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Controlled Decompression Attenuates Brain Injury in a Novel Rabbit Model of Acute Intracranial Hypertension

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: In the past, standard rapid decompressive craniectomy was used to alleviate the secondary damage caused by high intracranial pressure. Recent clinical studies showed that controlled decompression may have a better curative effect than rapid decompression. However, the effect on controlled decompression in animals is unclear.

Material/Methods: Totally 80 healthy male New Zealand rabbits were randomly divided into a sham group (n=20), a rapid decompression group (n=30), and a controlled decompression group (n=30). An intracranial hypertension model was induced by injecting saline into an epidural balloon catheter and reducing ICP slowly and gradually by use of a pressure pump. The model was evaluated and analyzed by general observations, imaging examination, ICP values, behavioral score, brain water content, Nissl staining, and caspase-3 protein detection.

Results: The mortality rate was 36.7% (11/30) in the rapid group, 20% (6/30) in the controlled group, and 5% (1/20) in the sham group. The incidence of epidural hematoma in the controlled group was lower than in the rapid group ($p<0.01$). The ICP was significantly lower in the controlled group than in the rapid group ($p<0.001$), and the behavioral score in the rapid group was higher than in the controlled group ($p<0.05$). There was a marked difference in brain water content between the controlled group and the rapid group ($p<0.01$). Nissl staining demonstrated that the ratio of Nissl body in the controlled group was significantly higher than in the rapid group ($p<0.01$). WB detection showed the expression of Caspase-3 in the controlled group was lower than in the rapid group ($p<0.05$).

Conclusions: The results show the advantages of use of controlled decompression with intracranial hypertension. The animal model we developed provides a platform for further research on controlled decompression.

MeSH Keywords: Decompression • Decompressive Craniectomy • Intracranial Hypertension • Models, Animal • Reperfusion Injury

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Background

Traumatic brain injury (TBI) is a primary cause of death and disability worldwide [1]. In addition to primary injury, it often leads to severe secondary brain damage, including intracranial hypertension [2]. Decompressive craniectomy is an effective measure to alleviate traumatic intracranial hypertension [3,4]. The standard rapid decompressive craniectomy is performed by designing a reversed question mark incision and exposing the skull. After a large bone flap is quickly removed, the dura mater is cut open to form a large window through which the hematoma and contusion tissue are removed. The whole process of decompression craniectomy needs to be carried out as soon as possible and the ICP released rapidly and entirely [5]. Despite surgical intervention, TBI is associated with high rates of disability and mortality.

Our previous research indicated that controlled decompression can improve prognosis for severe TBI patients. Controlled decompression requires monitoring the changes in intracranial pressure (ICP) during surgery by using various measures to perform decompression gradually so that brain tissue can be slowly reperfused. In contrast to the traditional rapid decompression, brain tissue reperfusion is carried out step by step to reduce cerebral ischemia-reperfusion injury and intraoperative encephalocele. Ultimately, use of controlled decompression reduces the mortality rate and improves the prognosis of patients with severe TBI [6].

Although the concept of controlled decompression has been proposed researchers in China and elsewhere [6,7], there has been no published animal research on controlled decompression. The purpose of the present study was to assess the therapeutic effect of controlled decompression in a novel model of acute intracranial hypertension in rabbits in which ICP is reduced slowly and gradually.

Material and Methods

Animals and drugs

Animal care was approved by the Ethics Committee of Wuxi Clinical College of Anhui Medical University (Heifei, China) and the experiment performed in accordance with the guidelines for the Care and Use of Laboratory Animals of the National Institutes of Health. We used male rabbits weighing 2.0–2.5 kg. The animals were placed in a room with the temperature of 22°C and standard air humidity and had free access to water and standard rabbit chow for 1 week. We stopped access to food and water 12 h before the operation.

Experimental design

We randomly divided 80 New Zealand white rabbits into 3 groups: a sham operation group (n=20), a rapid decompression group (n=30), and a controlled decompression group (n=30). Anesthesia was induced with 1–2 ml propofol (5 mg/kg) after endotracheal intubation, and anesthesia was maintained with inhaled isoflurane (1.2–2.0% MAC). A ventilator (Matrx VIP 3000, USA) was used for inhaled anesthetic transmission and adjusted ventilation. The depth of anesthesia was judged by loss of the postural reaction, corneal reflex, and having a gentle respiratory rate. Then, the animal was carefully fixed to the rabbit platform in a prone position and its head was disinfected with 75% alcohol and hypodermic injection with 0.5 ml lidocaine for local anesthetic. Vital signs were kept stable and body temperature was maintained at 37°C with a constant-temperature blanket throughout the process. When fully anesthetized, we stripped the subcutaneous tissue and periosteum to the root of the ear after making a scalp incision about 5 cm along the midline. We used a burr drill (JSDA, JD700, China) to make 2 round holes 0.5 cm in diameter beside the sagittal suture and the coronal suture The distance between the center of the holes and the gaps was 0.5 cm. Maintaining the integrity of the dura mater and removing the bone fragments carefully, a balloon catheter (Euromedical Industries Sdn. Bhd, 6 ch/fr, 53120605, Malaysia) was inserted into the epidural space toward the frontotemporal side through the right hole, and the subdural ICP transducer was inserted vertically into the brain tissue about 1.0 cm through the other hole (Figure 1). The catheter was connected to the pressure pump and the ICP transducer was connected to an ICP monitoring device (Codman, Johnson and Johnson Medical, 82-6635, USA), and we sealed the holes with dental cement (Dentsply, Jeltrate Alginate Impression Material, USA). The sham group was maintained for 30 min without injecting saline. The rapid group and controlled group were injected with saline by pressure pump (Merit Basix Touch Inflation Device, IN4130, USA) for 5 min to increase ICP to 38 mmHg. After maintaining at the ICP for 30 min [8], we instantaneously pumped out the saline to reduce ICP quickly in the rapid group, but ICP was reduced gradually over a period of 30 min in the controlled group. If there was respiratory distress or Cushing reaction during the operation, the experiment was stopped and the animal was immediately assisted.

After the operation, the catheter was removed and the holes were resealed, retaining the ICP transducer to record the ICP value. Animals were unpinned from the platform and carefully returned to the same feeding room in which they had stayed for 24 h before the operation (the animals that died during the period were counted as failed modeling). During the first 24 h after surgery, the rabbits were also given carprofen (Rimadyl®, Pfizer) 10 mg/kg, and enrofloxacin (Baytril®, Bayer) 20 mg/kg

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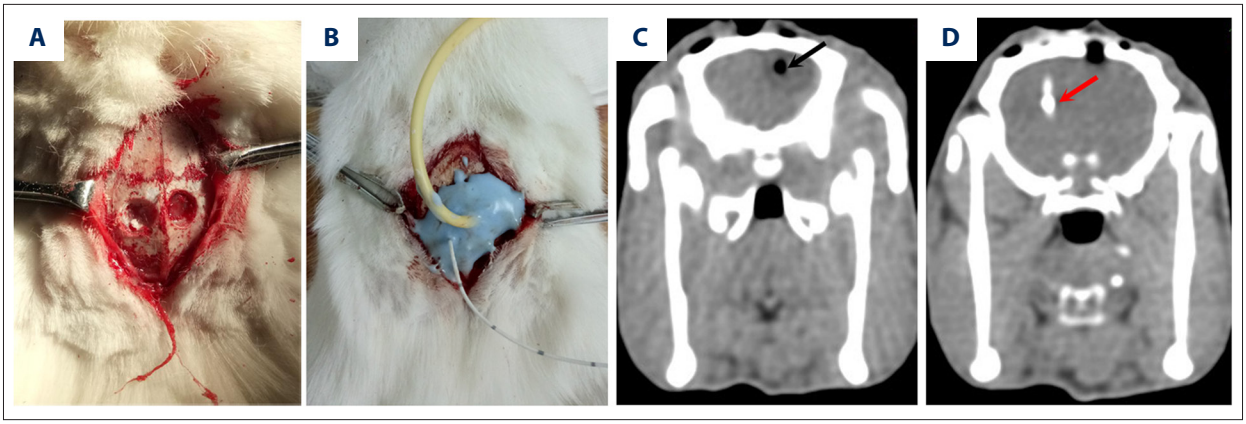

Figure 1. Intraprocedural image of the 2 holes on the rabbit skull (**A**) and insertion of the balloon catheter and ICP probe (**B**). CT image showing the position of the balloon (black arrow) (**C**), and the probe (red arrow) (**D**).

hypodermically for anti-inflammatory and antibacterial treatment [9]. ICP was recorded and behavioral scores were assessed at the 24th h, then the rabbits were killed by injecting pentobarbital sodium (100 mg/kg) into the ear vein. A combination of cessation of heartbeat, breathing, and bilateral pupil dilation was used to confirm death. The brain cortex of the compression area was isolated on ice and some were placed in a –80°C cryogenic freezer, while others were stored in formalin solution for further biochemical assessment.

Behavioral scoring

Behavioral scores were recorded by an evaluator who did not participate in the experiment. A scoring table was used to assess neural function at 24 h after the operation [10,11]. The behavioral study included the following 3 tests: I) Appetite. Scores indicate the following: 2, scarcely ate; 1, left meal unfinished; 0, finished meal. II) Activity. Scores indicate the following: 2, almost always lying down; 1, lying down, will stand and walk with some stimulation; 0, active, alert or standing. III) Deficits. Scores indicate the following: 2, impossible to walk and stand due to ataxia and paresis; 1, unable to walk due to ataxia or paresis; 0, no deficits.

Brain water content

As an independent prognostic variable, the degree of brain edema is closely related to patient mortality [12]. Wet and dry weight method was applied to assess brain water content. Partial fresh cortex tissue was removed 24 h after the operation and weighed immediately (wet weight), after which we weighed it again after being dried in an oven (DHG101-0) at 110°C for 24 h (dry weight).The percentage brain water content was calculated as follows: (wet weight–dry weight)/wet weight×100%, which was assessed in 12 rabbits in each group: sham group (n=12), rapid group (n=12), and controlled group (n=12).

Nissl staining

The brain cortex tissues stored in formalin solution were subjected to Nissl staining. Tissues were dehydrated, paraffin-embedded, and sliced (thickness, 10 mm/slice), followed by dewaxing 3 times in xylene for 5 min each time and then placing them in anhydrous ethanol for 5 min, 90% ethanol for 2 min, 70% ethanol for 2 min, and distilled water for 2 min. Specimens underwent Nissl staining for 10 min and then were rinsed twice with distilled water for a few seconds each time. They were then dehydrated twice in 95% ethanol for 2 min each time and made transparent by treatment with xylene twice for 5 min each time, followed by sealing with neutral gum. Specimens were viewed under an Olympus light microscope (Olympus Corporation) and ImageJ 1.51j8 software (USA) was used for data analysis. Specimens from 6 rabbits from each group were randomly selected for staining. A total of 5 regions were analyzed and the experiment was repeated 3 times. The Nissl bodies were stained dark blue and the nucleus was blue against a background of light blue. Nissl bodies were confirmed with the help of pathologists and counted in each region (magnification, ×40) by a researcher who was blinded to the study.

Western blot analysis

Western blot analysis was used to evaluate the expression level of caspase-3 proteins [13]. Caspase as a family of cysteine proteases that play an important part in apoptosis. Caspases-3 influences the process of neuronal apoptosis, and has a correlation with patient prognosis and mortality [14,15]. A total of 6 rabbits from each group were assessed. Cell lysis buffer (300 ul; Bogoo Biotech Co., Shanghai, China) was added to each sample for complete cracking, followed by heating at 100°C for 5 min and centrifuging at 12 000×*g* for 5 min to remove cell debris, then cooled on ice. We separated 20 µl protein per hole by 10% SDS-PAGE and transferred it to a nitrocellulose

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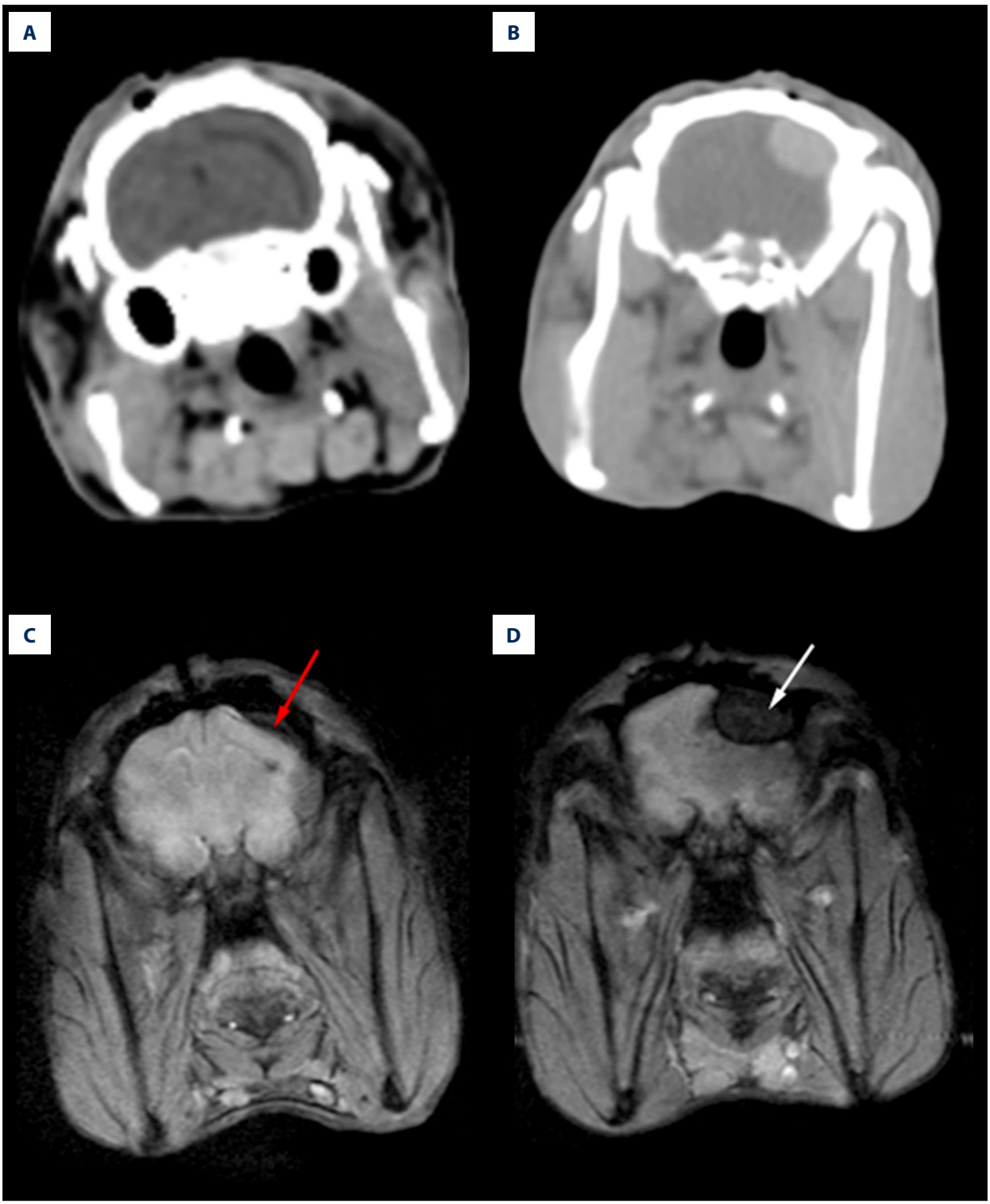
membrane. We used rabbit anti-caspase-3 (1: 1000; ab44976; Abcam) primary antibody and glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (diluted in 1: 5000; Sigma) was used as a loading control. Following incubation with the primary antibodies for 2 h, membranes were cleaned with TBST and incubated with appropriate horseradish peroxidase-labeled secondary antibodies (1: 1000) for 2 h. Super-GL ECL hypersensitive photoluminescence solution was used for chemiluminescence detection, followed by exposure of X-ray film. After developing and fixing, the dried film was photographed



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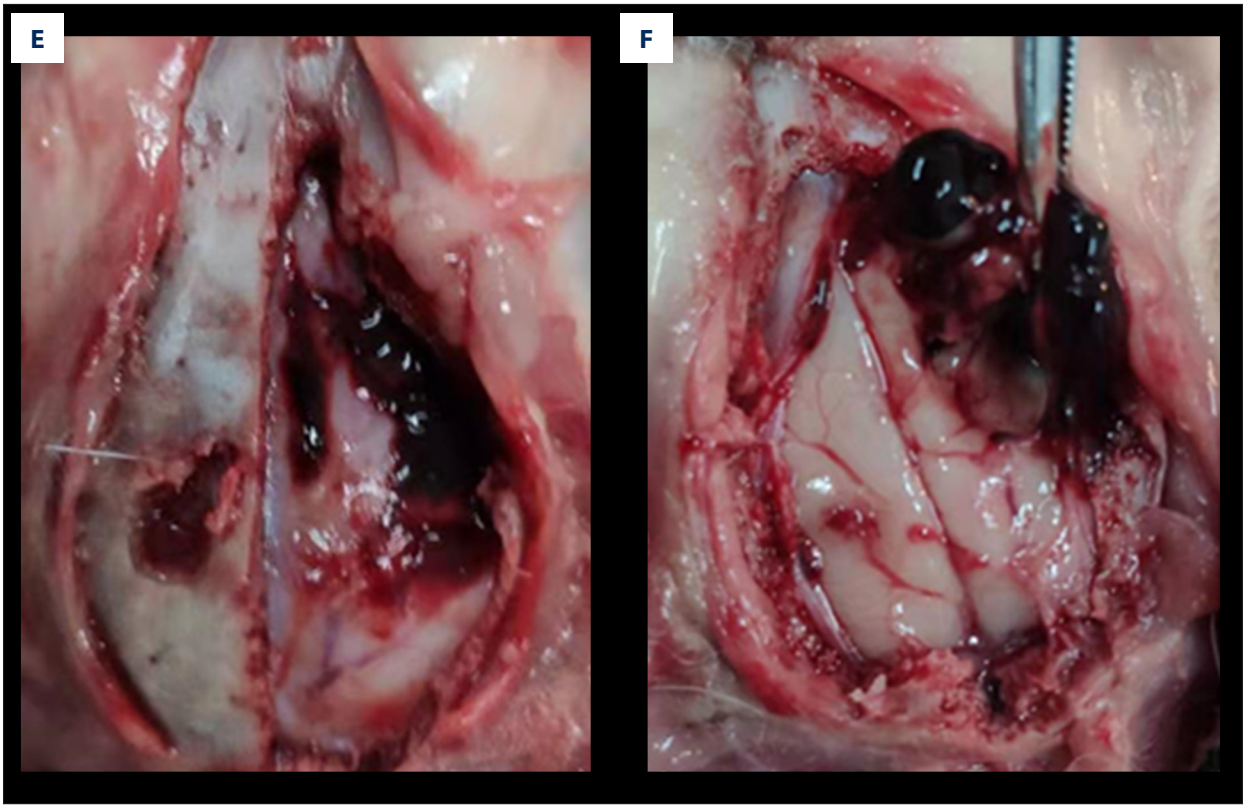

Figure 2. Imaging examination of the rabbit brain. CT (computed tomography) image of controlled group (**A**) and rapid group (**B**). Magnetic resonance imaging (MRI) T2 star weighted angiography (SWAN) shows an oval epidural hematoma (white arrow) on the oppressed zone and the center line was significantly shifted in the rapid decompression group (**D**). However, the picture of the controlled decompression group (**C**) showed hematoma (red arrow) was significantly less and the center line shifted slightly. The anatomical image of 2 groups (**E, F**). The incidence of epidural hematoma in the controlled group was lower than in the rapid group (** p<0.01).

using a gel imaging analysis system. The Gel-Pro Analyzer software (Media Cybernetics, Inc.) was used to analyze the results.

Statistical analysis

The results are expressed as the mean±standard deviation. SPSS 17.0 statistical software (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Differences among multiple groups were assessed by one-way analysis of variance (ANOVA) followed by Tukey post hoc analysis. Differences with P value <0.05 were considered as statistically significant.

Results

General observations

The total mortality in the model was 22.5% (18/80). The mortality rate was 36.7% (11/30) in the rapid group, 20% (6/30) in the controlled group, and 5% (1/20) in the sham group, and the mortality rate in the controlled group was obviously lower than in the rapid group. When establishing the model, animals that died during the operation or within 24 h afterwards were excluded from the model and included in the mortality rate.

Imaging examination

The imaging of the rabbit brain showed the brain tissue and hematoma at 24 h after the operation (Figure 2). Hematoma was identified in the epidural space. In this image, the rabbits that underwent the controlled decompressive operation had little hemorrhage and the center line shifted slightly. However, rabbits that underwent rapid decompressive had huge epidural hematomas (EDH) and the center line was clearly shifted. The incidence of epidural hematoma in the rapid group was 63.3% (19/30) *vs.* 40% (12/30) in the controlled group.

ICP state

We recorded the ICP values of the rabbits 24 h after surgery. The ICP in the sham operation group (6.00±1.76) was obviously lower than in the other groups (p<0.001), and the controlled

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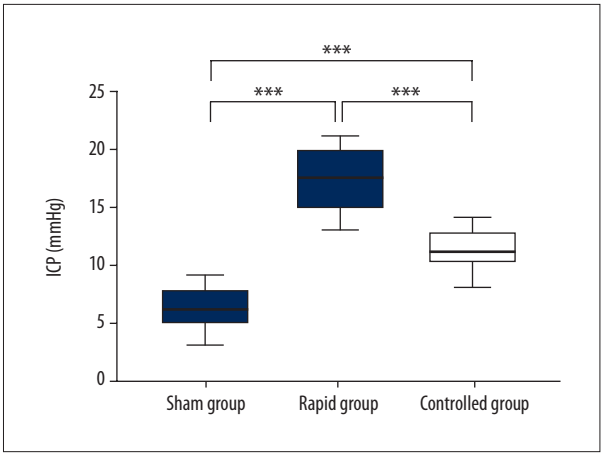

Figure 3. The box and whisker plots showing the average ICP at the 24th h after operation in all groups (n=12), where the middle line represents mean, upper, the lower level of box represents 25% and 75% quartiles, and whiskers represent the maximum and minimum value. Sham group *vs.* rapid group *vs.* controlled group; there were clear differences among the 3 groups (*** p<0.001).

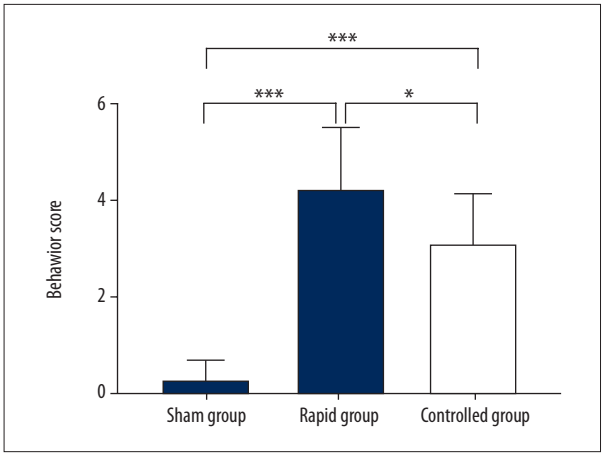

Figure 4. Behavior scores in the experimental groups after operation (n=12). Bar graphs represent means±standard deviation (SD). The results showed that the behavior scores were significantly higher in the rapid group compared with the controlled group (* p<0.05) and sham group (*** p<0.001).

decompression group (11.42±1.83) had clearly lower ICP than in the rapid decompression group (17.17±2.59; p<0.001) (Figure 3).

Behavior scoring

The behavior scores in the sham group (0.25±0.45; p<0.001) were significantly lower than in other groups (ANOVA), and the behavior scores in the rapid group were significantly higher than in the than controlled group (4.25±1.29 *vs.* 3.08±1.08; p<0.05) (Figure 4), indicating that controlled decompression improved neurological function better than with rapid decompression.

Brain water content

The brain water content of the rapid decompression group was significantly higher than in the sham group (81.64±0.91 *vs.* 79.91±0.74; p<0.001) and controlled group (81.64±0.91 *vs.* 80.52±0.66; p<0.01) (Figure 5), but there was no obvious difference between the sham operation group and the controlled group (79.91±0.74 *vs.* 80.52±0.66; p=0.15), indicating that controlled decompression results in less brain edema than with rapid decompression.

Nissl staining

The oppressed part of brain cortex of rabbits received Nissl staining. It was found that Nissl bodies were expressed in all groups, but the expression of Nissl bodies was highest in the sham group, and the cytoplasm of neurons was covered with dark blue granular Nissl bodies with deep coloring.

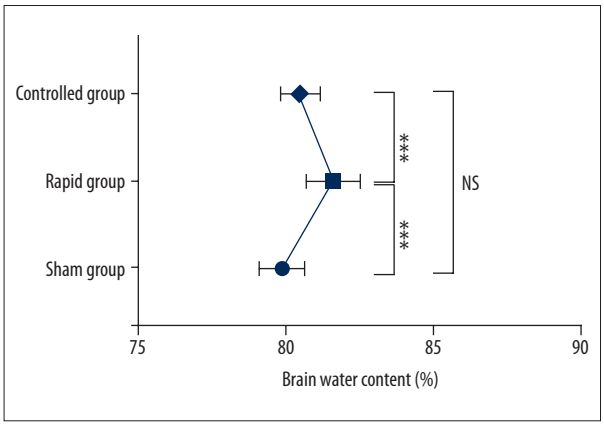

Figure 5. Water content of brain cortex of rabbits in each group (n=12) at 24 h following operation. Line chart shows the averaged values of brain water content; data are represented as the means±SD. The sham operation group *vs.* the rapid group (*** p<0.001); The sham operation group *vs.* controlled group. NS (not significant; =0.15); the rapid group *vs.* the controlled group (** p<0.01).

In the rapid group, there were significantly fewer Nissl bodies in the cytoplasm of neurons compared with the sham operation group (20.95±6.11 *vs.* 53.88±10.10; p<0.001) and there was light staining. However, the ratio in the controlled group was markedly higher than in the rapid group (36.80±7.31 *vs.* 20.95±6.11; p<0.01) (Figure 6) and the granules were abundant with deep coloring. These results show that controlled decompression alleviated neuron cell injury.

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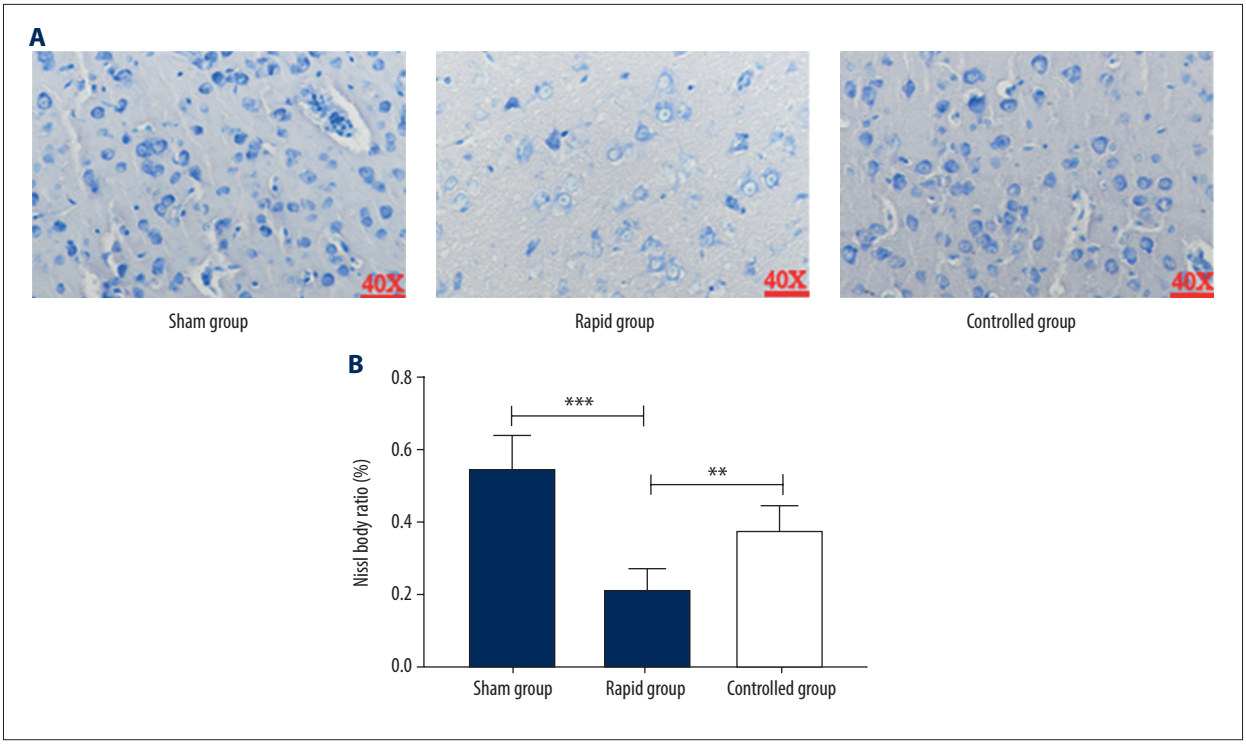

Figure 6. (**A**) Nissl staining of brain cortex after 24 h of modeling (n=6). Abundant Nissl bodies were found in the sham group. Comparison of Nissl cell ratio. Data are presented as the mean±SD. (**B**) Nissl staining was markedly reduced in rapid group (*** p<0.001 *vs.* the sham group). Nissl bodies markedly increased in controlled decompression group (** p<0.01 *vs.* the rapid decompression group).

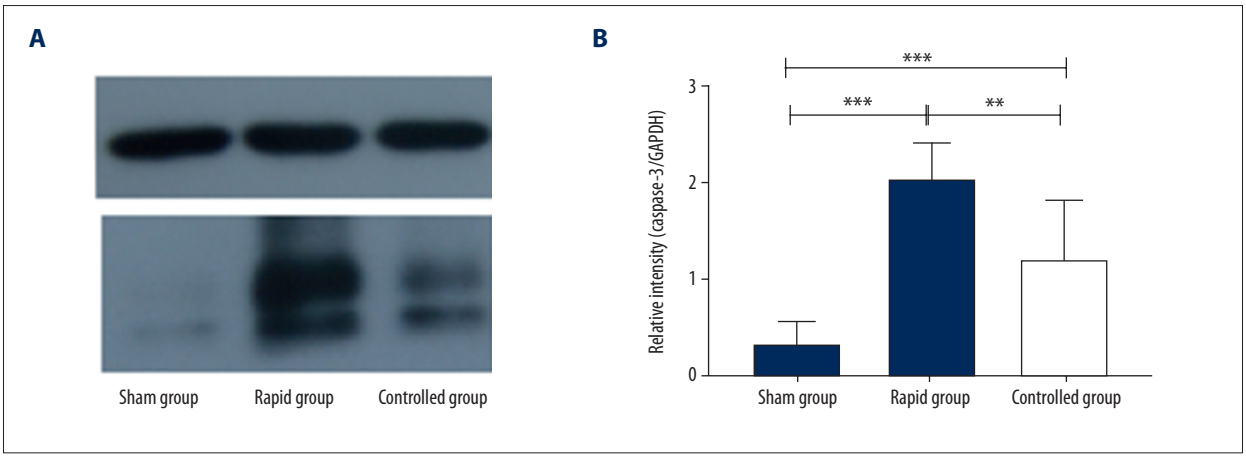

Figure 7. Caspase-3 protein content in cerebral cortex of oppressed area (n=6). (**A**) Representative Western blot of caspase-3 protein expression. (**B**) Quantification of caspase-3 protein expression. Data are presented as the mean±SD. The content of caspase-3 in the sham group was evidently lower than rapid group and controlled group (*** p<0.001). Caspase-3 expression levels were significantly decreased in controlled decompression group (* p<0.05 *vs.* the rapid decompression group).

Caspase-3 protein expression

Western blot analysis was used for testing the expression of caspase-3 protein in the cerebral cortex of the oppressed area at 24 h after modeling to observe the apoptosis of neurons. The relative intensity of caspase-3 protein in the rapid decompression group was obviously higher than in the sham group (2.04±0.39 *vs.* 0.32±0.27; p<0.001), while it was significantly lower in the controlled group (2.04±0.39 *vs.* 1.19±0.84; p<0.05) (Figure 7).

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Discussion

At present, decompressive craniectomy is the last option to save the life of patients with traumatic craniocerebral injury [16]. After conservative treatment fails to control refractory intracranial hypertension (e.g., ICP >25 mmHg for a long period of time), there is sufficient evidence to support the use of decompression as a life-saving intervention [17]. Rapid decompressive craniectomy can reduce ICP, thus improving cerebrovascular compliance [18], cerebral oxygenation [19,20], and cerebral perfusion [21,22], and can also reduce postoperative brain edema [11], but it also leads to a high probability of rebleeding and brain swelling during surgery or post-operatively. Flint et al. reported that 58% of patients (n=40) experienced acute encephalocele and ipsilateral or contralateral rebleeding with rapid decompressive craniectomy [23], which sharply increases ICP and aggravates cytotoxicity and angiogenic brain edema [24,25]. The purpose of this operation is not only to save the patient's life, but also, and perhaps more importantly, to reduce disability and improve prognosis of patients who survive surgery and to help them have better long-term quality of life. Although the mortality rate decreases in patients who have their uncontrolled intracranial hypertension treated by rapid decompressive craniectomy, they have higher rates of complications [25], severe disabilities, and vegetative state [26,27], which seriously affect subsequent quality of life. Clinical researchers have recently introduced the idea and method of controlled decompression. It gradually releases ICP by placing a ventricular probe to release cerebrospinal fluid slowly, and a suction device is placed in the small dural incision to suck out part of the hematoma, after which the contusion tissue is slowly removed [6]. In contrast to the traditional rapid decompressive craniectomy method, controlled decompression is performed slowly so that the brain tissue can be perfused gradually and ischemia-reperfusion injury can be minimized. In agreement with a study by Jiang et al., Wang et al. reported that mortality in the controlled decompression group (23.4%, 15/64) was significantly lower than in the rapid decompression group (35.9%, 23/64), but both studies found that the prognosis was not improved [6,7]. Multicenter research is needed to better evaluate the clinical therapeutic effect of controlled decompression. In animal research, mortality was reduced and the behavioral prognosis was improved. The result of mortality was in line with previous clinical studies, but there are differences in the prognostic performance of animals, which was probably related to differences in physiological conditions and neurobehavioral evaluation systems between animals and humans.

Severe TBI often leads to acute traumatic intracranial hypertension. To animal models, the intracranial hypertension is extremely mature. Konstantinos Kasapas et al. successfully studied the invasive and ultrasound-based monitoring of intracranial pressure in an experimental model of epidural hematoma in rabbits [28]. Joacil Carlos da Silva et al. studied the efficacy of hypertonic saline and mannitol in a model of fatal cranial hypertension [29]. M Janda et al. researched the surgical treatment of advanced intracranial hypertension in pig models of intracranial hypertension [30]. Uldal et al. studied an idiopathic intracranial hypertension model in obese rats [31]. However, there have been few animal experiments on controlled decompression. To study controlled decompression in greater detail, we developed a new intracranial hypertension model to release ICP gradually and slowly by use of a pressure filling pump.

In the present study, the initial pressure after inserting the probe in rabbits was generally 4–12 mmHg, and the pressure value remained stable after the catheter was inserted. In the process of pressurization, the ICP did not rise until about 0.8 ml of normal saline had been injected. The speed gradually accelerated as more normal saline was injected in the catheter, which is in agreement with the law of intracranial pressure-volume curves [32]. In our experiment, the catheter was connected with the pressure filling pump so that we can control the rotating axis to change the direction of infusion so that ICP can be slowly increased or decreased. We found that ICP became unstable when it exceeded 38 mmHg, after which, addition of a small amount of fluid led to greatly increased ICP, and the mortality rate of rabbits also increased significantly when ICP exceeded 40 mmHg. We found that 38.8% (7/18) of rabbit deaths occurred when ICP was higher than 40 mmHg during modeling. Of course, the other factors contributing to mortality were the enormous intracranial hemorrhages, mistakes in inhalation, and over-anesthetization. The initial ICP was closely correlated with mortality and poor prognosis, which is an independent predictor of poor prognosis [33]. In Hua Liu's study [34], it was demonstrated that the proportion of mortality and adverse outcomes increased with the increase of ICP. The mortality rate rose from 0% to 13% when ICP was above 40 mmHg, which was consistent with our animal experiment results. Some studies [35,36] suggested that the mortality rate begins to rise when ICP reaches 20–25 mmHg. Therefore, the target ICP set at 38 mmHg would be appropriate in the model, which not only caused brain injury, but ensured a low mortality rate. The present study found that the proportion of epidural hematoma in the rapid decompression group (63.3%) was significantly higher than in the controlled decompression group (40%), and the amount of hematoma in the rapid decompression group was also higher. The amount of hematoma was associated with the occurrence of delayed hemorrhage after the operation [37], and controlled decompression appears to reduce the incidence of delayed hemorrhage.

In the controlled group, the survival rate was higher and the neurobehavioral performance of animals was

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significantly improved. Controlled decompression slowed the recovery of cerebral blood flow by slowly reducing ICP. On the one hand, it attenuated the cerebral ischemia-reperfusion injury during decompression and reduced the risk and severity of delayed intracranial hemorrhage. On the other hand, it alleviated the brain edema and diffuse brain swelling caused by excessive perfusion after rapid decompression. Comparing the 2 surgical methods, we found that controlled decompression reduced the expression of apoptotic genes and slowed the progression of cell necrosis and apoptosis. These results indicate that the overall behavioral prognosis was improved. The present results indicate that ischemia-reperfusion injury was the major mechanism involved, and apoptosis, programmed necrosis, and other mechanisms may also be involved in this process.

In our study, the controlled decompression occurred over a period of 30 min. However, the time allowed is limited because excessive time of decompression can aggravate brain injury instead. We suggest that controlled decompression within 1 h is appropriate, but the best time at which to protect the brain needs more exploration.

Conclusions

We found that controlled decompression can reduce neuronal apoptosis and brain edema, decrease mortality, and improve prognosis, which provides a new surgical concept for the therapy of traumatic intracranial hypertension. In addition, the improved animal model facilitates clinical research on controlled decompression surgery. However, the appropriate time at which to perform controlled decompression and the specific molecular mechanism need further study.

Conflicts of interest

None.

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