doi: 10.13241/j.cnki.pmb.2019.16.024

丙种球蛋白联合美罗培南治疗新生儿败血症的疗效及对血清 IL-6、GM-CSF、PCT 水平的影响 *

方 瑞 赵青松 汪 燕 梁 霞 都鹏飞△

(安徽医科大学第二附属医院 儿科 安徽 合肥 230000)

摘要 目的：探讨丙种球蛋白联合美罗培南治疗新生儿败血症的疗效及对血清白介素 -6 (IL-6)、粒细胞巨噬细胞集落刺激因子(GM-CSF)、降钙素原(PCT)水平的影响。**方法**：选择 2017 年 1 月至 2018 年 12 月我院接诊的 80 例新生败血症患儿作为本研究对象，通过随机数表法将其分为观察组和对照组，每组 40 例。对照组在常规处理基础上给予美罗培南治疗，观察组在对照组的基础上联合丙种球蛋白治疗。比较两组的临床疗效、症状改善时间、住院时间、治疗前后血清免疫球蛋白 G(IgG)、IL-6、GM-CSF、PCT 水平的变化及不良反应的发生情况。**结果**：治疗后 7d，观察组临床疗效总有效率显著高于对照组(95% vs. 80%，*P<0.05*)；观察组拒奶改善时间、皮肤颜色及体温正常时间、住院时间均短于对照组(*P<0.05*)；观察组血清 IgG 高于对照组，血清 IL-6、GM-CSF、PCT 均低于对照组(*P<0.05*)。两组治疗治疗期间均无死亡病例和严重不良反应发生。**结论**：丙种球蛋白联合美罗培南治疗新生儿败血症的疗效显著优于单用美罗培南治疗，其可有效降低血清 IL-6、GM-CSF、PCT 的表达，促进患儿恢复。

关键词：丙种球蛋白；美罗培南；新生儿败血症；白介素 -6；粒细胞巨噬细胞集落刺激因子

中图分类号：R722.131 **文献标识码**：A **文章编号**：1673-6273(2019)16-3124-04

Curative Efficacy of Gamma Globulin Combined with Meropenem in the Treatment of Neonatal Sepsis and Its Effects on the Serum IL-6, GM-CSF and PCT Levels*

FANG Rui, ZHAO Qing-song, WANG Yan, LIANG Xia, DU Peng-fei△

(Department of Pediatrics, Second Affiliated Hospital of Anhui Medical University, Hefei, Anhui, 230000, China)

ABSTRACT Objective: To study the curative efficacy of gamma globulin combined with meropenem in the treatment of neonatal sepsis and its effects on the serum interleukin-6 (IL-6), granulocyte macrophage colony-stimulating factor (GM-CSF) and procalcitonin (PCT) levels. **Methods:** 80 patients of neonatal sepsis who were treated from January 2017 to December 2018 in our hospital were selected and divided into the observation group and the control group according to the random number table, with 40 cases in each group. The control group was treated with meropenem on the basis of conventional treatment, while the observation group was combined with gamma globulin on the basis of control group. The clinical efficacy, symptoms improvement time, hospitalization time, changes of the serum immunoglobulin G(IgG), IL-6, GM-CSF, PCT levels before and after treatment and incidence of adverse reactions were compared between the two groups. **Results:** After 7 days treatment, the total effective rate of observation group was significantly higher than those in the control group. (95% vs. 80%, *P<0.05*); the refusal improvement time, skin and body temperature normal time, hospitalization time in the observation group were shorter than those in the control group (*P<0.05*); the serum IgG in observation group was higher than those in the control group, the serum IL-6, GM-CSF and PCT were lower than those in the control group (*P<0.05*). There was no deaths and serious adverse reactions during treatment in two groups. **Conclusion:** The efficacy of gamma globulin combined with meropenem in the treatment of neonatal sepsis was significantly better than meropenem alone, it can effectively reduce the expression of serum IL-6, GM-CSF, PCT levels.

Key words: Gamma globulin; Meropenem; Neonatal sepsis; Interleukin -6; Granulocyte macrophage colony-stimulating factor

Chinese Library Classification(CLC): R722.131 Document code: A

Article ID: 1673-6273(2019)16-3124-04

前言

新生儿败血症主要是由于病原体侵入血液并迅速生长、繁殖所致的一种全身炎症反应，是新生儿时期的严重感染性疾病，患儿若得不到及时有效的治疗，极易出现呼吸窘迫、呼吸暂停等严重并发症，甚至危及生命[1,2]。目前，该病的治疗首选抗生

* 基金项目：安徽省自然科学基金项目(20130151)

作者简介：方瑞(1982-)，男，硕士，主治医师，主要研究方向：儿科疾病，电话：13866104609，E-mail：jiandandian07@163.com

△ 通讯作者：都鹏飞(1957-)，男，硕士，主任医师，主要研究方向：儿科疾病

(收稿日期：2019-02-17 接受日期：2019-03-12)

素。美罗培南是一种碳青霉素烯类抗生素，是新生儿败血症的常用药物，具有抗菌谱广、抗菌活性强等优势，但单独使用抗生素仍有部分患儿无法获得满意疗效[3,4]。

近年来研究表明新生儿败血症的发病和机体免疫系统发育不完善密切相关，而通过增加免疫辅助疗法可促进该病转归。丙种球蛋白属免疫增强剂，具有强化机体免疫力、抗感染能力等作用[5,6]。白介素 -6(IL-6)、粒细胞巨噬细胞集落刺激因子(GM-CSF)、降钙素原(PCT)在机体炎症反应中作用关键[7,8]。因此，本研究主要探讨了丙种球蛋白联合美罗培南治疗新生儿败血症的疗效及其对血清 IL-6、GM-CSF、PCT 水平的影响。

1 资料与方法

1.1 一般资料

选择 2017 年 1 月至 2018 年 12 月我院接诊的 80 例新生败血症患儿作为本研究对象。纳入标准[9]：① 符合新生儿败血症检查诊断标准，出现拒奶、烦躁不安、发热、面色苍白等临床症状，有外周血象改变，经过病原菌培养结果呈阳性；② 患儿家属知情同意本研究。排除标准[10]：① 并发严重内分泌系统、自身免疫性系统病变；② 合并严重肝肾功能障碍；③ 合并病毒感染；④ 纳入研究前已使用过抗生素；⑤ 对研究药物过敏。通过随机数表法将患儿分为观察组和对照组，每组 40 例。两组一般资料见表 1，差异无统计学意义($P>0.05$)。

表 1 两组一般资料的比较[$\bar{x}\pm s$，n(%)]

Table 1 Comparison of the general information between two groups[$\bar{x}\pm s$, n(%)]

Groups	Sex(M/F)	Age(d)	Weight(kg)	Term infant	Premature infant	Primary infection	Secondary infection
Observation group(n=40)	22/18	14.84± 2.70	3.24± 0.28	15(37.50)	25(62.50)	24(60.00)	16(40.00)
Control group (n=40)	19/21	14.49± 2.82	3.20± 0.30	17(42.50)	23(57.50)	26(65.00)	14(35.00)

1.2 治疗方法

两组均接受常规处理，包括维持水电解质平衡、改善微循环等，并积极给予其余对症治疗。对照组在此基础上给予美罗培南 (规格 0.5 g，厂家：苏州佳友制药有限公司，国药准字 J20140169)治疗，剂量 20 mg/kg 稀释于 5~10 mL 氯化钠溶液中静脉滴注，每 12h 给药一次；连续用药 7d。观察组在对照组基础上，联合丙种球蛋白(规格，厂家，国药准字)治疗，剂量 400 mg/kg/d，初始滴注速度 4~6 滴 /min，30 min 后若患儿无不良反应可逐渐增加滴注速度，2~3h 内滴注完毕，连续用药 3d。

1.3 观察指标

记录两组临床症状改善时间和住院时间；采集治疗前、治疗后 7d 时静脉血 2 mL，使用 3000 r/min 的速度离心 10 min 后，提取上层血清液，使用日立全自动生化分析仪 7600-020 型检测血清免疫球蛋白 G(IgG)、IL-6、GM-CSF、PCT 的表达，其中 IgG、IL-6、GM-CSF 酶联免疫吸附法(ELISA)购于武汉博士德生物技术有限公司，PCT 循环增强荧光免疫法试剂盒购于星童医疗技术有限公司；并评价安全性。

1.4 疗效评价标准

治疗 7d 后根据文献[11]评价，显效：拒奶、烦躁不安等症状消失，体温正常，皮肤红润，可正常进食，经过病原菌培养显示为阴性；有效：拒奶、烦躁不安、面色苍白等症状部分改善，体温未得到正常恢复，病原菌培养呈阴性；无效：未至上述标准。显效 + 有效为总效率。

1.5 统计学分析

以 spss18.0 软件包处理实验数据，计量资料用均数± 标准差($\bar{x}\pm s$)表示，组间比较采用 t 检验，计数资料组间比较采用 x^2 检验，以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组临床疗效的比较

治疗后，观察组总有效率显著高于对照组(95% vs. 80%，$P<0.05$)，见表 2。

表 2 两组临床疗效比较[例(%)]

Table 2 Comparison of the clinical efficacy between two groups[n(%)]

Groups	Excellence	Valid	Invalid	Total effective rate
Observation group(n=40)	22(55.00)	16(40.00)	2(5.00)	38(95.00)*
Control group(n=40)	17(42.50)	15(37.50)	8(20.00)	32(80.00)

Note: compared with the control group, *$P<0.05$.

2.2 两组症状改善时间、住院时间的比较

观察组拒奶改善时间、皮肤颜色及体温正常时间、住院时间较对照组均显著缩短($P<0.05$)，见表 3。

2.3 两组治疗前后血清 IgG 水平的比较

治疗后，两组血清 IgG 水平均较治疗前显著升高，且观察组明显高于对照组($P<0.05$)，见表 4。

2.4 两组治疗前后血清 IL-6、GM-CSF、PCT 水平的比较

两组治疗前血清 IL-6、GM-CSF、PCT 比较差异无统计学

意义(*P<0.05*)；治疗后，两组血清 IL-6、GM-CSF、PCT 均低于治疗前，且观察组以上指标均明显低于对照组(*P<0.05*)，见表 5。

表 3 两组症状改善时间、住院时间的比较($\bar{x}\pm s$，d)

Table 3 Comparison of the symptom improvement time and hospitalization time between two groups ($\bar{x}\pm s$, d)

Groups	Refusal improvement time	Skin normal time	Body temperature normal time	hospitalization time
Observation group(n=40)	4.89± 0.50*	5.79± 0.62*	3.87± 0.39*	7.89± 1.05*
Control group(n=40)	6.11± 0.65	7.04± 0.70	6.20± 0.40	10.05± 1.47

Note: compared with the control group, **P<0.05*.

表 4 两组治疗前后血清 IgG 水平的比较($\bar{x}\pm s$，g/L)

Table 4 Comparison of the serum IgG level between two groups before and after treatment($\bar{x}\pm s$, g/L)

Groups		IgG
Observation group(n=40)	Before treatment	7.04± 1.28
	After treatment	14.85± 1.70*#
Control group(n=40)	Before treatment	7.08± 1.26
	After treatment	10.01± 1.37*

Note: compared with before treatment, **P<0.05*; compared with the control group, #*P<0.05*

表 5 两组治疗前后血清 IL-6、GM-CSF、PCT 水平的比较($\bar{x}\pm s$)

Table 5 Comparison of the serum IL-6, GM-CSF and PCT levels between two groups before and after treatment($\bar{x}\pm s$)

Groups		IL-6(ng/L)	GM-CSF(μg/L)	PCT(μg/L)
Observation group(n=40)	Before treatment	32.92± 3.74	0.20± 0.05	6.86± 1.20
	After treatment	10.31± 1.63*#	0.07± 0.01*#	1.02± 0.23*#
Control group(n=40)	Before treatment	32.84± 3.78	0.21± 0.05	6.93± 1.16
	After treatment	16.29± 1.90*	0.11± 0.02*	1.67± 0.29*

Note: compared with before treatment, **P<0.05*; compared with the control group, #*P<0.05*.

2.5 安全性评价

两组治疗治疗期间均无死亡病例和严重不良反应发生。

3 讨论

败血症是新生儿较为严重的一种感染性疾病，病原菌以格兰阳性菌为主，所占比例高达 80%以上。致病菌侵入机体后，在血液中大量繁殖并产生毒素，造成机体出现全身炎症反应综合征[12,13]。新生儿败血症若得不到有效的治疗，病死率可高达 10%~50%，即便是存活的部分患儿也会出现后遗症，严重影响着新生儿的生活质量和生命安全[14,15]。合理的抗生素治疗是新生儿败血症的首要治疗方案，而美罗培南是目前治疗新生儿败血症的常用药物，属第 2 代碳青霉烯类抗生素，主要抗菌活性是通过对细菌细胞壁的合成产生抑制作用的途径发挥，对大多数β内酰胺酶等均具有稳定的水解作用，抗菌谱广。但随着近年来细菌耐药的加重，部分患儿难以获得满意疗效[16,17]。

研究表明除了早期给予抗生素治疗外，免疫治疗也是提高新生儿败血症预后的重要因素。新生败血症患儿免疫功能较差，IgG 抗体在受到感染后明显降低，削弱 T 细胞功能，而通过被动免疫调节在提高抗感染能力中十分关键[18,19]。丙种球蛋白属 IgG 抗体的免疫增强剂，具有免疫调节、免疫替代的双重作用，在给药后可令血液中 IgG 的表达迅速增加[20,21]。Łysenko L 等[22]报道显示丙种球蛋白可和败血症患儿的病原分泌毒素或病原相互结合，并发挥中和作用，削弱细胞毒性，且可提高中性粒细胞的调理和吞噬作用。

IL-6 是一种具有多种生物学活性的因子，与 IL-8、肿瘤坏死因子 -α(TNF-α)等共同参与者机体的炎症介导反应。由于新生败血患儿存在着明显的细胞免疫缺陷，血清中有较高的循环免疫复合物，可刺激到 IL-6 的大量表达[23,24]。GM-CSF 主要分泌来自于损伤的内皮细胞，属一类多肽类激素样造血生长因子，是反映单核 - 巨噬细胞生长、增殖、分化的敏感性指标，目前已有研究证实新生败血患儿血清 GM-CSF 表达明显升高，其原因和淋巴细胞活化、细胞免疫遭受到抑制等相关[25,26]。PCT 在反映机体细菌感染中具有较高的敏感性，且随着感染的加剧，表达水平升高[27,28]。

本研究结果显示联合丙种球蛋白治疗的患儿血清 IgG 的升高程度和 IL-6、GM-CSF、PCT 均明显优于单独使用美罗培南的患儿，通过分析是由于丙种球蛋白在给药后可迅速提高 IgG 表达，影响微生物和靶细胞受体之间的结合，并通过和病原体的结合，降低毒素能力，激活补体，改善细胞免疫缺陷，提高抗感染能力，且丙种球免疫蛋白中包含着 IL-6 等自身抗体，对此类细胞因子具有中和作用，可抑制炎症进展[29,30]；而联合美罗培南的抗菌机制在于进一步降低 IL-6、GM-CSF、PCT 的表达。本研究中，联合丙种球蛋白的患儿在临床疗效及症状改善时间、住院时间结果上也更有优势，显示联合丙种球蛋白治疗可缩短症状恢复时间，提高治疗效果。

综上所述，丙种球蛋白联合美罗培南治疗新生儿败血症的

疗效显著优于单用美罗培南治疗，其可有效降低血清 IL-6、GM-CSF、PCT 的表达，促进患儿恢复。

参 考 文 献(References)

[1] El Manouni El, Hassani S, Berkhout DJC, et al. Risk Factors for Late-Onset Sepsis in Preterm Infants: A Multicenter Case-Control Study[J]. Neonatology, 2019, 116(1): 42-51

[2] Prout AJ, Talisa VB, Carcillo JA, et al. Epidemiology of Readmissions After Sepsis Hospitalization in Children[J]. Hosp Pediatr, 2019, 9(4): 249-255

[3] Germovsek E, Lutsar I, Kipper K, et al. Plasma and CSF pharmacokinetics of meropenem in neonates and young infants: results from the NeoMero studies [J]. J Antimicrob Chemother, 2018, 73(7): 1908-1916

[4] Liem TBY, Slob EMA, Termote JUM, et al. Comparison of antibiotic dosing recommendations for neonatal sepsis from established reference sources[J]. Int J Clin Pharm, 2018, 40(2): 436-443

[5] Badawy M, Mosallam DS, Saber D, et al. Use of Mannose-Binding Lectin Gene Polymorphisms and the Serum MBL Level for the Early Detection of Neonatal Sepsis[J]. J Pediatr Genet, 2018, 7(4): 150-157

[6] Ezzelarab MB, Zhang H, Guo H, et al. Regulatory T Cell Infusion Can Enhance Memory T Cell and Alloantibody Responses in Lymphodepleted Nonhuman Primate Heart Allograft Recipients [J]. Am J Transplant, 2016, 16(7): 1999-2015

[7] Al Hazzani AA, Bawazeer RAB, Shehata AI. Epidemiological characterization of serotype group B Streptococci neonatal infections associated with interleukin-6 level as a sensitive parameter for the early diagnosis[J]. Saudi J Biol Sci, 2018, 25(7): 1356-1364

[8] Kumar J, Singh A. A Comparative Evaluation of Presepsin with Procalcitonin and CRP in Diagnosing Neonatal Sepsis: Correspondence[J]. Indian J Pediatr, 2019, 86(3): 313-314

[9] Subspecialty Group of Neonatology, the Society of Pediatric, Chinese Medical Association; Professional Committee of Infectious Diseases, Neonatology Society, Chinese Medical Doctor Association[J]. Expert consensus on the diagnosis and management of neonatal sepsis (version 2019)[J]. Zhonghua Er Ke Za Zhi, 2019, 57(4): 252-257

[10] Parri N, Trippella G, Lisi C, et al. Accuracy of presepsin in neonatal sepsis: systematic review and meta-analysis[J]. Expert Rev Anti Infect Ther, 2019, 17(4): 223-232

[11] Nabi SN, Basak AK, Kamruzzaman M, et al. Performance of Haematological Parameters in Early Diagnosis of Clinically Suspected Neonatal Sepsis[J]. Mymensingh Med J, 2019, 28(1): 193-199

[12] Gelano TF, Bacha YD, Abate D. Effect of chlorhexidine cord application on prevention of neonatal sepsis in developing countries: Systematic review and meta-analysis [J]. Int J Health Sci (Qassim), 2019, 13(1): 40-51

[13] Rohit A, Suresh Kumar D, Dhinakaran I, et al. Whole-genome-based analysis reveals multiclone Serratia marcescens outbreaks in a non-Neonatal Intensive Care Unit setting in a tertiary care hospital in India[J]. J Med Microbiol, 2019, 68(4): 616-621

[14] Good PI, Hooven TA. Evaluating Newborns at Risk for Early-Onset Sepsis[J]. Pediatr Clin North Am, 2019, 66(2): 321-331

[15] Al-Mouqdad MM, Aljobair F, Alaklobi FA, et al. The consequences of prolonged duration of antibiotics in premature infants with suspected sepsis in a large tertiary referral hospital: a retrospective cohort study[J]. Int J Pediatr Adolesc Med, 2018, 5(3): 110-115

[16] Softi ć I, Tahirovi ć H, Di Ciommo V, et al. Bacterial sepsis in neonates: Single centre study in a Neonatal intensive care unit in Bosnia and Herzegovina[J]. Acta Med Acad, 2017, 46(1): 7-15

[17] Shobowale EO, Solarin AU, Elikwu CJ, et al. Neonatal sepsis in a Nigerian private tertiary hospital: Bacterial isolates, risk factors, and antibiotic susceptibility patterns[J]. Ann Afr Med, 2017, 16(2): 52-58

[18] Saboohi E, Saeed F, Khan RN, et al. Immature to total neutrophil ratio as an early indicator of early neonatal sepsis [J]. Pak J Med Sci, 2019, 35(1): 241-246

[19] Giorgakoudi K, O'Sullivan C, Heath PT, et al. Cost-effectiveness analysis of maternal immunisation against group B Streptococcus (GBS) disease: A modelling study [J]. Vaccine, 2018, 36 (46): 7033-7042

[20] Poujol F, Monneret G, Gallet-Gorius E, et al. Ex vivo Stimulation of Lymphocytes with IL-10 Mimics Sepsis-Induced Intrinsic T-Cell Alterations[J]. Immunol Invest, 2018, 47(2): 154-168

[21] Bernardo L, Yu H, Amash A, et al. IgG-Mediated Immune Suppression to Erythrocytes by Polyclonal Antibodies Can Occur in the Absence of Activating or Inhibitory Fcγ Receptors in a Full Mouse Model[J]. J Immunol, 2015, 195(5): 2224-2230

[22] Łysenko L, Leśnik P, Nelke K, et al. Immune disorders in sepsis and their treatment as a significant problem of modern intensive care [J]. Postepy Hig Med Dosw (Online), 2017, 71(1): 703-712

[23] Raymond SL, Hawkins RB, Murphy TJ, et al. Impact of toll-like receptor 4 stimulation on human neonatal neutrophil spontaneous migration, transcriptomics, and cytokine production [J]. J Mol Med (Berl), 2018, 96(7): 673-684

[24] Falck M, Osredkar D, Wood TR, et al. Neonatal Systemic Inflammation Induces Inflammatory Reactions and Brain Apoptosis in a Pathogen-Specific Manner[J]. Neonatology, 2018, 113(3): 212-220

[25] Deshmukh HS, Liu Y, Menkiti OR, et al. The microbiota regulates neutrophil homeostasis and host resistance to *Escherichia coli* K1 sepsis in neonatal mice[J]. Nat Med, 2014, 20(5): 524-30

[26] Shane AL, Sánchez PJ, Stoll BJ. Neonatal sepsis [J]. Lancet, 2017, 390(10104): 1770-1780

[27] Kumar N, Dayal R, Singh P, et al. A Comparative Evaluation of Presepsin with Procalcitonin and CRP in Diagnosing Neonatal Sepsis [J]. Indian J Pediatr, 2019, 86(2): 177-179

[28] Quadir AF, Britton PN. Procalcitonin and C-reactive protein as biomarkers for neonatal bacterial infection[J]. J Paediatr Child Health, 2018, 54(6): 695-699

[29] Tashiro Y, Murakami A, Goizuka R, et al. An asymmetric antibody repertoire is shaped between plasmablasts and plasma cells after secondary immunization with (4-hydroxy-3-nitrophenyl)acetyl chicken γ-globulin[J]. Int Immunol, 2015, 27(12): 609-620

[30] Ruvinsky S, Taicz M, Pérez MG, et al. Varicella at "Casa Garrahan", 2008-2013: Assessment of postexposure prophylaxis measures [J]. Arch Argent Pediatr, 2015, 113(3): 237-243