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促红细胞生成素对脑损伤早产儿 NBNA 评分、肝肾功能 以及脑干听觉诱发电位的影响 *

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摘要 目的:探讨促红细胞生成素(EPO)对脑损伤早产儿新生儿神经行为测定(NBNA)评分、肝肾功能以及脑干听觉诱发电位的影响。**方法:**选取 2015 年 2 月~2018 年 7 月期间我院收治的脑损伤早产儿 117 例,将上述研究对象根据随机数字表法将其分为对照组(n=58)和观察组(n=59),对照组患儿给予常规对症治疗,观察组在对照组的基础上联合 EPO 治疗,比较两组 NBNA 评分、肝肾功能以及脑干听觉诱发电位,记录两组患儿治疗期间并发症发生情况。**结果:**观察组纠正胎龄 40 周时 NBNA 评分高于对照组($P<0.05$)。两组患儿治疗后峰间期(I~III波、III~IV波、I~IV波)、潜伏期(I波、III波、IV波)均较治疗前降低,且观察组低于对照组($P<0.05$)。两组患儿治疗前、后尿素氮(BUN)、肌酐(Cr)、血清谷丙转氨酶(SGPT)、总胆红素(TBIL)比较差异均无统计学意义($P>0.05$)。两组患儿动脉导管未闭、新生儿败血症发生率比较差异无统计学意义($P>0.05$),而观察组支气管肺发育不良、颅内出血、脑干听觉诱发电位异常等发生率低于对照组($P<0.05$)。**结论:**EPO 对脑损伤早产儿具有一定的神经保护作用,能够有效保护受损神经细胞与听觉神经通路,降低脑损伤并发症的发生率,且不影响患儿的肝肾功能。

关键词:促红细胞生成素;脑损伤;早产儿;新生儿神经行为测定评分;肝功能;肾功能;脑干听觉诱发电位

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Effect of Erythropoietin on NBNA Score, Liver and Kidney Function and Brainstem Auditory Evoked Potential in Premature Infants with Brain Injury*

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ABSTRACT Objective: To investigate the effects of erythropoietin (EPO) on neonatal neurobehavioral assessment (NBNA) score, liver and kidney function and brainstem auditory evoked potential in premature infants with brain injury. **Methods:** 117 premature infants with brain injury who were admitted to our hospital from February 2015 to July 2018 were selected, and the subjects were divided into control group (n=58) and observation group (n=59) according to the digital table method. The control group was given routine symptomatic treatment. The observation group was treated with EPO on the basis of the control group. The NBNA score, liver and kidney function and brainstem auditory evoked potentials were compared between the two groups, and the complications of the two groups were recorded during the treatment. **Results:** The NBNA score of the observation group at 40 weeks of corrected gestational age was higher than that of the control group ($P<0.05$). The peak interval (I~III wave, III~IV wave, I~IV wave) and incubation period (I wave, III wave, IV wave) of the two groups after treatment were lower than those before treatment, and those of the observation group were lower than those of the control group ($P<0.05$). There were no significant differences in urea nitrogen (BUN), creatinine (Cr), serum glutamic-pyruvic transaminase (SGPT) and total bilirubin (TBIL) between the two groups before and after treatment ($P>0.05$). There were no significant differences in the incidence of patent ductus arteriosus and neonatal sepsis between the two groups ($P>0.05$), while the incidence of bronchopulmonary dysplasia, intracranial hemorrhage and abnormal brainstem auditory evoked potential in the observation group were lower than those in the control group ($P<0.05$). **Conclusion:** EPO has a certain neuroprotective effect on premature infants with brain injury. It can effectively protect the injured nerve cells and auditory nerve pathways, reduce the incidence of complications of brain injury, and it do not affect the liver and kidney function of the infants.

Key words: Erythropoietin; Brain injury; Premature infants; Neonatal neurobehavioral assessment score; Liver function; Kidney function; Brainstem auditory evoked potential

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前言

早产儿是指胎龄在 37 周以前出生的活产婴儿,其器官功能以及适应能力均较足月儿差,应给予早产儿特殊护理。伴随着临床新生儿重症监护技术的发展,早产儿存活率有所提升,但早产儿并发症却难以避免,其中最主要同时也是后果最严重的并发症为脑损伤^[1-3]。据统计^[4],存活的早产儿中约有 5%~10% 的患儿可出现脑损伤,该类患儿临床主要表现为认知、运动、行为等出现神经功能障碍,给患儿及其家庭带来沉重的影响。促红细胞生成素(Erythropoietin,EPO)是一种激素类物质,可促进红细胞生成,主要由肝脏、肾脏分泌,其在肾性贫血以及早产儿贫血中的疗效已得到证实^[5-7]。随着研究的深入,已有不少研究发现^[8,9],EPO 可保护神经并促进神经发育。本研究通过探讨 EPO 对脑损伤早产儿新生儿神经行为测定(Neonatal neurobehavioral assessment,NBNA)评分、脑干听觉诱发电位、肝肾功能的影响,旨在为临床提供参考。

1 资料与方法

1.1 一般资料

选取 2015 年 2 月~2018 年 7 月期间我院收治的脑损伤早产儿 117 例,纳入标准:(1)均符合《实用新生儿学》^[10]中相关诊断标准;(2)胎龄范围 28 周~36 周,出生体重 ≤ 2500 g;(3)患儿家长或监护人知情本次研究并签署了知情同意书。排除标准:(1)合并先天性心脏病患儿;(2)合并遗传性代谢疾病患儿;(3)伴有严重先天性畸形患儿;(4)合并凝血功能障碍、溶血症、红细胞增多症患儿;(5)合并严重感染患儿。将上述研究对象根据随机数字表法将其分为对照组($n=58$)和观察组($n=59$),其中对照组男 28 例,女 30 例,胎龄 28~36 周,平均(32.48 ± 1.27)周;出生体重 1800~2500g,平均(2148.69 ± 42.76)g;分娩方式:顺产 20 例,剖宫产 38 例。观察组男 27 例,女 32 例,胎龄 29~36 周,平均(32.55 ± 1.36)周;出生体重 1700~2500 g,平均(2156.49 ± 49.61)g;分娩方式:顺产 18 例,剖宫产 41 例。两组患儿一般资料比较无差异($P>0.05$),组间可比。本次研究已经我院伦理学委员会批准同意。

1.2 方法

均放置于新生儿保温箱,给予心电监护,维持内环境稳定,加强呼吸管理等,同时进行常规对症治疗。观察组在对照组基础上加用 EPO(沈阳三生制药有限责任公司,国药准字:S19980074,规格:3000IU/支)治疗,皮下注射,500U/kg,隔日一次。两组患儿均治疗 3~4 周。

1.3 观察指标

于纠正胎龄 40 周时采用 NBNA 评分^[11]评价两组患儿神经功能,均由受过专业训练的同一新生儿专科医师进行评定,NBNA 评分包括被动肌张力、主动肌张力各 4 项,早产儿行为能力 6 项,原始反射、一般状况各 3 项,每项评分 0~2 分,总分 40 分,当评分小于 35 分时,提示有脑损伤。记录所有患儿治疗前后脑干听觉诱发电位峰间期(I~III波、III~IV波、I~IV波)、潜伏期(I波、III波、IV波)的情况。于治疗前后采集患儿肘静脉血 5 mL,2800 r/min 离心 12 min,离心半径 6 cm,分离血清,置于 -20℃ 冰箱中待测。采用 SysmexUF50 型全自动分析仪检测

尿素氮(Blood urea nitrogen,BUN)、肌酐(Creatinine,Cr)、血清谷丙转氨酶(Serum glutamic-pyruvic transaminase,SGPT)、总胆红素(Total bilirubin,TBIL)。记录两组患儿治疗期间并发症发生情况,包括支气管肺发育不良、颅内出血、脑干听觉诱发电位异常发生率、新生儿败血症、动脉导管未闭等。

1.4 统计学方法

数据分析选用 SPSS 26.0 统计软件,计数资料用[n(%)]表示,行 χ^2 检验,符合正态分布的计量资料用($\bar{x} \pm s$)表示,组间采用独立样本 t 检验,以 $P<0.05$ 为差异具有统计学意义。

2 结果

2.1 NBNA 评分比较

观察组纠正胎龄 40 周时 NBNA 评分为(36.95 ± 2.02)分,高于对照组的(33.26 ± 2.13)分,两组比较差异具有统计学意义($t=9.616, P=0.000$)。

2.2 脑干听觉诱发电位比较

两组患儿治疗前峰间期(I~III波、III~IV波、I~IV波)、潜伏期(I波、III波、IV波)比较无差异($P>0.05$),两组患儿治疗后峰间期(I~III波、III~IV波、I~IV波)、潜伏期(I波、III波、IV波)均较治疗前降低,且观察组低于对照组($P<0.05$),详见表 1。

2.3 两组患儿治疗前后肾功能指标比较

两组患儿治疗前、后 BUN、Cr、SGPT、TBIL 比较无差异($P>0.05$),详见表 2。

2.4 两组患儿治疗期间并发症发生情况

两组患儿动脉导管未闭、新生儿败血症发生率比较差异无统计学意义($P>0.05$),而观察组支气管肺发育不良、颅内出血、脑干听觉诱发电位异常等发生率低于对照组($P<0.05$),详见表 3。

3 讨论

早产儿由于其独特的脑解剖结构以及各项系统发育不成熟,易导致脑损伤。当发生脑损伤后,脑组织细胞凋亡、结构萎缩,破坏神经系统完整性^[12-14]。引起早产儿脑损伤的因素较多,目前临床就其发病机制尚无统一说法,已有不少学者认为其发病与早产儿脑血管发育不全、缺氧缺血、围生期窒息、免疫学机制以及宫内感染等有关^[15,16]。以往临床制定了一系列预防以及治疗措施,如脑源性神经营养因子、亚低温疗法、氧自由基清除剂等,但效果皆不尽如人意,故而寻求新的早产儿脑损伤的有效治疗方案已成为临床的研究热点^[17,18]。EPO 本质为糖蛋白,以其有效地促进骨髓造血而得名,早期常用于贫血类疾病治疗^[19]。以往的传统观点认为 EPO 分子量较大,无法顺利通过血脑屏障^[20],而徐发林等人^[21]动物实验研究结果却显示,未成熟鼠脑损伤后经 EPO 干预治疗后,出现了内源性的血管新生反应,且 EPO 可进一步促进该反应,说明 EPO 可成功通过血脑屏障发挥神经保护作用,本研究就此展开探讨。

本研究中观察组纠正胎龄 40 周时 NBNA 评分高于对照组,可见脑损伤早产儿应用 EPO 神经修复作用较好,由于早产儿各方面发育不成熟,其血脑屏障同样具备不成熟性,EPO 可顺利通过屏障,进而通过抑制神经细胞蛋白质的降解、活化线粒体功能等途径来发挥保护神经的作用^[22]。既往研究结果表

表 1 两组患儿治疗前后脑干听觉诱发电位比较($\bar{x} \pm s$, ms)Table 1 Comparison of brainstem auditory evoked potentials in two groups of children before and after treatment($\bar{x} \pm s$, ms)

Groups	Peak interval						Incubation period					
	I ~III wave		III~IV wave		I ~IV wave		I wave		IV wave		III wave	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=58)	2.92±0.17	2.82±0.13*	2.53±0.14	2.46±0.12*	5.51±0.27	5.20±0.36*	2.79±0.37	2.61±0.51*	5.64±0.47	5.33±0.44*	8.15±0.34	7.74±0.53*
Observation group (n=59)	2.88±0.18	2.71±0.21*	2.51±0.15	2.37±0.15*	5.54±0.35	4.56±0.35*	2.81±0.43	2.41±0.43*	5.63±0.52	4.92±0.57*	8.18±0.57	7.35±0.46*
t	1.235	3.400	0.745	3.580	0.518	9.750	0.269	2.295	0.109	4.350	0.345	4.253
P	0.219	0.001	0.458	0.001	0.605	0.000	0.788	0.024	0.913	0.000	0.731	0.000

Note: compared with before treatment, * $P < 0.05$.表 2 两组患儿治疗前后肝肾功能指标比较($\bar{x} \pm s$)Table 2 Comparison of liver and kidney function before and after treatment in two groups($\bar{x} \pm s$)

Groups	BUN (mmol/L)		Cr (μmol/L)		SGPT (U/L)		TBIL (μmol/L)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=58)	5.39±1.23	5.04±1.42	74.88±12.78	71.34±9.54	28.18±9.95	27.54±11.32	76.95±10.66	74.26±9.64
Observation group (n=59)	5.41±1.18	5.13±1.33	75.04±13.65	72.38±8.23	28.25±10.73	27.66±8.01	77.16±12.41	75.18±11.52
t	0.090	0.354	0.087	0.632	0.037	0.066	0.098	0.468
P	0.929	0.724	0.788	0.529	0.971	0.947	0.922	0.641

表 3 两组患儿治疗期间并发症发生情况[n(%)]

Table 3 Complications of the two groups during treatment[n (%)]

Groups	Bronchopulmonary dysplasia	Intracranial hemorrhage	Incidence of abnormal brainstem auditory evoked potential	Neonatal sepsis	Patent ductus arteriosus
Control group (n=58)	16 (27.59)	10 (17.24)	28 (48.28)	7 (12.07)	13 (22.41)
Observation group (n=59)	7 (11.86)	3 (5.08)	15 (25.42)	5 (8.47)	11 (18.64)
χ^2	2.577	2.376	3.571	0.411	0.255
P	0.032	0.036	0.010	0.522	0.614

明^[23],神经细胞损伤可造成机体电生理改变,而脑干听觉诱发电位可准确评价机体电生理改变,其主要反映的是外耳至脑干神经传导通路的功能,一般情况下脑损伤早产儿表现为峰间期(I~III波、III~IV波、I~IV波)、潜伏期(I波、III波、IV波)的延迟。本次研究结果中两组患儿治疗后峰间期、潜伏期均较治疗前降低,且观察组低于对照组,提示EPO干预后,脑损伤早产儿的脑干听觉诱发电位得到显著改善,EPO可在一定程度上缓解脑损伤进展,可在短时间内发挥抗氧化、抗炎、促进神经生长等,有助于脑功能尤其听觉神经传导系统的改善^[24-26]。同时两组

患儿治疗前后以及组内BUN、Cr、SGPT、TBIL比较差异均无统计学意义,可见EPO对患儿肝肾功能无影响,安全性较好。江燕丽等人^[27]动物实验研究结果表明,重组人促红细胞生成素对感染所致肝肾损伤和内质网应激具有保护作用,而有关其具体作用机制尚需进一步研究。另外,观察组支气管肺发育不良、颅内出血、脑干听觉诱发电位异常等发生率低于对照组,表明EPO的应用可有效减少脑损伤早产儿的并发症发生率,EPO对神经细胞起保护效果的主要机制可能是抑制细胞凋亡、促进神经细胞生成、促血管生成以及减轻兴奋性氨基酸毒性等,缓

解脑损伤破坏进程,进而有效减少并发症发生率^[28-30]。然而,本次研究受到对象来源以及数量的限制,并且对患儿的观察尚局限于静态记录,致使结果可能存在一定的偏倚,有待今后进一步的深入研究。

综上所述,EPO对神经组织有营养和保护作用,脑损伤早产儿应用EPO可有效改善其脑干听觉诱发电位,减少并发症发生率,且对肝肾功能无不良影响,安全可靠。

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