临床细胞生物学

重组人干扰素α-2b联合布地奈德、异丙托溴铵雾化对小儿毛细支气管炎疗效及IL-18、IL-33的影响

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摘要 该研究探讨重组人干扰素α-2b联合布地奈德、异丙托溴铵雾化治疗小儿毛细支气管炎的疗效及其对患儿IL-18、IL-33的影响。选取2016年1月至2017年1月我院收治的毛细支气管炎患儿88例, 采用随机数字表法分为对照组(44例)和观察组(44例)。两组患儿均给予止咳、祛痰、平喘、抗感染及抗病毒等常规治疗, 对照组在常规治疗基础上加用布地奈德、异丙托溴铵雾化治疗, 观察组在对照组治疗的基础上再加用重组人干扰素α-2b雾化治疗, 两组患儿均治疗7天。比较两组患儿的临床疗效及4个月内呼吸道合胞病毒(respiratory syncytial virus pneumonia, RSV)感染复发率, 同时比较两组患儿治疗前后血清白细胞介素-18(IL-18)、白细胞介素-33(IL-33)、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)、嗜酸粒细胞阳离子蛋白(eosinophilic cell cationic protein, ECP)、嗜酸粒细胞(eosinophilic cells, EOS)水平。研究结果显示, 观察组的治疗总有效率为95.45%, 高于对照组的81.82%, 差异具有统计学意义(P<0.05); 治疗前, 两组患儿血清IL-18、IL-33水平无显著差异(P>0.05); 治疗后观察组的IL-18、IL-33、TNF-α水平均显著低于对照组, 组间差异明显(P<0.05); 治疗前, 两组患儿ECP、EOS水平无显著差异(P>0.05); 治疗后观察组的ECP(7.22±4.48 μg/mL)、EOS(124.25±40.49 μg/mL)水平均显著低于对照组(11.72±4.81 μg/mL、177.18±50.08 μg/mL), 组间差异明显(P<0.05)。随访4个月中, 观察组的RSV复发率为4.55%, 明显低于对照组的22.73%, 组间差异显著(χ^2=6.18, P=0.01)。该研究得出, 重组人干扰素α-2b联合布地奈德、异丙托溴铵雾化治疗小儿毛细支气管炎效果良好, 可有效降低IL-18、IL-33水平, 且抗炎效果稳定、不易复发, 值得临床推广使用。

关键词 重组人干扰素α-2b; 布地奈德; 异丙托溴铵; 毛细支气管炎; 疗效; IL-18; IL-33

Effects of Recombinant Interferon α-2b Combined with Budesonide and Ipratropium Bromide on Efficacy of Bronchiolitis and IL-18 and IL-33 in Children

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Abstract The purpose of this study was to investigate the efficacy of recombinant human interferon α-2b combined with budesonide and ipratropium bromide in the treatment of bronchiolitis and its effects on IL-18 and

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IL-33 in children with bronchiolitis. Eighty-eight children with bronchiolitis treated in our hospital from January 2016 to January 2017 were randomly divided into control group (n=44) and observation group (n=44). The children in the two groups were given routine treatment such as antitussive, expectorant, antiasthmatic, anti-infective and antiviral therapy. The control group was treated with budesonide and ipratropium bromide on the basis of routine treatment. The observation group was treated with recombinant human interferon α-2b in addition to the control group. Both groups were treated for 7 days. The clinical efficacy and the recurrence rate of RSV (respiratory syncytial virus pneumonia) infection within 4 months were compared between the two groups. At the same time, the levels of serum IL-18 (interleukin-18), IL-33 (interleukin-33), TNF-α (tumor necrosis factor-α), ECP (eosinophilic cell cationic protein) and EOS (eosinophilic cells) were compared between the two groups before and after treatment. The results showed that the total effective rate of the observation group was 95.45%, which was higher than that of the control group (81.82%), and the difference was statistically significant. Before treatment, there was no significant difference in serum IL-18 and IL-33 levels between the two groups. After treatment, the levels of IL-18, IL-33 and TNF-α in the observation group were significantly lower than those in the control group, and there was significant difference between the two groups. Before treatment, there was no significant difference in the levels of ECP and EOS between the two groups, but after treatment, the levels of ECP and EOS in the observation group (7.22±4.48 μg/mL) and EOS (124.25±40.49 μg/mL) were significantly lower than those in the control group (11.72±4.81 μg/mL and 177.18±50.08 μg/mL). During the 4-months follow-up, the recurrence rate of RSV in the observation group was 4.55%, which was significantly lower than that in the control group (22.73%). There was significant difference between the two groups (χ^2=6.18, P<0.01). This study shows that recombinant human interferon α-2b combined with budesonide and ipratropium bromide atomization is effective in the treatment of bronchiolitis in children, which can effectively reduce IL-18 and IL-33, and has stable anti-inflammatory effect as well as is not easy to recur, so it is worthy of clinical application.

Keywords recombinant interferon alpha-2b; budesonide; ipratropium bromide; bronchiolitis; efficacy; IL-18; IL-33

毛细支气管炎是小儿常见的呼吸系统疾病, 该病多发于2岁以下婴幼儿, 大部分患儿年龄为1~6个月[1]。小儿毛细支气管炎80%以上是由呼吸道合胞病毒(respiratory syncytial virus, RSV)所致[3], 此外, 鼻病毒、流感病毒、腺病毒均可引起毛细支气管炎。其临床症状主要表现为咳嗽、呼吸困难、三凹征及喘息, 如未能及时治疗甚至会出现呼吸衰竭及心力衰竭等严重结果[2]。流行病学研究报道, 小儿毛细支气管炎发病率高达80%, 且约1/3的患儿发展为哮喘[3], 严重影响患儿的身体健康和生命安全, 及时发现病情和早期用药可有效预防哮喘疾病的发生[4], 从而提高患儿生活质量。目前, 尚未有根治小儿毛细支气管炎的方法, 广泛应用于临床的方法主要有抗感染药物、中药治疗、氧疗等, 但难以达到理想的治疗效果, 复发率较高。布地奈德、异丙托溴铵是小儿毛细支气管炎治疗中的常用药物, 可迅速缓解患儿病情。近年来, 相关研究报道, 重组人干扰素α-2b在毛细支气管炎的治疗中具有增强抗感染和调节免疫的作用[5]。本次研究旨在分析重组人干扰素α-2b联合布地奈德、异丙托溴铵雾化对小儿毛细支气管炎疗效及白细胞介素-18(interleukin-18, IL-18)、白细胞介素-33(interleukin-33, IL-33)的影响, 现汇报如下。

1 资料与方法

1.1 一般资料

采选我院88例2016年1月~2017年1月儿科收治的毛细支气管炎患儿。纳入标准: (1)所有患儿符合第6版《实用儿科学》中关于毛细支气管炎的诊断标准[6]; (2)患儿家属同意并签订知情同意书; (3)无心脏病、肝肾功能不全、肿瘤等重大疾病史, 无药物食物过敏史。排除标准: (1)伴有严重的血液系统、免疫系统疾病患儿; (2)病程过程中服用维生素D和使用过免疫调节剂者; (3)合并慢性肝肾疾病、重度

蛋白质–能量营养不良及先天性肺疾病者; (4)不配合治疗者。采用随机数字表法将88例患者分为对照组和观察组, 其中对照组患儿年龄为2~22个月, 平均年龄为(6.35±2.25)个月; 男21例, 女23例; 病程1~12天, 平均病程(4.33±2.45)天。观察组患儿年龄为3~25个月, 平均年龄为(7.12±3.23)个月; 男22例, 女22例; 病程1~15天, 平均病程(5.41±3.25)天。两组患者一般资料差异无统计学意义(P>0.05), 具有可比性(表1)。本研究经本院伦理委员会批准。

1.2 方法

两组患儿均给予止咳、祛痰、平喘、抗感染及抗病毒等常规治疗。对照组在常规治疗基础上加用0.5 mg布地奈德混悬液(阿斯利康制药有限公司, 国药准字H20140475, 2 mL:1 mg)、1 mL异丙托溴铵溶液(法国Laboratoire Unither, 批准文号H20150158, 250 μg:2 mL×10支)雾化治疗, 2次/天。

观察组在对照组治疗的基础上雾化吸入0.3 mL重组人干扰素(北京凯因科技股份有限公司提供, 批准文号201601002, 3 Million International Units/0.3 mL/支), 2次/天。两组患儿均治疗7天。

1.3 观察指标

(1)比较两组患儿的临床疗效; (2)比较两组患儿4个月内RSV感染复发率; (3)比较两组患儿治疗前后IL-18、IL-33、肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)水平; (4)比较两组患儿治疗前后嗜酸粒细胞阳离子蛋白(eosinophilic cell cationic protein, ECP)、嗜酸粒细胞(eosinophilic cells, EOS)水平。

1.4 检查方法及疗效标准

检查方法: 分别于治疗前1天及治疗7天后清晨空腹抽取患者静脉血3 mL, 3 000 r/min离心15 min分离血清, 用酶联免疫吸附法(ELISA)检测患者IL-18、IL-33、TNF-α、ECP、EOS水平, 所用试剂盒由森贝伽(南京)生物科技有限公司提供, 所有操作过程均严格按照使用说明书进行。

疗效标准(1)控制: 患儿5天内体温转归, 肺部湿啰音和喘鸣音、咳嗽、喘息等临床症状基本消失; (2)显效: 患儿5天后体温有所下降, 肺部湿啰音和喘鸣音、咳嗽、喘息等临床症状明显减轻; (3)有效: 患儿5天后体温有所改善但仍发热反复, 所有临床症状及体征有所减轻; (4)无效: 患儿5天后仍出现发热, 肺部湿啰音和喘鸣音、咳嗽、喘息等临床症状无改善或加重。

1.5 统计学方法

使用SPSS 21.0分析数据, 计量资料以($\bar{x}$±s)表示, 组间比较采用t检验。计数资料以率[n(%)]表示, 组间比较采用χ^2检验。P<0.05为差异有统计学意义。

2 结果

2.1 两组临床疗效的比较

观察组控制26例(59.09%), 显效12例(27.27%), 有效4例(9.09%), 无效2例(4.55%); 对照组控制19例(43.18%), 显效10例(22.73%), 有效7例(15.91%), 无效8例(18.18%)。两组疗效对比(观察组95.45% *vs* 对照组81.82%), 观察组显著优于对照组(χ^2=4.06, P=0.04), 有显著性差异。

2.2 两组患儿治疗前后IL-18、IL-33、TNF-α水平的比较

治疗前两组患儿IL-18、IL-33、TNF-α水平均无显著差异(P>0.05); 治疗后观察组IL-18、IL-33、TNF-α水平显著低于对照组, 组间差异明显(P<0.01)(表2)。

2.3 两组患儿治疗前后的ECP、EOS的比较

治疗前两组患儿的ECP、EOS均无显著差异(P>0.05); 治疗后观察组的ECP、EOS均显著低于对

表1 患者一般资料比较(两组)

Table 1 General data comparison of patients (two groups)

组别 Group	年龄/month Age /month	性别(n)/% Gender (n) /%		病程/天 Course of disease /d
		Male	Female	
Control group (n=44)	6.35±2.25	21 (47.72%)	23 (52.27%)	4.33±2.45
Observation group (n=44)	7.12±3.23	22 (50.00%)	22 (50.00%)	5.41±3.25
t/χ^2	t=1.40	χ^2=0.05	χ^2=0.05	t=1.76
P	0.166	0.831	0.831	0.082

两组患者一般资料对比, P>0.05。

Comparison of general information between two groups of patients, P>0.05.

表2 两组患儿治疗前后IL-18、IL-33、TNF-α水平的比较($\bar{x}\pm s$)

Table 2 Comparison of IL-18, IL-33 and TNF-alpha levels before and after treatment in two groups ($\bar{x}\pm s$)

组别 Group	IL-18 /ng·L^{-1}		IL-33 /ng·L^{-1}		TNF-α /pg·mL^{-1}	
	治疗前 Before treatment	治疗后 After treatment	治疗前 Before treatment	治疗后 After treatment	治疗前 Before treatment	治疗后 After treatment
Control group (n=44)	178.51±79.16	166.43±68.54*	189.65±82.32	163.16±65.44*	39.75±5.89	27.24±13.49*
Observation group (n=44)	177.87±79.02	142.37±32.67*	187.97±81.63	145.04±42.85*	40.74±4.89	18.63±12.86*
t	0.04	2.10	0.10	2.06	0.86	3.06
P	0.97	0.04	0.92	0.07	0.39	0

*P<0.05, 与治疗前比较。

*P<0.05 compared with before treatment.

表3 两组患儿治疗前后的ECP及EOS的比较($\bar{x}\pm s$)

Table 3 Comparison of ECP and EOS before and after treatment in two groups ($\bar{x}\pm s$)

组别 Group	ECP /μg·mL^{-1}		EOS /×10^3·mm^{-3}	
	治疗前 Before treatment	治疗后 After treatment	治疗前 Before treatment	治疗后 After treatment
Control group (n=44)	25.53±11.16	11.72±4.81*	204.82±71.18	177.18±50.08*
Observation group (n=44)	26.73±11.86	7.22±4.48*	210.58±100.25	124.25±40.49*
t	0.62	5.54	0.31	5.45
P	0.49	0	0.76	0

*P<0.05, 与治疗前比较。

*P<0.05 compared with before treatment .

照组, 组间差异明显(P<0.01)(表3)。

2.4 两组患儿4个月内RSV感染复发率的比较

随访4个月中, 对照组患儿共出现10例RSV感染复发, 复发率为22.73%; 研究组患儿共出现2例RSV感染复发, 复发率为4.55%, 研究组的复发率明显低于对照组, 组间差异显著(χ^2=6.18, P=0.01)。

3 讨论

毛细支气管炎发病年龄多见于1~6个月, 发病率高达80%。临床患儿可见发热、咳嗽、喘息、呼吸困难等临床症状, 如未能及时治疗, 患儿可出现肺气肿、心肌损伤甚至造成呼衰及心衰等严重结局[7-9]。目前, 尚未有根治毛细支气管炎的方法, 临床多采用抗感染药物、氧疗等治疗方法, 但往往不能达到理想的治疗效果, 病情容易反复发作, 严重影响患儿的身心健康和生命安全。解剖学分析发现, 婴幼儿的呼吸道黏膜抵抗力薄弱容易受到各种病原的感染, 且婴幼儿免疫机制不完善造成局部清除能力有限, 从而导致感染向下蔓延引起毛细支气管炎[10-12]。IL-8是一种小分子活性多肽, 其主要免疫作用是趋化、激活中性粒细胞, 增加外周血中组胺的释放, 从而刺激呼吸道分泌炎性介质, 引起炎症反应[13]。体外实验研究发现, 在小鼠鼻内滴入IL-33, 可导致气道高反应性和气道炎症的发生[14]。IL-33具有促使气道炎症的发生和肺泡巨噬细胞的活化作用, 阻断IL-33后, 肺泡巨噬细胞来源的细胞炎症因子显著减少, 气道炎症明显减轻[15]。TNF-α主要由单核巨噬细胞产生, 亦可经B细胞应答病毒后产生, 其主要结构是多肽链, 主要位于肝细胞胞质中, 能够增强多种黏附分子的表达, 从而增强炎症反应和细胞毒作用, 但是TNF-α的细胞毒作用是通过间接诱导IL-6、IL-8等细胞因子的高表达来引起的[16]。因此, 血清中IL-18、IL-33、TNF-α水平可一定程度反映毛细支气管炎患儿的炎症严重程度。

血清ECP是一种具有强大细胞毒性及神经毒性的嗜酸性粒细胞经活化释放的炎性介质, 其可导致呼吸道炎症, 诱发或加重喘息、气促等症状。因此, 血清ECP可作为判断喘息发作的特异性指标之一。相关研究表明, 患儿的EOS浓度因病毒感染而上升, 从而增加血清ECP合成分泌, 进而趋化EOS、T淋巴细胞、单核细胞而使炎症反应加剧[17-19]。糖皮质激素可有效治疗毛细支气管炎, 其对炎症细胞的活化、

迁移和生成及炎症介质的释放具有抑制作用, 同时抑制平滑肌的收缩。布地奈德作为一种吸入性糖皮质激素, 可特异性抑制嗜酸性粒细胞的增殖及分化, 其进入呼吸道后可有效减少嗜酸性粒细胞的生成从而减少循环中的炎性介质如IL-18、IL-33、TNF-α、ECP, 起到抗炎效果。异丙托溴铵气雾剂是一种抗胆碱药物, 对M胆碱受体具有阻断作用, 且可有效缓解器官平滑肌痉挛, 相关研究报道, 异丙托溴铵气雾剂与β_2受体激动剂联用对支气管的舒张具有增强作用且可延长持续时间[20]。重组人干扰素α-2b是病毒进入机体后诱导宿主细胞产生的反应物, 局部应用于病变部位, 具有促使病变部位及其邻近细胞抵抗病毒的感染和增强免疫功能的作用。布地奈德、异丙托溴铵、重组人干扰素α-2b三者联用雾化吸入可达到增强免疫力、抗炎平喘、减少毛细支气管炎的效果。本研究结果显示, 观察组的治疗总有效率为95.45%, 高于对照组的81.82%; 治疗后观察组的IL-18、IL-33、TNF-α水平均显著低于对照组; 治疗后观察组的ECP、EOS水平均显著低于对照组; 随访4个月中, 观察组的RVS复发率为4.55%, 明显低于对照组的22.73%。提示重组人干扰素α-2b联合布地奈德、异丙托溴铵雾化可有效降低毛细支气管炎患儿的IL-18、IL-33水平, 且抗炎效果稳定、不易复发。

综上所述, 重组人干扰素α-2b联合布地奈德、异丙托溴铵雾化治疗小儿毛细支气管炎效果良好, 可有效降低IL-18、IL-33水平, 且抗炎效果稳定、不易复发。该方法值得临床推广使用。

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