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小儿消积止咳口服液联合布地奈德对支气管哮喘患儿血清 IFN-γ,IL-4,TGF-β1,NO 水平的影响 *

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摘要 目的：研究小儿消积止咳口服液联合布地奈德对支气管哮喘患儿血清干扰素 -γ（Recombinant human interferon gamma，IFN-γ），白介素 -4（Interleukin-4，IL-4），转化生长因子 β1（Transforming growth factor beta 1，TGF-β1），一氧化氮（Nitric oxide，NO）水平的影响。**方法：**选择 2018 年 1 月～2019 年 12 月于我院诊治的 67 例支气管哮喘患儿，将其随机分为两组。对照组单用布地奈德，观察组采用小儿消积止咳口服液联合布地奈德治疗。**结果：**观察组的有效率 93.94 %明显高于对照组 70.59 %（*P*<0.05）；观察组患儿的哮鸣音消失时间、咳嗽消失时间、住院时间和喘憋消失时间明显短于对照组患儿（*P*<0.05）；治疗后，两组患儿的血清 NO 和 IL-4 水平明显降低（*P*<0.05），血清 TGF-β1 和 IFN-γ 水平明显升高（*P*<0.05），且观察组患儿的血清 NO 和 IL-4 水平明显低于对照组（*P*<0.05），血清 TGF-β1 和 IFN-γ 水平明显高于对照组（*P*<0.05）；治疗后，两组患儿的血清 IgM、IgA 和 IgG 水平明显降低（*P*<0.05），且观察组的血清 IgM、IgA 和 IgG 水平明显更低（*P*<0.05）。**结论：**小儿消积止咳口服液联合布地奈德对支气管哮喘患儿有显著的疗效，其机制可能与调节血清 IFN-γ，IL-4，TGF-β1，NO 水平有关。

关键词：小儿消积止咳口服液；布地奈德；支气管哮喘；干扰素 -γ；白介素 -4；转化生长因子 β1；一氧化氮

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Effect of Xiaoer Xiaoji Zhike Oral Liquid Combined with Budesonide on Serum IFN-γ, IL-4, TGF-β1, NO Levels in Children with Bronchial Asthma*

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ABSTRACT Objective: To study the effect of Xiaoer Xiaoji Zhike Oral Liquid combined with budesonide on serum interferon-γ (IFN-γ), interleukin-4 (IL-4), transforming growth factor β1 (TGF-β1), nitric oxide (NO) level in children with bronchial asthma. **Methods:** Selected 67 cases of patients with bronchial asthma who were treated in our hospital from January 2018 to December 2019, divided into two groups randomly. The control group was treated with budesonide alone, and the observation group was treated with Xiaoer Xiaoji Zhike Oral Liquid combined with budesonide. **Results:** The effective rate of the observation group 93.94 % was significantly higher than that of the control group 70.59 % (*P*<0.05). The disappearance time of wheezing, cough disappearance, hospital stay and wheezing disappearance time of the observation group were significantly shorter than control group (*P*<0.05). After treatment, the levels of serum NO and IL-4 of the two groups of children were significantly reduced (*P*<0.05), and the levels of serum TGF-β1 and IFN-γ were significantly increased (*P*<0.05), and the levels of serum NO and IL-4 in the observation group The level of IL-4 was significantly lower than that of the control group (*P*<0.05), and the levels of serum TGF-β1 and IFN-γ were significantly higher than that of the control group (*P*<0.05). After treatment, the serum IgM, IgA and IgG levels of the two groups of children were significantly reduced (*P*<0.05), and the serum IgM, IgA and IgG levels of the observation group were significantly lower (*P*<0.05). **Conclusion:** Erxiaoji Zhike Oral Liquid combined with budesonide has a significant effect on children with bronchial asthma. The mechanism may be related to the regulation of serum IFN-γ, IL-4, TGF-β1 and NO levels.

Key words: Xiaoer Xiaoji Cough Oral Liquid; Budesonide; Bronchial Asthma; Interferon-γ; Interleukin-4; Transforming Growth Factor β1; Nitric Oxide

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前言

支气管哮喘主要表现为喘息、胸闷和呼吸困难等，其发病机制是由多种的炎症细胞和炎症介质引发，患者会出现反应性的可逆性气流受阻和气道高反应性[1-3]。支气管哮喘具有持续时间长、发病率高、易复发和发病突然等特点。哮喘发病的周期性以及反复性，会使患儿和家长长时间处在紧张的状态，临床研究表明，增加患儿发病的严重程度和发病的次数，将影响其生命安全 [4,5]。临床治疗哮喘患儿以尽量降低哮喘的发作次数为主，以改善发病时患儿的症状表现，避免发生气道不可逆阻塞，防止患儿出现呼吸衰竭[6]。目前治疗哮喘患儿的方案主要是抗炎、解痉和抗过敏，常用治疗药物主要包括糖皮质激素、抗感染治疗、白三烯受体阻断剂以及 β2 受体激动剂治疗等[7]。布地奈德是一种比较有效的糖皮质激素类药物，具有比较强的抑制变态反应作用和非特异性抗炎作用，而且具有比较好的耐受性，大部分患者的不良反应均比较轻，口咽并发症以及全身作用与给药剂量有关[8]。小儿消积止咳口服液主要用于小儿慢性咳嗽、小儿支原体肺炎、小儿便秘、小儿上呼吸道感染后咳嗽、小儿急性支气管炎等疾病的治疗，目前尚未见将其应用于小儿支气管哮喘中的报道。因此，本研究分析了小儿消积止咳口服液联合布地奈德对支气管哮喘患儿的疗效，并分析可能的机制。

1 资料与方法

1.1 一般资料

选择 2018 年 1 月～2019 年 12 月于我院诊治的 67 例支气管哮喘患儿，纳入标准：(1)均符合相关的诊断标准[9]，(2)慢性持续期；(3)未合并严重的肝功能障碍、心功能障碍和肾功能障碍；(4)患儿的父母均知情同意。排除标准：(1)合并肺结核、肺炎等其他严重病；(2) 对小儿消积止咳口服液和布地奈德过敏的患儿；(3)合并内分泌系统、免疫系统、神经系统、血液系统病变的患儿；(4)近期有免疫调节剂、白三烯调节剂、糖皮质激素、支气管扩张剂使用史；(5)合并严重感染的患儿。用抽签法随机分为两组。观察组 34 例，男 19 例，女 15 例；年龄 3~13 岁，平均(6.27±1.39)岁；病程 0.4~5.9 年，平均(3.72±0.41)年；病情轻度患儿 22 例，病情中度患儿 12 例。对照组 33 例，男 19 例，女 14 例；年龄 3~13 岁，平均(6.31±1.42)岁；病程 0.4~5.9 年，平均(3.75±0.42)年；病情轻度患儿 23 例，病情中度患儿 10 例。两组的一般资料具有可比性(P>0.05)。

1.2 治疗方法

两组都采取吸氧、抗生素抗感染等常规治疗。对照组：雾化吸入布地奈德 1 mg，2 次 /d。观察组：联合口服小儿消积止咳口服液（鲁南厚普制药有限公司，国药准字 Z10970022，规格：10 mL/ 支），3~4 岁的支气管哮喘患儿每次服用 15 mL，5 岁以上的患儿每次服用 20 mL，3 次 /d。两组均应用至临床症状完全消失为止。

1.3 观察指标

疗效标准[9]：(1)显效：患儿的肺部鸣喘音和胸闷、反复喘息、气急或咳嗽等症状基本消失；(2)有效：患儿的肺部鸣喘音减少，胸闷、反复喘息、气急或咳嗽等症状有所减轻；(3)无效：患儿的肺部鸣喘音和胸闷、反复喘息、气急或咳嗽等症状无明显改变。

比较两组的哮鸣音、咳嗽、喘憋消失时间及住院时间。

治疗前后，均空腹采集患儿 3 mL 的上肢静脉血，采取硝酸还原酶法检测血清 NO 水平，采取 ELISA 法检测血清 IgM、IgA、IgG、IFN-γ，IL-4，TGF-β1 水平。

1.4 统计学分析

采用 SPSS 21.0，计量资料以($\bar{x}\pm s$)表示，对比用 t 检验，计数资料用%表示，对比 χ^2 检验，P<0.05 有统计学意义。

2 结果

2.1 两组疗效对比

观察组的有效率 93.94 %(24/34)，明显高于对照组 70.59 %(31/34)，对比有统计学意义(P<0.05)，见表 1。

表 1 两组疗效比较[例(%)]

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

Groups	n	Effective	Valid	Invalid	The total effect rate
Control group	34	15(44.12)	9(26.47)	10(29.41)	24(70.59)
Observation group	33	19(57.57)	12(36.36)	2(6.06)	31(93.94)*

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

2.2 两组症状消失时间对比

观察组哮鸣音、咳嗽、喘憋消失时间及住院时间和明显短于对照组，对比差异有统计学意义(P<0.05)，见表 2。

表 2 两组症状消失时间对比($\bar{x}\pm s$)

Table 2 Comparison of symptom disappearance time between the two groups ($\bar{x}\pm s$)

Groups	n	Wheezing disappearance time	Cough disappearance time	Hospitalization time	Wheezing disappearance time
Control group	34	4.87±1.46	4.73±1.58	8.49±2.36	3.98±1.25
Observation group	33	3.52±1.27*	3.31±1.07*	5.27±1.24*	2.85±0.43*

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

2.3 两组血清 IFN-γ,IL-4,TGF-β1,NO 水平对比

治疗后,两组的血清 NO 和 IL-4 水平明显降低(P<0.05),血清 TGF-β1 和 IFN-γ 水平明显升高(P<0.05),且观察组的血清 NO 和 IL-4 水平明显低于对照组 (P<0.05),血清 TGF-β1 和 IFN-γ 水平明显高于对照组(P<0.05),见表 3。

表 3 两组治疗前后的血清 IFN-γ,IL-4,TGF-β1,NO 水平对比 ($\bar{x}\pm s$)

Table 3 Comparison of serum IFN -γ, IL-4, TGF-β1, no levels between the two groups before and after treatment ($\bar{x}\pm s$)

Groups		IFN-γ(ng/L)	IL-4(pg/mL)	TGF-β1(ng/mL)	NO(μmol/L)
Control group(n=34)	Pretherapy	33.26±2.49	71.48±12.39	12.13±1.78	78.36±12.45
	Post-treatment	46.28±3.44 #	59.43±11.27 #	19.34±2.36 #	64.29±11.47 #
Observation group (n=33)	Pretherapy	33.57±2.58	72.25±13.46	12.24±1.46	79.13±11.36
	Post-treatment	54.13±10.27*#	41.36±10.44*#	25.38±2.47*#	53.48±10.13*#

Note: Compared with the control group, *P<0.05; compared with pretherapy, #P<0.05.

2.4 两组血清 IgM、IgA 和 IgG 水平对比

治疗后, 两组患儿的血清 IgM、IgA 和 IgG 水平明显降低(P<0.05),且观察组的血清 IgM、IgA 和 IgG 水平明显更低(P<0.05),见表 4。

表 4 两组治疗前后的血清 IgM、IgA 和 IgG 水平对比 ($\bar{x}\pm s$)

Table 4 Comparison of serum IgM, IgA and IgG levels between the two groups before and after treatment ($\bar{x}\pm s$)

Groups		IgM	IgA	IgG
Control group(n=34)	Pretherapy	1.89±0.33	1.09±0.14	10.93±2.24
	Post-treatment	1.62±0.27#	0.98±0.07#	8.73±1.46#
Observation group(n=33)	Pretherapy	1.87±0.31	1.10±0.15	10.97±2.15
	Post-treatment	1.34±0.15*#	0.87±0.04*#	7.49±1.14*#

Note: Compared with the control group, *P<0.05; compared with pretherapy, #P<0.05.

3 讨论

据报道,我国支气管哮喘的发病率大约是 1 %,其中儿童可占 3 %,据测算我国大约有超过一千万的支气管哮喘患者[10]。支气管哮喘是由嗜酸性粒细胞、T 淋巴细胞等多种细胞和气道结构细胞异常分布,导致慢性气道炎症[11-13]。这种慢性炎症会使易感者对于各种的激发因子产生气道高反应性,还能导致气道狭窄,患者以呼吸困难、喘息、咳嗽或胸闷等为主要症状[14-16]。一般来说,支气管哮喘患儿的病情加重能在数天甚至数小时内发生,偶尔可在短短数分钟内危及到其生命,因而,对支气管哮喘患儿进行及时有效的紧急治疗极为重要。布地奈德具有以下多种的作用:抑制细胞因子的生成;明显抑制支气管腺体内酸性轴多糖的合成;明显的抑制炎性细胞的趋化;增强平滑肌细胞 β 受体的反应性;减少炎性细胞介质的释放;抑制胶原酶以及弹性蛋白酶的分泌;减少血浆素原激活剂的释放;对组氨酸脱羧酶进行抑制,降低组胺的生成量等效果,进而明显减轻患者机体平滑肌的收缩反应[17-21]。

支气管哮喘属于 " 喘证 "、" 哮证 " 等范畴[22]。其病机大多为素体脾肺虚寒,水液敷布,影响肺气宣降,形成内饮外寒。小儿消积止咳口服液的成分主要为蝉蜕、槟榔、桔梗、瓜蒌、连翘、莱菔子、山楂、枇杷叶、枳实和葶苈子等。其中,蝉蜕利咽开音,疏散风热,息风止痉,明目退翳。槟榔能有效行水化湿,降气行滞。桔梗宣肺,排脓,祛痰。瓜蒌宽胸散结,清热涤痰。莱菔子降气化痰,消食除胀。连翘解毒,清热,消肿,散结。枇杷叶和胃利尿,清肺止咳,止渴。枳实化痰散痞,破气消积。葶苈子祛痰平喘,泻肺降气,泄热逐邪,利水消肿。诸药合用,共奏宣肺止咳、祛痰消积食之功效[23]。本研究发现,联用小儿消积止咳口服液能提高疗效。周璇[24]等学者的研究小儿消积止咳口服液联合西药治疗儿童支气管哮喘临床效果的远期影响,对照组在常规治疗基础上给予布地奈德雾化吸入和孟鲁司特钠颗粒口服治疗,观察组在观察组基础上加用小儿消积止咳口服液, 治疗 3 个月,观察组的治疗总有效率明显优于对照组,与本研究结果一致。其原因为,小儿消积止咳口服液能恢复患儿脾胃的运化功能,祛除积食,则可以有效截断生痰的来源,肺气通则有助于共奏祛痰平喘之功效。

IL-4 不但能促进 B 淋巴细胞的增殖和分化, 而且有助于 IgE 的合成;IL-4 可以对 Th1 细胞的效能产生一定的抑制效果,维持 Th2 细胞的增殖[25,26]。TGF-β1 能通过抑制初始 T 细胞分化为 Th1 及 Th2, 使患者的免疫功能维持于比较稳定的状态[27]。IFN-γ 能产生较强的免疫调节功能,使 Th1 细胞亚群和 Th2 细胞亚群处于一个平衡的状态,减轻气道炎症[28,29]。NO 能促进毛细血管的渗出,扩张支气管,促进气道黏膜水肿,进而使气道阻塞情况加重[30]。本研究发现,小儿消积止咳口服液联合布地奈德能明显降低患儿的血清 NO 和 IL-4 水平, 提高血清 TGF-β1 和 IFN-γ 水平,与刘冬岩[31]的研究类似,该学者探讨小儿消积止咳口服液联合丙卡特罗治疗小儿咳嗽变异性哮喘的临床疗效,治疗后,两组血清 IL-2,IFN-γ 水平均显著增高,治疗后治疗组 IL-6 水平低于对照组,而 IL-2,IFN-γ 高于对照组。表明小儿消积止咳口服液不但可以减轻哮喘患儿气道的黏膜水肿情况,调节 INF-γ 及 IL- 4 的表达而产生免疫炎症调节效果,

还能抑制中性粒细胞聚集于患者的气道黏膜,降低气道的高反应性,抑制炎性细胞释放过氧自由基以及氧化物,具有抗氧化和抗炎效果。本研究还发现,联用小儿消积止咳口服液能更加明显的降低血清 IgM、IgA 和 IgG 水平,改善免疫功能。王艳茹等[32]对 54 例支原体肺炎患儿联用小儿消积止咳口服液,对照组在常规治疗基础上使用阿奇霉素序贯疗法,观察组在对照组治疗方案基础上使用小儿消积止咳口服液,结果显示小儿消积止咳口服液联合阿奇霉素对支原体肺炎患儿的血清 IgM、IgA 和 IgG 水平明显低于阿奇霉素治疗,与本研究一致。本研究结果可为后期临床治疗支气管哮喘患儿提供药物,为其探究其机制提供思路,但是本研究也存在一定的不足,样本来源单一,病例数量少,结果可能存在一定的偏移,后续研究需要扩大样本量深入探究小儿消积止咳口服液治疗支气管哮喘患儿的机制。

综上所述,小儿消积止咳口服液联合布地奈德对支气管哮喘患儿有显著的疗效,其机制可能与调节血清 IFN-γ,IL-4,TGF-β1,NO 水平有关。

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