Abstract. – OBJECTIVE: This study examines the relationship between intracranial pressure (ICP) changes after skull injury repair and neurocognitive function before and after the repair.

PATIENTS AND METHODS: Sixty patients undergoing skull injury repair participated in the study. A non-invasive detection analyzer was used to detect the ICP 2 days before operation, 10 days after the operation and one month after the operation in all patients. Additionally, the mean cerebral blood flow velocities (MV) in the internal carotid and the medial cerebral arteries were detected using a transcranial Doppler ultrasound (TCD). The neurological and cognitive functions were assessed using the NIHSS and the MMSE scales, respectively. And finally, an ELISA assay was used to detect the plasma insulin-like growth factor (IGF)-1 and β-amyloid peptide (Aβ) levels.

RESULTS: The results showed that all parameters studied improved significantly and continuously after surgery.

CONCLUSIONS: We suggest that the improvement in the ICP values and the neurocognitive functions are related to the resulting decreased expression levels of IGF-1 and Aβ after the repair.

Key Words: Skull repair, Intracranial pressure, Neurocognitive function, Insulin-like growth factor-1, Aβ-amyloid peptide.

Introduction

There are many studies supporting the notion that skull defects larger than 3 cm in diameter may not only affect the integrity of the structure of the skull, but also aggravate the brain tissue injury and affect the intracranial pressure, cerebral perfusion and nerve regulation functions, leading to neurocognitive disfunction1,2. Fortunately, skull repairing procedures can reshape the skull and improve the quality of life of patients3; and the application of new repair materials, especially through progress in bone tissue engineering, will enable perfect repair of skull defects from a morphological and functional standpoint4. The idea is that skull repair will help stabilize the intracranial pressure with positive effects on the cerebral blood flow and a resulting promotion of neurocognitive function recovery5,6. However, there are less in-depth analyses on the influence of changing concentrations of molecular products that being differentially regulated could influence neurocognitive function. Recent works have confirmed the neurocognitive impairment is closely related to β-amyloid peptide (Aβ) deposition and a brain insulin-like growth factor-1 (IGF-1)-mediated signal transduction system disorder7. Accordingly, this study analyzes whether the improvement on neurocognitive function after skull injury repair is related to the expression levels of Aβ and IGF-1.

Patients and Methods

Patients

Sixty patients undergoing skull injury repair in our hospital from June 2014 to January 2016 were enrolled. Patients with neurocognitive dysfunction (such as dementia), anxiety and depression state, unsuccessful operation, large skull defect, inaccurate completion of scale scoring, and incomplete data caused by other causes were excluded. There were 40 males and 20 females, with ages from 34 to 68 years old and a mean age of 52.5 ± 14.6 years of age; the length of time with a skull defect ranged from 1 to 10 days, with a mean of 5.2 ± 2.3 days; the defect area span from 3.3 to 10.4 cm², with a mean of 6.5 ± 2.2 cm²; and there were 35 cases of cranial trauma, 7
cases with decreased intracranial pressure after acute cerebral hemorrhage, 15 cases with tumor resections and other three cases. Finally, 45 cases underwent titanium mesh repair, and 15 cases had autologous skull defect repairs. The study as approved by the Ethics Committee of our hospital and the informed consents from the patients’ families were obtained.

**Operation Method**

A skin flap incision was made making use of the original incision, and making sure to preserve the flap blood circulation as much as possible to prevent delayed wound healing due to poor postoperative blood circulation. The skin flap was peeled carefully to avoid injury to the cerebral dura mater and reduce the occurrence of postoperative incision cerebrospinal fluid leakage. After completely exposing the bone defect, a titanium mesh was shaped to allow the complete coverage of it. In the cases where the defect was too large for the mesh, the cerebral dura mater in the defect center was suspended and fixed on the metal titanium mesh with silk to reduce the dead space, and prevent postoperative hematoma or effusion occurrence. The titanium mesh was put in place on top of the defect and fixed by screws, to allow drainage of the subcutaneous and epidural effusions. The implant was placed under the epidural temporalis muscle, to avoid the referred pain due to repetitive movement of the temporalis muscle.

**Clinical Observation Indicators**

The intracranial pressure (ICP) was obtained by use of a MICP-IA type non-invasive intracranial pressure detection analyzer (Chongqing Mingxi Medical Devices Co., Ltd.). This device can calculate the intracranial pressure using the flash N2 wave latency variation in a positive correlation plot. The same skilled professional took all the measurements twice, with an interval of 6 h between measurements; an average was obtained. Briefly, the patients lied down and put on flash goggles that emit a standard yellow laser stimulation signal on the tester. The stimulus is then converted into electrical signals after the retinal photoreceptor, and a detection electrode then collects the message and sends it to a computer for processing. The result is a flash visual evoked potential characteristic curve from many waves that can be calibrated and allow for calculation of the ICP value. To reduce errors, if the difference between the two measured values was more than 20 mmHg, additional measurements would be carried out, and the two closest mean values would be taken as the ICP value data.

The cerebral mean blood flow velocity (MV) was measured with a transcranial Doppler ultrasound apparatus (TCD), namely the Doppler Box analyzer (DWL Compumedics Germany GmbH, Singen, Germany) with the QL system modular software. The standard configuration included a conventional single-channel detection software and M-Mode, with support for 1.2, 4, 8, and 16 MHzc probes. The bilateral internal carotid artery (ICA) measurements were detected through the ocular window. The mean velocity (MV) of the middle cerebral artery (MCA) was detected through the temporal window.

The NIH stroke scale from the National Institutes of Health (NIHSS) was adopted to assess neurological functions. There was a total of 11 items; the general score was from 0 to 42 points, and the scoring time was 2 min; the higher the score, the worse the neurological function.

The mini-mental state examination scale (MMSE) was chosen for cognitive functions. There were a total of five items, the maximum score was 30; and the lower the score, the worse the cognitive function.

Also, an ELISA assay was carried out to detect the plasma insulin-like growth factor (IGF) -1 and β-amyloid peptide (Aβ) levels. The procedure was done on three occasions (2 days before operation, 10 days after the operation and one month after the operation), and Beijing Zhongshan Biotechnology Co., Ltd, China, supplied the kits. All tests were carried out in accordance with the manufacturer’s instructions.

**Statistical Analysis**

The SPSS19.0 software (SPSS Inc., Chicago, IL, USA) was used for data entry and statistical analysis. The quantitative data were expressed as a mean ± standard deviation, and variance analysis was used for comparisons. The qualitative data was expressed as the number of cases or by a percentage (%) and the χ²-test was used for comparisons between groups. p < 0.05 indicated a statistically significant difference.

**Results**

**Comparison of Intracranial Pressure and Cerebral Blood Flow**

After treatment, the intracranial pressure, the MV of ICA and the MCA at the affected side were
Expression of IGF-1 and Aβ in patients with repaired skull injury

All significantly increased and kept increasing with time. The differences were statistically significant (p < 0.05) (Table I).

Comparison of NIHSS and MMSE Scores

The NIHSS scores in patients were decreased after treatment and the MMSE scores were increased significantly and continued to improve with the time (p < 0.05) (Table II).

Comparison of IGF 1 and Aβ Expression Levels

The IGF 1 and Aβ expression levels in patients decreased further after the treatment (p < 0.05) and the values continued to get lower with time (Table III).

Discussion

The skull bone is a membranous bone whose regeneration is poor. Skull defects lead to decreased intracranial pressure, in which cases the scalp covering the bone window sinks. When standing or walking, the intracranial pressure is further decreased and the depression deepens; while in the horizontal position, the local site bulges, causing blood vessels in the cerebral cortex to be distorted by changing tension states. The blood perfusion in the brain is affected and can even lead to cerebral atrophy. Patients often develop a skull defect syndrome due to the changing intracranial pressures that result from body position changes. The skull defect syndrome is characterized by symptoms such as headache, dizziness, fear of noise, fear of shock, difficulty concentrating, fatigue, anxiety, depression, local pain, physical disability, difficulty recovering from aphasia, and easily induced seizures. A study found that a neurocognitive function test 5 years after acquiring a skull defect showed a 30 to 50% comparative decline, and that secondary dementia affected about 5 to 10% of the patients.

Studies have also shown that different defect sites lead to different degrees of decreased neurocognitive function, and different repair materials may influence the outcome. However, the specific mechanisms are not very clear. In this work it was found that the neurological dysfunction symptoms were mainly manifested by dysarthria, language disorders, decreased limb muscle strength and sensation; and the cognitive dysfunction symptoms were mainly manifested by alterations of orientation, time, naming ability and short-term memory. After the treatment, all of the parameters studied improved significantly. The intracranial pressure, and the ipsila-

Table I. Comparison of intracranial pressure and cerebral blood flow.

<table>
<thead>
<tr>
<th></th>
<th>Intracranial pressure (mmH₂O)</th>
<th>ICA at affected side (MV (cm/s))</th>
<th>ICA at uninjured side (MV (cm/s))</th>
<th>MCA at affected side (MV (cm/s))</th>
<th>MCA at uninjured side (MV (cm/s))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before operation</td>
<td>105.3 ± 11.2</td>
<td>53.4 ± 12.6</td>
<td>57.8 ± 13.5</td>
<td>61.2 ± 14.5</td>
<td>66.9 ± 15.0</td>
</tr>
<tr>
<td>10 days after operation</td>
<td>116.4 ± 12.3</td>
<td>55.6 ± 13.3</td>
<td>57.9 ± 13.4</td>
<td>64.4 ± 14.6</td>
<td>67.0 ± 15.2</td>
</tr>
<tr>
<td>1 month after operation</td>
<td>125.5 ± 12.7</td>
<td>57.7 ± 13.4</td>
<td>58.0 ± 13.6</td>
<td>66.8 ± 14.7</td>
<td>67.2 ± 15.3</td>
</tr>
<tr>
<td>F</td>
<td>&lt;0.001</td>
<td>0.964</td>
<td>8.231</td>
<td>0.825</td>
<td></td>
</tr>
<tr>
<td>p</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.919</td>
</tr>
</tbody>
</table>

Note: MV: mean blood flow velocity; ICA: internal carotid artery; MCA: middle cerebral artery.

Table II. Comparison of NIHSS and MMSE scores.

<table>
<thead>
<tr>
<th></th>
<th>NIHSS</th>
<th>MMSE</th>
</tr>
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<tbody>
<tr>
<td>Before operation</td>
<td>27.8 ± 5.0</td>
<td>20.3 ± 4.2</td>
</tr>
<tr>
<td>10 days after operation</td>
<td>23.1 ± 4.2</td>
<td>23.7 ± 4.5</td>
</tr>
<tr>
<td>1 month after operation</td>
<td>18.3 ± 3.6</td>
<td>25.8 ± 4.7</td>
</tr>
<tr>
<td>F</td>
<td>10.325</td>
<td>8.524</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Table III. Comparison of IGF-1 and Aβ expression levels (ng/ml).

<table>
<thead>
<tr>
<th></th>
<th>NIHSS</th>
<th>MMSE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before operation</td>
<td>256.3 ± 42.3</td>
<td>45.8 ± 5.5</td>
</tr>
<tr>
<td>10 days after operation</td>
<td>214.7 ± 41.7</td>
<td>36.9 ± 4.7</td>
</tr>
<tr>
<td>1 month after operation</td>
<td>176.9 ± 35.8</td>
<td>31.7 ± 4.0</td>
</tr>
<tr>
<td>F</td>
<td>15.628</td>
<td>12.325</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Note: IGF-1, insulin-like growth factor-1; Aβ, β-amylloid peptide.
teral MV of ICA and MCA increased and also became higher overtime. The neurological and cognitive functions improved after treatment, and over time. And, finally, the IGF-1 and Aβ expression levels were decreased and also continued to do so with time. The mechanism by which skull repair could improve the blood flow may be related to the loosening of adhesions between the cerebral dura mater and the bone flap as well as the adhesion between the cerebral dura mater and the bone window. It is also possible that the traction, pulling, distortion and oppression of the cerebral vascular surface from scar tissues were relieved; or that the skull repair eliminates the deleterious effects of the atmospheric pressure on the defect site\(^{12}\). How did the increased intracranial pressure and cerebral perfusion improve the neurocognitive function? The study results suggest a link between the decreased IGF-1 and Aβ expression levels and the neurocognitive function improvement.

Aβ is a polypeptide containing 40 amino acids that is produced by hydrolysis of the amyloid precursor protein (APP)\(^{13}\). The aggregation of Aβ proteins seems to play an important role in the pathogenesis of Alzheimer’s disease (AD) and it has been signaled as one of the most important risk factors for it\(^{14,15}\). A study confirmed that the abnormal Aβ deposition, the expression of highly phosphorylated microtubule binding protein (Tau), and apolipoprotein (Apo) E4 could form amyloid plaques inside and outside of neurons, thereby causing neurodegenerative lesions\(^9\). IGF-1 is an important neurotrophic factor, its receptor, IGF-1R, is abundantly expressed in the nervous system\(^{11}\). Another study confirmed that IGF-1 might affect Aβ clearance and tau protein phosphorylation, could regulate PI3K/Akt and MAPK/ERK1/2 signal transduction pathway and could, therefore, play an important role in neurodegenerative diseases such as AD\(^{19}\).

**Conclusions**

To sum up, the skull repair operations can significantly improve intracranial pressure, cerebral blood flow and neurocognitive function, and the last effect may be associated with the decreased expression levels of IGF-1 and Aβ.

**Conflict of interest**

The authors declare no conflicts of interest.

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