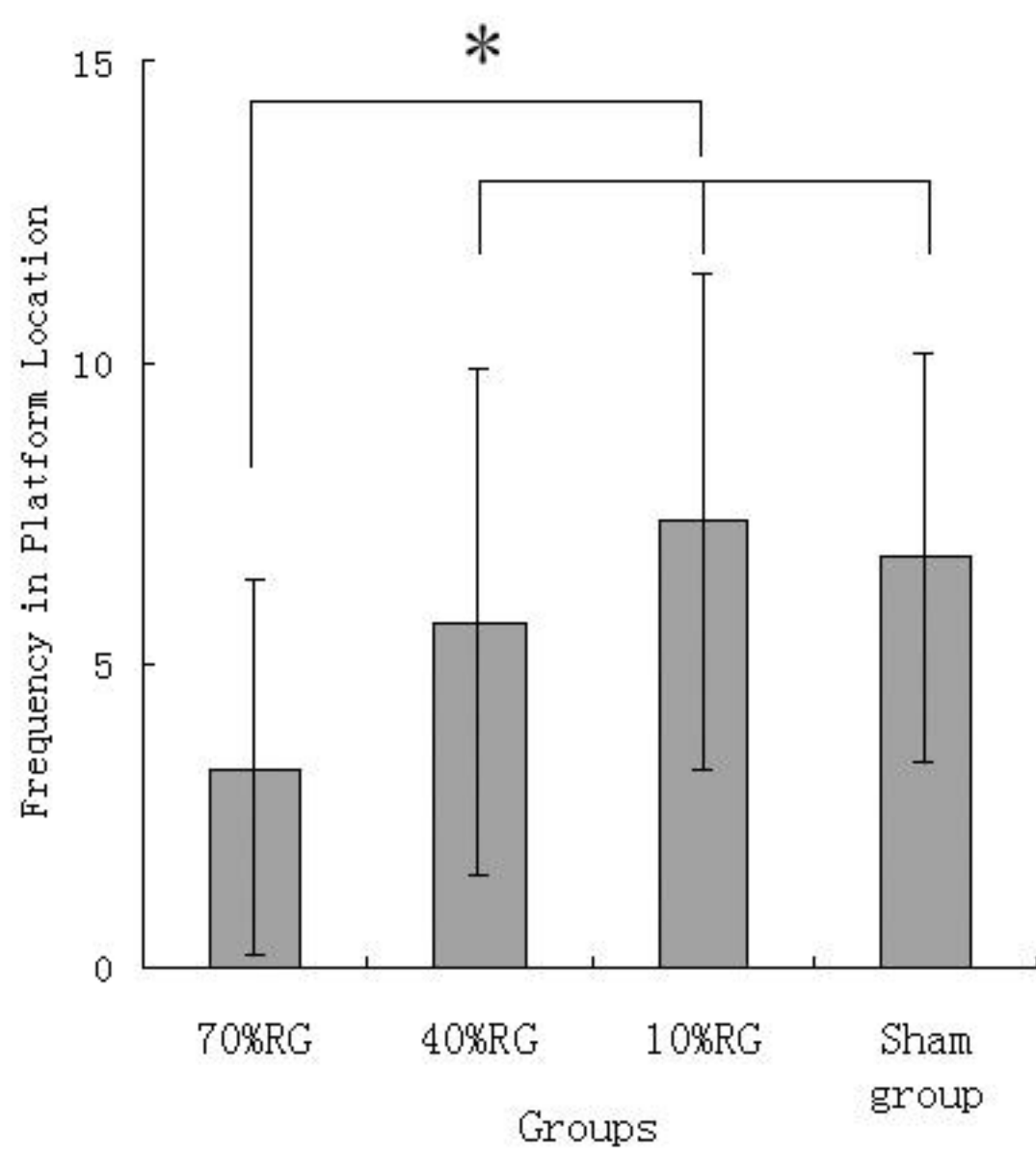
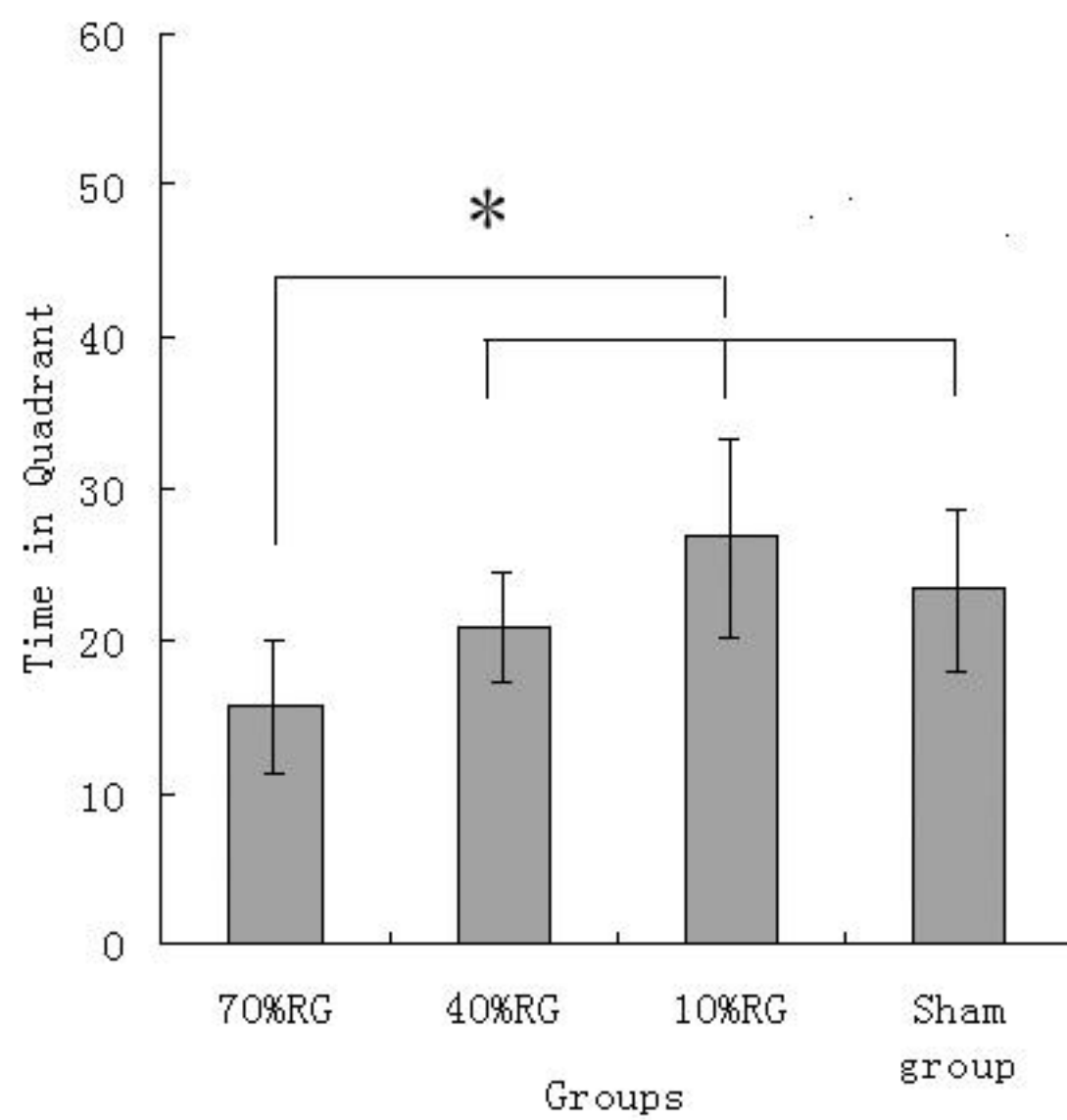
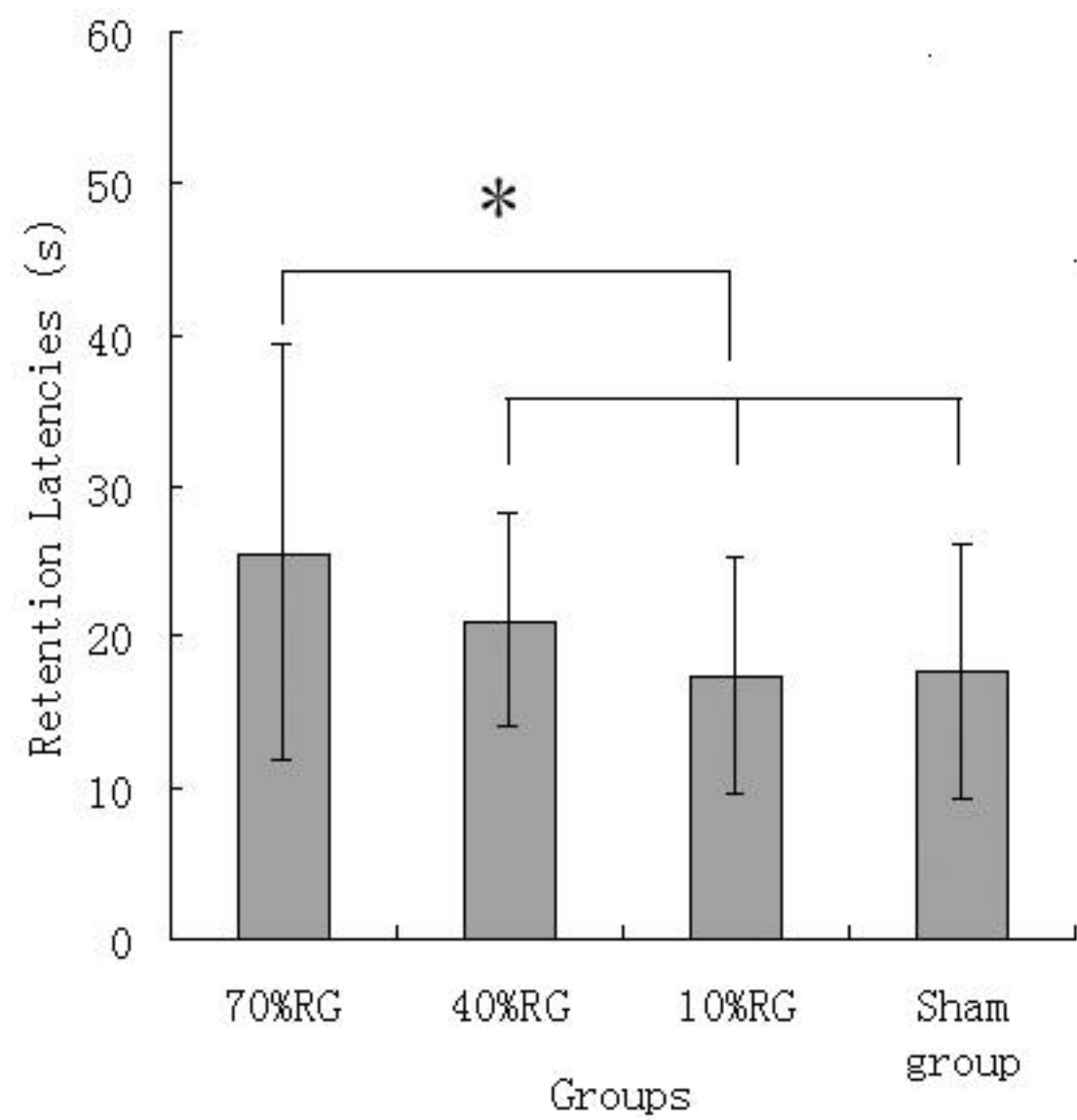


Figure 2.