

Evaluation of the role of 8-iso-PGF levels at multiple sites during intracranial hemorrhage in pediatric patients

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Abstract. – OBJECTIVE: The present study was planned to explore the role of 8-isomeric-prostaglandinF2 α (8-iso-PGF2 α) levels at the multiple sites of cerebrospinal fluid in children with intracranial hemorrhage.

PATIENTS AND METHODS: 90 children with intracranial hemorrhage were admitted to Surgery Intensive Care Unit (SICU) of our hospital from January to December 2013 and were selected as study subjects. They were divided into group A (n=30), group B (n=30) and group C (n=30). The group A was given conventional treatment, the group B was treated with minimally invasive puncture and the group C was treated with cerebrospinal fluid decompression. After 1 d, 2 d, 3 d, and 7 d of hospitalization, enzyme-linked immunosorbent assay (ELISA) was used to detect the 8-iso-PGF2 α levels in peripheral blood of children in all groups. On the day of admission and 10 d after treatment, 3 groups of children were implemented with brain nuclear magnetic resonance spectroscopy for metabolite analyses.

RESULTS: On the day of admission there were no significant differences in the 8-iso-PGF2 α levels among group A, B and C. Further, after 1 d, 3 d, 7 d of hospital stay, the 8-iso-PGF2 α levels in peripheral blood showed a gradual downward trend, and decline range of the group C was greater than that of group A and B ($p < 0.05$). After 10 days of treatment, there were significant differences in the bilateral temporal lobe and hippocampal NAA/Creatinine (Cr), Cho/Cr, ml/Cr and NAA/ml among group A, B, and C. The survival rate of group C was higher than that of group A and B ($p < 0.05$). On the other hand, the prevalence of sequelae was significantly lower than that of group A and B ($p < 0.05$). The amount of blood loss in children with intracranial hemorrhage was positively correlated with the levels of 8-iso-PGF2 α in peripheral blood ($r = 0.546, p < 0.05$) as observed by Spearman correlation analysis.

CONCLUSIONS: 8-iso-PGF2 α plays an important role in the pathogenesis of intracranial hemorrhage, and could be utilized as a biomarker of oxidative stress in children with intracranial hemorrhage. Further, cerebrospinal fluid decompression is a better method of treatment for intracranial hemorrhage.

Key Words:

Intracranial hemorrhage, Children, 8-iso-PGF2 α , Nuclear magnetic resonance spectroscopy, Prognosis.

Introduction

Intracranial hemorrhage is a severe disease characterized by intracranial hypertension, convulsions, jaundice and respiratory failure¹. Intracranial hemorrhage progress has been reported to be very fast but variable levels of long-term neurological sequelae exist². Important causes for intracranial hemorrhage included premature birth, hypoxia and a lack of vitamin K³⁻⁵. Further, the evolving development of the economy and the improvement of medical technology improved the survival rates of premature infants. However, this increased the occurrence of intracranial hemorrhage.

Late Vitamin K Deficiency Bleeding (LVKDB) is the major cause of intracranial hemorrhage for 1-6 month old infants. Further, China is one of the countries experiencing high morbidity. About 50% LVKDB has been reported to be intracerebral hemorrhage⁶. Reports showed that^{7,8} the incidence of intracerebral hemorrhage is (4.4-7.2)/100000. 2011. Netherlands reported that its

incidence was (0.5-3.3)/100000 in 2011. However, there are no large-scale clinical studies on intracranial hemorrhage in China.

8-iso-Prostaglandin F₂α (8-iso-PGF₂α) is the stabilized end product produced after free radicals induced impairment of lipid membranes polyunsaturated fatty acids (arachidonic acid)⁹. Further, this end product could accurately reflect the levels of lipid peroxidation, corresponding to the extent of damage in organ tissue. Moreover, it is an ideal biochemical index to evaluate the degree of oxidative damage¹⁰. Keeping in mind these views, the present study explored the role of 8-iso-PGF₂α levels at the multiple sites of cerebrospinal fluid in children with intracranial hemorrhage.

Patients and Methods

Patients

90 cases of intracranial hemorrhage children meeting the diagnostic standards of Late Vitamin K Deficiency Bleeding (LVKDB) (who were treated by SICU of our hospital from January to December 2013) were selected as study subjects. These cases included 50 male cases and 40 female cases. The onset age was 35 days to 4 months. The total duration from attack to treatment was 2-5 days. There were 42 cases of subarachnoid hemorrhage, 24 cases of subdural hemorrhage, 20 cases of parenchymal hemorrhage, and 4 cases of mixed hemorrhage. All children were purely on breast-feeding, and there was no history of trauma or hemorrhagic disease. Selected cases were randomly divided into three groups named A, B and C, with 30 cases in each group. In each group, general information difference had no statistical significance ($p > 0.05$). The study was approved by the Ethics Committee of Xuzhou Children's Hospital. Signed written informed consents were obtained from all participants before the study.

Methods

The group A subjects took the conventional treatment, group B was given minimal invasive puncture treatment and group C subjects were treated with decompression of intraventricular hemorrhage cerebrospinal fluid. Measurement of 8-iso-PGF₂α levels was performed in peripheral blood of all three groups on the 1st d, 2nd d, 3rd d, and 7th d of hospital stay by using Enzyme linked immunosorbent assay (ELISA) kit (Bioleaf Biotech Co. Ltd., Shanghai, China). NMR analysis

of head metabolites was performed by: 3.0 T Signa HDxt superconducting magnetic resonance apparatus (General Electric Company, NY, USA). Head quadrature coils were used in eight ways and sponge cushion was utilized for the stabilization of the subject. After 15 minutes' rest, the patient was put in the scanning position. Then, the conventional MRI Bruker Scientific Technology Co., Ltd. (Beijing, China) and multi-body 1H-MRS examination were conducted.

Observation Indicators

1. Measurement of the 8-iso-PGF₂α levels in peripheral blood of three groups after their admission to hospital on the 1st d, 2nd d, 3rd d, and 7th d, was made.
2. Analyses of head metabolites were performed in all three groups the first day of admission and on the day after the treatment by nuclear magnetic resonance. Through conventional Magnetic Resonance Imaging (MRI) scanning, eligible subjects were applied point resolved spectroscopy (PRESS) to obtain the 3D-CSI. The positions of chemical frequency shifts from main metabolites were associated with nerve the nervous system diseases (Figure 1).
3. After the discharge, these patients were followed up for 1 to 2 years so as to judge the relations between patients' result and prognosis and between the amount of bleeding and 8-iso-PGF₂α levels.

Statistical Analysis

SPSS 20.0 (IBM, Armonk, NY, USA) statistical software was utilized for statistical analyses. Measurement data were presented as ($\bar{x} \pm s$). Count data were shown by percentage. Correlation analysis was performed by Spearman analysis. $p < 0.05$, signified statistically significance.

Results

Comparison of 8-iso-PGF₂α Levels in Peripheral Blood of the Three Groups of Children

Comparison of 8-iso-PGF₂α levels of the group A, B, C on the first day of admission showed no statistical significance ($p > 0.05$). However, 8-iso-PGF₂α levels showed a declining trend after 1st, 2nd, 3rd, 7th d of hospital stay. Further, the decline range of group C was better than that of group A and B ($p < 0.05$), as shown in Figure 2.

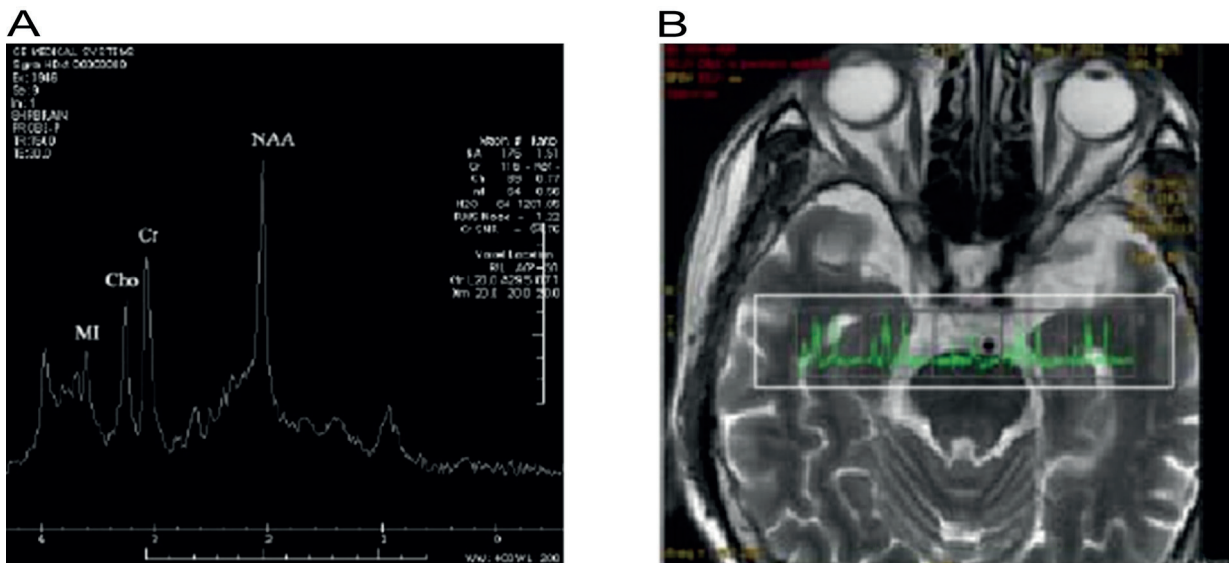


Figure 1. 1H-MRS showing the chemical frequency shift location of all metabolites: **A**, 1H-MRS wave; **B**, The location of the metabolites.

8-iso-PGF $_{2\alpha}$ Level Changes of Extracted Solution in Minimal Invasive Puncture in Group B

After the treatment, 8-iso-PGF $_{2\alpha}$ levels of extracted solution during minimal invasive puncture in group B showed a gradual declining trend, as shown in Figure 3.

C 8-iso-PGF $_{2\alpha}$ Level Changes of Cerebrospinal Fluid in Group C

After the treatment, 8-iso-PGF $_{2\alpha}$ levels of cerebrospinal fluid in group C showed a gradual declining trend, as shown in Figure 4.

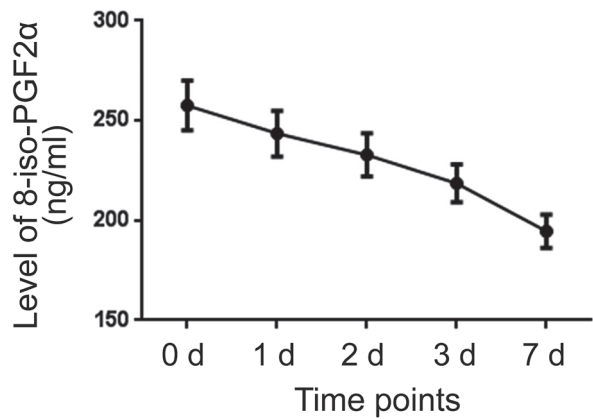


Figure 3. Levels of 8-iso-PGF $_{2\alpha}$ in extracted solution through a minimally invasive puncture in group B.

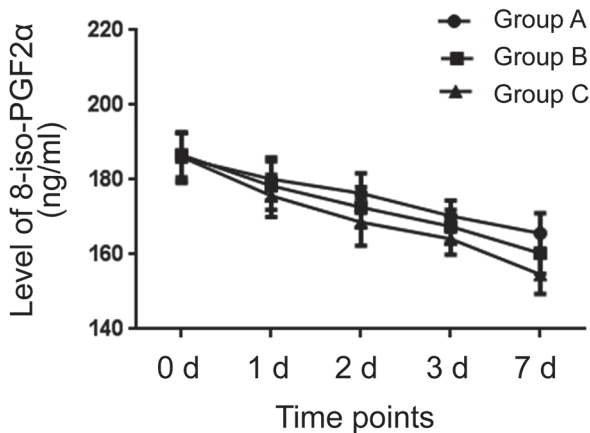


Figure 2. Levels of 8-iso-PGF $_{2\alpha}$ in peripheral blood for 3 different groups.

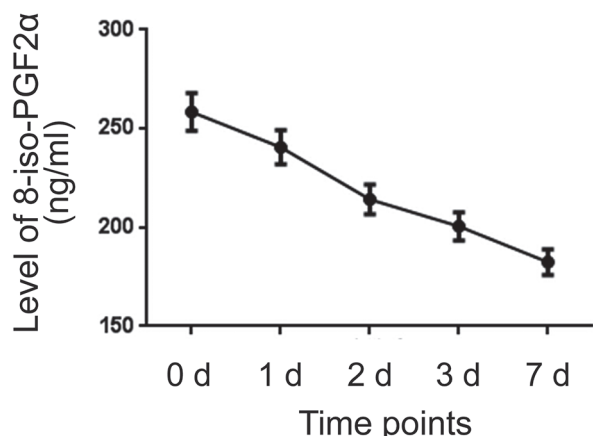


Figure 4. Levels of 8-iso-PGF $_{2\alpha}$ in cerebrospinal fluid in group C.

Concentration Comparison of Bilateral Medial Temporal Lobe Metabolite Between the Three Groups

On the first day of hospital stay, NAA/Cr, Cho/Cr, mI/Cr, NAA/mI between left and right medial temporal lobes in groups A, B and C had no statistical significance ($p > 0.05$). However, on the 10th day of hospital stay, the differences of NAA/Cr, Cho/Cr, mI/Cr, NAA/mI between left and right medial temporal lobe in group A, B, C were statistically significant ($p < 0.05$). Bilateral medial temporal lobe conventional MRI

and 1H-MRS wave spectrum of three groups are shown in Figure 5.

Concentration Comparisons of Bilateral Hippocampus Between the Three Groups

On the 10th day of treatment, the difference of NAA/Cr, Cho/Cr, mI/Cr, NAA/mI between left and right hippocampus in group A, B, C were statistically significant ($p < 0.05$). Hippocampus conventional MRI and 1H-MRS wave spectrum of three groups are shown in Figure 6.

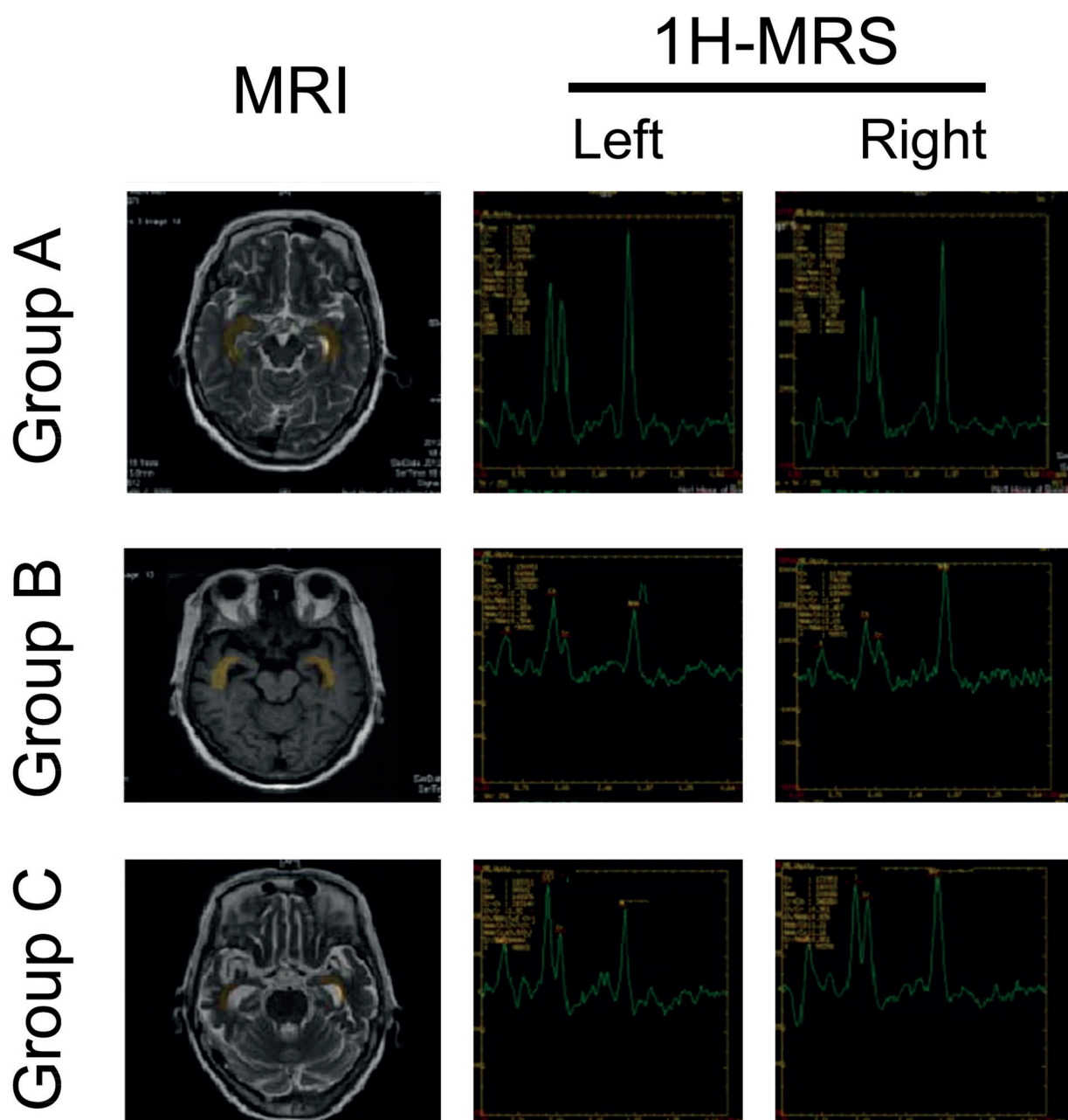


Figure 5. Bilateral medial temporal lobe conventional MRI and 1H-MRS wave spectrum in 3 different groups.

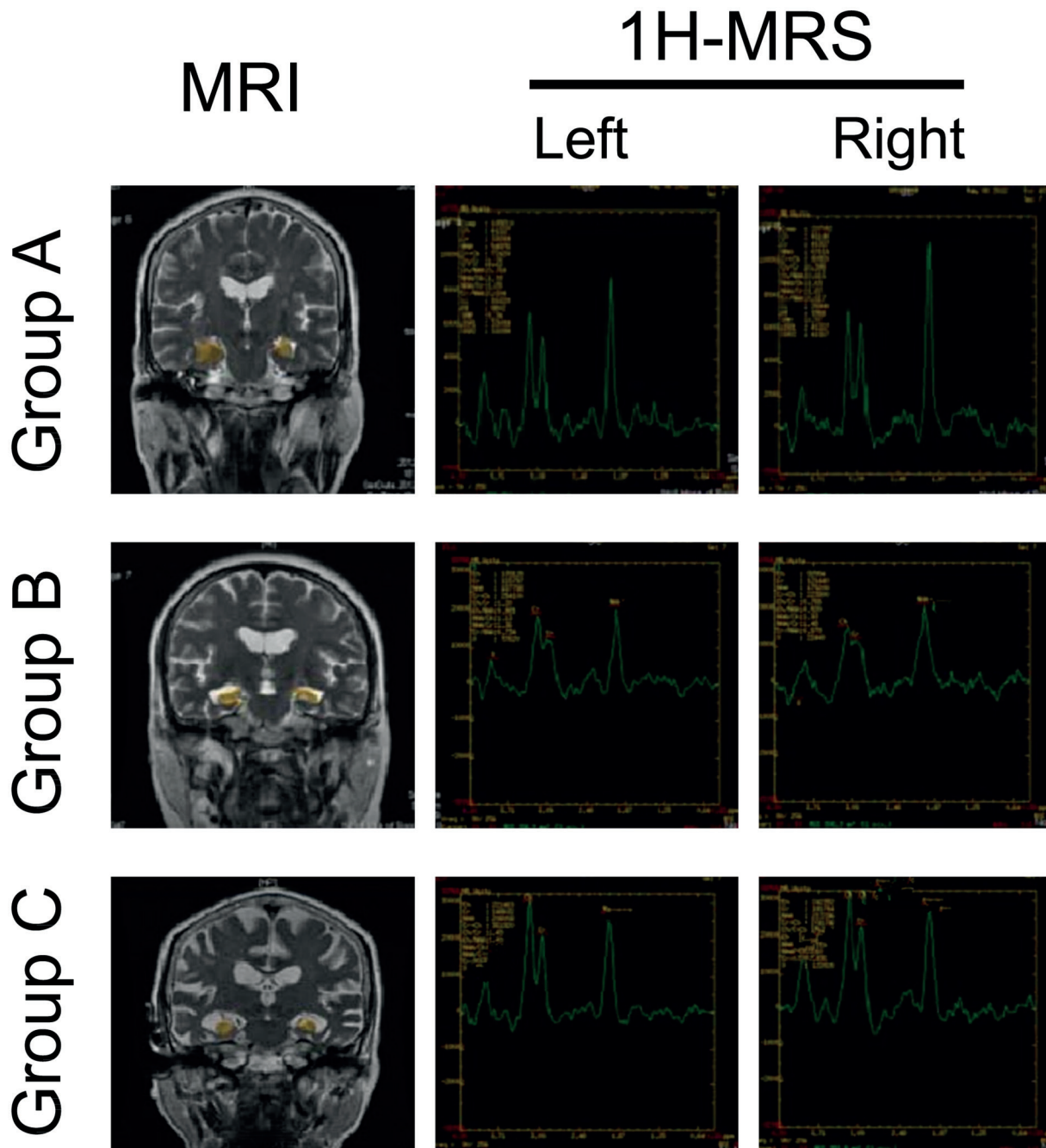


Figure 6. Bilateral hippocampus conventional MRI and 1H-MRS wave spectrum in 3 different groups.

Comparison of Disease Development and Prognosis in the Three Groups

The survival rates in group C were significantly higher than that of group A and B ($p < 0.05$). The incidence of the sequel was significantly lower than that of group A and B ($p < 0.05$) (Table I).

Correlation Analysis Between Peripheral Blood 8-iso-PGF $_{2\alpha}$ Levels and the Amount of Bleeding

The amount of bleeding in intracranial hemorrhage children was positively correlated with peripheral blood 8-iso-PGF $_{2\alpha}$ levels ($r = 0.546$, $p < 0.05$), as shown in Figure 7.

Table I. Comparison of disease development and prognosis in the three groups (examples).

| Group | No. | Death | Giving up treatment | Survival | Remaining sequela |
|-------|-----|-------|---------------------|-------------------|-------------------|
| A | 30 | 7 | 6 | 17 | 12 |
| B | 30 | 5 | 5 | 20 ^a | 9 ^a |
| C | 30 | 3 | 2 | 25 ^{a,b} | 6 ^{a,b} |

Note: Compared with group A, ^a $p < 0.05$; Compared with group B, ^b $p < 0.05$.

Discussion

Infant intracranial hemorrhage belongs to a common nerve injury disease in pediatrics. The main causes responsible for this pathological state included birth trauma, anoxia and suffocation¹¹⁻¹³. If the condition is serious, it leads to irreversible brain damages via intracranial hemorrhage. The above pathological state further results in cognitive dysfunction and movement disorders, affecting life quality of both children as well as their parents¹⁴. Late Vitamin K Deficiency Bleeding (LVKDB) is the main causative factor responsible for this deadly pathological state. It did so by lowering the activity of prothrombin, which leads to spontaneous intracranial hemorrhage¹⁵.

Related studies have shown that¹⁶ 8-iso-PGF₂α levels could reflect the lipid peroxidation after human ischemia reperfusion, and could be used for the assessment of oxidation intensity of free radicals in the human body. At present, 8-iso-PGF₂α level changes in neonatal cord blood are clear, but there are fewer reports on 8-iso-PGF₂α level changes during intracranial

hemorrhage in variable parts of infants. The present study showed that 8-iso-PGF₂α levels of group A, B, and C on the day of admission had no statistical significance ($p > 0.05$). However, 8-iso-PGF₂α levels of the three groups showed a significant declining trend in peripheral blood after the 1st, 2nd, 3rd and 7th d of hospital stay. Further, the declining range of group C was better than that of group A and B ($p < 0.05$). Post-treatment results also showed a declining trend in the levels of 8-iso-PGF₂α levels in both group B (minimal invasive puncture) and C. It could be inferred from above results that 8-iso-PGF₂α levels play an important role in the pathogenesis of intracerebral hemorrhage in infants. At the same time, the present study also confirmed that the amount of bleeding in intracranial hemorrhage affecting children was positively correlated with 8-iso-PGF₂α levels in peripheral blood ($r = 0.546$, $p < 0.05$) as observed by Spearman correlation analysis. So, peripheral blood 8-iso-PGF₂α levels are beneficial for the early diagnosis and timely treatment of children with intracranial hemorrhage.

MRS has the ability to analyze quantitatively the multiple trace metabolites in tissues, and could judge the local tissue metabolism and biochemical changes of nervous system^{17,18}. 1H-MRS is the preferred option for the quantitative assessment of metabolites in human brain tissue non-invasively^{19,20}. The present work also utilized above technology and showed that there were significant differences in the levels of NAA/Cr, Cho/Cr, mI/Cr, NAA/mI between bilateral medial temporal lobes and hippocampus in group A, B and C ($p < 0.05$). This signified the utilization of NAA/Cr, Cho/Cr, mI, NAA/Cr/mI for the diagnosis, identification and prognosis of intracranial hemorrhage in infants.

Further, the analysis of patients' disease development and prognosis observed that the survival rate in group C was significantly higher than that in group A and B ($p < 0.05$). On the other hand, the prevalence of sequela in group C was lower

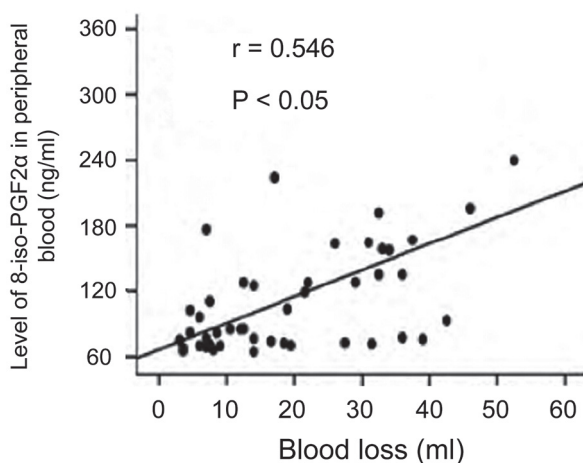


Figure 7. Correlation analysis between 8-iso-PGF₂α level in peripheral blood and blood loss.

than that in group A and B ($p < 0.05$). Thus, intraventricular hemorrhage cerebrospinal fluid decompression treatment had outstanding effects on children with intracranial hemorrhage.

Conclusions

8-iso-PGF 2α levels play an important role in the pathogenesis of intracranial hemorrhage and could be used for the early diagnosis and timely treatment. Further, intraventricular hemorrhage cerebrospinal fluid decompression treatment is a better treatment option with minimal invasion.

Acknowledgements

This study was supported by Grant No. KC15SH037.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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