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桑杏二陈汤与孟鲁司特钠治疗儿童感染后咳嗽的临床对照研究

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摘要 目的:观察和比较桑杏二陈汤(SEG)与孟鲁司特钠治疗儿童感染后咳嗽(PIC)的临床有效性及安全性。**方法:**选择 2015 年 3 月~2017 年 5 月就诊于西京医院儿科门诊的 PIC152 例患儿,将其分为观察组(76 例)与对照组(76 例)。观察组患儿口服 SEG 治疗 1 周,而对照组口服孟鲁司特钠咀嚼片治疗 1 周。比较两组患者治疗前后的咳嗽症状积分和疗效。**结果:**治疗 1 周后,观察组(SEG 组)患儿的咳嗽症状积分与治疗前相比明显下降($P<0.05$),而对照组患儿的咳嗽症状积分与治疗前比无明显变化($P>0.05$),观察组患儿咳嗽积分明显低于对照组($P<0.05$)。观察组患儿的治愈率、显效率均高于对照组($P<0.01$)。两组均无不良反应发生。**结论:**SEG 治疗儿童 PIC 的临床疗效明显优于孟鲁司特钠,且无不良反应发生。SEG 治疗可缩短部分 PIC 患儿的病程。

关键词:感染后咳嗽;儿童;桑杏二陈汤;孟鲁司特钠

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Effect of Sangxingerchen Granule and Montelukast on the Post-infection Cough in Children: a Controlled Clinical Study

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ABSTRACT Objective: To study the clinical efficacy and safety of Sangxingerchen granule (SEG) in the treatment of post-infection cough (PIC) in children. **Methods:** A prospective randomized controlled study was conducted in 152 cases of PIC children in the pediatric outpatient of Xijing Hospital from March 2015 to May 2017. They were assigned to the treatment group (76 cases) and controlled group (76 cases). Patients in the treatment group were given SEG orally for 1 week, while patients in the controlled group were given Montelukast chewable tablets for 1 week. Then the cough scores and efficacy were compared between the two groups. **Results:** After taking 1 week of SEG, the cough scores in the treatment group were significantly decreased compared with those before treatment ($P<0.05$), while the cough scores in the control group showed no significant decrease ($P>0.05$). After treatment, the cough scores of treatment group were significantly decreased compared with the control group ($P<0.05$). Both the recovery rate and excellence rate were higher in the treatment group than those in the control group ($P<0.01$). No adverse events was observed in both groups. **Conclusion:** SEG therapy was better than Montelukast in the treatment of PIC children with no serious adverse reactions, it could shorten the PIC course in part of children with PIC.

Key words: Post-infectious cough; Child; Sangxingerchen granule; Montelukast

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前言

感染后咳嗽(post-infection cough, PIC)是指急性呼吸道感染后持续存在的刺激性干咳,或伴有少量白色黏液痰,病程一般不超过 8 周^[1]。研究显示有 11%~25%的上呼吸道感染患者可能发生 PIC,占儿童慢性咳嗽的 39.4%^[23]。PIC 为自限性,无特效治疗药物。中国儿童慢性咳嗽诊断与治疗指南低度^[4]建议对于咳嗽严重者给予口服孟鲁司特钠或吸入性糖皮质激素(ICS)治疗。但持续数周的咳嗽往往影响患儿的生活、学习及睡眠质

量,家长因此反复带患儿就诊,既增加了患儿使用 ICS 的机会,也增加了反复感染的几率。研究表明中医药治疗 PIC 安全有效,不仅能有效减轻咳嗽症状,并且能缩短病程。桑杏汤是治疗急性咳嗽的经典方剂。而二陈汤是治疗慢性咳嗽的经典方剂,由陈皮、半夏、茯苓和甘草四味药物组成。因此,本研究主要观察和比较桑杏二陈汤对 PIC 患儿的治疗效果和安全性,现报道如下。

1 资料与方法

1.1 临床资料

采取前瞻性研究方法,选择 2015 年 3 月~2017 年 5 月就诊于西京医院儿科门诊的 PIC 患儿,纳入标准如下:(1)咳嗽持续>4 周,呈刺激性干咳或伴少量白色黏痰,血常规、CRP、胸部

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X线检查正常,支原体培养和支原体抗体均为阴性,肺通气功能正常;(2)1岁<年龄<14岁;(3)一、二级亲属及患儿均无过敏性疾病史;(4)患儿无慢性咳嗽病史和喘息病史。排除标准:(1)以咳嗽症状为主的其他疾病;(2)患者依从性差,未按规定用

药或疗程不足者;(3)治疗过程中发生药物不良反应;(4)治疗过程中继发其他疾病。入选152例患儿,随机分为观察组和对照组,两组的年龄、性别和病程比较差别无统计学意义($P>0.05$,见表1)。

表1 两组患者的基线资料比较($n, \bar{x} \pm s$)

Table 1 Comparison of the baseline characteristics between two groups($n, \bar{x} \pm s$)

Groups	Amount(n)	Age(year)	Boy/Girl	Duration of cough(week)
Control group	76	4.80± 2.12	36/40	5.13± 0.24
Treatment group	76	4.86± 2.20	37/39	5.28± 0.30

1.2 治疗方法

观察组口服 SEG(广州一方制药公司颗粒剂,组成为:桑叶10 g、杏仁10 g、前胡10 g、桔梗10 g、陈皮6 g、法半夏9 g、茯苓10 g、生甘草6 g),每日1付,用40-60 mL开水冲调,分2-3次口服。3岁以下,杏仁、桔梗和法半夏减半量。对照组口服孟鲁司特钠咀嚼片(杭州默沙东制药有限公司,国药准字

J20130053),4 mg/d(<6岁),5 mg/d(6~12岁),睡前服用。

1.3 观察指标

(1)咳嗽症状积分:采用2015年中国咳嗽诊断与治疗指南^[4]的咳嗽症状积分评估两组患儿治疗前后咳嗽症状积分情况,进行组间及自身治疗前后比较。咳嗽症状评分标准^[4]如表2所示。

表2 咳嗽症状积分表

Table 2 Cough symptom score table

Scores	Daytime cough symptom scores	Nighttime cough symptom scores
0	No cough during the day	No cough during the night
1	Few short episodes of coughing	Few short episodes of coughing
2	Occasional coughs or rare episodes of prolonged coughing,which did mild interfere with usual daytime activities	Occasional waking due to coughs
3	Frequent coughs or at least occasional episodes of prolonged coughing, which did interfere with usual daytime activities	Distressing coughs preventing any sleep

(2)疗效评价标准:根据治疗前后咳嗽症状积分计算咳嗽症状的改善率 $[(\text{治疗前积分} - \text{治疗后积分}) \div \text{治疗后积分} \times 100\%]$ ^[5]。咳嗽症状积分改善率 $>95\%$ 为治愈,70%-95%为显效,30%-70%为有效, $<30\%$ 为无效。总有效率=治愈+显效+有效。

1.4 统计学处理

采用 SPSS19.0 软件进行统计学处理。计量资料以 $\bar{x} \pm s$ 表示,计数资料用率(%)表示,分析用 t 检验和 χ^2 检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 两组患儿治疗前后咳嗽积分比较

如表3所示,两组患儿治疗前咳嗽症状积分比较无统计学差异($P>0.05$)。治疗1周后,治疗组患儿咳嗽积分较治疗前明显下降,差异有统计学意义($P<0.05$)。对照组患儿咳嗽症状积分略有下降,与治疗前比较无统计学意义($P>0.05$)。治疗组患儿治疗后咳嗽积分明显低于对照组,差异有统计学意义($P<0.05$)。

表3 两组治疗前后咳嗽症状积分比较

Table 3 Comparison of the cough symptom scores between the two groups before and after treatment

Groups	Amount(n)	Time	Daytime cough	Nighttime cough	Total integral
Control group	76	baseline	2.09± 0.72	1.45± 0.70	3.54± 1.20
		After treatment	2.03± 0.68	1.15± 0.60	3.18± 1.03
Treatment group	76	baseline	2.13± 0.68	1.23± 0.91	3.48± 1.46
		After treatment	1.07± 0.57 ^{ab}	0.42± 0.49 ^{ab}	1.49± 0.74 ^{ab}

Note: a. compared with baseline, $P<0.05$; b. compared with the after treatment in control group, $P<0.05$.

2.2 两组患儿的疗效比较

如表4所示,治疗组总有效率、治愈率、显效率和有效率均显著高于对照组($P<0.05$)。两组患儿在治疗期间进行动态随访,用药过程中均未发现不良反应。

3 讨论

PIC 是急性呼吸道感染控制后仍迁延不愈的一类慢性咳嗽,是幼儿和学龄前儿童慢性咳嗽的常见原因,其发病机制尚不明确。一般认为 PIC 的发生可能是各种病原体(包括呼吸道病毒、细菌和肺炎衣原体、支原体等)感染引起多种炎症介质及细胞因子释放,导致呼吸道上皮细胞广泛损伤,破坏了气道上皮完整性和(或)纤毛柱状上皮细胞鳞状化生,从而引起持续

表 4 两组临床疗效的比较(n,%)

Table 4 Comparison of the clinical efficacy between the two groups at one week after treatment (n,%)

Group	Cases	Cure	Excellence	Effective	Useless	Total effective rate
Control group	76	0(0%)	0(0%)	22(28.9%)	54(71.1%)	28.9%
Treatment group	76	23(30.3%) ^a	22(28.9%) ^a	26(34.2%)	5(6.5%) ^a	93.5% ^a

Note: a, compared with the control group, $P < 0.01$.

的气道炎症,并伴有暂时性的气道高反应性。有研究显示呼吸道上皮细胞损伤后导致神经纤维裸露,容易受到外界刺激,同时由于中性内肽酶减少,神经肽降解能力下降,在气道中逐渐蓄积,导致神经源性炎症而使咳嗽的敏感性增加^[6]。随着气道黏膜修复,气道反应性恢复正常,咳嗽可在数周内自然缓解。所以,PIC被形象地称之为“感染的尾巴”^[7,8]。

目前,PIC患儿尚缺乏疗效确切的治疗药物。PIC对抗生素治疗无反应。成人PIC可使用中枢性镇咳药缓解咳嗽症状,但不宜长期使用^[9]。儿童则不建议使用中枢性镇咳药,对于咳嗽严重的PIC患儿,指南建议给予ICS治疗或口服孟鲁斯特钠,但仅是低度建议(C)^[1]。由于指南对儿童慢性咳嗽的诊断性治疗顺序是:咳嗽变异性哮喘、上气道咳嗽综合征和PIC,临床上难免会把部分PIC患儿当作咳嗽变异性哮喘接受至少8周的ICS治疗。有研究观察随访了109例慢性非特异性咳嗽患儿,发现仅有30例确诊为咳嗽变异性哮喘或哮喘,因此认为对于无过敏体质和无慢性咳嗽病史的患儿,早期ICS是不必要的。该研究提示对于拟诊PIC的患儿,至少应观察随访2周,从而避免过度使用ICS^[9]。

孟鲁司特是一种选择性白三烯受体拮抗剂,通过竞争性结合半胱氨酸受体而抑制白三烯的活性,能有效地拮抗由白三烯导致的毛细血管通透性增加,减轻炎性细胞浸润和炎性介质的释放,从而降低气道高反应性^[10]。然而,一项双盲随机安慰剂对照的临床研究显示孟鲁司特治疗成人PIC是无效的,患者服用孟鲁司特2周和4周时,咳嗽症状积分与安慰剂对照组相比均无显著性差异^[11]。儿童感染后咳嗽很少单用孟鲁司特钠治疗,一般均与ICS或祛痰止咳药合用。

桑杏汤是治疗急性咳嗽的经典方剂。一篇系统评价文章分析了桑杏汤及其加减方对急慢性咳嗽的治疗效果,肯定了桑杏汤的疗效优势^[12]。研究表明桑杏汤可增加II型肺泡细胞合成表面活性物质,从而湿润气道、上调AQP5基因表达,抑制炎性细胞因子“级联反应”,减轻气道黏膜损伤和气道炎症^[13]。桑杏汤单味药的药理研究显示桑叶中黄酮类、生物碱类及多糖为其主要功效成分,其中生物碱具有抗病毒作用^[14];苦杏仁分解产生微量氢氰酸,对呼吸中枢呈抑制作用,对SO₂刺激诱导的咳嗽小鼠有明显的止咳效果^[15,16];前胡提取物有良好的祛痰效果,苦杏仁、桔梗均可减轻气道上皮损伤,减少炎性细胞浸润^[17]。二陈汤是治疗慢性咳嗽的经典方剂,由陈皮、半夏、茯苓和甘草四味药物组成。药理研究显示二陈汤中的陈皮、半夏均具有良好的止咳祛痰功效,尤其以止咳作用为著^[18],半夏的止咳作用仅稍弱于可待因^[15];茯苓酸是中药茯苓特有的药理成分,通过抑制磷酸酶、白三烯分泌,降低5-脂氧合酶、弹性蛋白酶、COX-2活性而发挥抗炎作用^[19];甘草作为传统的止咳平喘药物,不仅能镇咳祛痰,抑制多种细菌和病毒感染,而且具有免疫调节作用。

甘草的主要成分甘草甜素和甘草次酸具有肾上腺皮质激素样作用,可提高机体对外界刺激的适应性。有研究显示甘草酸可通过促进IL-12、IL-10和IFN- γ 的产生,抑制Th2极化反应,降低过敏性哮喘小鼠的气道高反应^[20,21]。

本研究所用的SEG为桑杏汤与二陈汤的合方,在本院儿科门诊长期用于治疗呼吸道感染后咳嗽,取得了良好的疗效^[22]。本研究用SEG治疗PIC患儿76例,用药1周后,患儿的咳嗽症状积分与治疗前相比明显降低,而对照组患儿的咳嗽积分与治疗前相比无显著性差异,表明SEG治疗儿童PIC能有效地缓解患儿的咳嗽症状,提高患儿的生活质量。本研究入选患儿的平均病程约为5周,服用SEG1周时,治愈率达(咳嗽症状积分改善率 $>95\%$)30.3%,对照组的治愈率为零,表明与单独服用孟鲁司特钠的患儿相比,SEG可缩短约1/3 PIC患儿的病程。用药1周时,服用SEG的患儿显效(咳嗽症状积分改善率达70~95%)率为28.9%,而服用孟鲁司特钠的对照组无一例显效。服用SEG的患儿咳嗽积分改善率 $<30\%$ (视为无效)者仅5例(6.5%),而对照组无效者占54例(71.1%)。以上结果表明SEG治疗儿童PIC的临床效果显著优于单独使用孟鲁司特钠。本研究纳入的病例年龄最小者1岁,最大者9岁,服药1周,两组患儿均未发生皮疹、厌食、腹痛、呕吐、腹泻等不良反应,表明SEG用于PIC安全性良好。

综上所述,SEG治疗儿童PIC的止咳效果好,安全性高,并且可缩短部分患儿的病程,避免过度使用糖皮质激素,减少因反复就诊而导致的重复感染。进一步的研究应关注SEG治疗儿童PIC的最佳疗程和停药后是否复发。对于SEG治疗无效的患儿以及咳嗽积分改善率不理想(30%~70%)的患儿,应予以较长期的随访,当患儿持续咳嗽超过8周时,应重新评估病情,及时纠正诊断。

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