Critical Care

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# The impact of different rates of sodium reduction on the central nervous system in acute hypernatremia in rabbits

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## Abstract

**Background** Acute hypernatremia is a prevalent electrolyte imbalance in the intensive care unit (ICU), closely associated with the severity of patients' conditions. This study employs animal experimentation to investigate the effects of varying sodium reduction rates on the central nervous system in acute hypernatremia, aiming to identify the optimal rate of sodium reduction.

**Methods** A stepwise sodium titration approach was used to establish an acute hypernatremia model, targeting a sodium increase of 0.5 mEq/L per hour (target serum sodium: a rise of 15 mEq/L within 48 h from baseline). Subsequently, a stepwise sodium decrement method was applied to reduce sodium levels to baseline. The study included four groups with different target sodium reduction rates: 1 mEq/L/h (Slow group), 2 mEq/L/h (Middle group), 3 mEq/L/h (Fast group), and Sham surgery group. Blood sodium and potassium levels, as well as urine sodium and potassium, were measured at various time points; central venous pressure (CVP) and intracranial pressure (ICP) were monitored; fluid intake and output were recorded to calculate fluid balance. After sodium reduction, brain tissue was extracted for pathological examination.

**Results** Twenty adult, healthy male rabbits were randomly assigned to four groups (five rabbits per group). Before and after sodium reduction, the ICP significantly increased in the Fast group from $7.00 \pm 0.71$ to $13.20 \pm 2.95$ and in the Middle group from $6.80 \pm 0.45$ to $11.40 \pm 0.89$ ($p = 0.015$ and $p = 0.000$, respectively); the Slow group showed no significant change in ICP. Pathological findings revealed edema and disorganized brain tissue in the cerebral cortex and brainstem in the Fast and Middle groups, with statistically significant differences compared to the sham-operated group in semi-quantitative analysis.

**Conclusion** For acute hypernatremia that develops within 48 h, sodium reduction rates exceeding 1 mEq/L/h are associated with greater increases in ICP and more severe brain edema. Therefore, for managing acute hypernatremia,our result prompted that sodium reduction rates might not exceed 1 mEq/L/h.

**Keywords** Hypernatremia, Rabbit, Intracranial pressure, Sodium reduction rate, Brain edema

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## Introduction

Hypernatremia is defined as a plasma sodium ion concentration > 145 mEq/L [1] and is closely associated with the severity of patients' conditions. It is relatively common in intensive care units, with an incidence rate of hypernatremia in critically ill patients ranging from 4 to 26% [2, 3], and it is an independent risk factor affecting patient prognosis [4]. Based on the duration of hypernatremia, it can be divided into acute and chronic hypernatremia, with hypernatremia lasting less than 48 h referred to as acute hypernatremia [5], and hypernatremia lasting more than 48 h referred to as chronic hypernatremia.

In terms of the rate of sodium reduction, there has been a lack of clear guidelines and consensus, presenting challenges for clinical physicians in practice. Some studies have indicated that rapid correction of hypernatremia is not associated with seizure occurrence, brain edema, or mortality [6]. Other studies have suggested that too slow correction can lead to higher mortality rates [7, 8]. For acute hypernatremia, some recommend rapidly reducing serum sodium to normal levels at a rate of 2 mEq/L/h [9], while others suggest that a reduction rate of 1 mEq/L/h is safe [10].

This study uses animal experiments as a means to delve into the impact of different rates of sodium reduction on the central nervous system during acute hypernatremia. By simulating different sodium reduction conditions in the experiment and measuring neurological indicators such as intracranial pressure, the study clarifies the damage to the central nervous system caused by different sodium reduction rates. Finally, by observing pathological changes in brain tissue, the types of central nervous system damage caused by different sodium reduction rates are identified.

## Methods

### Experimental animals and grouping

Twenty healthy adult male Japanese white rabbits, weighing 2.0 to 2.5 kg, were randomly and evenly divided into 4 groups. The target sodium reduction rates were 1 mEq/L/h (Slow group), 2 mEq/L/h (Middle group), and 3 mEq/L/h (Fast group), as well as a sham surgery control group. The preliminary experiment showed that the ICP difference between the Fast and Slow groups reached 5.2 mmHg, with an extremely large effect size (Cohen's d = 2.42). According to the formula, only 4 rabbits per group were needed (with a power of 80%), but we actually used 5 rabbits per group to account for potential experimental attrition. The actual power reached 99%, which is far beyond the conventional threshold, indicating that the sample size was sufficient. In accordance with the "3R principles" of animal experiments (reduction, refinement, replacement), we used the minimum sample size.The experimental animals were provided by Liaoning Changsheng Biotechnology Co., Ltd., with a license number: SCXK (Liao) 2020–0001. This experiment was approved by the Ethics Committee of Dalian Central Hospital: Approval Number: YN2022-039–37.

### Anesthesia

The monitor was connected to the rabbit, an oxygen mask was applied, oxygen supply was initiated (flow rate 4–5L/min). Once the rabbit ceased struggling, the oxygen flow rate was decreased to 3L/min, isoflurane was administered and set at 1%, then the isoflurane concentration was escalated to 4–5%. Upon disappearance of the rabbit's corneal reflex and confirmation of a deep anesthesia state, a laryngeal mask was inserted to maintain continuous gas anesthesia.

### Jugular vein catheterization

The neck and back were prepared and disinfected. An incision was made in the left neck area, and subcutaneous tissue was separated to locate the external jugular vein. After isolating a section of the vein, a puncture needle was inserted parallel to the direction of the vessel. A single-lumen catheter was then inserted using the Seldinger technique and sutured in place, with the catheter fixed to the rabbit's back.

### ICP monitoring probe placement

A 1.5 cm incision was made in the rabbit brain skin, 0.5 cm from the labial side of the coronal suture and 0.5 cm to the left of the midline, and the periosteum was removed. A hole with a diameter of about 2 mm was drilled in the incision, and a 1 cm deep ICP monitoring catheter was inserted at a 30° angle with the horizontal plane as the baseline. In this experiment, the Codman MicroSensor™ ICP Transducer (Johnson & Johnson Professional, Inc., Raynham, MA) and the ICP Express™ Transducer Control Unit (Johnson & Johnson Professional, Inc., Raynham, MA) were used to monitor changes in intracranial pressure in real time. The ICP probe is placed in the cranial subdural space.

Dental cement was used to seal the hole, and the guide wire was fixed to the skull. The protective sleeve of the ICP monitoring catheter was sutured to the muscle on the top of the skull using 5–0 sutures, and the catheter was led out through a subcutaneous tunnel between the ears, finally fixed in place on the back for later use.

### Establishment of acute hypernatremia model

This study used a stepwise sodium increment method to establish an acute hypernatremia model. This approach takes into account the rabbits' adaptability to sodium and changes in urinary sodium, increasing the concentration

and infusion rate of sodium chloride solution in different stages to gradually raise the serum sodium levels. This method overcomes the issue of rabbits adapting to a fixed hypertonic fluid, allowing serum sodium to reach the desired level. During the model establishment, urine sodium and volume were closely monitored, and subsequent infusions were adjusted based on intermediate measurements to ensure the successful establishment of the acute hypernatremia model. (See Fig. 1) The 1.3% sodium chloride solution is made by mixing 60 ml of 10% concentrated sodium chloride with 400 ml of 5% glucose. The 2% sodium chloride solution is made by mixing 100 ml of 10% concentrated sodium chloride with 400 ml of 5% glucose. The 3% sodium chloride solution is made by mixing 115 ml of 10% concentrated sodium chloride with 385 ml of 5% glucose.

#### Stepwise sodium reduction method

This study employed a stepwise sodium reduction method to smoothly reduce sodium levels. Initially, a constant target rate of sodium reduction was set, such as a decrease of 1 mEq/L per hour. Based on the initial serum sodium value, the total time required to reduce to a normal level was calculated. Sodium reduction was carried out in stages, with the concentration and rate of the infusion solution adjusted according to the actual decrease in serum sodium at each stage, while maintaining the predetermined rate of sodium reduction. Blood and urinary sodium values were regularly monitored to ensure a smooth reduction process and avoid complications from rapid sodium reduction. This method requires strict monitoring and adjustment to ensure that serum sodium is gradually and smoothly reduced to the normal range. (See Fig. 2).

#### Sample collection

The 20 rabbits were divided into different sodium reduction rates: the Fast group with a sodium reduction rate of 3 mEq/L/h, the Middle group with a rate of 2 mEq/L/h, the Slow group with a rate of 1 mEq/L/h, and the sham surgery control group, which did not undergo sodium increase or reduction. During the sodium increase phase, blood was drawn every 10–15 h to measure serum sodium, potassium, urinary sodium, urinary potassium,

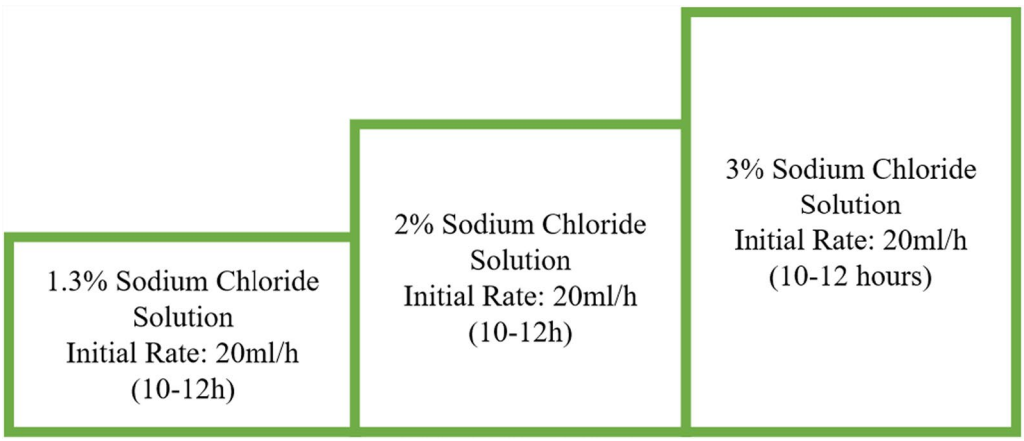


**Fig. 1** Schematic diagram of the stepwise sodium increment method

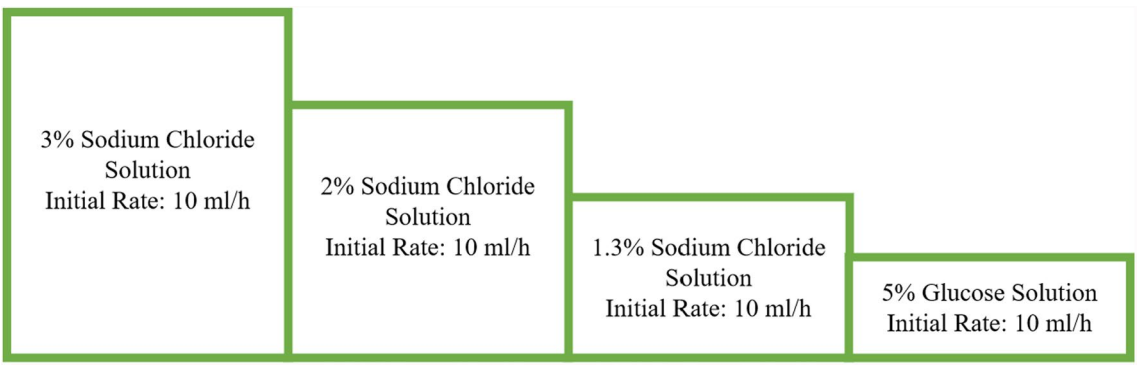


**Fig. 2** Schematic diagram of the stepwise sodium reduction method

CVP, and ICP. During the sodium reduction phase, the Fast group had measurements taken at 1 h, 3 h, and 5 h; the Middle group at 1 h, 5 h, and 7 h; and the Slow group at 5 h, 10 h, and 15 h.

### Pathological section preparation

After the completion of sodium reduction, the rabbits were euthanized using an air embolism method, and the brain tissue was rinsed with buffer solution, fixed, deparaffinized, and stained. Hematoxylin and Eosin (HE) staining: Sections were placed in hematoxylin stain for 3–5 min, then rinsed and dehydrated, followed by staining in eosin solution for 5 min. Luxol Fast Blue (LFB) staining: ① Sections were first stained in LFB stain 1 in a microwave repair box for 3–4 h, then washed with tap water until colorless; ② Then, sections were placed in LFB stain 2 in a microwave repair box for rapid differentiation for 3–5 s, followed by washing 2–3 times with water; ③ Next, sections were placed in LFB stain 3 for rapid differentiation for 3–5 s, then washed 2–3 times with water until the nerve myelin sheath was clearly visible in blue, and other components were light blue or even colorless. If not, step 2 and 3 should be repeated. Finally, the sections were dehydrated and mounted for photography.

### Statistical analysis and graphing methods

Experimental data were analyzed using SPSS 27.0 software. Quantitative data were expressed as mean ± standard deviation (X ± S). One-way ANOVA was used for multiple group comparisons, and t-tests were used for pairwise comparisons of multiple sample means. Repeated measures design ANOVA was used for time-based measurements of group data, and Pearson correlation analysis was used for variable correlation analysis. A *p*-value of less than 0.05 was considered statistically significant. The graph was generated using GraphPad Prism 10.1.2.

**Table 1** Comparison of indicators after establishment of acute hypernatremia model ($\overline{X} \pm S$, n = 15)

| Group category | Slow group | Middle group | Fast group | *p* |
|---|---|---|---|---|
| Serum sodium | 153.40 ± 1.96 | 152.60 ± 1.34 | 154.00 ± 2.74 | 0.542 |
| Serum potassium | 3.03 ± 0.46 | 2.82 ± 0.65 | 2.73 ± 0.37 | 0.649 |
| Urine sodium | 392.00 ± 34.41 | 451.20 ± 113.40 | 388.00 ± 63.44 | 0.383 |
| Urine potassium | 25.43 ± 14.27 | 32.87 ± 10.25 | 24.22 ± 6.90 | 0.424 |
| CVP | 7.80 ± 0.45 | 7.00 ± 1.41 | 7.00 ± 1.00 | 0.397 |
| ICP | 7.07 ± 0.59 | 6.80 ± 0.45 | 7.00 ± 0.70 | 0.284 |

## Results

Within 36–48 h, after increasing the sodium level in the experimental group at a target rate of 0.5 mEq/L/h, statistical analysis and comparison of key indicators of the experiment were conducted. There were no significant statistical differences in the various laboratory indicators among the Fast group, Middle group, and Slow group, as shown in Table 1. During the establishment of the acute hypernatremia model, serum sodium concentrations were measured at various timepoints. (Timepoint 1 is measured before sodium increase; timepoint 2 is measured around 12 h after sodium increase; timepoint 3 is measured around 24 h after sodium increase; timepoint 4 represents the measurement at the end of sodium increase). As shown in Fig. 3, the serum sodium concentration of the experimental group rabbits increased smoothly according to the experimental design.

The Barrs indicate the standard deviation.

Statistical analysis and comparison of ICP before and after the establishment of the acute hypernatremia model (Timepoint 1 and timepoint 4) showed no statistical difference among the four groups, see Fig. 4. During the establishment of the acute hypernatremia model, ICP was measured in rabbits from the four groups, and statistical analysis and comparison of the overall change in ICP revealed no statistical difference in the overall change of ICP among the four groups of rabbits, see Fig. 4.

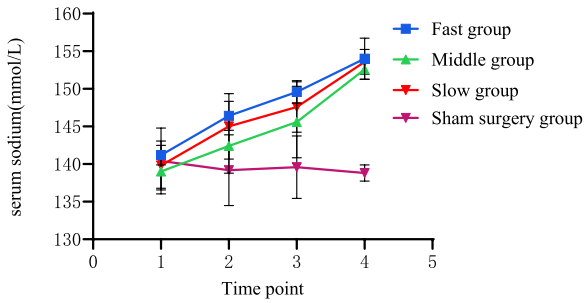


**Fig. 3** The graph of serum sodium concentration changes

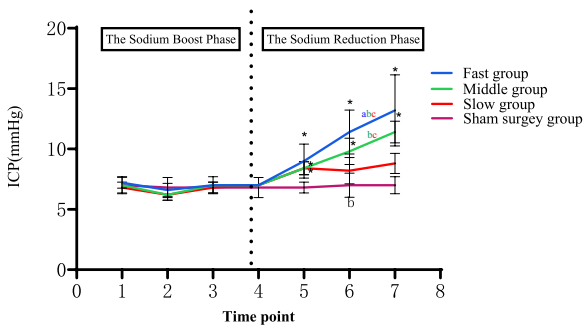


**Fig. 4** Overall trend chart of ICP changes

During the sodium reduction process, the ICP of rabbits in the four groups was observed and recorded. Statistical analysis of the ICP in rabbits from the four groups during the sodium reduction period showed that there were statistical differences in the ICP at timepoint 5, timepoint 6, and timepoint 7 for the four groups of rabbits, see Fig. 4.

Throughout the entire experimental process, statistical analysis and comparison of the overall trend of ICP changes in rabbits from the four groups were conducted, revealing that there was a statistical difference in the overall trend of ICP changes among the four groups of rabbits, as shown in Fig. 4: the horizontal axis represents the timepoints of the laboratory measurements, and the vertical axis represents the values of ICP, indicating that ICP differences occurred during the sodium reduction phase, and the faster the rate of sodium reduction, the faster the increase in ICP. Statistical analysis and comparison of the ICP during the sodium reduction period between the experimental groups showed that there was no statistical difference in ICP between the Fast group and the Middle group; there was a statistical difference in ICP between the Fast group and the Slow group; and there was a statistical difference in ICP changes between the Middle group and the Slow group during the sodium reduction period.

Comparing the experimental groups with the sham surgery group, it was found that there was a statistical difference in ICP changes between the Fast group and the Middle group and the sham surgery group during the sodium reduction period; there was no statistical difference in ICP changes between the Slow group and the sham surgery group during the sodium reduction period。As shown in Table 2, the *p*-values obtained from the comparisons between each group are presented.

Statistical analysis and comparison of ICP before (Timepoint 4) and after (Timepoint 7) sodium reduction revealed that there was a statistically significant difference in ICP before and after sodium reduction in both the Fast and Middle groups. In contrast, no statistically significant difference was found in ICP before and after sodium reduction in the Slow group. Similarly, no statistically significant difference was observed in the sham surgery group, as depicted in Fig. 5.

In the legend, the "Fast group" represents the group with a sodium—lowering rate of 3 mmol/L per hour. The "Middle group" stands for the group with a sodium—lowering rate of 2 mmol/L per hour. The "Slow group" refers to the group with a sodium—lowering rate of 1 mmol/L per hour. And the "Sham surgery group" denotes the sham—operated control group. The asterisk (*) indicates that there is a statistically significant difference between the experimental group and the control group at this point; "abc" represents that there are statistically significant differences between the Fast group and both the Middle group and the Slow group during the sodium reduction phase; "bc" represents that there is a statistically significant difference between the Middle group and the Slow group during the sodium reduction phase. The Barrs indicate the standard deviation.

For the Slow group, Middle group, and Fast group, there were no statistical differences in the volume of fluid input, output, or fluid balance during the sodium increase and decrease processes, as shown in Fig. 6

During the acute hypernatremia model development, varied NaCl solutions were used, likely elevating serum chloride levels. Upon entering the sodium—reduction phase, lower—chloride or glucose solutions were administered, gradually decreasing serum chloride levels. This trend aligns with the solution administration and electrolyte regulation in the experimental design, as shown in Fig. 7.

The Barrs indicate the standard deviation.

*Pathological changes*: The cerebral cortex and brainstem regions of the Fast group, as well as the Middle and Slow groups, exhibited pathological phenomena such as interstitial edema, perivascular edema, and nuclear vacuolation. Under the same magnification, the interstitial edema in the Fast and Middle groups was more severe than in the Slow group, indicating that faster sodium

**Table 2** Pairwise comparison of ICP among four groups during the sodium reduction period

| Group category | Fast group | Middle group | Slow group | Sham surgery group |
|---|---|---|---|---|
| Fast group | 1 | 0.188 | 0.020 | 0.001 |
| Middle group | 0.188 | 1 | 0.005 | 0.008 |
| Slow group | 0.020 | 0.005 | 1 | 0.885 |
| Sham surgery group | 0.001 | 0.008 | 0.885 | 1 |

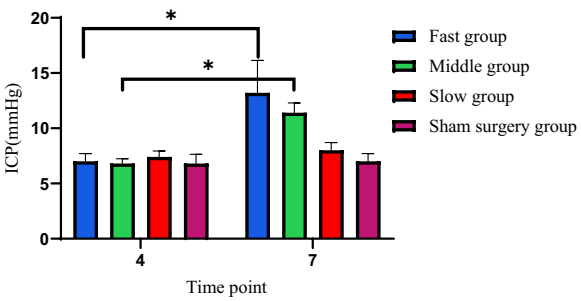


**Fig. 5** Comparison between time point 4 and time point 7

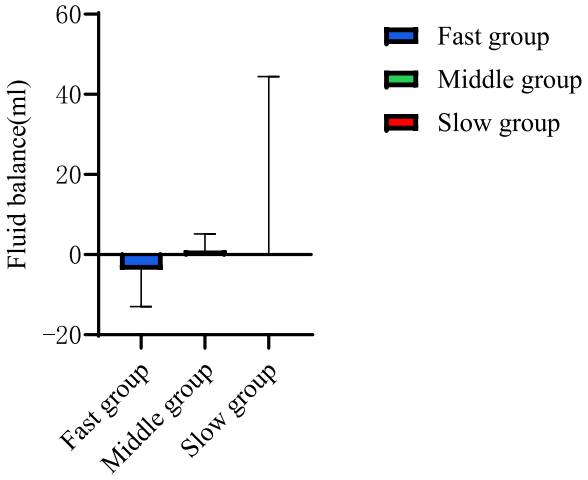


**Fig. 6** Statistical chart of fluid balance in the three groups

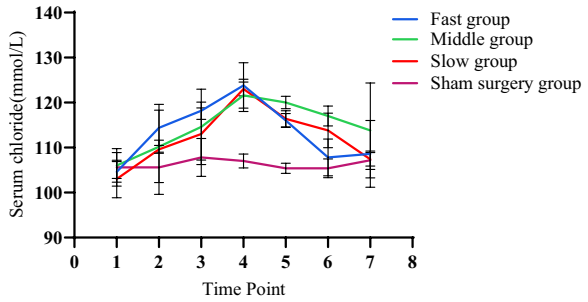


**Fig. 7** Serum chloride changes chart

reduction led to more severe edema, see Figs. 8 and 9. LFB staining of the brain tissue revealed no significant demyelination, see Fig. 10.

Semi-quantitative analysis of pathological changes in the cerebral cortex and brainstem was performed, with an arbitrarily defined grading standard based on the same anatomical location, magnification, and visual estimation of tissue edema: severe if the lesion occupies more than 2/3 of the field of view, moderate if it occupies 1/3 to 2/3, and mild if less than 1/3. The Fast and Middle groups showed more severe damage compared to the Slow group and the sham surgery group, with statistical differences. There was no significant difference between the Slow group and the sham surgery group. This further confirms that sodium reduction at a rate exceeding 1 mEq/L impacts the central nervous system, with more rapid reduction leading to more severe effects.

Elevated ICP is closely related to pathological changes of brain edema. In this experiment, interstitial edema, perivascular edema, and nuclear vacuolization in the brain tissue of the Fast group (Figs. 8–9) suggest the combined effect of blood–brain barrier disruption and cytotoxic damage. This kind of damage may be associated with the osmotic imbalance caused by rapid sodium reduction: the sharp decrease in plasma osmolarity leads to water entering the brain parenchyma against the gradient, and the delayed regulation of brain tissue osmolarity further exacerbates edema formation. Even after blood sodium concentration returns to normal, the continuous disturbance of brain tissue ion homeostasis may cause delayed neurological damage, which provides important insights for the individualized treatment of clinical hypernatremia.

## Discussion

The harmfulness of hypernatremia is mainly due to the degree of hypernatremia, the duration of hypernatremia, and the dangers brought by incorrect correction of hypernatremia. Studies have found that hypernatremia increases the 28-day mortality rate of patients [4]. The focus of treating hypernatremia is to address the cause, supplement free water, and closely monitor serum sodium concentrations. A study analysis found that current recommendations for treating acute and chronic hypernatremia are not based on high-quality research [11]. For chronic hypernatremia, Richard et al. proposed that no more than 8–10 mEq/L should be corrected in chronic hypernatremia patients every 24 h, with a maximum correction rate of 0.5 mEq/L/h, and regular assessment of serum sodium concentration should be required during the correction phase. In 1995, Borra et al. concluded through experiments that the correction rate of hypernatremia is related to the improvement of mental status, and the frequency of improvement in the level of consciousness is higher when hypernatremia is corrected within 4 days [12]. A retrospective study found that rapid correction of hypernatremia is not related to a higher mortality rate of hypernatremia [13], defining "rapid correction" as greater than 0.5 mEq/L. Other studies have shown that the mortality rate of hypernatremia is often related to insufficient correction [14]. There are currently no guidelines or consensuses for the rate of sodium reduction during the treatment of acute hypernatremia for clinical reference. It is recommended to quickly reduce serum sodium to normal at a rate of 2 mEq/L/h [9], and experts in the literature do not mention the reason for reducing sodium at this rate, but consider that it is necessary to quickly reduce serum sodium to normal levels for acute hypernatremia, as persistent hypernatremia itself will have an impact on patients. Some experts also state that reducing sodium at a rate of 1 mEq/L/h is safe [10], and this is based on case reports. According to pathophysiological theory, some experts also recommend using glucose-based hypotonic solutions to quickly correct acute hypernatremia and reduce

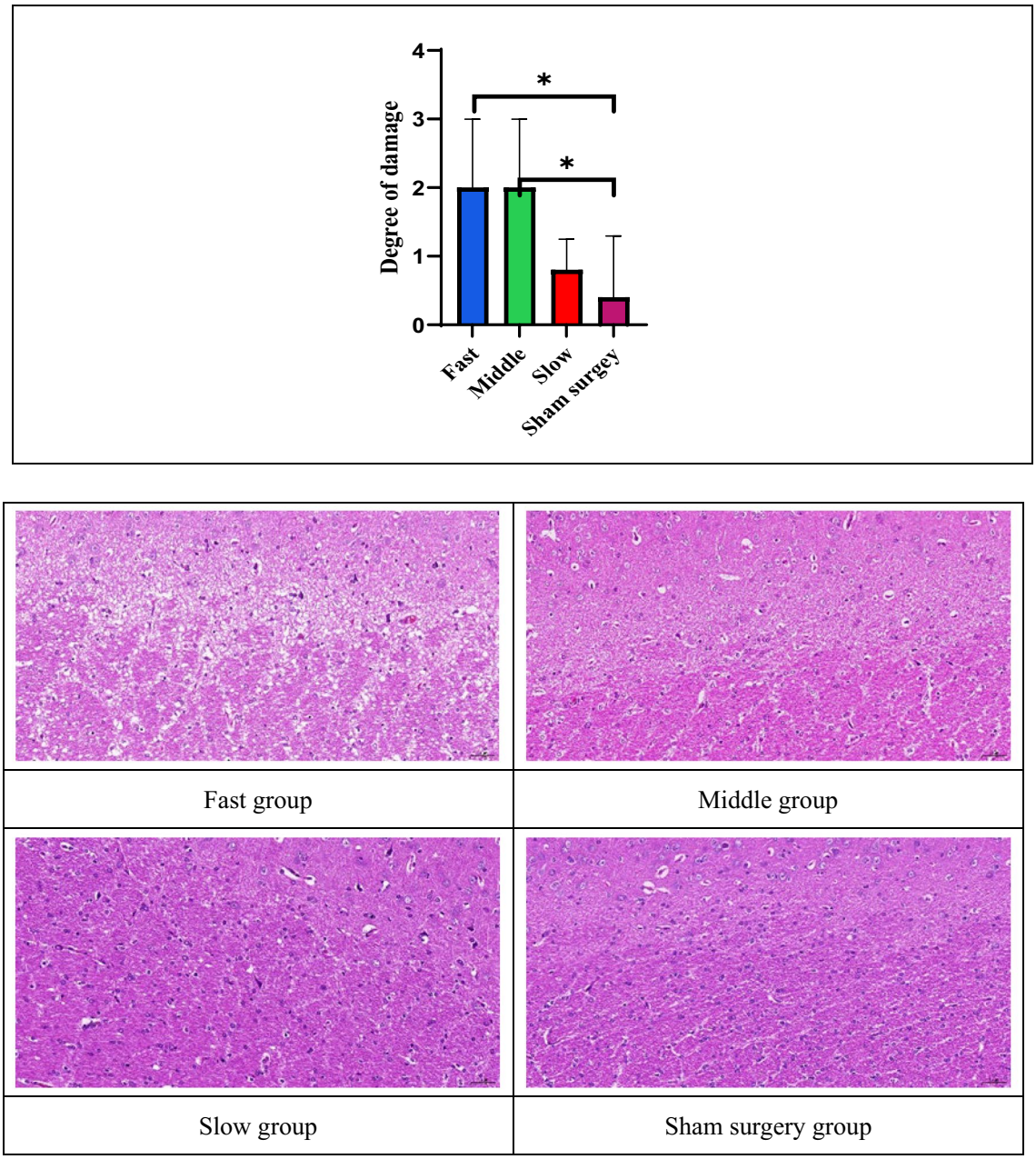


**Fig. 8** Semi-quantitative analysis and pathological presentation of the cerebral cortex

it to 145 mEq/L within 24 h [15]. A retrospective study showed that the 30-day and 1-year mortality rates after rapid correction of hypernatremia were lower than those after slow correction [16].

These recommendations for correcting hypernatremia are mostly based on studies of children and intensive care unit inpatients, and further evidence is needed to clarify the rate of sodium reduction. This experiment suggests a sodium reduction rate not exceeding 1 mEq/L/h through animal experiments. This experiment mainly explores the treatment of hypernatremia formed within 48 h (acute hypernatremia). The results show that under different rates of sodium reduction, both the Fast group and the Middle group had increased ICP, which was statistically different compared to the Slow group and the sham surgery group. Comparing the ICP before and after sodium reduction, both the Fast group and the Middle group showed statistical differences, but there was no significant difference in the overall comparison during the reduction period between the two groups, indicating that

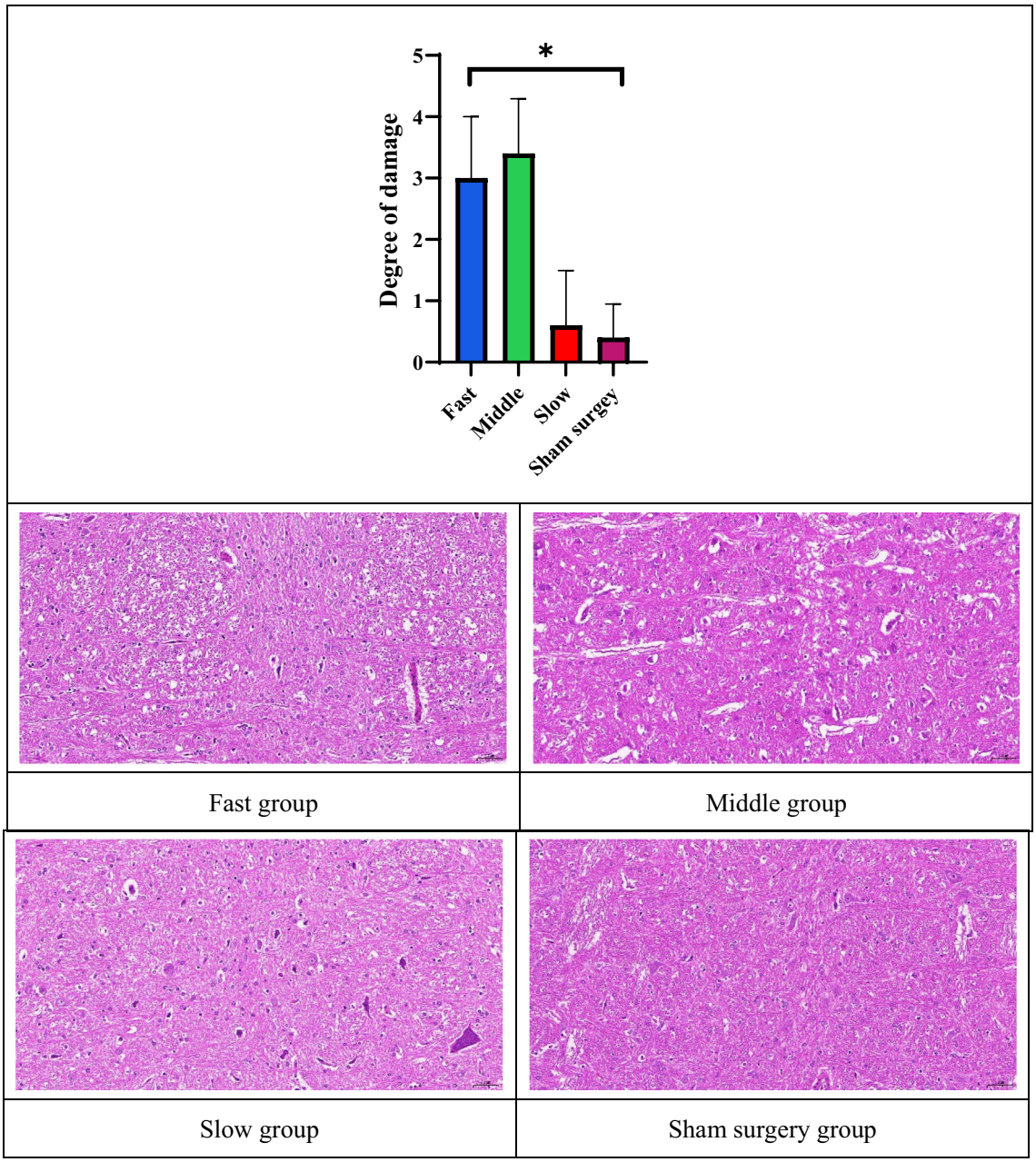


**Fig. 9** Semi-quantitative analysis and pathological presentation of the brainstem

a sodium reduction rate greater than 1 mEq/L/h affects the central nervous system of rabbits. By comparing the overall changes in ICP during sodium reduction in the Slow group and the sham surgery group, there was no statistical difference between the two. This indicates that a sodium reduction rate of 1 mEq/L/h is safe, compared to faster rates of 2—3 mEq/L/h. Regarding the mechanism of ICP increase, it may be due to rapid sodium reduction leading to a lower sodium balance in the blood than in the tissue fluid, causing fluid to enter brain cells from the blood, resulting in increased ICP. Conversely, during slow sodium reduction, there is enough compensation time to balance the sodium ions inside and outside the vessels, so there will be no excessive fluid entering the tissue, and ICP will not increase. Statistical analysis of the amount of fluid in the three groups found no statistical difference among the three groups in terms of input, output, and fluid balance. This indicates that the increase in ICP in the Fast group and Middle group in this experiment was not caused by fluid balance but by rapid

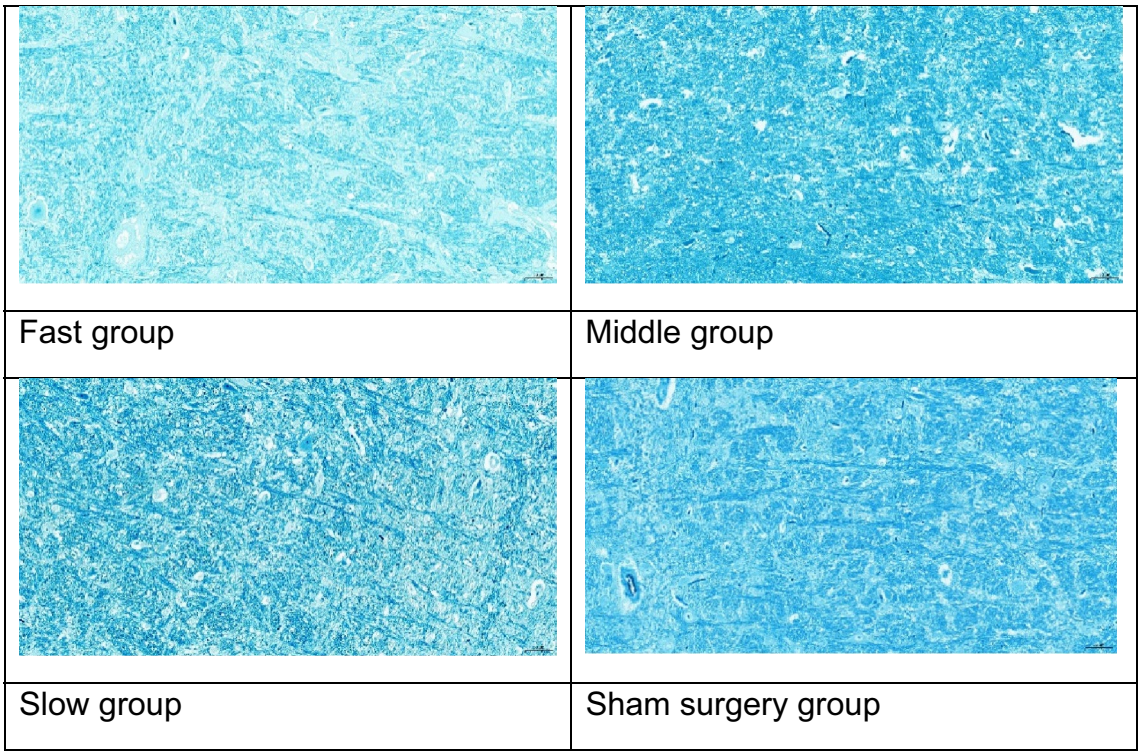


**Fig. 10** Pathological presentation with LFB staining

sodium reduction, and cerebral edema was not caused by fluid infusion.

Acute hypernatremia can be severely harmful, leading to cerebral hemorrhage or osmotic demyelination [17], but these changes can be avoided with a sodium reduction rate of less than 0.5 mEq/L/h [9, 14, 18]. Although no demyelination changes were found in the pathological sections of this experiment, it does not mean that there are no demyelination changes, and further research is still needed.

The results of this study further emphasize that the rate of sodium reduction during the treatment of acute hypernatremia has different effects on the central nervous system. The changes in ICP observed in the animal model may have implications for clinical practice. Rapid sodium reduction, while quickly correcting electrolyte imbalances, may increase ICP and pose a risk to the central nervous system. This suggests that doctors should carefully choose the rate of sodium reduction in clinical practice, especially for acute hypernatremia formed within 48 h, and it is appropriate to reduce sodium at a rate of less than 1 mEq/L/h.

This study found that rapid sodium reduction (3 mmol/L/h) caused the ICP (Intracranial Pressure) in rabbits to increase to 13.2 mmHg, which is an increase of 89% from the baseline value. Although this absolute value is lower than the pathological threshold of human ICP (>20 mmHg), rabbits have a small cranial cavity volume and a sensitive osmotic response of the blood–brain barrier. Therefore, the same proportion of increase may be more clinically significant. In addition, rabbits have a fast metabolic rate and weak compensatory ability of brain tissue, which may amplify the damaging effects of sodium reduction speed on the central nervous system. Future research needs to combine large animal models (such as pigs) or clinical observations to further verify the safe range of sodium reduction speed.

## Limitation

This study still has some limitations. Due to the relatively small sample size and the experimental conditions not covering all possible clinical situations, future studies could consider expanding the sample size and introducing more experimental designs to more comprehensively understand the impact of different rates of sodium reduction on ICP in acute hypernatremia. The results of this study were formed in animal experiments, and further experiments are needed to determine if this phenomenon occurs in clinical settings. For a specific model like rabbits, rapid sodium reduction may have adverse effects on the central nervous system, but it may not necessarily produce the same results in humans, which

also highlights the importance of individualized treatment strategies. Since the sodium levels in this study did not exceed 160 mEq/L during the sodium increase process, this study cannot make reliable recommendations for hypernatremia with concentrations exceeding 160 mEq/L, and future research can make further efforts in this direction. At the same time, this study only investigated acute hypernatremia, and we cannot provide a basis for the treatment rate of chronic hypernatremia, which could be a direction for future research.

## Conclusion

For acute hypernatremia formed within 48 h, the faster the rate of decrease in sodium levels exceeds 1 mEq/L per hour, the greater the increase in intracranial pressure (ICP) and the more severe the cerebral edema.

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13054-025-05377-9.

Additional file 1.

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**Author contributions**
Geng Xue and Hongyu Wu are the main authors and participated in the writing of the paper. Lin Ma,Ruidong Feng, andRui Cao participated in the experiment. Rongli Yang and Shuo Wu, as supervisors, provided guidance on papers and experiments.

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**Availability of data and materials**
No datasets were generated or analysed during the current study.

## Declarations

**Ethics approval and consent to participate**
Not applicable.

**Consent for publication**
Not applicable.

**Competing interests**
The authors declare no competing interests.

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