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葡萄糖酸锌颗粒联合消旋卡多曲颗粒对轮状病毒性肠炎患儿血浆炎症因子、心肌酶指标及免疫功能的影响*

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摘要 目的:探讨葡萄糖酸锌颗粒联合消旋卡多曲颗粒对轮状病毒性肠炎患儿血浆炎症因子、心肌酶指标及免疫功能的影响。**方法:**选取2017年2月~2019年7月期间于我院门诊就诊的轮状病毒性肠炎患儿97例,根据随机数字表法分为对照组(n=48)和研究组(n=49),在常规治疗的基础上对照组患儿给予消旋卡多曲颗粒治疗,研究组在对照组的基础上联合葡萄糖酸锌颗粒治疗,比较两组患儿疗效、血浆炎症因子[白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)]、血清心肌酶指标[乳酸脱氢酶(LDH)、磷酸肌酸激酶同工酶(CK-MB)和磷酸肌酸激酶(CK)]及免疫功能指标(CD4⁺、CD8⁺、CD4⁺/CD8⁺)的变化情况,记录两组治疗期间不良反应发生情况。**结果:**研究组治疗7d后的临床总有效率为91.84%(45/49),高于对照组的75.00%(36/48)($P<0.05$)。两组治疗7d后血浆IL-6、TNF- α 水平均下降,且研究组低于对照组($P<0.05$)。两组治疗7d后血清LDH、CK、CK-MB水平均下降,且研究组低于对照组($P<0.05$)。两组治疗7d后CD8⁺下降,且研究组低于对照组($P<0.05$);CD4⁺、CD4⁺/CD8⁺升高,且研究组高于对照组($P<0.05$)。两组不良反应发生率对比未见统计学差异($P>0.05$)。**结论:**葡萄糖酸锌颗粒联合消旋卡多曲颗粒治疗轮状病毒性肠炎患儿疗效显著,可改善患儿炎症因子、心肌酶指标,提升患儿免疫功能,且未见严重不良反应发生。

关键词:葡萄糖酸锌颗粒;消旋卡多曲颗粒;轮状病毒性肠炎;炎症因子;心肌酶指标;免疫功能

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Effects of Zinc Gluconate Combined with Racecadotril on Plasma Inflammatory Factors, Myocardial Enzymes and Immune Function in Children with Rotavirus Enteritis*

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ABSTRACT Objective: To investigate the effect of zinc gluconate combined with racecadotril on plasma inflammatory factors, myocardial enzymes and immune function in children with rotavirus enteritis. **Methods:** A total of 97 children with rotavirus enteritis who were admitted to our hospital from February 2017 to July 2019 were selected, they were randomly divided into control group (n=48) and study group (n=49) according to the random number table method. On the basis of routine treatment, the control group was treated with racecadotril granules. The study group was treated with zinc gluconate oral solution on the basis of the control group. The efficacy and plasma inflammatory factors [interleukin-6 (IL-6), tumor necrosis factor- α (TNF- α), serum myocardial enzyme indexes [lactate dehydrogenase (LDH), creatine phosphokinase-isoenzyme-MB (CK-MB) and creatine phosphokinase (CK)] and immune function indexes (CD4⁺, CD8⁺, CD4⁺/CD8⁺) changes of two groups were compared. **Results:** The total clinical effective rate of the study group at 7 d after treatment was 91.84% (45/49), which was higher than 75.00% (36/48) of the control group ($P<0.05$). The levels of plasma IL-6 and TNF- α of the two groups decreased at 7 days after treatment, and the levels of the study group were lower than those of the control group ($P<0.05$). The levels of LDH, CK and CK-MB of the two groups decreased at 7 days after treatment, and the levels of the study group were lower than those of the control group ($P<0.05$). 7 days after treatment, CD8⁺ of the two groups decreased at 7 days after treatment, and that of the study group was lower than that of the control group ($P<0.05$). CD4⁺, CD4⁺/CD8⁺ were increased, and that of the study group were higher than that of the control group ($P<0.05$). No serious adverse reactions were found in the two groups ($P>0.05$).

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Conclusion: Zinc gluconate combined with racecadotril in the treatment of rotavirus enteritis children has a significant effect, which can improve the inflammatory factors and myocardial enzyme indexes, and enhance the immune function of children, and no serious adverse reactions have been observed.

Key words: Zinc gluconate; Racecadotril granules; Rotavirus enteritis; Inflammatory factors; Myocardial enzyme index; Immune function

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前言

轮状病毒性肠炎是婴幼儿常见的病症之一,该病起病急、病情进展快,以腹泻、高热为主要症状,若未能及时予以治疗,患儿易因电解质紊乱、脱水等问题引发死亡^[1-3]。目前临床针对该病的治疗尚无特异性方案,多以抗病毒、纠正电解质、补液为主^[4]。消旋卡多曲颗粒是临床常见的脑肽酶抑制剂,可减少水电介质的过度分泌,是治疗轮状病毒性肠炎的常用药物^[5],但部分患儿经该药治疗后疗效并不理想。随着对该疾病研究的深入,不少研究发现腹泻会引起机体锌元素大量丢失,且锌元素的丢失程度与疾病预后、转归息息相关^[6,7]。葡萄糖酸锌颗粒为临床常见的补锌药物,锌具有修复肠粘膜、促进肠粘膜细胞再生等作用,继而缓解腹泻^[8]。鉴于此,本研究通过对病毒性肠炎患儿采用葡萄糖酸锌颗粒联合消旋卡多曲颗粒治疗,探讨其对轮状血浆炎症因子、心肌酶指标及免疫功能的影响,以期临床治疗小儿轮状病毒性肠炎提供参考。

1 资料与方法

1.1 一般资料

选取2017年2月~2019年7月期间我院门诊就诊的轮状病毒性肠炎患儿97例,纳入标准:(1)均符合病毒性肠炎的诊断标准,临床表现为不同程度的呕吐、腹泻,大便为水样或蛋花样,经实验室相关检查检测出轮状病毒;(2)发病时间 ≤ 72 h;(3)年龄6~24个月;(4)已签署了同意书。排除标准:(1)重度脱水或存在频繁呕吐,无法进行口服补液治疗;(2)近期服用过抗生素等类药物;(3)合并其他感染性疾病;(4)存在营养不良的患儿;(5)中途退出本次研究,无法观察疗效者;(6)对本次研究用药存在禁忌症者。根据随机数字表法分为对照组($n=48$)和研究组($n=49$),对照组男28例,女20例,年龄6~24个月,平均 (13.48 ± 2.17) 个月;体质指数 $8\sim 14\text{ kg/m}^2$,平均 $(11.38\pm 0.93)\text{ kg/m}^2$;发病至入院时间 $7\sim 72\text{ h}$,平均 $(38.57\pm 4.29)\text{ h}$;无脱水19例,轻度脱水15例,中度脱水14例。研究组男30例,女19例,年龄6~23个月,平均 (14.15 ± 2.38) 个月;体质指数 $7\sim 14\text{ kg/m}^2$,平均 $(11.19\pm 0.86)\text{ kg/m}^2$;发病至入院时间 $8\sim 70\text{ h}$,平均 $(38.12\pm 6.37)\text{ h}$;无脱水20例,轻度脱水13例,中度脱水16例。两组患儿一般资料对比未见统计学差异($P>0.05$),具有可比性。此次研究已获取我院伦理学委员会批准进行。

1.2 方法

两组均给予退热、维持酸碱平衡等常规治疗,在此基础上,对照组给予消旋卡多曲颗粒(国药准字H20051055,江苏正大丰海制药有限公司,规格:10 mg)治疗,温水冲服,3次/d,1~9月龄剂量每次10 mg,9~24月龄剂量每次20 mg。研究组在

对照组基础上联合葡萄糖酸锌颗粒(苏药制字H04003197,徐州市儿童医院,规格:60 mg)治疗,6~12月剂量为40 mg/d,1~2岁剂量为60 mg/d,温水冲服,分早晚两次饭后口服。两组均治疗7d。

1.3 观察指标

(1)记录两组临床疗效。疗效判定标准参考《现代实用儿科学》^[9]。具体如下:治疗后2~3d,体征、临床症状消失,大便次数得到正常恢复或减少到2次/d,大便性状正常(显效);治疗后2~3d,临床症状、体征基本消失,大便次数减少到2次/d,大便性状有所改善(有效);临床体征、症状、大便次数及性状未见改善甚至加重(无效)。总有效率=显效率+有效率。(2)于治疗前、治疗7d后抽取患儿空腹静脉血4 mL,置于涂有肝素钠的试管中,室温下静置0.5 h,经离心处理(离心半径7 cm,3500 r/min离心12 min),分离血清、血浆,置于 -40°C 冰箱中待测。参考试剂盒(江西赛基生物技术有限公司)说明书,采用流式荧光法检测血浆白介素-6(IL-6)、肿瘤坏死因子- α (TNF- α)水平。采用全自动生化分析(日立7600)检测血清心肌酶指标水平:乳酸脱氢酶(Lactate dehydrogenase, LDH)、磷酸肌酸激酶同工酶(Creatine phosphokinase-isoenzyme-MB, CK-MB)和磷酸肌酸激酶(Creatine phosphokinase, CK)。采用流式细胞仪检测免疫功能指标 CD4^{+} 、 CD8^{+} ,并计算 $\text{CD4}^{+}/\text{CD8}^{+}$ 。(3)记录两组不良反应。

1.4 统计学方法

采用SPSS25.0进行统计分析,计数资料以率的形式表示,采用卡方检验,计量资料以 $(\bar{x}\pm s)$ 的形式表示,采用t检验。以 $\alpha=0.05$ 为检验标准。

2 结果

2.1 临床疗效比较

治疗7d后研究组的临床总有效率为91.84%(45/49),高于对照组的75.00%(36/48)($P<0.05$),详见表1。

2.2 炎症因子水平比较

治疗前两组血浆IL-6、TNF- α 水平比较无差异($P>0.05$);两组治疗7d后血浆IL-6、TNF- α 水平均下降,且研究组低于对照组($P<0.05$),详见表2。

2.3 两组心肌酶指标比较

两组治疗前血清LDH、CK、CK-MB水平比较无差异($P>0.05$);两组治疗7d后血清LDH、CK、CK-MB水平均下降,且研究组低于对照组($P<0.05$),详见表3。

2.4 两组免疫功能指标比较

两组治疗前 CD4^{+} 、 CD8^{+} 、 $\text{CD4}^{+}/\text{CD8}^{+}$ 比较无差异($P>0.05$);两组治疗7d后 CD8^{+} 下降,且研究组低于对照组($P<0.05$)。

05);CD4⁺、CD4⁺/CD8⁺ 升高, 且研究组高于对照组($P<0.05$), 详见表 4。

表 1 两组临床疗效比较 例(%)

Table 1 Comparison of clinical effects between the two groups n(%)

Groups	Markedly effective	Effective	Invalid	Total effective rate
Control group(n=48)	13(27.08)	23(47.92)	12(25.00)	36(75.00)
Study group(n=49)	19(38.76)	26(53.06)	4(8.16)	45(91.84)
χ^2				4.993
P				0.026

表 2 两组炎症因子水平比较($\bar{x}\pm s$)Table 2 Comparison of inflammatory factors between the two groups($\bar{x}\pm s$)

Groups	IL-6($\mu\text{g/L}$)		TNF- α (ng/L)	
	Before treatment	7 d after treatment	Before treatment	7 d after treatment
Control group(n=48)	53.54 $\pm$ 3.64	34.07 $\pm$ 4.35*	73.12 $\pm$ 6.89	57.35 $\pm$ 7.56*
Study group(n=49)	52.89 $\pm$ 4.93	19.10 $\pm$ 3.27*	72.93 $\pm$ 5.43	38.41 $\pm$ 6.12*
t	0.737	19.184	0.151	13.575
P	0.463	0.000	0.880	0.000

Note: compared with before treatment, * $P<0.05$.

表 3 两组心肌酶指标比较($\bar{x}\pm s$)Table 3 Comparison of myocardial enzyme indexes between the two groups($\bar{x}\pm s$)

Groups	LDH(U/L)		CK(U/L)		CK-MB(U/L)	
	Before treatment	7 d after treatment	Before treatment	7 d after treatment	Before treatment	7 d after treatment
Control group (n=48)	212.54 $\pm$ 10.83	159.15 $\pm$ 11.71*	61.28 $\pm$ 5.31	47.64 $\pm$ 6.57*	144.52 $\pm$ 12.41	97.16 $\pm$ 9.32*
Study group(n=49)	213.03 $\pm$ 14.94	105.74 $\pm$ 13.55*	62.02 $\pm$ 6.34	32.57 $\pm$ 5.61*	142.47 $\pm$ 14.32	69.75 $\pm$ 8.69*
t	0.185	20.753	0.623	12.157	0.753	14.985
P	0.854	0.000	0.535	0.000	0.453	0.000

Note: compared with before treatment, * $P<0.05$.

表 4 两组免疫功能指标比较($\bar{x}\pm s$)Table 4 Comparison of immune function indexes between the two groups($\bar{x}\pm s$)

Groups	CD4 ⁺ (%)		CD8 ⁺ (%)		CD4 ⁺ /CD8 ⁺	
	Before treatment	7d after treatment	Before treatment	7d after treatment	Before treatment	7d after treatment
Control group (n=48)	37.77 $\pm$ 6.81	42.76 $\pm$ 6.31*	33.21 $\pm$ 5.73	28.03 $\pm$ 4.38*	1.44 $\pm$ 0.27	1.88 $\pm$ 0.38*
Study group(n=49)	36.71 $\pm$ 7.92	47.38 $\pm$ 7.27*	32.28 $\pm$ 4.96	23.45 $\pm$ 3.44*	1.45 $\pm$ 0.29	2.45 $\pm$ 0.41*
t	0.759	4.736	0.855	5.734	0.176	8.315
P	0.436	0.000	0.395	0.000	0.861	0.000

Note: compared with before treatment, * $P<0.05$.

2.5 两组不良反应比较

治疗期间,对照组出现嗜睡 1 例、便秘 1 例、恶心 2 例,不良反应发生率为 8.33%(4/48);研究组出现轻度恶心 2 例、呕吐 1 例、便秘 2 例等消化道反应,不良反应发生率为 10.20%(5/49);两组不良反应发生率对比未见统计学差异($\chi^2=0.101$, $P=0.751$)。

3 讨论

腹泻是婴幼儿的常见疾病,小儿由于各项器官发育并不成熟,其肠道免疫力低下,极易受到致病微生物的侵袭而引起各种感染性腹泻病^[10,11]。小儿腹泻主要由轮状病毒和产毒性大肠埃希菌感染引起,其中以轮状病毒性肠炎较为多见^[12]。轮状病毒通过感染小肠粘膜的上皮细胞,致使微绒毛变短、破坏、排列不规则或肿胀,进而引起小肠的吸收功能障碍;此外,发生病变的肠粘膜细胞双糖酶分泌不足,食物中糖类消化彻底,导致其于肠腔内积滞,超过结肠吸收功能而引起水样腹泻^[13-15]。轮状病

毒性肠炎具有一定的自限性,但其带来的并发症如酸碱代谢紊乱、脱水、发热、酸中毒等均会对患儿造成一定影响^[16]。消旋卡多曲颗粒为选择性的外周脑啡肽酶抑制剂,近年来已被广泛应用于治疗急性水样腹泻,疗效已得到广大临床医师的认可^[17,18]。自2004年世界卫生组织建议对急性腹泻病儿童每天给予锌治疗后,临床实践也证实了补锌治疗效果较好,还可在一定程度上缩短病程^[19,20]。葡萄糖酸锌颗粒是临床常见的补锌药物,现逐渐用于轮状病毒性肠炎患儿的辅助治疗中^[21,22]。

本次研究中,研究组治疗后的疗效明显优于对照组,可见轮状病毒性肠炎患儿经葡萄糖酸锌颗粒联合消旋卡多曲颗粒治疗后,治疗效果提高。提示消旋卡多曲颗粒具有较强的亲脂性,进入人体后可快速水解,并选择性地抑制脑啡肽酶,从而延长消化道内源性脑啡肽酶生理活性,维持水、电解质平衡^[23]。此外,消旋卡多曲颗粒对肠蠕动的的影响较轻,可快速改善腹泻症状^[24]。葡萄糖酸锌颗粒可预防腹泻过程中小儿锌元素过度流失,锌元素可防止液体的流失,并通过多种途径维持肠道粘膜的完整性,同时还可促进肠道粘膜细胞的生长发育,恢复消化功能^[25]。轮状病毒感染不仅会导致患者出现消化道类的症状,还会导致心肌细胞受损,导致血浆中心肌酶含量如CK、LDH、CK-MB迅速升高^[26]。此外,轮状病毒性肠炎可引起患儿持续性腹泻,导致蛋白质的生物合成受到影响,间接造成患儿免疫力低下的情况,免疫应答被激活后,可刺激中性粒细胞大量分泌IL-6、TNF- α 等炎症因子,引起炎症扩大级联化,进一步加重病情^[27]。T淋巴细胞为介导免疫功能的重要细胞,其中CD8⁺可抑制机体免疫功能,CD4⁺则可增强机体免疫功能,在轮状病毒感染后,可导致CD4⁺/CD8⁺比值下降^[28]。本研究中两组患儿血浆炎症因子、心肌酶指标及免疫功能均有所改善,且联合治疗者改善效果更佳。这可能是由于患儿补充锌元素后,肠道内消化性酶及胸腺肽等锌依赖因子的活性被激活,有利于肠道内蛋白质的合成,进而可提高机体的免疫功能。同时,锌作为抗氧化剂,可减少毒素吸取和细胞损伤,进而减少机体损伤,改善炎症因子及心肌酶指标^[29,30]。两组不良反应发生率对比未见统计学差异,可见联合治疗安全性较好。

综上所述,轮状病毒性肠炎患儿经葡萄糖酸锌颗粒联合消旋卡多曲颗粒治疗后,患儿血浆炎症因子、心肌酶指标及免疫功能等得到显著改善,且未见严重不良反应发生,疗效显著。

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