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布地奈德雾化吸入对毛细支气管炎患儿血清 IL-4、IFN- γ 、TNF- α 及 T 淋巴细胞亚群的影响 *

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摘要 目的:研究布地奈德雾化吸入治疗小儿毛细支气管炎的临床疗效及对血清白介素-4(IL-4)和 γ 干扰素(IFN- γ)、肿瘤坏死因子- α (TNF- α)及T淋巴细胞亚群的影响。**方法:**研究对象选取我院2014年1月到2017年1月收治的毛细支气管炎患儿70例,采用随机数字法将其分为对照组和观察组,每组35例。对照组患者给予吸氧、控制喘憋和抗病原体等常规治疗,观察组患者在对照组的基础上雾化吸入布地奈德联合特布他林及异丙托溴铵治疗。比较两组患者的治疗总有效率,各症状和体征缓解时间和住院时间,治疗前后的血清IL-4、IFN- γ 、TNF- α 和T淋巴细胞亚群CD3⁺、CD4⁺、CD8⁺及CD4⁺/CD8⁺水平的变化。**结果:**治疗后,观察组的治疗总有效率(97.14%)明显高于对照组(71.43%)($P=0.00$);观察组气促缓解时间、哮鸣音消失时间、湿啰音消失时间、咳嗽消失时间、心率正常时间、住院时间明显短于对照组($P<0.01$);观察组患者的CD3⁺、CD4⁺及CD4⁺/CD8⁺细胞比值、血清IFN- γ 水平均明显低于高于对照组,CD8⁺、血清IL-4、TNF- α 水平明显低于对照组($P<0.05$)。**结论:**布地奈德雾化吸入治疗毛细支气管炎的临床疗效显著,可有效抑制炎症,增强机体免疫功能,且治疗安全性较高。

关键词:布地奈德;毛细支气管炎;疗效;白介素-4(IL-4); γ 干扰素(IFN- γ);儿童

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Effects of Aerosol Inhalation of Budesonide on the Serum IL-4, IFN- γ , TNF- α and T Lymphocyte Subsets of Children with Bronchiolitis*

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ABSTRACT Objective: To study the clinical effect of budesonide inhalation on the children with bronchiolitis and its effect on the serum Interleukin-4 (IL-4) and interferon gamma (IFN- γ), tumor necrosis factor alpha (TNF- α) and T lymphocyte subsets. **Methods:** 70 patients with bronchiolitis treated in our hospital from January 2014 to January 2017 were selected and divided into the control group and observation group by random number method. In the control group, patients were given oxygen, controlled wheezing and anti-pathogens and other conventional treatment, on this basis, the observation group were treated with nebulized budesonide combined with terbutaline and ipratropium bromide. The total effective rate of treatment was compared between the two groups of patients. The remission time of symptoms and signs and hospitalization time were compared. The levels of serum inflammatory factors and T lymphocyte subsets were also compared before and after treatment. **Results:** The total effective rate (97.14%) was significantly higher in the observation group than that of the control group (71.43%)($P=0.00$); the remission duration of anhelation, the disappearance time of wheezing, rale, moist rale, cough, normal time of heart rate, hospitalization time of observation group were dominantly shorter than those of the control group ($P<0.01$). After treatment, the ratio of CD3⁺, CD4⁺, CD4⁺/CD8⁺ cells in the observation group were significantly lower than those of the control group, CD8⁺ was significantly lower than that of the control group ($P<0.01$). The level of serum IL-4 and TNF- α in both groups were significantly lower than those of the control group, and the level of serum IFN- γ was significantly higher than that of the control group ($P<0.05$). **Conclusion:** Inhalation of budesonide was effective in the treatment of bronchiolitis, it effectively inhibit the inflammation, enhance the immune function, lower the adverse reactions with high safety.

Key words: Budesonide; Bronchiolitis; Efficacy; Interleukin-4 (IL-4) and interferon gamma (IFN- γ); Children

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前言

毛细支气管炎是由于毛细支气管炎性肿胀和分泌物阻塞引起通气功能异常,出现肺气肿或不张的下呼吸道感染疾病。

患儿伴有的临床症状多为发热、咳嗽、呼吸困难、肺部湿啰音等^[1],若得不到有效治疗,可导致哮喘的发生,甚至引起机体多器官并发症,严重威胁患儿的生命健康。由于小儿的肺部和支气管尚处于生长发育阶段,免疫功能低下,对外来微生物引起的

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感染免疫应答较弱,因此易诱发毛细支气管炎^[2]。目前,药物治疗仍是毛细支气管炎的首选治疗方案,抗生素、支气管扩张剂、糖皮质激素都是临床上常用药物^[3]。相关研究表明^[4]毛细支气管炎尤其是病毒性细支气管炎应用支气管扩张剂无明显疗效;抗生素的使用可能会引起患儿腹泻率增加。

布地奈德(Budesonide,BUD)是糖皮质激素类药物,其不含卤素,与倍氯米松有相似的局部抗炎作用,目前临床上多采用雾化吸入布地奈德来治疗毛细支气管炎。雾化吸入可使布地奈德直接到达患儿的呼吸道及肺部,因此比口服药物起效快。目前研究显示^[5]辅助性T细胞在毛细支气管炎发病中起着重要的作用,其水平下降可导致支气管哮喘的发生。本研究主要探讨了布地奈德治疗小儿毛细支气管炎的临床疗效及其对患儿血清IL-4、IFN- γ 、TNF- α 水平及体内辅助性T细胞的影响。

1 资料与方法

1.1 一般资料

研究对象选取我院2014年1月到2017年1月收治的毛细支气管炎患儿70例,纳入标准^①:均符合《APP临床实践指南》2014年版中诊断小儿毛细支气管炎的标准;^②患儿年龄 ≤ 2 岁;^③无合并严重的心脑血管、肝肾肺等器官组织疾病;^④家属均自愿参加并签署知情同意书。排除标准:^①患有严重血液、免疫系统疾病或恶性肿瘤者;^②近期服用免疫抑制剂、其他抗菌药物治疗者;^③对本研究药物过敏者;^④合并有其他影响治疗疗效的疾病者。采用随机数字法将其分为对照组和观察组,每组35例。对照组患者男性20例、女性15例,年龄在2个月~2岁,平均年龄为(10.28 $\pm$ 0.32)个月,病程在1~3d,平均病程为(1.89 $\pm$ 0.42)d。观察组患者男性21例、女性14例,月龄在2~23个月,平均年龄为(10.32 $\pm$ 0.41)个月,病程在1~3d,平均病程是(1.91 $\pm$ 0.49)d。两组患儿的性别、年龄、病程等一般资料比较,差异无统计学意义($P>0.05$),具有可比性。

1.2 治疗方法

两组患儿均接受平喘吸氧、抗病毒及抗感染等常规治疗。在对照组的基础上,观察组雾化吸入布地奈德(AstraZenecaPtyLtd公司,L0T3034595,2 mL:1mg),联合采用特布他林

(AstraZeneca AB公司,H00042391,2 mL:5 mg)、异丙托溴铵(Laboratoire Unither公司,H20100682,2 mL:500 μ g)治疗。具体方法:将布地奈德、特布他林和异丙托溴铵加入到空气压缩式雾化吸入器中,对患儿进行雾化吸入治疗,剂量依次为:0.5 mg/次、1.7 mg/次、125 μ g/次,治疗时间:10~15 min/次,频率:2次/d,两组患儿均连续接受治疗3~5天,观察病情变化并记录。

1.3 观察指标

① 两组患儿治疗后的疗效比较;② 两组患儿的气促缓解、哮鸣音消失、湿啰音消失、咳嗽消失、心率正常、住院等时间的比较;③ 比较两组患儿的治疗前后CD3⁺、CD4⁺、CD8⁺及CD4⁺/CD8⁺细胞比值;④ 两组患者治疗前后的血清白介素-4(IL-4)、干扰素- γ (IFN- γ)、肿瘤坏死因子(TNF- α)水平。

1.4 疗效评价标准及检测方法

① 治愈:治疗后患儿气喘、咳嗽、肺部啰音等症状完全消失,血常规检查恢复正常;② 有效:治疗后患儿气喘、咳嗽、肺部啰音等症状有所改善,血常规检查基本正常;③ 无效:治疗后患儿喘憋、咳嗽、肺部湿啰音等临床典型症状无明显好转或加重。治疗总有效率=(治愈率+显效率)*100%^[7]。

治疗前后分别采集患儿空腹静脉血2 mL,室温下静置20 min后3000 r/min离心15 min后取上清液,-80℃保存待测。采用酶联免疫吸附试验(ELISA)检测T淋巴细胞亚群(CD3⁺、CD4⁺、CD8⁺及CD4⁺/CD8⁺细胞比值)水平和血清IL-4、IFN- γ 、TNF- α 水平,试剂盒分别由北京方程生物科技有限公司、上海万疆生物科技有限公司、上海晶抗生物工程有限公司提供,所有步骤均严格参照操作说明书进行。

1.5 统计学方法

所有数据均经SPSS21.0系统处理,计量资料均采用均数 $\pm$ 标准差表示,并给予t检验。而计数资料以率(n%)表示,采用 χ^2 检验,以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组患儿治疗后的疗效比较

对照组患者的治疗总有效率(71.43%)明显低于观察组(97.14%)($P=0.00$),详情见表1。

表1 两组患者的治疗疗效比较[n(%)]

Table 1 Comparison of the curative effect between the two groups [n(%)]

Group	Cure	Effective	Invalid	Total effective rate(%)
Control group(n=35)	13(37.14)	12(34.29)	10(28.57)	71.43
Observation group(n=35)	20(57.14)	14(40.00)	1(2.86)	97.14
P	-			0.00

2.2 两组患儿临床相应症状缓解/消失、心率恢复正常和住院的时间比较

对照组气促缓解、哮鸣音消失、湿啰音消失、咳嗽消失、心率正常、住院等时间明显长于观察组($P<0.05$),详情见表2。

2.3 两组患儿治疗前后的T淋巴细胞亚群比较

两组患儿治疗前的血CD3⁺、CD4⁺及CD4⁺/CD8⁺细胞比值水平比较差异无统计学意义($P>0.05$);治疗后,两组患儿的血CD3⁺、CD4⁺及CD4⁺/CD8⁺细胞比值水平均明显升高,CD8⁺水

平明显降低。同时,观察组CD3⁺、CD4⁺及CD4⁺/CD8⁺细胞比值水平明显高于对照组($P<0.01$),CD8⁺水平明显低于对照组($P<0.01$),详情见表3。

2.4 两组患儿治疗前后的血清IL-4、IFN- γ 、TNF- α 水平比较($\bar{x}\pm s$)

两组患儿治疗前血清IL-4、IFN- γ 、TNF- α 水平比较均差异无统计学意义($p>0.05$);治疗后,观察组患儿血清IL-4、TNF- α 水平明显低于对照组($P<0.01$),血清IFN- γ 水平明显高

于对照组($P<0.01$),详情见表 4。

表 2 两组各临床症状缓解 / 消失时间、心率恢复正常时间及住院时间比较($\bar{x}\pm s$, d)

Table 2 Comparison of the clinical symptom relief time, heart rate recovery time and hospitalization time between two groups($\bar{x}\pm s$, d)

Group	Shortness of breath time	Wheezing disappearance time	Wet rale disappearance time	Cough disappearance time	Normal heart rate	Hospital stay
Control group (n=35)	3.13± 0.78	4.38± 0.96	6.42± 0.92	6.21± 1.28	2.82± 0.72	8.15± 2.03
Observation group (n=35)	2.26± 0.58	3.01± 0.75	4.74± 0.97	5.18± 0.89	2.16± 0.65	6.57± 1.19
P	0.79	0.00	0.85	0.00	0.82	0.00

表 3 两组患儿治疗前后的 T 淋巴细胞亚群比较($\bar{x}\pm s$)

Tab 3 Comparison of the T lymphocyte subsets before and after treatment between the two groups($\bar{x}\pm s$)

Group	CD3 ⁺		CD4 ⁺		CD8 ⁺		CD4 ⁺ /CD8 ⁺	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=35)	42.08± 7.14	56.01± 8.92 ^⓪	27.39± 5.32	32.24± 6.58 ^⓪	32.98± 7.21	30.68± 3.38 ^⓪	0.96± 0.20	1.32± 0.36 ^⓪
Observation group(n=35)	41.96± 7.11	64.31± 10.21 ^⓪	27.38± 5.41	39.76± 7.16 ^⓪	33.42± 7.16	24.86± 3.79 ^⓪	0.92± 0.19	1.90± 0.72 ^⓪
P	0.85	0.00	0.90	0.00	0.86	0.00	0.81	0.00

Note: ⓪ compared with before treatment, $P<0.05$.

表 4 两组患者治疗前后的血清 IL-4、IFN- γ 、TNF- α 水平比较($\bar{x}\pm s$)

Table 4 Comparison of the serum IL-4, IFN- and TNF- levels before and after treatment between the two groups($\bar{x}\pm s$)

Group	IL-4($\mu\text{g/L}$)		IFN- γ ($\mu\text{g/L}$)		TNF- α ($\mu\text{g/L}$)	
	Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Control group (n=35)	29.72± 4.26	22.31± 3.11 ^⓪	136.54± 15.42	158.98± 16.12 ^⓪	199.73± 53.11	163.57± 49.46 ^⓪
Observation group (n=35)	29.42± 4.01	8.14± 1.36 ^⓪	135.79± 14.76	205.98± 21.96 ^⓪	204.96± 45.79	125.10± 38.96 ^⓪
P	0.83	0.00	0.87	0.00	0.90	0.00

Note: ⓪ compared with before treatment, $P<0.05$.

3 讨论

毛细支气管炎是小儿出生一年内最常见的下呼吸道感染,是一岁内儿童住院的常见原因^[8]。由于婴幼儿气道较成年人狭窄^[9],气流速度慢,病原微生物易滞留,且免疫系统发育不完善,黏膜表面 IgA 水平低,因此易发生感染^[10]。且婴幼儿细支气管壁无软骨支撑,直径只有 75~300 μm 左右^[11],当炎症发生时毛细支气管纤毛上皮坏死,局部充血,部分黏膜上皮细胞坏死脱落,引起管腔部分或完全堵塞,导致肺通气和血流灌注失调产生低氧血症^[12],故患儿常伴有喘息样呼吸困难,其严重危害患儿的生命健康。有研究指出^[13]体内某些细胞因子可诱发毛细支气管炎。Th1 细胞可产生 INF- γ , INF- γ 与 IL-4 呈拮抗作用,故可以抑制 IL-4 诱导 B 细胞增殖和 IgE 的分泌^[14],从而减缓患儿喘息、咳嗽。Th2 细胞可产生 IL-4, IL-4 趋化嗜酸性粒细胞浸润患儿呼吸道^[15],抑制 INF- γ 的产生,促使 B 细胞合成分泌 IgE 从而诱发患儿喘息、咳嗽^[16]。TNF- α 可诱导血小板活化因子和白介素的释放^[17],从而加重炎症反应,诱发喘息。正常机体中 T

细胞平衡分化发育为 Th1/Th2^[18],共同调节机体稳态, Th1/Th2 失衡已经被证明是哮喘的发病机制^[19],也与毛细支气管炎的发病有关^[20]。研究表明^[21]小儿在患毛细支气管期间血浆内 CD3⁺、CD4⁺ 细胞水平减少, CD8⁺ 细胞水平增多, 因此机体内 IgE 合成过多时,可诱导某种气道反应增加,说明 T 细胞参与了毛细支气管炎过程。

目前,布地奈德广泛应用于临床上慢性咽炎、喉炎、鼻炎、支气管炎等疾病的治疗^[22],其抑制炎症介质和细胞因子的合成的同时促使机体合成抗炎性蛋白质,故具有良好的疗效。布地奈德属于糖皮质激素类药物,因其与糖皮质激素的受体结合能力强,故具有抗炎抗过敏的作用,是地塞米松的 980 倍^[23]。雾化吸入可使药物到达全肺,药物可附着在气道黏膜上,与糖皮质激素相关受体特异性结合,从而激活受体,诱导自身抗体的产生,同时通过抑制气道的高反应性,增强支气管、平滑肌对儿茶酚胺的敏感性来发挥作用,可缓解支气管痉挛、黏膜水肿,修复气道损伤以及降低毛细血管通透性^[24],最终达到治疗毛细支气管炎的作用。特布他林属于肾上腺素 β_2 - 受体激动剂,作用于中

小气道,辅助布地奈德增强抗炎、平喘作用^[25];异丙托溴铵是一种四价铵化合物,具有抗胆碱能作用,可辅助布地奈德增强支气管扩张作用。

采用雾化吸入给药方式使药物直接进入呼吸道,可湿化气道、稀释痰液,其用量只需其他给药方式的十分之一^[26],明显减少了药物的毒副作用,同时也避免了口服或静脉给药对患儿非病变器官的影响,优于其他治疗方式。在本研究中,观察组患儿治疗后的 IL-4、TNF- α 水平明显低于对照组,IFN- γ 水平明显高于对照组,表明布地奈德有纠正 Th1/Th2 比例与功能失衡的作用,降低患儿机体的炎症反应;观察组儿血浆中 CD3⁺、CD4⁺、及 CD4⁺/CD8⁺ 细胞比值均明显高于对照组,CD8⁺ 明显低于对照组,表明布地奈德有改善患儿机体免疫功能的作用。同时研究显示观察组患儿的气促、咳嗽、肺部哮鸣音等症状缓解或消失的时间明显低于对照组,可能与布地奈德抑制炎症反应,改善机体免疫功能有关。

综上所述,布地奈德雾化吸入治疗小儿毛细支气管炎疗效显著,在有效抑制炎症的同时,增强机体免疫功能,治疗安全性较高。

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