BIOCELL
2019 43(1): 7-11

ISSN 1667-5746 (on-line)
ISSN 0327-9545 (printed)

Meta-analysis evaluation of the treatment of neonatal hypoxic–ischemic encephalopathy with ganglioside

Wen LI; Junli YANG; Dong ZHOU; Jinghui ZHANG; Qingcui ZHUO

Department of Pediatrics, Qilu Hospital of Shandong University, Jinan, 250012, China

Key words: Ganglioside, Hypoxic–ischemic encephalopathy, Meta-analysis, Neonate

Abstract: The efficacy and safety of ganglioside in the treatment of neonates who suffer from hypoxic–ischemic encephalopathy (HIE) needs to be fully evaluated. We searched the following databases: PubMed, ScienceDirect, LISTA, CNKI, Chinese biomedical literature database and Wanfang digital journals of full-text database to determine the inclusion and exclusion criteria of papers and a total of 12 papers were included after quality evaluation. Then we conducted the meta-analysis with RevMan5.0 software. The results showed that compared with the control group, the abnormal rate declined in the ganglioside-treated group (relative risk (RR)=0.27, 95% confidence interval (CI)= 0.05–1.96). NBNA records of the 7, 10–14d neonates were improved effectively: RR (95% CI) were 2.28 (0.86–3.42) and 2.53 (1.04–2.92) respectively. Neural system sequelae incidence was reduced significantly: RR (95% CI) = 0.35: (0.15–0.79). Ganglioside treatment could effectively reduce the abnormality rate of head size, improve the neurological score, reduce the incidence of neurological sequelae, and significantly prompt clinical recovery for neonates with HIE.

Introduction

Neonatal hypoxic–ischemic encephalopathy (HIE) is a serious complication of neonatal asphyxia, which could cause neonatal cerebral palsy, chronic neurological damage of mental dysplasia, and even lead to death (Li and Yin, 2005). The pathogenesis of HIE is complicated, because apoptosis, NO synthesis, oxygen free radical, excitatory amino acid, and other physiological or biochemical mechanisms may be involved (Wu, 2003). To date, there are no accepted neuroprotective agents with definite clinical effects in clinical practices. The main therapeutic strategies to treat HIE rely on neuroprotective drugs that can relieve the functional nerve injury and the reduction of the rate of sequelae.

Studies have found that gangliosides, as a neurotrophic factor enhancer are present normally in the mammalian cell membrane and play important roles in hypoxic–ischemic brain damage with functions of protecting cell membrane, antagonizing the neurotoxicity of excitatory amino and also promoting the recovery of neural function (Palmano *et al.*, 2015; Sheng and Li, 2017). Gangliosides are thought to significantly participate in maintaining the self-renewal capacity of neural stem cells, and hence neurogenesis, through sustaining EFG-induced EFGR signaling byinteracting EFGR in lipid raft micro domains (Wang and Yu, 2013). It has been reported that gangliosides are involved in modulating the ion channel function and receptor signal transduction, both of which are vital functions of neuronal excitability and synaptic transmission (Nowycky *et al.*, 2014). Gangliosides have been also shown to play key roles in activity-dependent long time potentiation in CA1 neurons of guinea pig hippocampal slices by modulating NMDA receptors/Ca^{2+} channels (Fujii *et al.*, 2002). The development of neonatal blood brain barrier is not complete, so exogenous gangliosides could cross the blood-brain barrier easily to regulate regeneration, differentiation of neurons, and repair of damaged neurons.

It has been indicated that treatment with gangliosides could strengthen efficacy and improve the prognosis (Mu, 2011; Lin and Geng, 2011). Currently gangliosides have been widely used in the treatment of HIE, but there are also some limitations such as expensive prices, empirical uses, and uncertain efficacy (Huang, 2011). This paper evaluated the efficacy and safety of gangliosides in the treatment of HIE systematically by Meta-analysis, hoping to provide theoretical bases and reference in clinical application of gangliosides.

Material and Methods

Inclusion and exclusion criteria

Inclusion criteria: Admitting neonates who suffered from hypoxic-ischemic encephalopathy was performed according to the diagnostic criteria that have been established by the Chinese Medical Science Society (Han, 1997) with no race, nationality, gender or age requirements.

*Address correspondence to: Wen Li,
wenliwll@sina.com

Exclusion criteria: Neonates who suffered from congenital malformation, intracranial hemorrhage, meningitis, other inherited metabolic diseases or were exposed to gangliosides 1-2 weeks before delivery.

All the papers included in this study met the following criteria: 1. Similar research hypotheses and methods. 2. Definite beginning time of studies or publication. 3. Explicit stipulation in sample size. 4. Clear criteria for patient selection, diagnosis and staging of cases. Definite measures of intervention and control. 5. Studies providing odd ratio (OR), relative risk (RR), rate variance (RV), hazard rate (HR) and 95% confidence interval (CI), or transferable OR (RR, RV, HR) and 95% CI. Measurement data should provide the means, standard deviation and sample size. Research papers with the following features were excluded: 1. Repeated report. 2. Deficient study design and poor quality. 3. Incomplete data and unclear outcome effect. 4. False statistical method, and no OR (RR, RV, HR) and 95% CI or measurement data not providing the mean and standard deviation. Papers or reviews from which data could not be extracted were not included.

Paper collection

To retrieve foreign language databases with the keywords: hypoxic-ischemic encephalopathy, HIE, hypoxic–ischemic, gangliosides, brain and neonate. And to retrieval databases in China with the keywords: gangliosides, hypoxia ischemic encephalopathy, neonatal. Using a retrieval strategy of combination with subject headings and free terms, the related papers published from June 1985 to June 2015 were explored from databases of PubMed, ScienceDirect, LISTA, CNKI, Chinese biomedical literature database, and Wanfang Digital Full Text Database, as well as manual retrieval of *Chinese Journal of Practical Pediatrics*, *The Journal of Clinical Pediatrics*, *International Journal of Pediatrics* and other related magazines.

Treatment methods and indexes

Treatment group adopted ganglioside intravenous injection plus conventional therapy while the control group only received conventional treatment. Conventional treatment is based on the guidelines for Evidence-based treatment of Hypoxic-Ischemic Encephalopathy in term infants (2011) developed by key Laboratory of Neonatal Diseases of the Ministry of Health (www.cjebp.net), including oxygen inhalation, improving ventilation, relieving hypercapnia, improving acidosis, keeping heart rate and blood pressure normal, mild hypothermia for the treatment of moderate to severe HIE infants. The efficacy parameters included the abnormal rate of head computed tomography (CT), neonatal behavioral neurological assessment (NBNA) score, incidence of neurological sequelae, and adverse drug reactions (ADRs).

Data extraction and quality evaluation

First, two researchers with the ability of paper retrieval read paper titles, abstracts and experiment conclusions parts independently, and then extracted data from these papers according to the inclusion and exclusion criteria. If their opinions differed, decisions were made after their discussion or judged by a third party. The incomplete data could be supplemented by email or telephone contact with the original authors. The quality evaluation referred to the criteria of systematic evaluation manual Cochrane 5.0 RCT (Higgins and Green, 2008). Evaluation contents included the stochastic method, blind method, integrity of data and results.

Statistical analysis

Meta-analysis was performed using RevMan 5.0 software provided by Cochrane collaboration. Heterogeneity test followed by Chi-square test was conducted for extracted data. $P \geq 0.1$, $I^2 < 50\%$ indicated statistical homogeneity reliability and stochastic model analysis. Descriptive analysis was used when data could not be analyzed with meta-analysis. The abnormal rate of CT, NBNA score, and incidence of neurological sequelae were analyzed by using RR, and each statistic was represented by 95% CI.

Results

General information of the papers included in the study

There were 128 papers obtained from the preliminary search, 26 of which were retrieved from PubMed, 18 from ScienceDirect, 6 from LISTA, 54 from CNKI, 12 from Chinese biomedical paper database, and 12 from Wanfang digital journals of full-text database. According to the exclusion criteria, 12 papers were included. There were 563 cases in control groups and 578 cases in treatment groups in this study (Tab. 1).

Comparison of abnormal rate of head CT

Comparisons of abnormal rate of head CT were found in two searching items (Wen, 2011; Li and Yin, 2005) and there was no statistical heterogeneity between the two studies (P=0.69, I^2=0). The analysis of fixed effects model was adopted. The results showed that there was a statistically significant difference in the incidence of HIE between the two groups (RR=0.27, 95% CI: 0.05-1.96) (Tab. 2).

NBNA scores

There were two papers (Yan *et al.*, 2010; Zhu, 2010) that contained comparison of NBNA scores after treatment with gangliosides for 7 days, and six papers (Li and Yin, 2005; Yang, 2012; Wang, 2009; Zhao, 2012; Sun and Wang, 2013; Song *et al.*, 2009)' that included comparison of NBNA scores after treatment with gangliosides for 14 days. The doses of gangliosides varied among different papers. There was no statistical heterogeneity among the studies (P=0.69, I^2=0). The analyzed results showed that there were statistically significant differences in the incidence of HIE between the groups (Tab. 3).

Neurological sequelae

Comparisons of neurological sequelae incidence between treatment and control groups were found in two items of research (Xiang and Wang, 2005; Zeng, 2009) and there was no statistical heterogeneity between the two studies (P=0.73, I^2=0) with fixed effect model analysis. The results indicated that statistically significant differences in the incidence of neurological sequelae between the two groups (RR=0.35, 95% CI: 0.15-0.79), suggesting that the application of gangliosides could significantly reduce the occurrence of HIE in neonates with neurological sequelae (Tab. 4).

Adverse reactions

Three studies found no adverse reactions (Xiang and Wang, 2005; Zhao, 2012; Zhu, 2010) and adverse reactions were not mentioned in other studies.

TABLE 1
The general information of the papers included in the study

Papers	Samples		Treatment methods		Curative effect index
	Control group	Observation group	Control group	Observation group	
Yan CH[10]	30	30	conventional therapy	Gangliosides 20 mg plus conventional therapy, once-daily, 7-10d/course	NBNA score, curative effect
Yang HJ[11]	75	75	conventional therapy	Gangliosides 20 mg plus conventional therapy, once-daily, 7-10d/course	NBNA score
Li L[1]	20	20	conventional therapy	Gangliosides 20mg plus conventional therapy, once-daily, 10d/course	NBNA score, head CT
Wen BX[12]	30	30	conventional therapy	Gangliosides 20mg plus conventional therapy, once-daily, 10-14d/course	Effective rate
Wang LZ[13]	30	35	conventional therapy	Gangliosides 20mg plus conventional therapy, once-daily, 10-12d/course	10-14d, 28d NBNA score, abnormal rate of head CT
Xiang JJ[14]	30	36	conventional therapy	Gangliosides 20mg plus conventional therapy, once-daily, 7d/course	neurological sequelae, ADRs
Guo WB[15]	39	39	conventional therapy	Gangliosides 20mg plus conventional therapy, once-daily, 10d/course	curative effect,TNF-α,IL-6
Zhao YH[16]	55	55	conventional therapy	Gangliosides 20mg plus conventional therapy, once-daily, 10d/course	NBNA score, ADRs, overall response rate
Sun SX[17]	150	150	conventional therapy	Gangliosides 20mg plus conventional therapy, once-daily, 7,10-14d, 3-4weeks/course	14,28d NBNA score
Zhu YW[18]	26	28	conventional therapy	Gangliosides 20mg plus conventional therapy, once-daily, 10-14d/course	3,7,14d NBNA score, ADRs
Song H[19]	38	40	conventional therapy	Gangliosides 20mg plus conventional therapy, once-daily, 10-14d/course	10-14d NBNA score
Zeng L[20]	40	40	conventional therapy	Gangliosides 20mg plus conventional therapy, once-daily, 7d/course	case-fatality rate, Neurological sequelae

TABLE 2
Comparison of abnormal rate of head CT in neonates with HIE

Studies	Control group		Observation group		Weight	RR	95%CI
	Abnormal cases	Total cases	Abnormal cases	Total cases			
Li L[1]	13	20	6	20	44%	0.3	[0.05-2.11]
Wang LZ[13]	15	30	9	35	56%	0.25	[0.03-2.14]
Total 95%CI		50		55	100%	0.27	[0.05-1.96]
Total cases	28		15				
Heterogeneity	Chi^2=0.13, df=1(P=0.69), I^2=0%						
Overall effect quantity test	Z=2.30, (P=0.03)						

Discussion

This article evaluated systematically the treatment of neonatal HIE with gangliosides and the results of meta–analysis showed that the application of gangliosides can effectively reduce the abnormal rate of head CT, improve the NBNA scores in different periods after treatment, and effectively reduce the occurrence of nervous system sequelae. There were statistical differences in the indexes above between the treatment group with gangliosides and conventional one. On the basis of conventional treatment, the application of gangliosides can improve the prognosis of patients with HIE and promote recovery.

There may be some methodological defects owing to different qualities of the 12 papers included in this study. For example, studies using random methods and ambiguous grouping may lead to certain selective biases (Yan *et al.*, 2010). It is necessary to use single or double blind methods, due to the subjective measurable indexes of neurobehavioral scores and head CT. In particular, the study by Xiang and Wang (2005) used no language limits in the retrieval process. However, the existence of certain publication biases cannot be excluded, as all the papers included in that study were in Chinese. According to the results of systematical evaluation, at present, methodology practices of random grouping, concealed grouping, single/double blind method, and follow-ups are still insufficient in clinical trial studies on the treatment of HIE with ganglioside as the effective evidences

are absent in evaluations of efficacy and adverse reactions in the treatment of HIE with gangliosides. For case inclusion, descriptions of inclusion and exclusion criteria should be valued while conducting, according to accepted diagnostic criteria. In addition, the severity of the disease about cases included should be controlled or grouped.

TABLE 3
Meta-analysis of NBNA scores between the treatment group and control group

Studies	Control group		Observation group		Weight	RR	95% CI
	Mean (SD)	Total cases	Mean (SD)	Total cases			
7d NBNA							
Zhu YW[18]	32.09(2.55)	26	34.47(2.79)	28	7.7%	2.38	[0.96-3.80]
Yan CH[10]	34.61(2.32)	30	36.28(2.65)	30	8.5%	2.19	[0.76-3.01]
Total 95%CI		56		58	16.2%	2.28	[0.86-3.42]
Heterogeneity	Chi^2=2.38,df=1(P=0.44),I^2=0%						
Overall effect quantity test	Z=6.30,(P<0.0001)						
10-14d NBNA							
Wang LZ[13]	32.28(2.62)	30	34.12(2.47)	35	9.3%	1.84	[0.60-3.08]
Song H[19]	34.62(2.51)	38	28.16(1.8)	40	11.1%	3.54	[2.57-4.51]
Sun SX[17]	32.11(2.13)	150	34.78(2.46)	150	32.6%	1.92	[0.85-2.99]
Zhao YH[16]	32.1(2.34)	55	37.2(2.17)	55	8.7%	2.37	[1.25-2.89]
Yang HJ[11]	33.72(2.24)	75	35.25(2.12)	75	16.4%	2.45	[0.98-2.91]
Li L[1]	35.26(2.21)	20	38.37(2.19)	20	5.7%	2.81	[1.13-3.02]
Total 95%CI		368		375	83.8%	2.53	[1.04-2.92]
Heterogeneity	Chi^2=12.8, df=5(P=0.13), I^2=37%						
Overall effect quantity test	Z=13.37, (P<0.0001)						
Total 95%CI		424		433	100%	2.37	[2.21-3.05]
Heterogeneity	Chi^2=16.35, df=7(P=0.21), I^2=18%						
Overall effect quantity test	Z=17.45, (P<0.0001)						

TABLE 4
Comparisons of neurological sequelae incidence in neonate with HIE between observation group and control group

Studies	Control group		Observation group		Weight	RR	95%CI
	Abnormal cases	Total cases	Abnormal cases	Total cases			
Xiang JJ[14]	11	30	5	36	75%	0.38	[0.14-0.96]
Zeng L[20]	4	40	1	40	25%	0.25	[0.03-2.14]
Total 95%CI		70		76	100%	0.35	[0.15-0.79]
Total cases	15		6				
Heterogeneity	Chi^2=0.12, df=1(P=0.73), I^2=0%						
Overall effect quantity test	Z=2.39, (P=0.02)						

Conclusion

Gangliosides are a kind of the agents used in comprehensive treatment of HIE. The usage of medication, including the dose, drug combination, duration and numbers of treatment course, should be adjusted according to the patient's condition when lacking of sufficient evidences. The blind, conventional and big loading usage of medication is discouraged. In the future of clinical studies, researchers should adopt more random, double-blind trials with good design, larger scale to continuously improve the quality of studies and describe the process of researches clearly according to the international general curative effect evaluation of scale and end-point measurement, in order to provide basis for gangliosides application in clinical treatment.

References

Fujii S, Igarashi K, Sasaki H, Furuse H, Ito K, Kaneko K, Kato H, Inokuchi J, Waki H, Ando S (2002). Effects of the mono- and tetrasialogangliosides GM1 and GQ1b on ATP-induced long-term potentiation in hippocampal CA1 neurons. *Glycobiology* **12**: 339-344.

Guo WB, Hu PL, Li SY, Wang XP (2011). Analysis on the therapeutic effect of ganglioside in treatment of neonatal hypoxic ischemic encephalopathy and its effect on TNF-α and IL-6. *Maternal and Child Health Care of China* **25**: 3908-3910.

Han YK (1997). Diagnostic basis and clinical classification of neonatal hypoxic ischemic encephalopathy. *Chinese Journal of Pediatrics* **35**: 2.

Higgins JP, Green S (2008). *Cochrane handbook for systematic reviews of interventions*. Cochrane Book Series 1-649.

Huang XH (2011). Research progress in neonatal hypoxic ischemic encephalopathy. *Guide of China Medicine* **22**: 213-215.

Li L, Yin XM (2005). Clinical observation of treatment of severe neonatal hypoxic ischemic encephalopathy with gangliosides. *Journal of Pediatric Pharmacy* **4**: 30-31.

Lin CG, Geng RJ (2011). Research progress in the assessment of prognosis of hypoxic ischemic encephalopathy. *Medical Recapitulate* **17**: 1502-1504.

Mu DZ (2011). The diagnosis and treatment of neonatal hypoxic ischemic encephalopathy. *Journal of Applied Clinical Pediatrics* **14**: 1144-1147.

Nowycky MC, Wu G, Ledeen RW (2014). Glycobiology of ion transport in the nervous system. *Advances in Neurobiology* **9**: 321-342.

Palmano K, Rowan A, Guillermo R, Guan J, McJarrow P (2015). The

role of gangliosides in neurodevelopment. *Nutrients* **7**: 3891-3913.

Sheng L, Li Z (2017). Adjuvant treatment with monosialoganglioside may improve neurological outcomes in neonatal hypoxic-ischemic encephalopathy: A meta-analysis of randomized controlled trials. *PLoS One* **12**: e0183490.

Song H, Song HQ, Li ZJ, Bao R (2009). Observation of ganglioside treatment of mediate and hard neonatal hypoxic ischemic encephalopathy. *Chinese Journal of Practical Nervous Diseases* **12**: 62-64.

Sun SX, Wang CH (2013). Clinical observation of ganglioside treatment of neonatal hypoxic ischemic encephalopathy in 150 cases. *Chinese Journal of Practical Medicine* **33**: 194-195.

Xiang JJ, Wang P (2005). Observation of clinical efficacy of ganglioside treatment of neonatal hypoxic ischemic encephalopathy. *Journal of Clinical Research* **22**: 812-813.

Wang J, Yu RK (2013). Interaction of ganglioside GD3 with an EGF receptor sustains the self-renewal ability of mouse neural stem cells in vitro. *Proceedings of the National Academy of Sciences* **110**: 19137-19142.

Wang LZ (2009). Observation of clinical efficacy of ganglioside treatment of mediate and hard neonatal hypoxic ischemic encephalopathy. *Strait Pharmaceutical Journal* **5**: 178-179.

Wen BX (2011). Observation of clinical efficacy of ganglioside treatment of neonatal hypoxic ischemic encephalopathy in 60 cases. *Contemporary Medicine* **17**: 256-257.

Wu P (2003). Progress in the pathogenesis and treatment of neonatal hypoxic ischemic encephalopathy. *International Medicine & Health Guidance News* **Z3**: 75-77.

Yan CH, Jiang Y, Liu HX (2010). Effects of GM1 treatment on TNF-αand IL-6 in neonates with hypoxic-ischemic encephalopathy. *Guangdong Medical Journal* **24**: 3263-3265.

Yang HJ (2012). The effects of ganglioside on neonatal hypoxic-ischemic encephalopathy and the serum TNF-α, IL-6. *China Modern Doctors* **12**: 47-49.

Zeng L (2009). Observation of ganglioside treatment efficacy of neonatal hypoxic ischemic encephalopathy. *Chinese Journal of Practical Nervous Diseases* **12**: 84-85.

Zhao YH (2012). Analysis of efficacy of ganglioside treatment of neonatal hypoxic ischemic encephalopathy. Medical laboratory sciences. China health industry **24**: 94-95.

Zhu YW (2010). Clinical observation of single sialic acid four hexose ganglioside treatment of neonatal hypoxic ischemic encephalopathy. *Chinese Journal of Clinical Research* **23**: 52-53.