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还原型谷胱甘肽治疗儿童葡萄糖-6-磷酸脱氢酶缺乏症中的临床效果研究*

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摘要 目的:研究还原型谷胱甘肽治疗儿童葡萄糖-6-磷酸脱氢酶(G-6-P-D)缺乏症并发急性溶血的临床疗效,为临床治疗提供参考。**方法:**选取我院2015年6月-2017年6月因葡萄糖-6-磷酸脱氢酶(G-6-P-D)缺乏症并发急性溶血的患儿78例并将其随机分为两组,每组39例。对照组予以停用氧化类药物,卧床休息,水化、碱化尿液,贫血严重者输注去白红细胞治疗;观察组在对照组基础上加用还原型谷胱甘肽治疗。观察和比较两组患儿第1天、第2天、第3天小便恢复率以及平均恢复时间,血清总胆红素第3天、第5天恢复率、平均恢复时间及平均住院时间。**结果:**治疗后,观察组第1天、第2天、第3天小便恢复率分别为51.3%、92.3%、100%,对照组分别为25.6%、64.1%、89.7%,观察组第1天、第2天、第3天小便恢复率均显著高于对照组(P<0.05);观察组及对照组小便恢复正常平均时间分别为1.8± 0.7天、2.6± 0.9天,观察组明显短于对照组(P<0.05);观察组第3天、第5天血清总胆红素恢复率分别为71.8%、100%,对照组为46.2%、97.4%;观察组和对照组血清总胆红素恢复正常平均时间分别为3.6± 0.9天、4.1± 1.0天;平均住院时间分别为2.3± 0.6天、2.8± 0.6天;观察组小便及血清总胆红素平均恢复时间(P<0.05)、平均住院时间均显著短于对照组(P<0.05)。**结论:**在儿童葡萄糖-6-磷酸脱氢酶缺乏并发急性溶血中应用还原型谷胱甘肽可增强其治疗疗效,缩短治疗疗程。

关键词:还原型谷胱甘肽;葡萄糖-6-磷酸脱氢酶缺乏症;急性溶血;治疗

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Clinical Study on the Efficacy of Reduced Glutathione in the Treatment of Children with Glucose-6-phosphate Dehydrogenase Deficiency*

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ABSTRACT Objective: To investigate the therapeutic effect of reduced glutathione(GSH) on the children with Glucose-6-phosphate dehydrogenase deficiency (G6PD) complicated by acute hemolysis. **Methods:** 78 cases of children with G6PD deficiency complicated with acute hemolysis were recruited into this study over a period of two years (2015.7-2017.7). We randomly assigned the patients in a 1:1 ratio to receive routine treatment combined of reduced glutathione per day (GSH group) or routine treatment alone as the control. Routine therapy included discontinued usage of oxidative drugs, bed rest, hydration, and alkalization of urine, and patients with severe anemia were given transfusion of leukocyte-depleted red blood cells. On the first day, second day, and the third day, we record the rate of patients who attain normal urine output. On the third day and fifth day, the rate of patients who attain normal serum total bilirubin(STB) level was recorded. In addition, the average time it takes for urine output and STB level returned to normal and the average duration of hospital stay was compared between the GSH group and the control. **Results:** In the GSH group, the urine recovery rates on the first day, the second day and the third day were 51.3%, 92.3% and 100% respectively, which were 25.6%, 64.1% and 89.7% respectively in the control group and were significantly lower than those of the GSH group (P<0.05). The average urine recovery time was 1.8± 0.7 days and 2.6± 0.9 days in the observation group and control group, which was significantly shorter in the observation group than that of the control group (P<0.05). The STB recovery rate of observation group was 71.8% and 100% on the third and fifth days respectively, which was 46.2% and 97.4% in the control croup and significantly lower than those of the GSH group. In the observation group, the average bilirubin recovery time was 3.6± 0.9 days, which was 4.1± 1.0 days in the control group. The average duration of hospital stay was 2.3± 0.6 days and 2.8± 0.6 days respectively. The average recovery time of urine and serum total bilirubin and average hospitalization in the observation group(P<0.05) were significantly shorter than those of the control group (P<0.05). **Conclusion:** Among children with G6PD complicated by acute hemolysis, reduced glutathione combined with routine therapy could shorten the treatment duration, and it is more effective than the routine therapy alone.

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前言

葡萄糖 -6- 磷酸脱氢酶 (glucose-6-phosphatedehy droge-nase,G6PD) 缺乏症是一种与红细胞酶异常相关的遗传性溶血性疾病,其遗传方式为 X 连锁不完全显性遗传。目前,全世界约 4 亿人患病[1],男性多于女性,我国以云南、贵州、四川、广东等地区多见。G6PD 缺乏症患儿平时大多无症状,在摄入蚕豆或暴露于某些感染或药物时会引起急性溶血性贫血[2,3];不同性别和基因型临床表现无明显差异[4,5]。但在新生儿期间可能会发生严重的黄疸,严重者遗留神经系统后遗症[6,7]。

还原型谷胱甘肽(glutathione,GSH)是一种三肽,参与体内三羧酸循环及糖代谢。红细胞中 GSH 的含量高,对维持细胞的正常代谢、红细胞膜的完整性和保护红细胞免受氧化剂的损害具有重要的意义。有研究显示在 G6PD 活性降低的患儿红细胞中,GSH 含量明显降低,严重影响正常红细胞代谢、细胞膜完整性以及稳定性[8]。本研究主要探讨了 GSH 治疗 G6PD 缺乏症并发急性溶血的临床效果,结果报道如下。

1 资料与方法

1.1 一般资料

选取我院 2015 年 6 月至 2017 年 6 月因葡萄糖 -6- 磷酸脱氢酶(G-6-P-D)缺乏症并发急性溶血的患儿 78 例,随机分为两组。观察组 39 例,包括男性 34 例,女性 5 例,年龄 7 月到 6 岁,平均年龄 3.2± 0.8 岁;对照组 39 例,包括男性 33 例,女性 6 例,年龄 1 岁到 6 岁,平均年龄 3.5± 0.6 岁。两组患儿发病前均有进食蚕豆及蚕豆类食物病史,其中 1 例母乳喂养的患儿其母亲有进食蚕豆病史。所有资料均符合伦理学规定,并签署相关知情同意书。

1.2 诊断标准

葡萄糖 -6- 磷酸脱氢酶缺乏并发急性溶血:检测 G6PD 活性小于 0.3,有血红蛋白尿、黄疸、贫血临床表现,网织红细胞百分比增高。

1.3 排除标准

合并发热、肾脏损害、肝功能损害、慢性肝病、慢性肾病等疾病的患儿。

1.4 临床表现

所有患儿均有酱油色小便或葡萄酒样小便、黄疸、不同程度的贫血。其中,重度贫血共 65 例。

1.5 治疗方法

对照组 39 例,予以停用氧化类药物,卧床休息、水化、碱化尿液,贫血严重者输注去白红细胞治疗;观察组 39 例,在对照组基础上加用还原型谷胱甘肽(山东绿叶制药有限公司)治疗,剂量:体重大于等于 10 kg,600 mg/d;体重小于 10 kg,1500 mg/m²·d。

1.6 观察指标

观察每次小便颜色,每日监测血常规及小便常规,隔日复查血清胆红素,记录出院时间。

1.7 疗效标准判定

临床观察 7 d;治愈:一般情况明显好转,黄疸消失,小便颜色正常,贫血恢复,血红蛋白尿消失,血清总胆红素正常,血红蛋白≥ 110 g/L。好转:一般情况好转,黄疸减轻,贫血改善,血红蛋白尿消失,血红蛋白≥ 80 g /L。无效:黄疸、贫血、血红蛋白尿仍存在,血红蛋白< 60 g/L。

1.8 统计学分析

采用 SPSS13.0 软件进行统计分析, 计量资料以 $\bar{x}\pm s$ 表示,组间比较采用 t 检验,计数资料组间比较采用 x^2 验,以 P<0.05 为差异有统计学意义

2 结果

本研究所有患儿观察 7 天后,黄疸均消失,小便颜色正常,复查小便常规血红蛋白尿消失,血清胆红素恢复正常,血红蛋白≥ 110 g/L,均达到治愈标准。

2.1 两组小便恢复时间比较

观察组小便第 1 天、第 2 天、第 3 天恢复率分别为 51.3%、92.3%、100%;对照组分别为 25.6%、64.1%、89.7%。观察组小便恢复率明显高于对照组,差异具有统计学意义(P<0.05),见表 1。

2.2 两组胆红素恢复率比较

观察组第 3 天、第 5 天胆红素恢复率分别为 71.8%、100%,对照组第 3 天、第 5 天胆红素恢复率分别为 46.2%、97.4%;观察组胆红素恢复时间明显短于对照组, 差异具有统计学意义(P<0.05),见表 2。

2.3 两组小便颜色、胆红素平均恢复天数及平均住院天数比较

观察组小便颜色平均恢复时间、胆红素平均恢复时间、平均住院天数分别为 1.8± 0.7 天、3.6± 0.9 天、2.3± 0.6 天, 对照组分别为 2.6± 0.9 天、4.1± 1.0 天、2.8± 0.6 天。观察组小便恢复平均时间、胆红素恢复平均时间、平均住院时间均短于对照组,差异具有统计学意义(P<0.05),见表 3。

表 1 两组小便恢复率的比较

Table 1 Comparison of the urinary recovery rate between two groups

Days	Observation Group n(%)	Control Group n(%)	x^2	P
1 d	20(51.3)	10(25.6)	5.417	0.020
2 d	36(92.3)	25(64.1)	9.101	0.003
3 d	39(100.0)	35(89.7)	4.216	0.124

表 2 两组血清总胆红素恢复率的比较

Table 2 Comparison of the total bilirubin recovery rate between two groups

Days	Observation Group n(%)	Control Groupn(%)	x^2	P
3 d	28(71.8)	18(46.2)	5.299	0.021
5 d	39(100.0)	38(97.4)	1.013	0.314

表 3 两组平均恢复天数及平均住院天数的比较

Table 3 Comparison of the average recovery Time and duration of hospital stay between two groups

Index	Observation Group n	Control Group n	t	P
Average urinary recovery Time (d)	1.8± 0.7	2.6± 0.9	5.466	＜0.001
Average total bilirubin bilirubin recovery Time(d)	3.6± 0.9	4.1± 1.0	2.227	0.029
Average duration of hospital stay(d)	2.3± 0.6	2.8± 0.6	4.768	＜0.001

3 讨论

G6PD 基因位于 Xq28，由 13 个外显子和 12 个内含子组成，全长 20114bP，编码 515 个氨基酸，目前约 200 种基因突类型被鉴定[9,10]。中国人 G6PD 的突变型主要为 G1376T、G1388A、A95G 三种[11]。G6PD 在所有细胞中均有表达，是细胞能量代谢磷酸己糖途径的限速酶，其主要生理作用是提供 NADPH。NADPH 作为供氢体，能够将氧化型的 GSSG 还原为 GSH，维持谷胱甘肽的还原状态，保护红细胞膜的完整性，避免过氧化氢的氧化性损伤[12]。G6PD 不足的红细胞不能产生足够的 NADPH，不能保护血液中红细胞免受外源性氧化剂的氧化及机体产生氧自由基的损害，同时对其它细胞氧化损伤也有较大的影响[13]。G6PD 缺乏除直接影响红细胞的抗氧化能力导致溶血性贫血外，还可影响红细胞膜的稳定性，进一步加重溶血[14,15]。谷胱甘肽在人体红细胞中含量较高，能够与进入体内的药物、毒素等结合，对防治红细胞溶血具有重要意义，其主要的生理功能是作为一种重要的抗氧化剂，清除体内的自由基，保护细胞免受氧化损伤[16,17]。

G6PD 缺乏症是人类最常见的酶病[18]，有研究发现其可与镰状细胞病同时存在[19]，且可能是肺动脉高压发生的高危因素[20]。根据诱发溶血的不同原因，G6PD 缺乏症目前可分为 5 种临床类型：伯氨喹型药物性贫血、蚕豆病、新生儿黄疸、感染诱发的溶血、先天性非球形红细胞溶血性贫血，以蚕豆病最为多见，以浓茶色小便或者葡萄酒样小便、黄疸、贫血为主要表现，部分患儿伴有呕吐、腹痛、少尿、中枢神经系统症状等。有报道称该病可并发肾功能损害，但本研究中患儿均未出现[21]。本研究中所有患儿均有酱油色小便、黄疸、贫血表现，发病前均有进食蚕豆及蚕豆类食物病史，符合蚕豆病临床表现类型。

还原型 GSH 作为体内一种重要的抗氧化剂，可通过直接清除自由基，减少自由基生成，调节离子分布，抑制细胞因子生成，从而减轻靶细胞损伤。有研究表明还原型 GSH 可对抗细胞的免疫性损害[22]。也有报道称 G6PD 缺乏症的患儿血液中还原型 GSH 的含量与 G6PD 活性相关，在此病中补充外源性 GSH 有助于维持红细胞膜的正常形态和完整性[13,23]。本研究中，观察组患儿第一天、第二天、第三天小便恢复率、血清总胆红素恢复率均明显优于对照组，平均住院时间少于对照组，提示加用还原型 GSH 治疗的患者小便恢复时间、血清总胆红素恢复时间、住院时间明显缩短，疗效更优，与叶军等[24]研究结果一致。

G6PD 缺乏症是一种常见病，临床上常以急性溶血为主要表现，还原型谷胱甘肽用于治疗 G6PD 缺乏症能有效减少小便中的血红蛋白尿及血清胆红素恢复正常的时间，增强治疗疗效，有效缩短治疗疗程。

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