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重组人干扰素 α-2b 注射液雾化吸入与重组人干扰素 α-2b 喷雾剂局部外用喷咽部治疗手足口病的疗效 *

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摘要 目的：探讨重组人干扰素 α-2b 注射液雾化吸入与重组人干扰素 α-2b 喷雾剂局部外用喷咽部治疗手足口病的疗效。**方法：**选择 2016 年 1 月至 2017 年 12 月就诊于河北省儿童医院的 160 例手足口病患儿作为研究对象，通过随机数表法分为对照组和试验组，每组 80 例。2 组均给予手足口病常规治疗措施，对照组在此常规治疗基础上给予重组人干扰素 α-2b 喷雾剂治疗，喷涂于咽喉部，每次 1 喷，3 次 /d，试验组在常规治疗基础上，给予重组人干扰素 α-2b 注射液 10 万 U（kg·次）加入生理盐水 2 mL 中进行雾化吸入治疗，2 次 /d；2 组疗程均为 3~5d。比较 2 组临床疗效、临床症状改善时间、血清指标及不良反应。**结果：**治疗后，试验组和对照组临床疗效总有效率分别为 91.25%（73/80）和 76.25%（61/80），差异具有统计学意义（*P<0.05*）；试验组和对照组体温正常时间分别为（2.78± 0.42）和（4.13± 0.58）d，皮疹消退时间分别为（3.53± 0.55）和（5.05± 0.63）d，口腔溃疡愈合时间分别为（3.35± 0.58）和（4.80± 0.58）d，正常进食时间分别为（3.91± 0.58）和（4.98± 0.50）d，住院时间分别为（5.91± 0.92）和（8.14± 0.81）d，差异均具有统计学意义（*P<0.05*）；治疗后，试验组和对照组血清淀粉样蛋白 A（SAA）分别为（133.43± 25.74）和（178.53± 26.96）mg·L^{-1}，C 反应蛋白（CRP）分别为（4.75± 0.71）和（8.54± 1.29）mg·L^{-1}，差异均具有统计学意义（*P<0.05*）；治疗期间，对照组出现恶心呕吐 5 例，皮疹 1 例，试验组出现 7 例恶心呕吐，2 例腹泻，2 组不良反应总发生率分别为 7.50（6/80）、11.25%（9/80），比较无显著差异（*P>0.05*）。**结论：**在手足口病患儿中使用重组人干扰素 α-2b 注射液雾化吸入效果显著，可有效促进疾病缓解，且用药安全性高，值得应用推广。

关键词：手足口病；重组人干扰素 α-2b；雾化吸入；喷雾剂

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Efficacy of Nebulization Inhalation of Interferon α-2b Injection Atomization Inhalation and Recombinant Human Interferon α-2b Spray in the Local External Use of the Sprayed Pharynx in the Treatment of Hand Foot and Mouth Disease*

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ABSTRACT Objective: To study the efficacy of nebulization inhalation of interferon α-2b injection atomization inhalation and recombinant human interferon α-2b sprayin the local external use of the sprayed pharynx in the treatment of hand foot and mouth disease. **Methods:** 160 children of hand foot and mouth disease who received therapy from January 2016 to December 2017 in the Hebei children's Hospital were selected as research objects, according to random number table, those patients were divided into the control group group and the treatment group group, 80 cases in each group. he 2 groups were given routine treatment for hand foot and mouth disease, on the basis of the routine treatment, the control group was treated with recombinant human interferon α-2b spray, spraying on the throat, one spraying each time, and 3 times/d, on the basis of routine treatment, the treatment group was given interferon α-2b injection 10 million U (kg·time) into the saline 2 mL for nebulization and inhalation, 2 times/d; the 2 groups were all 3~5d. The clinical curative effect, clinical symptom improvement time, serum index and adverse reaction of two groups were compared. **Results:** After treatment, the total effective effective rate of the treatment group and the control group was 91.25% (73/80) and 76.25% (61/80) respectively, the differences was statistically significant (*P<0.05*); the temperature normal time of the treatment group and the control group was（2.78± 0.42）and（4.13± 0.58）d respectively, the rash subsided time was（3.53± 0.55）and（5.05± 0.63）d respectively, the oral ulcer healing time（3.35± 0.58）and（4.80± 0.58）d respectively, the normal feeding time was（3.91± 0.58）and（4.98± 0.50）d, the

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hospitalization time was(5.91± 0.92)and(8.14± 0.81)d, the differences was statistically significant(*P<0.05*); after treatment, the serum amyloid A (SAA) in the treatment group and the control group was (133.43± 25.74)and (178.53± 26.96)mg·L^{-1} respectively, the C reactive protein (CRP) was(4.75± 0.71)and(8.54± 1.29)mg·L^{-1} respectively, the differences was statistically significant(*P<0.05*); during the treatment period, there were 5 cases of nausea and vomiting and 1 cases of rash in the control group, 7 cases of nausea and vomiting and 2 cases of diarrhea in the treatment group, the total incidence of adverse reactions in the 2 groups were 7.50 (6/80) and 11.25% (9/80), respectively, and there was no significant difference(*P>0.05*). **Conclusion:** Interferon α-2b injection atomization inhalation is well for children with hand foot and mouth disease, which can effectively promote the remission of the disease, and the safety of drug use is high, and it is worthy of application and promotion.

Key words: Hand foot and mouth disease; Recombinant human interferon α-2b; Atomization inhalation; Spray

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前言

小儿手足口病主要是由于感染肠道病毒所致一种传染性疾病,好发于 3 岁以下儿童,主要特征为手足口、臀部等出现疱疹、丘疹等,若未得到及时控制,极易诱发心肌炎、脑脊髓炎、肺水肿等严重并发症[1,2]。近年来,较多报道证实,重组人干扰素α-2b 注射液具有广谱抗病毒、抑制细胞增殖等作用,且对机体免疫力具有调节作用[3,4]。因此,本研究分别在手足口病患儿中应用重组人干扰素α-2b 注射液雾化吸入和喷雾剂局部外用喷咽部治疗,探讨 2 种方式的治疗差异,现报道如下。

1 材料与方法

1.1 研究设计

本研究按前瞻性、随机、双盲、安慰剂对照、单中心临床研究方法设计。

1.2 病例选择

选择 2016 年 1 月至 2017 年 12 月就诊于河北省儿童医院的 160 例手足口病患儿作为研究对象。本研究已获得我院伦理委员会批准实施,患儿家属对此研究均知情同意。

诊断与入选标准:① 符合《手足口病诊疗指南(2010 版)》[5]中对手足口病的诊断标准,均为急性起病,患儿手足口、臀部有丘疹、疱疹出现,疱疹周围有炎性红晕,疱内液体较少,合并发烧、咳嗽、食欲降低、流涕等症状,合并精神萎靡、昏迷、呕吐、呼吸困难、四肢发凉等神经系统、呼吸系统、循环系统症状,并通过肠道细菌检查结果得以确诊;② 年龄<10 岁。

排除标准:① 合并严重精神系统损伤或精神疾病者;② 合并心脏系统疾病;③ 近期接受过手术;④ 合并艾滋病、肺结核等传染性疾病;⑤ 肝纤维化,肝功能严重障碍;⑥ 对本研究药物过敏。

1.3 药品与仪器

重组人干扰素α-2b 注射液,规格:每支 1 mL:300 万 U,批号 S20010050,厂家:沈阳三生制药股份有限公司;重组人干扰素α-2b 喷雾剂,规格:每支 10 mL,批号 151119,厂家:天津未名生物医药有限公司;德国百瑞氧源驱动雾化吸入。

血清淀粉样蛋白 A(SAA)酶联免疫吸附法(ELISA)试剂盒,上海信裕生物科技有限公司;C 反应蛋白(CRP)ELISA 试剂盒,上海西塘生物科技有限公司;全自动生化分析仪 8000,德国罗氏诊断有限公司。

1.4 分组与治疗

将 160 例患儿通过随机数表法分为 2 组,每组 80 例。对照组给予重组人干扰素α-2b 喷雾剂治疗,喷涂于咽喉部,每次 1 喷,3 次 /d;试验组在常规治疗基础上,给予重组人干扰素 α-2b 注射液 10 万 U(kg/ 次)加入生理盐水 2 mL 中进行雾化吸入治疗,2 次 /d;2 组疗程均为 3~5d。

1.5 观察指标和疗效评价

记录 2 组患儿体温正常、皮疹消退、口腔溃疡愈合、正常进食时间和住院时间;并于治疗前、治疗后 5d 时,采集 3 mL 空腹静脉血,置于无菌抗凝管内,静置 30 min,使用 3000 r·min^{-1} 的速度离心 10 min, 提取上层清液置于冷冻箱内储存以备检测,检测 SAA、CRP 的变化;并记录治疗期间不良反应。

疗效评价标准参照文献[6],显效:48h 内体温恢复至正常,手足口疱疹基本或完全消失,溃疡愈合,不流涎,可以正常进食,精神状态佳;显效:72h 内体温恢复至正常,手足口疱疹、溃疡大部分愈合,可精神,精神状态较好;无效:治疗 5d 后,仍有发炎、难以进食、流涎等症状,口腔疱疹、溃疡等无明显减少或增加,甚至出现细菌感染等并发症。以显效 + 有效为总有效率。

1.6 统计学处理

用 SPSS 18.0 软件进行统计分析。计量资料用表示,组间比较用独立样本 t 检验,计数资料用率表示,比较用 x^2 检验,*P<0.05* 表示差异具有统计学意义。

2 结果

2.1 一般资料

2 组一般资料比较无显著差异(*P>0.05*),见表 1。

2.2 组临床疗效比较

试验组临床疗效总有效率明显比对照组高 (*P<0.05*),见表2。

2.3 两组临床症状改善时间比较

试验组体温正常、皮疹消退、口腔溃疡愈合、正常进食时间和住院时间均明显短于对照组(*P<0.05*),见表 3。

2.4 两组血清因子比较

治疗前,2 组血清 SAA、CRP 比较均无显著差异(*P>0.05*);治疗后,2 组血清 SAA、CRP 较治疗前均显著降低(*P<0.05*),试验组血清 SAA、CRP 均明显比对照组低(*P<0.05*),见表 4。

2.5 安全性评价

2 组治疗期间均未出现神经系统功能紊乱、肝肾功能异

表 1 2 组患者的一般资料比较($\bar{x}\pm s$)

Table 1 Comparison of general information in 2 groups($\bar{x}\pm s$)

Item		Control group(n=80)	Treatment group(n=80)
Sex(M/F)		47/33	45/35
Age(year)		3.71± 1.08	3.80± 1.08
HR(beat·min^{-1})		101.07± 16.36	101.82± 17.34
RR(beat·min^{-1})		45.07± 7.40	44.95± 7.02
SBP(mmHg)		130.06± 13.64	129.30± 14.56
DBP(mmHg)		86.99± 8.52	86.38± 8.79
Course of disease(d)		4.36± 0.37	4.34± 0.34
Temperature(℃)		37.74± 1.45	37.86± 1.18
Severity(n,%)	Slight	43(53.75)	46(57.50)
	Severe	37(46.25)	34(42.50)

Note: HR: Heart rate; RR: Respiratory rate; SBP: Systolic pressure; DBP: Diastolic pressure;
Control group: Conventional therapy+Recombinant human interferon α-2b spray; Treatment group: Conventional therapy+ Recombinant human interferon α-2b injection atomization inhalation.

表 2 2 组临床疗效比较[n(%)]

Table 2 Comparison of the clinical efficacy between two groups[n(%)]

Item	Control group(n=80)	Treatment group(n=80)
Effective	33(41.25)	47(58.75)
Valid	28(35.00)	26(32.50)
Invalid	19(23.75)	7(8.75)
Total effective rate	61(76.25)	73(91.25)*

Note: Compared with control group, *P<0.05. Total effective rate= Effective+ Valid.

表 3 2 组临床症状改善时间比较($\bar{x}\pm s$, d)

Table 3 Comparison of the clinical symptoms improvement time between two groups($\bar{x}\pm s$, d)

Item	Control group(n=80)	Treatment group(n=80)
Temperature normal time	4.13± 0.58	2.78± 0.42*
Rash subsided time	5.05± 0.63	3.53± 0.55*
Oral ulcer healing time	4.80± 0.58	3.35± 0.58*
Normal feeding time	4.98± 0.50	3.91± 0.58*
Hospitalization time	8.14± 0.81	5.91± 0.92*

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

表 4 2 组血清因子比较($\bar{x}\pm s$)

Table 4 Comparison of the serum factor between two groups($\bar{x}\pm s$)

Item	Control group(n=80)		Treatment group(n=80)	
	Before treatment	After treatment	Before treatment	After treatment
SAA(mg·L^{-1})	413.59± 55.83	178.53± 26.96*	412.05± 58.78	133.43± 25.74*#
CRP(mg·L^{-1})	20.41± 2.93	8.54± 1.29*	20.46± 2.59	4.75± 0.71*#

Note: Compared with before treatment, *$P<0.05$; Compared with control group, #$P<0.05$. SAA: Serum amyloid A; CRP: C reactive protein.

常、血常规异常等不良反应;对照组出现恶心呕吐 5 例,皮疹 1 例,试验组出现 7 例恶心呕吐,2 例腹泻,症状均较为轻微,停药后自行缓解,无需特殊处理,2 组不良反应总发生率分别为 7.50(6/80)、11.25%(9/80),比较无显著差异($P>0.05$)。

3 讨论

手足口病是种由多种肠道病毒所引发的传染疾病,主要感染途径包括呼吸道、消化道和解除传染等,多为急性起病[7,8]。

导致常见的病原体主要包括肠道病毒 71 型(EV71)、柯萨奇 A 组 16 型(CoxA16),而其中 EV71 感染的患儿极易出现严重的神经系统并发症,短时间内可引发永久性肌麻痹和死亡,预后较差[9,10]。

干扰素是人和动物细胞受到适当刺激时所生成的一种微量且具有高度生物活性的糖蛋白,具有较强的抗病毒作用[11,12]。其可通过和细胞表面特异性的膜受体相互结合,对病毒 DNA、RNA 及蛋白质的合成产生抑制作用,可防止病毒在感染的细胞中的复制和释放,对细胞增殖具有抑制作用[13,14]。且干扰素可通过增加 T 细胞和 NK 细胞活性,诱导淋巴因子的生成,发挥消灭病毒的作用,增加机体抗病毒活性[15,16]。并有研究指出,在婴幼儿中自体生成干扰素的能力较弱,内源性干扰素不足,而通过给予外源性干扰素可提高机体抗病毒能力[17,18]。重组人干扰素 α-2b 是由携带有人白细胞干扰素 a-2b 基因质粒的重组假单胞菌中提取而成,具有提高机体干扰素的含量的作用[19,20]。既往临床上给予重组人干扰素 α-2b 多以大剂量全身给药为主[21]。但有报道发现,高浓度的干扰素无论实在体内或体外均对抗体形成具有抑制作用,在一定范围中,干扰素浓度越高,抑制效应也会更强[22,23]。并有学者认为,在使用重组人干扰素 α-2b 时应注意干扰素的聚射效应,即作用于病毒的侵犯部位,才可发挥其最有效的抗病毒疗效[24,25]。有实验指出,局部给药可减少全身用药所产生的头痛、高热、肌肉酸痛等不良反应,安全性较好[26,27]。但目前关于何种方式用于手足口病患儿效果更佳的方式较少。

本研究结果显示,使用重组人干扰素 α-2b 雾化吸入的患儿血清 SAA、CRP 的降低程度更明显,通过分析是由于雾化吸入利用高速氧气气流,直接在病毒侵袭的部位发生作用并抵达靶细胞,获得更高的局部抑制病毒浓度,加强局部的抗抗炎、抗感染能力,且雾化吸入较局部外用相比,作用时间很长,生物利用度更高,抗炎效果更持久[28,29]。Teo KW,等[30]报道也得出相似结论。且本研究中,使用重组人干扰素 α-2b 雾化吸入的患儿临床疗效、临床症状改善时间均优于局部外用的患儿,显示出该方式在发挥更有效的抗炎作用的同时,可进一步促进患儿疾病的恢复,提高临床疗效。

综上所述,在手足口病患儿中使用重组人干扰素 α-2b 注射液雾化吸入效果显著,可有效促进疾病缓解,且用药安全性高,值得应用推广。

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