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rh-INFα2b 治疗儿童毛细支气管炎的疗效及对免疫功能的调节作用 *

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摘要 目的:探讨重组人干扰素 α2b(rh-INFα2b)治疗儿童毛细支气管炎的临床效果及对免疫功能的调节作用。**方法:**选取我院儿科收治的毛细支气管炎患儿 134 例作为研究对象,采用随机数字表法将其分为观察组和对照组,每组各 67 例。两组均给予基础治疗措施,观察组采用雾化 rh-INFα2b 治疗,疗程均为一周。对比两组治疗前后的咳嗽、喘息、哮鸣音、三凹征症状评分、外周血 T 淋巴细胞分布、血清白细胞介素 -4(IL-4)、γ- 干扰素(IFN-γ)、白细胞介素 -2(IL-2)水平的变化。**结果:**观察组治疗后的咳嗽、喘息、哮鸣音、三凹征症状评分均显著低于对照组(P<0.05),$CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 均明显高于对照组(P<0.05),而 $CD8^+$ 测定值、血清 IL-4、IFN-γ、IL-2 水平均显著低于对照组(P<0.05);治疗 7d 后,观察组的痊愈率 53.73%、显效率 32.84%、有效率 11.94%、无效率 1.49%,对照组的痊愈率 37.31%、显效率 38.81%、有效率 19.40%、无效率 4.48%,观察组的痊愈率显著优于对照组(P<0.05)。**结论:**雾化 rh-INFα2b 可显著提高儿童毛细支气管炎的临床疗效,增强其免疫功能。

关键词:重组人干扰素 α2b;毛细支气管炎;免疫调节

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Therapeutic Effect of rh-INFα2b on the Children with Bronchiolitis and Its Regulation of Immune Function*

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ABSTRACT Objective: To investigate the clinical effect of rh-INFα2b in the treatment of bronchiolitis in children and its regulating effect on immune function. **Methods:** A total of 134 children with bronchiolitis treated in our hospital's pediatric department were selected as research objects, and they were divided into the observation group and the control group by random number table method, with 67 cases in each group. Both groups were given conventional treatment, and the observation group was treated with nebulized rh-INFα2b for one week. The changes of cough, wheezing, wheezing, tricuspid symptom score, peripheral blood T lymphocyte distribution, serum IL-4, IFN-γ, and IL-2 levels were compared between the two groups before and after treatment. **Results:** The cough, wheezing, wheezing, and trident sign scores of the observation group after treatment were significantly lower than those of the control group (P <0.05), $CD3^+$, $CD4^+$, $CD4^+$ / $CD8^+$ were significantly higher than the control group (P <0.05). The $CD8^+$ measured value, serum IL-4, IFN-γ, IL-2 levels were significantly lower than the control group (P <0.05). After 7 days of treatment, the recovery rate of the observation group was 53.73%, the apparent efficiency was 32.84%, the effective rate was 11.94%, and the ineffective rate was 1.49%. The cure rate of the control group was 37.31%, the apparent efficiency was 38.81%, the effective rate was 19.40%, and the inefficiency was 4.48%. The recovery rate of observation group was better than that in the control group (P<0.05). **Conclusion:** Nebulizing rh-INFα2b can significantly improve the clinical efficacy of bronchiolitis in children and enhance its immune function.

Key words: Recombinant human interferon alpha 2b; Bronchiolitis; Immunomodulatory effects

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前言

毛细支气管炎的基础发病率较高，在不同免疫力的儿童中,毛细支气管炎的发病率均可呈现出较高的发病态势。临床上,毛细支气管炎能够导致患者重症肺部感染的发生,提高远期多脏器功能致残的发生风险[1,2]。药物治疗能够在毛细支气管炎的整体性治疗过程中发挥作用,支气管扩张剂或者糖皮质激素能够显著缓解毛细支气管炎的临床症状,促进患儿肺功能的

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恢复。但长期临床观察显示采用糖皮质激素或者支气管扩张剂治疗后，毛细支气管炎患者的病情缓解率仍然偏低，治疗后患儿疾病的复发率仍然较高，自身免疫力抑制的表现仍然明显[3]。

重组人干扰素 α2b(rh-INFα2b)作为抗病毒药物，能够能够通过拮抗病毒 RNA 的合成，促进病毒颗粒蛋白的合成障碍，最终促进呼吸道病毒的凋亡和分解[4,5]。本次研究选取我院儿科收治的毛细支气管炎患儿 134 例作为研究对象，探讨了 rh-INFα2b 治疗毛细支气管炎的临床效果，现报道如下。

1 资料与方法

1.1 临床资料

选取我院儿科收治的毛细支气管炎患儿 134 例作为研究对象，采用随机数字表法将其分为观察组和对照组各 67 例，研究对象纳入间段为 2017 年 1 月～2019 年 3 月。纳入标准：(1)毛细支气管炎的诊断标准参考中华医学会制定的标准[6]；(2)患儿年龄 6 个月～3 岁；(3)发病至就诊时间 <96 h；(4)近 2 周未使用抗生素、抗病毒药物治疗；(5)研究方案获得医学伦理委员会审批后同意，经患儿家长同意。排除标准：(1)先心病患儿；(2)脓毒血症、全身感染疾病；(3)心衰、肺水肿；(4)近 3 个月具有糖皮质激素类药物治疗史；(5)对治疗药物具有过敏反应。

观察组：男 37 例、女 30 例，年龄 6 个月 ~3 岁，平均 16.9±5.2 个月；病程 1~3 天，平均 1.63±0.40 天；体质量 12.9±2.0 kg。对照组：男 32 例、女 35 例，年龄 6 个月 ~3 岁，平均 17.3±5.8 个月；病程 1~3 天，平均 1.55±0.47 天；体质量 13.2±2.5 kg。两组患儿的年龄、性别、病程、体质量比较差异无统计学意义(P>0.05)，具有可比性。

1.2 方法

1.2.1 治疗方法 对照组：吸入硫酸沙丁胺醇悬液(阿斯利康公司 批号：306877)，0.25 mL，布地奈德悬液(AstraZenecaPtyLtd 公司 批号：H20170902)，0.5 mg，每日 2 次，连续治疗 7d；观察组在硫酸沙丁胺醇 + 布地奈德治疗的基础上，联合使用 rh-INFα2b 注射液(天津华立达生物公司，批号：20178494)，雾化吸入，每日 2 次，间隔时间大于 6h，连续治疗 7d。具体雾化方法：将硫酸沙丁胺醇、布地奈德或者 rh-INFα2b，加入 9g/L 的生理盐水中雾化吸入，总体积控制为 2.5 mL，流量大于 5 L/min，20 min 内雾化吸入完。

1.2.2 观察指标 对比两组治疗前、治疗 1 周后的咳嗽、喘息、哮鸣音、三凹征症状评分(均划分为 0、1、2、3 分四个等级，评分越高表示患儿的临床症状越严重)，治疗前后的外周血 T 淋巴细胞($CD3^+$、$CD4^+$、$CD8^+$)、血清白细胞介素 -4(IL-4)、γ- 干扰素(IFN-γ)、白细胞介素 -2(IL-2)。

采用外周静脉血 3-5 mL，室温下放置 5-10 min，自然分层后抽取上层清亮液体待测。采用 ELISA 法进行 IL-4、IFN-γ、IL-2 的检测，BioTek 酶标仪购自美国伯腾仪器有限公司；采用流式细胞仪法进行 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$T 淋巴细胞的检测，流式细胞仪 Attune NxT 购自赛默飞公司。

临床疗效评价：痊愈：患儿的咳嗽、喘息、哮鸣音等临床症状体征完全消失，实验室检查各项指标及胸片检测均恢复正常；显效：患儿的咳嗽、喘息、哮鸣音等临床症状体征得到显著缓解或者消失，实验室指标基本恢复正常；有效：患儿的咳嗽、喘息、哮鸣音等临床症状体征较治疗前有所改善但是需要进一步治疗，实验室指标尚未完全恢复正常；无效：未达到上述标准的患儿；总有效率 = 痊愈 + 显效 + 有效。

1.3 统计学处理

统计分析采用 SPSS 21.0 软件，计量资料指标采用 $\bar{x}\pm s$ 表示，两组间比较采用 t 检验，计数资料组间比较采用 x^2 检验或非参数检验，以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组临床症状评分的比较

观察组治疗后的咳嗽、喘息、哮鸣音、三凹征症状评分均显著低于对照组(P<0.05)，见表 1。

2.2 两组治疗前后的外周血 T 淋巴细胞亚群指标比较

观察组治疗后的 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 测定值高于对照

表 1 两组治疗前后临床症状评分的比较($\bar{x}\pm s$，分)

Table 1 Comparison of the clinical symptoms score between observation group and control group before and after treatment($\bar{x}\pm s$, scores)

Groups	n	Cough		Respite	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	67	2.21±0.58	0.39±0.16	1.90±0.48	0.30±0.11
Control group	67	2.15±0.63	0.60±0.23	1.82±0.51	0.51±0.19
t		0.574	-6.135	0.935	-7.829
P		0.567	0.000	0.351	0.000

Groups	n	Wheeze		Trident	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	37	2.04±0.61	0.40±0.17	1.44±0.38	0.20±0.07
Control group	36	1.96±0.58	0.58±0.21	1.51±0.43	0.35±0.12
t		0.778	-5.453	-0.998	-8.838
P		0.438	0.000	0.320	0.000

组(P<0.05)，$CD8^+$ 测定值低于对照组(P<0.05)，见表 2。

表 2 两组治疗前后外周血 T 淋巴细胞亚群指标的比较($\bar{x}\pm s$)

Table 2 Comparison of the T lymphocyte subsets in peripheral blood between observation group and control group before and after treatment($\bar{x}\pm s$)

Groups	n	$CD3^+$(%)		$CD4^+$(%)	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	67	56.12±5.59	65.20±4.73	34.81±3.30	39.65±4.12
Control group	67	57.06±5.25	63.66±5.04	35.20±3.48	38.11±4.56
t		-1.003	1.824	-0.666	2.051
P		0.318	0.070	0.507	0.042

Groups	n	$CD8^+$(%)		$CD4^+/CD8^+$	
		Before treatment	After treatment	Before treatment	After treatment
Observation group	37	27.74±2.86	24.20±2.55	1.25±0.20	1.64±0.25
Control group	36	27.60±2.92	25.91±2.73	1.28±0.19	1.48±0.22
t		0.280	-3.747	-0.890	3.933
P		0.780	0.000	0.375	0.000

2.3 两组治疗前后的血清 Th1/Th2 细胞因子水平比较

观察组治疗后的血清 IL-4、IFN-γ、IL-2 测定值均显著低于对照组(P<0.05)，见表 3。

表 3 两组治疗前后的血清 Th1/Th2 细胞因子水平比较($\bar{x}\pm s$)

Table 3 Comparison of the serum Th1 / Th2 levels between observation group and control group before and after treatment($\bar{x}\pm s$)

Groups	n	IL-4(ng/L)		IFN-γ(ng/L)		IL-2(pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	67	740.5±209.5	485.9±98.7	966.8±220.4	518.3±138.0	2.90±0.78	1.52±0.58
Control group	67	727.1±198.8	569.3±122.6	931.4±243.0	600.5±163.7	2.81±0.72	1.85±0.51
t		0.380	-4.337	0.883	-3.143	0.694	-3.497
P		0.705	0.000	0.379	0.002	0.489	0.001

2.4 两组的临床疗效比较

治疗 7d 后，观察组的痊愈率 53.73%、显效率 32.84%、有效率 11.94%、无效率 1.49%，对照组的痊愈率 37.31%、显效率 38.81%、有效率 19.40%、无效率 4.48%，观察组的痊愈率显著优于对照组(P<0.05)；见表 4。

表 4 两组的临床疗效比较[例(%)]

Table 4 Comparison of the clinical efficacy between observation group and control group[n(%)]

Groups	n	Recovery	Markedly effective	Effective	invalid
Observation group	67	36(53.73)	22(32.84)	8(11.94)	1(1.49)
Control group	67	25(37.31)	26(38.81)	13(19.4)	3(4.48)
Z			-2.083		
P			0.037		

2.5 两组的不良反应对比

治疗过程中，两组均未出现严重的不良反应，观察组有 1 例出现一过性皮疹，对照组未见特殊不良反应发生。

3 讨论

支气管炎系指支气管发生炎症，小儿最常见且较严重的是毛细支气管炎，好发于冬季，可引起局部流行[7]。毛细支气管炎的病变主要发生在肺部的细小支气管，也就是毛细支气管，所以病名为 " 毛细支气管炎 "，通常是由普通感冒，流行性感冒等病毒性感染引起的并发症，也可能由细菌感染所致，是小儿常见的一种急性下呼吸道感染[8]。呼吸道合胞病毒感染、流感病毒感染，均能够通过下呼吸道毛细支气管结构的破坏，加剧局部炎症反应，促进毛细支气管炎的发生[9]。毛细支气管炎的病原主要为呼吸道合胞病毒，可占 80%或更多；其它依次为腺病毒、副流

感病毒、鼻病毒、流感病毒等;少数病例可由肺炎支原体引起。

感染病毒后,细小的毛细支气管充血,水肿,粘液分泌增多,加上坏死的粘膜上皮细胞脱落而堵塞管腔,导致明显的肺气肿和肺不张[10]。炎症常可累及肺泡,肺泡壁和肺间质,故可以认为它是肺炎的一种特殊类型[11]。毛细支气管炎不同于一般的气管炎或支气管炎,临床症状像肺炎,但以喘憋为主,此病多发生在 2.5 岁以下的小儿,80%在 1 岁以内,多数是 6 个月以下的小儿[12,13]。在具有自身 T 淋巴细胞功能紊乱或者功能障碍的儿童中,毛细支气管炎的发病程度可持续加重,其整体临床结局可显著恶化。持续的毛细支气管炎病情进展,还能够增加肺心病或者支气管哮喘的发病风险[14,15]。通过针对性扩张毛细支气管,能够显著改善支气管阻塞及平滑肌痉挛表现,改善肺通气和肺换气过程。而糖皮质激素能够通过抑制局部炎症因子的释放,缓解局部呼吸道粘膜上皮细胞的炎症损伤,进而稳定病情。但包括多项非多中心的相关报道研究认为,采用布地奈德 + 沙丁胺醇等药物治疗后,毛细支气管炎患者的咳嗽和喘息等临床症状仍然较为明显,治疗后患者肺部啰音的消失时间仍然较长[16]。

rh-INFα2b 是人工合成的干扰素药物,能够通过结合体细胞膜上皮的配体,诱导抗病毒效果[17],具有广谱抗病毒、抗肿瘤、抑制细胞增殖以及提高免疫功能等作用[18]。干扰素与细胞表面受体结合诱导细胞产生多种抗病毒蛋白,抑制病毒在细胞内繁殖,提高免疫功能包括增强巨噬细胞的吞噬功能,增强淋巴细胞对靶细胞的细胞毒性和天然杀伤性细胞的功能[19]。rh-INFα2b 对于病毒组蛋白受体的阻断作用能够抑制单核细胞或者巨噬细胞对于病毒颗粒蛋白的合成[20]。rh-INFα2b 诱导的机体干扰素体系的激活还能够促进细胞免疫的激活,提高 T 淋巴细胞对于病毒颗粒的吞噬作用。目前研究表明 rh-INFα2b 能够在毛细支气管炎临床疗效的改善过程中发挥作用[21,22],但对于治疗后外周血 T 淋巴细胞、血清白细胞介素 -4(IL-4)、γ- 干扰素(IFN-γ)、白细胞介素 -2(IL-2)等的分析不足[23]。rh-INFα2b 对于机体炎症因子的下调得益于 rh-INFα2b 对呼吸道粘膜屏障的改善及其对于呼吸道合胞病毒或者流感病毒的拮抗作用[24]。rh-INFα2b 对不同呼吸道病毒的免疫屏障作用能够避免呼吸道病毒对于机体炎症应激体系的激活,减轻炎症因子的释放程度[25]。本研究结果显示 rh-INFα2b 能够显著改善毛细支气管炎患儿的临床症状,促进患者病情的改善和疾病的恢复。这主要由于 rh-INFα2b 能够显著抑制毛细支气管局部炎症反应,抑制局部病毒的复制,改善高病毒载量导致的毛细支气管痉挛表现。$CD3^+$、$CD4^+$、$CD4^+/CD8^+$T 淋巴细胞是评估患者细胞免疫功能的指标,$CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 比例越高,患者细胞免疫功能越为完善,而 $CD8^+$T 淋巴细胞比例越高,患者细胞免疫抑制越为明显[26,27]。本研究中,观察组患者治疗后 $CD3^+$、$CD4^+$、$CD4^+/CD8^+$ 比例明显上升,而 $CD8^+$T 淋巴细胞比例明显下降,表明 rh-INFα2b 能够显著改善毛细支气管炎患者的细胞免疫平衡。rh-INFα2b 对于患者免疫功能的调节作用,主要由于 rh-INFα2b 能够诱导抗原提呈细胞或者树突状细胞的激活,促进 $CD4^+$、$CD8^+$T 淋巴细胞的分化成熟,最终改善相关 T 淋巴细胞平衡。其他类似的研究也显示 rh-INFα2b 辅助治疗支气管炎患者后,支气管炎患者的 $CD4^+$T 淋巴细胞可上升 30%以上,在 rh-INFα2b 治疗疗程越长或者治疗越为规范的患者中,支气管炎患者免疫功能的改善更为显著[28]。

白细胞介素(interleukin,IL)即是由多种细胞产生并作用于多种细胞的一类细胞因子,至少发现了 38 个白细胞介素,分别命名为 IL-1~IL38,功能复杂,成网络,复杂重叠[29];在免疫细胞的成熟、活化、增殖和免疫调节等一系列过程中均发挥重要作用,此外它们还参与机体的多种生理及病理反应,IL-4 是 II 型辅助 T 细胞(Th2 细胞)分泌的细胞因子,IL-4 的生物作用,包括刺激活化 B 细胞和 T 细胞增殖、$CD4^+$T 细胞分化成 II 型辅助 T 细胞,它也在调节体液免疫和适应性免疫中起关键作用[30],IL-4 诱导 B 细胞抗体类别转换向 IgE,上调第二型主要组织兼容性复合体的产生;IL-2 能诱导和增强细胞毒活性,应用 IL-2 治疗某些疾病、特别是对肿瘤治疗的研究得到了广泛开展,单独使用 IL-2 或与 LAK 细胞等联合使用治疗肿瘤取得了一定的疗效,还可望用于病毒感染、免疫缺陷病及自身免疫病的治疗;IFN-γ 是Ⅱ型干扰素,又称 γ-IFN 或免疫干扰素是由有丝分裂原刺激 T 淋巴细胞产生,干扰素是一种高效的抗病毒生物活性物质,又是一种具有广泛免疫调节作用的淋巴因子。IL-4、IFN-γ、IL-2 对于下游炎症细胞和炎症因子的激活,能够加剧毛细支气管的功能障碍。本研究结果显示 rh-INFα2b 能够显著抑制机体的炎症反应。随后的疗效分析显示,观察组患者治疗疗效显著高于对照组,提示雾化 rh-INFα2b 吸入是一种有效的儿童毛细支气管炎治疗方案。

综上所述,雾化 rh-INFα2b 可显著提高儿童毛细支气管炎的临床疗效,增强其免疫功能,其具体机制仍有待于进一步的研究证实。

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