

# Clinical Application of Intracranial Pressure Monitoring Based on Flash Visual Evoked Potential in Treatment of Patients with Hypertensive Intracerebral Hemorrhage

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## Research article

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# Abstract

**Objective** To investigate the application value of flash visual evoked potential (FVEP) noninvasive intracranial pressure (nICP) monitoring technology in patients with hypertensive intracerebral hemorrhage (HICH).

**Methods** There were 116 eligible subjects included in the experiment, the final sample size was 102 for this study. They were randomly divided into FVEP nICP monitoring group (experimental group) and the non-monitoring group (control group). The experimental group were examined lumbar puncture immediately after intracranial pressure was monitored by FVEP. Mannitol was used in reducing the elevated intracranial pressure. The serum concentrations of creatinine and urea nitrogen were recorded to assess the renal function. To evaluate the efficacy of FVEP nICP monitoring technique for clinical adjustment of mannitol. The Glasgow prognosis scores (GOS) were evaluated for patients' prognosis between two groups.

**Results** There was no statistical significance between FVEP nICP measurement and lumbar puncture intracranial pressure measurement ( $195.76 \pm 58.88$  mmH<sub>2</sub>O vs  $197.04 \pm 53.72$  mmH<sub>2</sub>O,  $P > 0.05$ ). Linear correlation analysis indicated that there was a strong positive relationship between the measurements ( $r = 0.950$ ,  $P < 0.01$ ). The duration prescription time and the average usage amount of mannitol in the experimental group was significantly less than that in the control group ( $P < 0.05$ ), and the serum creatinine and urea nitrogen concentrations in the two groups were not statistically significant ( $P > 0.05$ ). The cure rate of the experimental group was higher than that of the control group ( $\chi^2 = 3.889$ ,  $P = 0.048$ ).

**Conclusion** FVEP nICP monitoring technology could replace invasive intracranial pressure monitoring technology in part HICH patients. The application of FVEP nICP technique can reduce the dosage of mannitol and improve the prognosis of patients with HICH.

## Background

Hypertension intracerebral hemorrhage (HICH) with the characteristic of high morbidity, mortality and disability is one of the major diseases that endanger the health of the elderly <sup>1</sup>. High intracranial pressure (ICP) caused by HICH is a common critical condition in neurology. The elevated ICP leads to the displacement of local brain tissue or the formation of brain herniation, which is the direct cause of the rapid deterioration of patients' condition and even death <sup>2</sup>. Headache, vomiting, and disturbance consciousness are the symptoms of the elevated ICP, but these clinical symptoms are not specific. At present, most of the ICP monitoring methods are invasive. Some limitations of the invasive methods include short-term monitoring, risk of infection and intracranial hemorrhage, restricted mobility of the subject, etc <sup>3</sup>. Therefore, it is necessary to find a noninvasive and reliable monitoring method to replace invasive intracranial pressure (iICP) to help clinical diagnosis and treatment. Flash visual evoked potential (FVEP) has been applied in clinical diagnosis due to its noninvasive and easy to perform <sup>4</sup>. Most clinical studies on FVEP noninvasive intracranial pressure (nICP) monitoring technology focus on

patients with elevated ICP caused by craniocerebral trauma, subarachnoid hemorrhage and HICH<sup>5,6</sup>. HICH is the most common disease of elevated ICP in neurology department. Mannitol is usually used in reducing the elevated ICP, but it can also cause side effects such as renal function damage and electrolyte disorder. In addition, under pathological conditions, mannitol crystals can form a hypertonic state locally through penetrating the damaged blood-brain barrier and aggravate cerebral edema<sup>7</sup>. The absence of published studies showing that management of elevated ICP has an effect on ICH outcome makes the decision whether to monitor and treat elevated ICP unclear in patients with ICH. Here, we monitored the changes of ICP with FVEP nICP monitoring technology in HICH patients, and evaluate whether the technique is beneficial for clinical practice and reduces complications.

## Methods

### Study design and participants

This study was a prospective registry designed to include consecutive patients with HICH. Only patients with mild to moderate intracerebral hemorrhage were eligible for this study. All subjects were recruited from the emergency department of Neurology, and hospitalized in the department of Neurology and Geriatric department of our hospital from November 2016 to December 2017. All subjects who had a history of hypertension or elevated blood pressure at onset met the diagnostic criteria of the American adult intracerebral hemorrhage treatment guidelines (2015)<sup>8</sup>. They were confirmed by cranial computed tomography (CT) with supratentorial hematoma without or only a small amount of intraventricular hemorrhage, and the amount of hematoma was less than 30 mL according to the Tada (ABC/2) formula<sup>9</sup>, with midline shift < 1 cm. The vital signs of subjects were relatively stable when they admitted to the hospital. Conservative treatment plan was first adopted after admission with the consent of the family. Exclusion criteria included local infection of the lumbar spine, severe liver and kidney dysfunction, pituitary tumor and all diseases associated with damage to visual pathways. Among 116 patients recruited from the emergency department of Neurology, the final sample size was 102 for this study. Because individuals were further excluded for the following reasons: hematoma enlargement requires surgery (n=9), intracranial aneurysm ruptured (n=2), transfer to the superior hospital (n=2), haematuria (n=1). Subjects were randomly divided into FVEP nICP monitoring group (experimental group) and the non-monitoring group (control group). This was in congruence with the local ethics committee requirements. The study was approved by the local ethics committees of our institutions, and subjects informed consent.

### Therapeutic methods

All HICH patients with elevated ICP were placed in a recumbent position, with elevation of the head of the bed to 30 degrees, kept the airway unobstructed, took sedatives as appropriate to keep the patients calm and kept the surrounding environment quiet, maintained the body temperature below 38.0 °C and strictly controlled blood pressure. For HICH patients presenting with SBP between 150 and 220 mmHg and without contraindication to acute BP treatment, acute lowering of the SBP to 140 mmHg. For HICH

patients presenting with SBP >220 mmHg, antihypertension agents were intermittent or continuous intravenous administration until SBP to 140 mmHg. Clinical symptoms and signs were observed every 30 minutes. 20% mannitol (Sichuan Kelun Pharmaceutical Co.Ltd, Sichun, China, batch no. A17103207-1) was used in reducing the elevated ICP in patients with HICH. Cranial CT was reviewed within 24h after admission, and were re-examined at any time according to the changes of the patient's condition. Patients of the experimental group received the first FVEP noninvasive and lumbar puncture iICP measurement within 1 h after admission. ICP values were monitored by FVEP nICP monitoring device within 24 hours, 3th day, 7th day and 14th day after admission, and mannitol dosage was timely adjusted according to the level of ICP. According to ICP values, the cases were divided into groups as normal (5.0 to 15.0mmHg), mildly increased (15.1 to 20.0 mmHg), moderately increased (20.1 to 40.0 mmHg) and severely increased (more than 40.1 mmHg). 1 mmHg is converted to mmH<sub>2</sub>O by multiplying with 13.6. Patients with mildly elevated ICP were observed closely without using mannitol usually. Patients with moderate elevated ICP lasting more than 10 minutes were offered 125 ml 20% mannitol, every 8 hours. The patients with severely elevated ICP were offered 125 ml 20% mannitol, every 6 hours. ICP values of patients in the control group were not monitored. The usage amount of mannitol was adjusted according to clinical symptoms, signs, hematoma size shown by CT. Mannitol, 125 ml 20% every 6 hours, was used in patients with consciousness disorders and hematoma enlargement by reviewing of cranial CT, and 125 ml 20% mannitol, every 8 hours in the other patients. The usage amount of mannitol and renal function were recorded in both groups. All patients were followed up to 3 months after discharge and their GOS scores were recorded.

### **FVEP non-invasive intracranial pressure monitoring**

FVEP nICP was determined using the MIP-310 nICP monitor (Chongqing Haiweikang Medical Instrument Co. Ltd, Chongqing, China) before treatment within 1 h after admission. Patients were supine in quiet state, excluding mental factors and environmental interference. The grounding electrode (black line) was placed on the eyebrows, left record electrode (orange line) and the right record electrode (brown line) were respectively placed on the external occipital protuberance 2 cm, and the reference electrode (red line) was placed at the hairline. After wearing the eye mask, the subject was given flash stimulation (the light source was blue neon light with a frequency of 1.0 Hz and a pulse width of 2ms for 50 times). The latency and amplitude of N2 wave were recorded after the stimulation, then calculated the ICP. With the relation function between N2 wave and ICP:  $ICP = 1.0371 * \text{latency} - 3.7106$  (mmH<sub>2</sub>O), the ICP values of both left and right channels can be obtained. The testing process should be measured for 3 consecutive times within 15 min for each measurement, and the mean value of 3 times should be taken. The normal ICP range is 80-180 mmH<sub>2</sub>O,  $\geq 200$  mmH<sub>2</sub>O means the elevated ICP.

### **Lumbar puncture**

In our work, cerebrospinal fluid (CSF) lumbar pressure was used in this protocol as a surrogate measurement of ICP. After FVEP nICP monitoring, the lumbar puncture immediately operated in patients of experimental group in order to evaluate the accuracy of the FVEP nICP monitoring values. The patient

was lying horizontally in the left lateral position. Once the appropriate location was palpated, after local anesthesia a non-traumatic lumbar needle was inserted in the L3-L4 or L4-L5 interspinous space and was left in place during the whole procedure. The CSF pressure was measured with a graduated fluid transducer. The zero reference pressure was the atmospheric pressure at the level of the foramen of Monro. In our study, local infection of the lumbar spine and brain herniation were contraindications to lumbar puncture.

### **Clinical efficacy evaluation**

Prognosis was evaluated using Glasgow Outcome Scale (GOS) standard <sup>10</sup>. level 1: death; Level 2: plant survival state; Level 3: severely disabled, unable to take care of himself; Level 4: mild disability, self-care; Level 5: return to good health and normal life. Level 1 and level 2 were considered invalid, level 3 and level 4 were considered disabled, and level 5 was considered cured. Cure rate = number of patients of level 5 / total number of cases ×100%.

### **Statistical analysis**

Statistical analysis was performed using SPSS software (Version 22.0, Chicago, IL, USA). Measurement data was given as mean ± standard deviation (S.D.) of the mean. Enumeration data was expressed as the count and percentage. Differences between study groups were examined with the  $\chi^2$ -test for categorical variables, and t-test for continuous variables. Pearson correlation analysis was used to analyze the correlation of ICP between the experimental group and the control group.  $P<0.05$  was considered statistically significant.

## **Results**

### **Study flow chart**

There were 116 eligible subjects included in the experiment, the final sample size was 102 for this study. They were randomly divided into the experimental group (n=52) and the control group (n=50). FVEP nICP monitoring and lumbar puncture test were performed in the experimental group. Cranial CT was examined and renal function was tested in all subjects. In the two groups, different treatment plans were given according to the severity of patients to reduce intracranial pressure. There was no loss of subjects during the experiment (Figure 1).

### **Status of patients and and outcome of their monitoring**

There were 52 cases in the experimental group including 28 males and 24 females, mean age  $61.15 \pm 5.84$  years. The volume of bleeding was mean  $21.16 \pm 4.27$  mL calculated by Multi-field formula. There were 50 cases in the control group including 27 males and 23 females, mean age  $60.82 \pm 4.18$  years, and the mean bleeding volume was mean  $20.73 \pm 5.96$  mL. There were no statistically significant differences in the two groups of patients in age, gender and blood loss. The value of FVEP nICP monitoring was

195.76 ± 58.88 mmH2O and the value of lumbar puncture measurement was 197.04 ± 53.72 mmH2O. There was no statistically significant difference ( $P > 0.05$ ).

Then, we used Pearson correlation analysis to analyze the correlation of FVEP nICP monitoring values and lumbar puncture measurement values. The analyses via Pearson's correlation coefficient demonstrated that FVEP nICP monitoring values was positively correlated with lumbar puncture measurement values ( $r=0.950$ ), the difference was significantly significant ( $P<0.01$ ) (Figure 2).

### Comparison of renal function and mannitol treatment between two groups

There were two cases who suffered kidney dysfunction in the control group, manifested as elevated creatinine and urea nitrogen values, but no statistical significance was found between the experimental group and the control group ( $P > 0.05$ ). Compared with the control group,

the duration prescription time and the average of mannitol usage in the experimental group was significantly decreased ( $P < 0.05$ ) (Table 1).

**Table 1. Comparison of kidney function and mannitol usage between two groups**

Variables	experimental group	control group
Cr (μmol/L)	120.38 ± 5.93	127.83 ± 6.72
BUN (mmol/L)	7.69 ± 0.97	8.97 ± 1.23
20% mannitol usage (mL)	3509.54 ± 289.18	4569.25 ± 308.74*

Cr, creatinine; BUN, blood urea nitrogen. Compared to the experimental group, \* $P \leq 0.05$

### Comparison of GOS scores between two groups

There were 35 patients with GOS grade 5 in the experimental group and 23 patients with GOS grade 5 in the control group. The cure rate in the experimental group was higher than that in the control group (67.3% vs. 46.0%,  $\chi^2 = 3.889$ ,  $P=0.048$ ) (Table 2).

**Table 2. comparison of GOS scores between the two groups, n (%)**

group	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
experimental group (n=52)	2(3.8)	3(5.8)	5(9.6)	7(13.5)	35(67.3)
control group (n=50)	4(8.0)	6(12.0)	8(16.0)	9(18.0)	23(46.0)

## Discussion

This study showed that there was no statistically significant difference between the FVEP nICP monitoring values ( $195.76 \pm 58.88$  mmH<sub>2</sub>O) and lumbar puncture measurement values ( $197.04 \pm 53.72$  mmH<sub>2</sub>O) in mild to moderate HICH patients ( $P > 0.05$ ). Pearson correlation analysis demonstrated that FVEP nICP monitoring values was positively correlated with lumbar puncture measurement values, the difference was significant ( $r=0.950$ ,  $P<0.01$ ). Through monitoring the change of ICP values by FVEP nICP monitoring technology, the duration prescription time and the average usage amount of mannitol in the experimental group was significantly less than that in the control group. The complications of kidney function impairment caused by drugs were also rare than those in the control group. Our research also showed that the recovery rate of the experimental group was significantly higher than that of the control group (67.3% vs. 46.0%,  $P=0.048$ ), and the prognosis of the HICH patients could be improved by closely monitoring the change of ICP value and timely adopting reasonable treatment plan.

HICH is an acute and severe disease in department of neurology. Elevated ICP after intracerebral hemorrhage plays an important role in secondary brain injury and is associated with increased mortality<sup>11</sup>. Timely detecting of ICP changes is the key to successful rescue of critically ill patients. Nowadays, most methods of ICP monitoring are invasive, but it's more likely to occur intracranial infection, intracranial hemorrhage and other complications<sup>12,13,14</sup>. Mizutani et al.<sup>15</sup> attempted to evaluate the sizes of intracranial hematoma, subdural hematoma, ventricular, and the degrees of subarachnoid hemorrhage and brain trauma injury through CT imaging, and established the relationship equation between CT imaging and elevated ICP by applying multiple regression analysis. But the results showed that the difference of ICP value was more than 40 mmH<sub>2</sub>O. Magnetic resonance imaging (MRI) examination is not convenient to be used in critically ill patients, nor can it be used to monitor ICP in a timely and dynamic manner<sup>16,17</sup>. FVEP nICP monitoring technology had been applied in clinical practice since 1986<sup>18</sup>. FVEP is the electrical activity generated by the occipital cortex to the visual stimulation induced by the diffuse non-mode light source. The delay time of the second negative wave (N2 wave) of the brain FVEP is directly related to ICP<sup>19</sup>. A microcomputer device can be used to perform visual stimulation and measure the delay time of N2 wave, then we can obtained the ICP value by comparing the relation table of N2 wave delay time and ICP value<sup>20</sup>. York et al. confirmed in the study of pediatric hydrocephalus and non-open craniocerebral trauma that there was a strong linear relationship between elevated ICP and prolonged latency of N2 wave of visual evoked potential (the correlation coefficient was 0.8-0.9)<sup>19</sup>. Visual evoked potential is best predicted when cranial hypertension is greater than or equal to 300 mmH<sub>2</sub>O<sup>21</sup>.

When a technique is applied to the clinic practice, the first consideration is accuracy. The correlation coefficient between nICP and ICP describes Whether nICP is a good proxy for the ICP. To assess the accuracy of a noninvasive method, the Association of Advancement of Medical Instrumentation stated that when the ICP that ranges between 0-20 mmHg, a difference of 2 mmHg is acceptable when compared to an invasive method<sup>22</sup>. Our study showed that the difference between the invasive and noninvasive ICP value within 2mmHg. Therefore, we can admit that FVEP nICP monitoring technology is accurate.

Similar to our research, ultrasonographic optic nerve sheath diameter (ONSD) is another noninvasive ICP monitoring technology through detecting optic nerve. Though it is a simple bedside ocular ultrasound used in detecting the elevated ICP, the ONSD is moderately correlated with ICP in both right and left eyes respectively and Pearson correlation of ONSD between two eyes (right and left) was 0.749 and 0.726<sup>23</sup>. The optimal ONSD cut-off for the identification of ICP has controversial, it fluctuates from 0.48-0.5cm<sup>24,25</sup>.

The majority of patients with intracerebral hemorrhage experienced further increase in ICP due to hematoma enlargement within 24h after the onset of intracerebral hemorrhage. Some researchers showed that the increase of ICP is significantly earlier than the clinically observed changes in consciousness and vital signs<sup>26,27</sup>. Especially applicable to patients with mild to moderate HICH without invasive ICP monitoring, FVEP nICP monitoring technology can be used as an effective means of early warning of further increase of ICP and further enlargement of hematoma<sup>28</sup>. Moreover, lumbar puncture manometry has been limited due to contraindications and clinical complications<sup>29</sup>. Therefore, the use of FVEP nICP monitoring is particularly important for HICH patients, especially for monitoring the change of ICP on the hematoma side and for early evaluating the degree of cerebral hemorrhage and cerebral edema.

In HICH patients, intracranial hematoma and cerebral edema will lead to elevated intracranial hypertension in 70% of patients. If not timely intervention will seriously affect the recovery of neurological function and prognosis of patients. Mannitol is the most commonly dehydrating agents which lower ICP by reducing blood viscosity and increasing plasma osmotic pressure<sup>30</sup>. However, clinical usage amount lacks scientific standards and often relies only on clinical experience, as for mannitol to achieve the expected effect is more difficult to determine. In addition, mannitol can cause kidney function damage and electrolyte disturbance. In order to reduce the possible damage caused by using of high doses of mannitol blindly, the American stroke Association recommends that mannitol should not be used prophylactically and should not be used for more than 5 days during first aid<sup>31,32</sup>. Clinical data showed that mannitol could shorten the incubation period of FVEP N2 wave, and FVEP could observe the changes of ICP after mannitol application<sup>33</sup>. In our experiment, the duration prescription time and the average usage amount of mannitol was significantly reduced in the experimental group by applying the FVEP nICP monitoring technology. The ICP changes monitored by FVEP nICP monitoring technology conducive to guide clinical treatment.

## Limitations

Certain limitations of this report need to be acknowledged. Firstly, the study was performed in a small population and in a limited area. There may be a bias in drawing conclusions. Secondly, this study only carried out in mild to moderate HICH patients, and the application of FVEP nICP monitoring technology in critically ill patients has not been experienced, so further experiments can be attempted.



# Conclusions

Our research showed that the recovery rate of the experimental group was significantly higher than that of the control group, and the prognosis of the HICH patients could be improved by closely monitoring the change of ICP value and timely adopting reasonable treatment plan. Based on the noninvasive and security of FVEP nICP monitoring technology, it can be considered to be applied to HICH patients with relatively mild to moderate clinical conditions, good patient compliance, and stability of the disease. The dynamic monitoring of ICP in HICH patients can guide the clinical timely adjustment of the dosage of mannitol and improve the condition and prognosis of HICH patients. However, the limitations and influencing factors of FEVP nICP monitoring technology should also be considered during clinical use, so as to better understand its indications and provide more reliable methods and means for clinical treatment of patients with HICH intracranial hypertension.

# Abbreviations

FVEP: flash visual evoked potential; nICP: noninvasive intracranial pressure; HICH: hypertensive intracerebral hemorrhage; GOS: glasgow prognosis scores; ICP: intracranial pressure; nICP: noninvasive intracranial pressure; iICP: invasive intracranial pressure; CT: computed tomography; MRI: magnetic resonance imaging; Cr: creatinine; BUN: blood urea nitrogen.

# Declarations

## Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Songjiang Hospital Affiliated to Shanghai Jiaotong University School of Medicine. Written informed consent was obtained from all participants following a detailed explanation of the study. The study was done in accordance with the principles outlined in the Declaration of Helsinki (1964).

## Consent for publication

Not applicable.

## Availability of data and materials

The data supporting our findings can be found in our article and its additional files.

## Competing interests

The authors declare that they have no competing interests.

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### Authors' contributions

FP-Y participated in the design of the study, statistical analysis, and drafted the manuscript. YC-Z participated in the design and conduct of the study. Y-Z carried out the operation of the experiment. Y-W provided management and operational assistance to the patients. XH-L helped to modify the manuscript. All authors read and approved the final manuscript.

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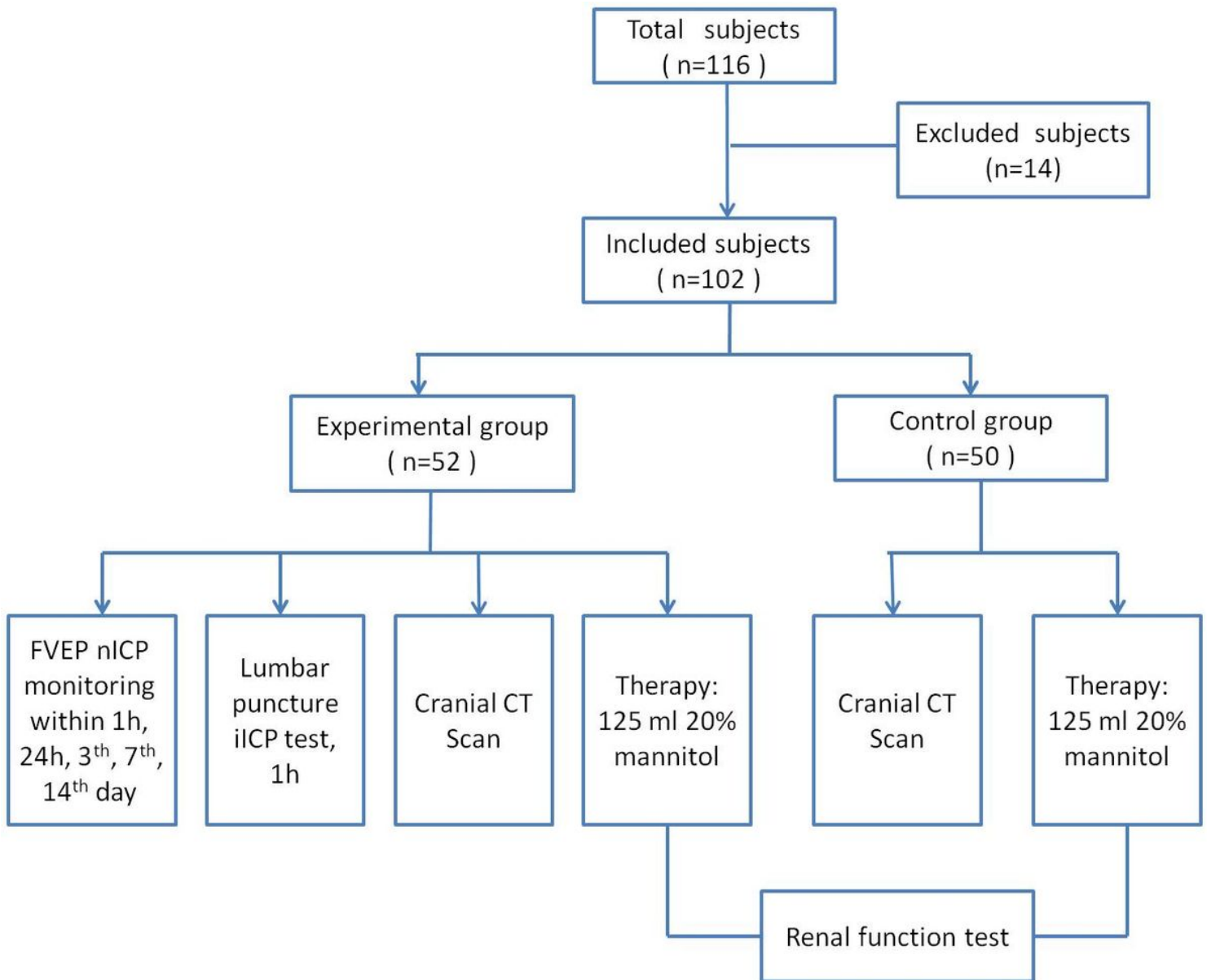
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## Figures



**Figure 1**

Flow chart of our study. FVEP, flash visual evoked potential; nICP, noninvasive intracranial pressure; iICP, invasive intracranial pressure; ICP, intracranial pressure.

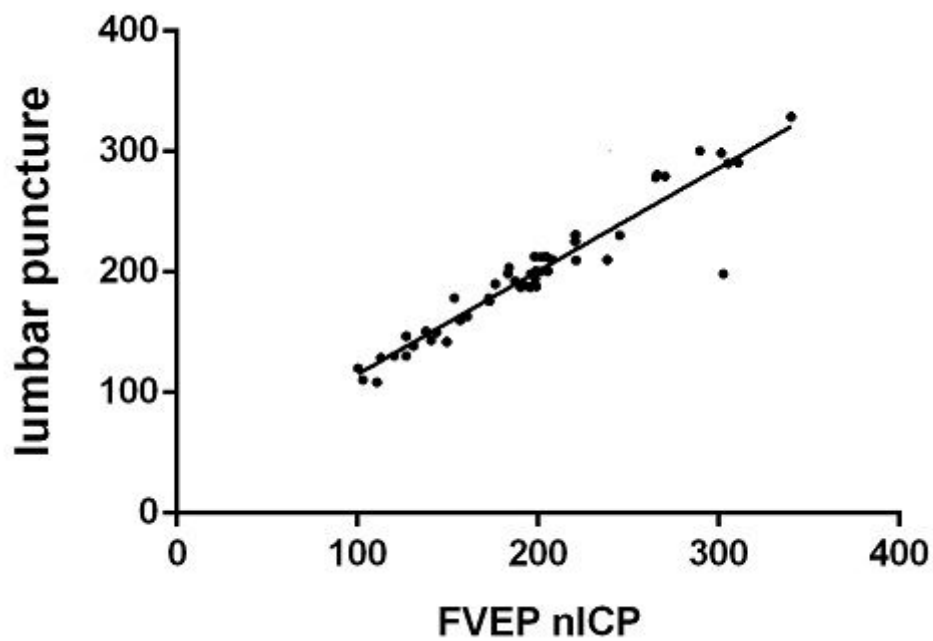


Figure 2

The correlation of ICP between the experimental group and the control group. FVEP, flash visual evoked potential; nICP, noninvasive intracranial pressure.