

Original Article

Ultrasound findings of mild neonatal periventricular-intraventricular hemorrhage after different treatments

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Abstract: Objective: To investigate the ultrasound findings of mild neonatal periventricular-intraventricular hemorrhage (PIVH) after different treatments, and to evaluate the neurological outcomes of mild PIVH with Gesell Development Diagnosis Scale (GDDS). Methods: A total of 194 newborns with grade I-II PIVH were recruited, and findings of cranial ultrasound examination before and 1 month after birth were included for analysis. The echo intensity and size of the lesions were recorded. Results: There was no significant difference in the echo intensity among three groups of grade I PIVH patients ($P>0.05$). There was significant difference in the echo intensity among three groups of grade II PIVH patients, and the ganglioside had the best therapeutic efficacy ($P<0.05$). No significant difference was observed in the area change among three groups of grade I PIVH patients ($P>0.05$). However, significant difference was observed in the area change among three groups of grade II PIVH patients, and ganglioside had a better efficacy than cerebrolysin and control agent ($P<0.05$), but there was no significant difference between cerebrolysin and control groups ($P>0.05$). GDDS evaluation showed no significant difference among three groups ($P>0.05$), and all the patients recovered completely. Conclusion: The efficacy of different treatments for mild PIVH can be reflected in the ultrasound findings. Mild PIVH children generally have a good neurological prognosis.

Keywords: Periventricular-intraventricular hemorrhage, Gesell Development Diagnosis Scale, neonatal, ultrasound

Introduction

Periventricular-intraventricular hemorrhage (PIVH) has the highest incidence among neonatal intracranial hemorrhagic diseases, and severe hemorrhage usually results in adverse neurodevelopment [1, 2]. There are a variety of methods used to detect the neonatal cranial lesions, such as computed tomography (CT), magnetic resonance imaging (MRI) and ultrasonography [3, 4]. With the development of neonatal cranial ultrasound technology, cranial ultrasound has become an important means in screening PIVH in newborns. Ultrasound has many advantages such as convenience, dynamic observation and no radiation. It has a high sensitivity in the diagnosis of subependymal hemorrhage and intraventricular hemorrhage [5-7]. At present, neonatal PIVH requires a comprehensive treatment. Gangliosides belong to a class of sialic acid-containing glycosphingolipid that is widely

present in the cell membrane of vertebrates, especially in the brain of fetus and newborn infants. Ganglioside therefore plays a crucial role in the neuronal differentiation, neurite outgrowth, and synapse formation [8, 9]. Some studies have shown that ganglioside is the only nerve glycosides that can pass through the blood brain barrier (BBB) [9]. In recent years, its therapeutic effect on neonatal hypoxic-ischemic encephalopathy has been reported in clinical practice and animal studies [10, 11], but its effect on neonatal PIVH is less reported. Due to the progression of diagnostic imaging methods, the clinical diagnosis rate of PIVH is increasing. The symptoms of neonatal PIVH are various, and it was reported that about 25%-50% PIVH children were not diagnosed due to absence of evident symptoms. Recently, long-term follow-up and investigations have pointed out that PIVH children have risk for cerebral palsy, mental retardation and other significant adverse

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Table 1. General information of children in three groups

Item	Control group (n=63)	Ganglioside group (n=60)	Cerebrolysin group (n=71)	P value
Gestational age (weeks)	35.8 ± 3.9	36.6 ± 2.5	37.1 ± 3.2	0.342
Birth weight (g)	2915.2 ± 883.6	2915.2 ± 883.6	2778.6 ± 689.6	0.968
Asphyxia degree (n, %)				
Mild	43, 68.3%	42, 70%	48, 67.6%	0.075
Severe	20, 31.7%	18, 30%	23, 32.4%	0.067

outcomes in school age and adolescence, even they have mild PIVH [12]. Thus, some investigators concern about whether PIVH affects the children's intellectual development. Currently, there are a variety of methods used to evaluate the intellectual development of children, such as the Wechsler scale, Raven's Standard Progressive Matrices, Bayley Scales of Infant Development, and Gesell Development Diagnosis Scale (GDDS). In the present study, the ultrasound findings of grade I-II PIVH before and after different treatments were evaluated, and GDDS scores were employed for the assessment of therapeutic outcomes.

Materials and methods

General information

Patients who were hospitalized in the Department of Neonatology of the First Affiliated Hospital of Guangxi Medical University between May 2012 and August 2014 were recruited into present study. Inclusion criteria: asphyxia of varying degrees, initial cranial ultrasound examination within 7 days after birth, cranial ultrasound examination showing grade I-II PIVH (mild PIVH, Papile's classification), a second cranial ultrasound examination performed after therapy and GDDS available at 1 month after birth. Exclusion criteria: Concomitant primary diseases. A total of 194 newborns (105 boys, 89 girls) with a total of 350 lesions were included for final analysis.

The gestational age at birth, birth weight and asphyxia degree were recorded. In this study, gestational age at birth was 28 to 41 weeks (mean: 36 ± 3 weeks). There were 58 preterm children and 101 full-term children. The birth weight was 1100-4190 g (average: 2768.1 ± 790.8 g). There were 65 low birth weight children and 129 normal birth weight children. A total of 133 children had mild asphyxia and 61 had severe asphyxia. There were no significant differences in the gestational age, birth weight and asphyxia degree among three groups

($P > 0.05$, **Table 1**). The effects of different treatments were comparable in the present study.

Diagnostic criteria

PIVH neonate were classified into grade I-II according to the Papile's classification [13]: Grade I: subependymal (germinal matrix) hemorrhage; Grade II: Hemorrhage extending to the ventricular system and occupying <50% of one lateral ventricle; no acute ventriculomegaly. According to the findings of cranial ultrasound and treatments, PIVH neonates were divided into following groups: A group was 51 grade I PIVH patients treated with ganglioside treatment (14.5%); B group was 48 grade II PIVH patients treated with ganglioside treatment (13.7%); C group was 74 grade I PIVH patients treated with cerebrolysin (21.1%); D group was 73 grade II PIVH patients treated with cerebrolysin (20.9%); E group was 52 grade I PIVH patients received support therapy alone (14.9%); F group was 52 grade II PIVH patients received support therapy alone (14.9%).

Instruments and methods

Protocol for ultrasonography: Routine cranial ultrasonography was performed by technicians using a portable, real time scanner (GE LOGIQ E9, US) with a digital high frequency transducers (9 MHz). Ultrasound scanning was done at six standard quasi-coronal views and five sagittal views through the anterior fontanel as the sonographic window [14]. The ultrasound examination was performed within 7 days and 1 month after birth, the echo intensity and size on the largest section of the lesion was recorded, and the ultrasound findings were compared among groups.

Treatment: same symptomatic and supportive treatments were given before ultrasound examination (maintaining a neutral temperature, normal breathing, blood glucose, blood pressure, acid-base balance, and reducing cerebral edema treatment, etc). On the first day after the

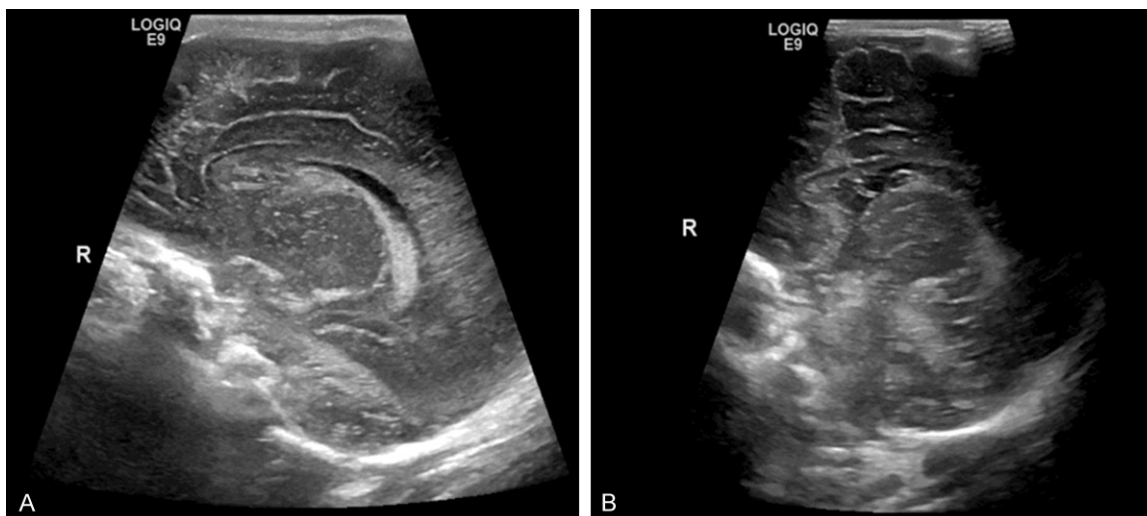


Figure 1. Ganglioside group: A preterm infant (female) with the gestational age at birth of 34⁺⁴ weeks and birth weight of 2450 g. A. Grade I PIVH lesion in the right thalamic-caudate groove was hyperechoic on the 4th day after birth and had a size of 0.74 cm × 0.34 cm on the largest section. B. Grade I PIVH lesion in the right thalamic-caudate groove was echoless on the 30th day after birth and had a size of 0.64 cm × 0.30 cm on the largest section.

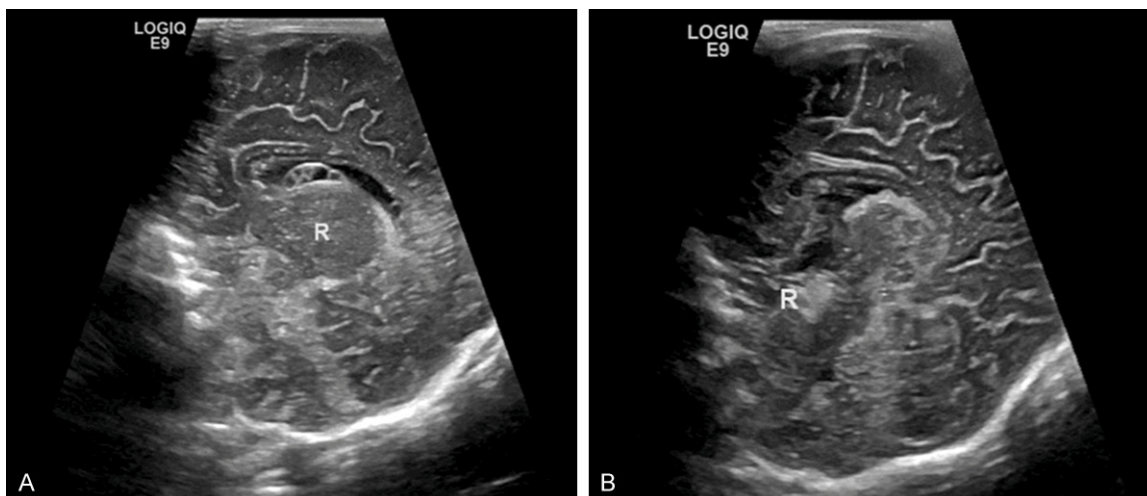


Figure 2. Cerebrolysin group: A neonate (male) with the gestational age at birth of 40⁺⁵ weeks and birth weight of 3050 g. A. Grade I PIVH lesion in the right thalamic-caudate groove was echoless on the 3th day after birth and had a size of 1.60 cm × 0.49 cm on the largest section. B. Grade I PIVH lesion disappeared on the 34th day after birth.

diagnosis of PIVH by ultrasound examination, patients of ganglioside groups received mono-sialotetrahexosyl ganglioside sodium injection (H20120458) at 20 mg once daily; patients of cerebrolysin groups received cerebrolysin injection (H20100440) at 0.03 g once daily; patients of control groups received intravenous 20 ml of 5% glucose solution injection daily. Treatments were performed for 14 days in one course.

Gesell Development Diagnosis Scale [15]: Professional psychologist evaluated the adaptability, gross motor movement, fine movement and

social contact abilities of the children. The developmental quotient (DQ) scores were recorded for analysis. GDDS results were expressed as DQ. DQ of ≥76 was normal, DQ of 55-75 showed mild retardation, DQ of 40-54 indicated moderate retardation and DQ of ≤39 suggested severe retardation.

Curative effect evaluation

The lesion size was measured at two examinations, and the therapeutic efficacy was assessed by the change in the lesion area. The

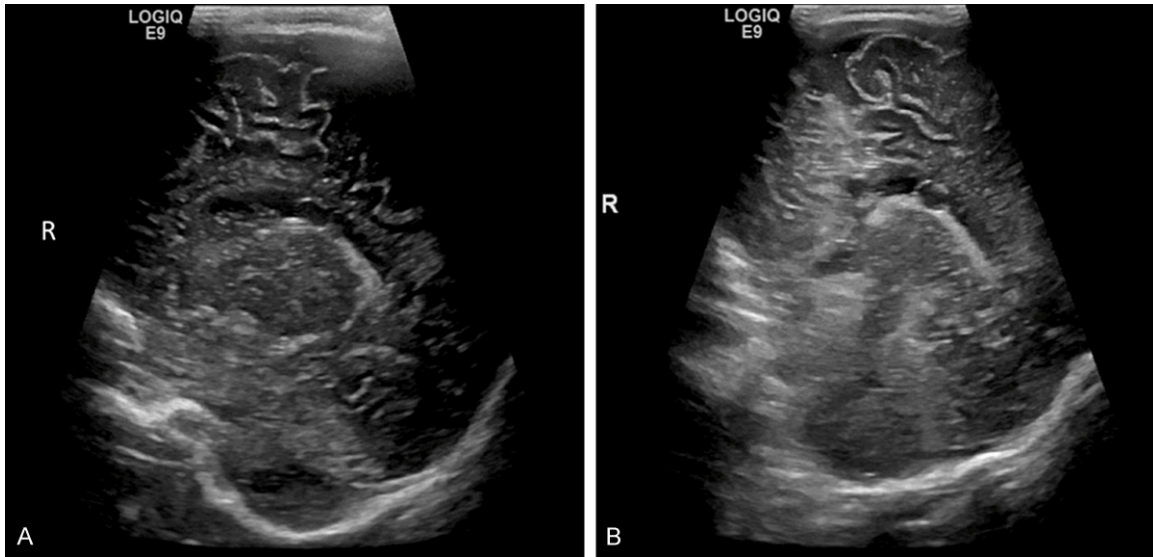


Figure 3. Control group: A preterm infant (female) with the gestational age at birth of 34^{+1} weeks and birth weight of 2200 g. A. Grade I PIVH lesion in the right thalamic-caudate groove was echoless on the 4th day after birth and had a size of 1.02 cm × 0.80 cm on the largest section. B. Grade I PIVH lesion in the right thalamic-caudate groove was echoless on the 32th day after birth and had a size of 1.01 cm × 0.61 cm on the largest section.

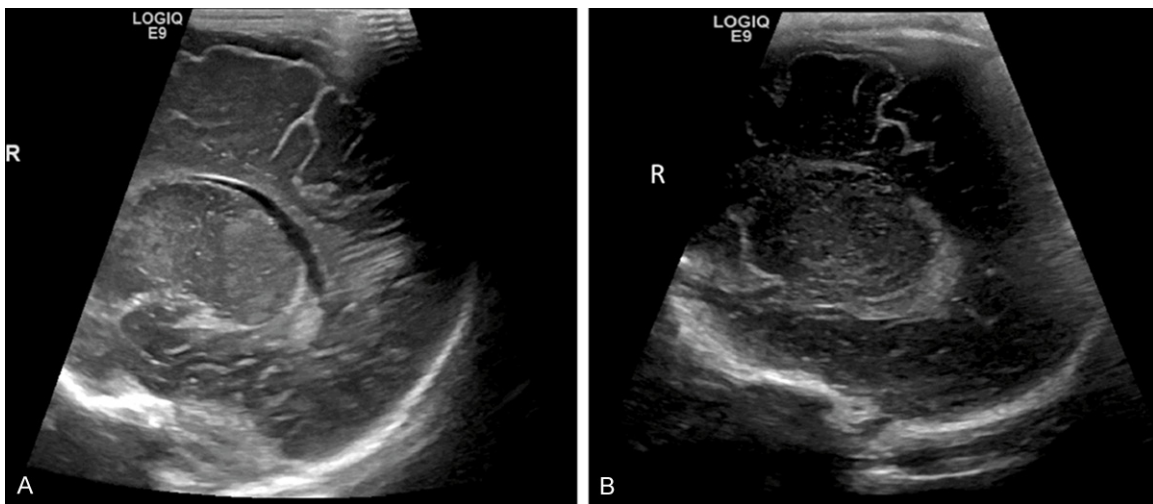


Figure 4. Ganglioside group: A preterm infant (male) with gestational age at birth of 35^{+2} weeks and birth weight of 2300 g. A. Grade II PIVH lesion in the right choroid plexus was hyperechoic on the 6th day after birth and had a size of 0.58 × 0.43 cm on the largest section. B. Grade II PIVH lesion disappeared on the 33th day after birth.

data were expressed as count data. For grade I PIVH lesions, the therapy was considered as “valid” when grade I PIVH lesion changed from hyperechoic area (first diagnosis) to echoless area (second diagnosis) (**Figure 1A, 1B**) or grade I PIVH lesion changed from echoless area (first diagnosis) to disappearance (second diagnosis) (**Figure 2A, 2B**); the therapy was considered as “invalid” when there was no significant change in echo intensity (**Figure 3A, 3B**). For grade II PIVH lesions, the therapy was

considered as “valid” when grade II PIVH lesion changed from hyperechoic area (first diagnosis) to disappearance (second diagnosis) (**Figure 4A, 4B**); the therapy was considered as “less valid” when grade II PIVH lesion changed from hyperechoic area (first diagnosis) to hypoechoic area (second diagnosis) (**Figure 5A, 5B**); the efficacy was considered as “invalid” when there was no significant change in echo intensity (**Figure 6A, 6B**). The data were expressed as ranked data.

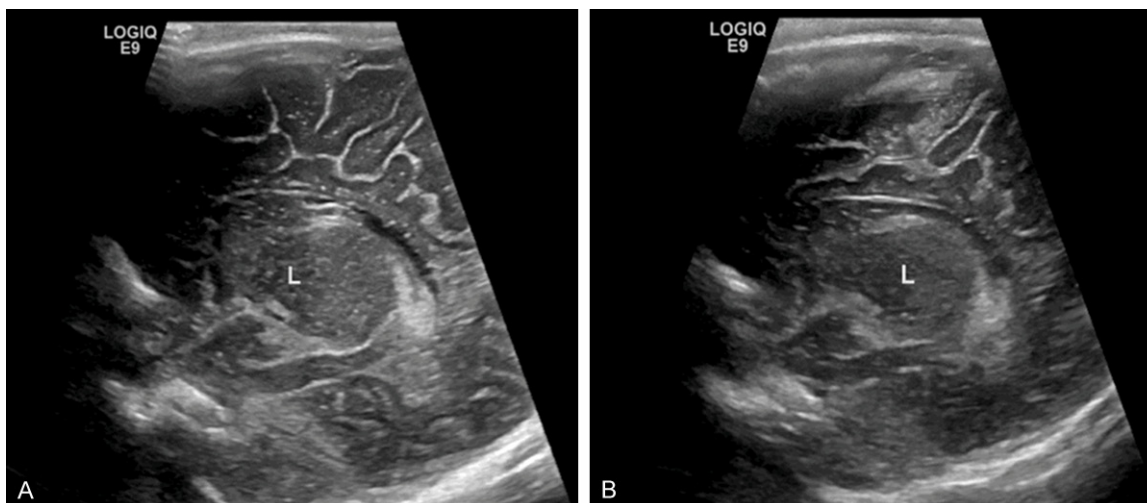


Figure 5. Cerebrolysin group: A neonate (female) with the gestational age at birth of 39⁺⁴ weeks and birth weight of 2950 g. A. Grade II PIVH lesion in the left choroid plexus was hyperechoic on the 5th day after birth and had a size of 1.08 cm×0.46 cm on the largest section. B. Grade II PIVH lesion in the left choroid plexus was hypoechoic on the 31th day after birth, and had a size of 0.94 cm×0.39 cm on the largest section.

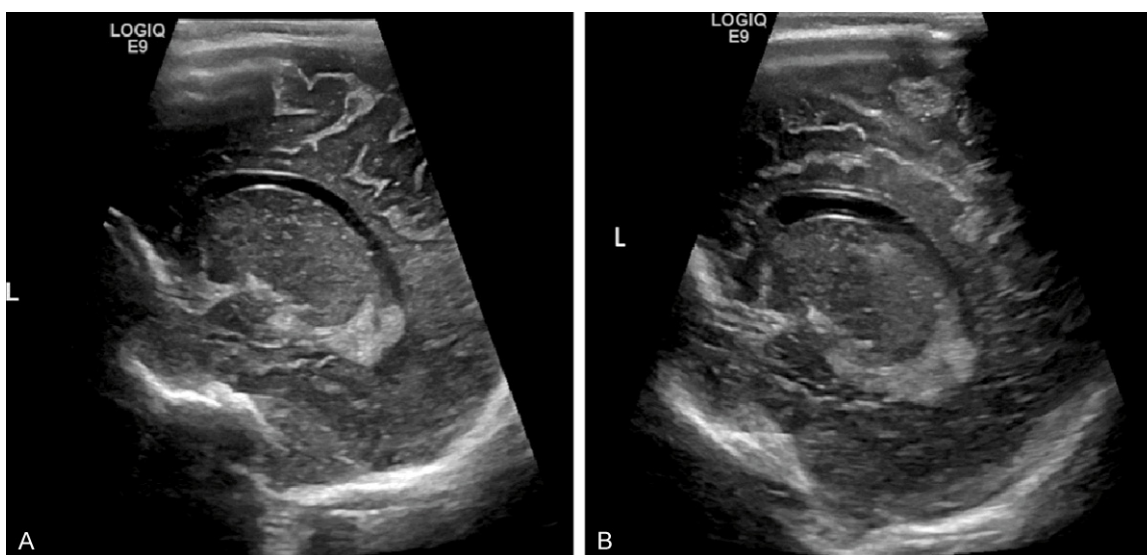


Figure 6. Control group: A neonate (male) with the gestational age at birth of 41⁺¹ weeks and birth weight of 3200 g. A. Grade II PIVH lesion in the left choroid plexus was hyperechoic on the 4th day after birth and had a size of 0.90 × 0.78 cm on the largest section. B. Grade II PIVH lesion in the left choroid plexus was still hyperechoic on the 34th day after birth, and had a size of 0.85 cm × 0.73 cm on the largest section.

Statistical analysis

For ranked data, a completely randomized design rank test was applied for comparison and a value of $P < 0.05$ was considered statistically significant.

Count data are expressed as means \pm standard deviation. Completely randomized design analysis of variance and SNK test were applied

for comparisons and a value of $P < 0.05$ was considered statistically significant.

Results

PIVH lesions

A total of 177 grade I PIVH lesions were assessed in this study. For 51 lesions in ganglioside group, 6 changed from hyperechoic area

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Table 2. Changes in echo intensity in grade I PIVH groups

Efficacy	Ganglioside group (n, %)	Cerebrolysin group (n, %)	Control group (n, %)	X	P
Valid	14, 27.5%	23, 31.1%	20, 38.5%	1.053	0.472*
Invalid	37, 72.5%	51, 68.9%	32, 61.5%		

Footnote: *A completely randomized design rank test was applied for ranked data comparison in the grade I PIVH groups. The echo intensity changes were not statistically significant in the grade I PIVH groups.

Table 3. Therapeutic efficacy in grade II PIVH groups

Efficacy	Ganglioside group (n, %)	Cerebrolysin group (n, %)	Control group (n, %)	P
Valid	9, 18.8%	2, 2.7%	2, 3.8%	0.002*
Less valid	12, 25.0%	13, 17.8%	4, 7.7%	
Invalid	27, 56.2%	58, 79.5%	46, 88.5%	
Mean Rank	65.12	85.42	88.37	

Footnotes: *A completely randomized design rank test was applied for ranked data comparison in the grade II PIVH groups. The lower values of the mean rank meant a better curative effect of the group: Ganglioside group > Cerebrolysin group > Control group.

(first diagnosis) to echoless area (second diagnosis), 8 from echoless area (first diagnosis) to disappearance (second diagnosis) and 37 remained unchanged in echo intensity. For 74 lesions in cerebrolysin group, 9 changed from hyperechoic area (first diagnosis) to echoless area (second diagnosis), 14 from echoless area (first diagnosis) to disappearance (second diagnosis) and 51 remained unchanged in echo intensity. For 52 lesions in control group, 6 changed from hyperechoic area (first diagnosis) to echoless area (second diagnosis), 14 changed from echoless area (first diagnosis) to disappearance (second diagnosis) and 32 remained unchanged in echo intensity.

A total of 173 grade II PIVH lesions were evaluated in this study. For 48 lesions in ganglioside group, 9 changed from hyperechoic area (first diagnosis) to disappearance (second diagnosis), 12 from hyperechoic area (first diagnosis) to hypoechoic area (second diagnosis) and 27 remained unchanged in echo intensity. For 73 lesions in cerebrolysin group, 2 changed from hyperechoic area (first diagnosis) to disappearance (second diagnosis), 13 from hyperechoic area (first diagnosis) to hypoechoic area (second diagnosis) and 58 remained unchanged in echo intensity. For 52 lesions in control group, 2 changed from hyperechoic area (first diagnosis) to disappearance (second diagnosis), 4 from hyperechoic area (first diagnosis) to hypo-

echoic area (second diagnosis) and 46 remained unchanged in echo intensity.

Therapeutic efficacy

In grade I PIVH groups, there was no significant difference in the changes in echo intensity among A, C and E groups ($P > 0.05$, **Table 2**). In grade II PIVH groups, significant difference in the changes of echo intensity was observed among B, D and F groups, and ganglioside had the best therapeutic efficacy, followed by cerebrolysin therapy and support therapy ($P < 0.05$, **Table 3**).

For the changes in lesion area of grade I PIVH groups, there was no significant difference among A, C and E groups ($P > 0.05$). For the changes in lesion area of grade II PIVH groups, there was marked difference among B, D and F groups (SNK test) and ganglioside had better efficacy than cerebrolysin therapy and support therapy ($P < 0.05$), but the therapeutic efficacy was comparable between cerebrolysin group and control group ($P < 0.05$, **Table 4**).

GDSS scores

GDSS scoring was conducted 1 month after birth. Results showed that there was no significant difference in the DQ among three groups ($P > 0.05$), and the DQ of all children reached a normal level (detailed in **Table 5**).

Discussion

PIVH is a relatively common disease for neonates in perinatal period. With the improvement of medical techniques, the survival rate of newborns is increasing, the mortality of premature and neonates with abnormal perinatal history are decreasing, however, the incidence of brain dysfunction in the survivor is still on the rise.

Cranial CT, MRI and ultrasound are the major tools used for the diagnosis of PIVH. However, CT and MRI have lower diagnostic specificity and sensitivity due to the location, size or other factors of the lesions [16]. With the advantages like less cost, no radiation, continuous scanning of the ventricular system, dynamic obser-

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Table 4. Changes in lesion area of different groups

	Lesion area (cm ²)			F	P
	Ganglioside group	Cerebrolysin group	Control group		
Grade I PIVH	0.33 ± 0.49	0.25 ± 0.37	0.24 ± 0.25	0.913	0.403
Grade II PIVH	0.26 ± 0.35	0.12 ± 0.31	0.44 ± 0.23	6.7	0.002*

Footnotes: *Completely randomized design analysis of variance and SNK test were applied for comparisons of the changes in lesion area. The lesion area changes in grade II PIVH groups were statistically significant: Ganglioside group > Cerebrolysin group > Control group.

Table 5. GDDS score of different treatment groups

Score	Control group (n=63)	Ganglioside group (n=60)	Cerebrolysin group (n=71)	P value
Adaptability	86.69 ± 15.77	86.50 ± 14.27	87.42 ± 16.88	0.706
Gross motor movement	89.07 ± 13.07	90.39 ± 12.01	91.68 ± 12.55	0.518
Fine movement	90.57 ± 12.39	89.63 ± 13.58	90.63 ± 15.76	0.712
Social contact	90.97 ± 11.87	89.91 ± 12.55	88.13 ± 11.26	0.405

Footnotes: The differences of the GDDS score in the three groups were not statistically significant.

vation and bedside application, cranial ultrasound has become a non-substitutable tool for the detection of neonatal intracranial lesions.

Currently, neonatal PIVH treatment required a comprehensive treatment which is still controversial, especially in mild PIVH. The supportive treatments include oxygen supply, maintenance of blood glucose, use of hemostatic agents, increasing intracranial pressure, and reducing movement. The treatment also includes the use of cerebrolysin and citicoline to protect brain cells, as well involves the introduction of the special nerve growth factor like ganglioside, which plays a key role in repairing damaged central nervous system. In addition, there are invasive treatments such as puncture and surgery. This study was to investigate the ultrasound findings of PIVH after different treatments. The therapeutic effect of ganglioside on the neonatal hypoxic-ischemic encephalopathy has been reported in previous studies, but its efficacy on neonatal PIVH is less studied. As an imported drug in China, ganglioside is relatively expensive and currently has prudent application in clinical practice. However, for mild PIVH, to our knowledge, the prognosis is usually good, and whether special pharmacotherapy is needed remains controversial.

In this study, ultrasound was employed for the detection of neonatal PIVH. Wen et al [17] found that the incidence of PIVH in high risk infants was 92% in utero, intrapartum or 1 day after birth, and the remaining percenta-

ge of PIVH occurred within 1-3 days after birth; more than 90% of PIVH could be identified within 4-5 days after birth. In this study, the initial ultrasound examination was done one week after birth, when the incidence newborn PIVH is high, and the lesions can be clearly identified.

Grade I PIVH is originated from the germinal matrix, especially in preterm neonates. The germinal matrix is present in 24-32 weeks fetus. It is an

immature thin-walled capillary network locating in the thalamic-caudate groove between caudate nucleus and thalamus. Approximately 30-55% of germinal matrix hemorrhage occurs in newborns less than 32 weeks in gestational age or lower than 1500 g in birth weight [7]. This subependymal hemorrhagic remain isolated or may expand into the lateral ventricle. Ultrasonography shows focal hyperechoic area locating in the thalamic-caudate groove between caudate nucleus and thalamus. When the subependymal hemorrhage begins to absorb, ultrasonography shows focal hypoechoic area or echoless area surrounding by hyperechoic line. Large hemorrhage may narrow and deform the anterior horn lateral ventricular. Neonates with isolated grade I PIVH generally have no obvious clinical symptoms or abnormal perinatal history. This hemorrhage has relatively good prognosis and no significant neurological sequelae.

Grade II PIVH might be isolated or developed from grade I PIVH. Ultrasonography shows focal hyperechoic area, located in the choroid plexus triangular, which may occupy partially or completely the entire lateral ventricle. Ultrasonography also shows significant thickening (usually >1.20 cm), extension or surface roughness of the choroid plexus. Neurological outcome is generally good.

The natural absorption, liquefaction and formation of grade I PIVH cysts usually take about 2-3 weeks. In the present study, the changes in

echo intensity and size of lesions in each treatment group, and there was no significant difference among each group for grade I PIVH patients ($P>0.05$). This means that, for the mild PIVH, general supportive therapy in the liquefaction and absorption periods is sufficient.

However, the absorption period of grade II PIVH is generally longer. Fresh hemorrhagic lesions appear hyperechoic, and reduction in echo intensity means that the lesions are entering the absorption and remission stage. In this study, the changes in echo intensity were compared among patients with grade II lesions. Results showed that ganglioside had the best therapeutic efficacy, followed by cerebrolysin therapy and support treatment ($P<0.05$). The changes in lesion size were also compared among three groups, and results revealed that the therapeutic efficacy of ganglioside was better than that in other two groups ($P<0.05$), while there was significant difference between cerebrolysin group and control group ($P>0.05$). It demonstrates that, for grade II PIVH, there is a longer absorption period, and pharmacotherapeutic interventions are important adjuvant strategies. Ganglioside is a nerve growth factor with significant effect, and can be used according to the actual situation of children.

In the present study, GDDS scoring showed that mild PIVH children generally had good neurological outcomes. DQ scores in each group were above the normal level, and differences in the DQ scores were not observed among three groups ($P>0.05$). Kang et al [18] investigated 22 PIVH premature infants treated with ganglioside by neonatal behavioral neurological assessment, and found that ganglioside could improve the neurological behaviors and neuro-motor symptoms of PIVH. The sample size of Kang's study was small as in our study. The effect of ganglioside on the neurological outcomes still is needed to confirm in more clinical investigations with large sample size and longer follow-up period.

There are several issues in this study that need further exploration. Firstly, unlike in CT and MRI, standard sections of ultrasonography are usually controlled manually, and thus it is not easy to control the accuracy of measurement. Although there are relatively standard sections for ultrasonography, the detection is easier to be affected by human factors to some extents.

The determination of echo intensity and lesion size varies among investigators. In the present study, a number of methods were employed for quality control: a doctor with rich experience in ultrasound examination performed ultrasonography, and the determination of echo intensity and measurement of lesion size had relatively uniform standards; the largest section of the lesions was used for assessments and measurements, and three measurements were done for averages; the ultrasound images were two-dimensional, but the hemorrhagic lesions were three-dimensional, which might make the lesion size measurements incomplete. In clinical application, three-dimensional ultrasound can be considered for accurate assessments and measurements.

Conclusion

The efficacy of different treatments for mild PIVH can be reflected by ultrasound findings. Mild PIVH children generally have a good neurological prognosis.

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Disclosure of conflict of interest

None.

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