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霉酚酸酯联合糖皮质激素治疗小儿紫癜性肾炎的疗效观察

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摘要 目的:探究霉酚酸酯联合糖皮质激素治疗小儿紫癜性肾炎的疗效及安全性。**方法:**选择 2012 年 3 月～2015 年 9 月 70 例于我院就诊的紫癜性肾炎儿童,按照不同的治疗方法将其分为观察组(35 例)和对照组(35 例)。两组患者入院后均给予常规治疗,在此基础上观察组患者给予泼尼松联合霉酚酸酯治疗,对照组给予泼尼松联合环磷酰胺治疗。比较两组的总有效率、临床症状消失时间、生化指标、免疫功能及不良反应发生情况。**结果:**观察组的临床总有效率为 94.29%(33/35),对照组的总有效率为 85.17%(30/35),两组比较差异无统计学意义(P=0.232)。治疗后,观察组蛋白尿、血尿等临床症状消失时间与对照组比较差异无显著意义(P＞0.05);两组患儿的 24 h 蛋白定量、$CD19^+$ 水平均较治疗前显著降低,且观察组 $CD19^+$ 水平显著低于对照组(P＜0.05),两组的血清白蛋白、总蛋白含量、$CD3^+$、$CD3^+CD4^+$ 水平在均较治疗前明显上升,且观察组的 $CD3^+$、$CD3^+CD4^+$ 水平显著高于对照组(P＜0.05)。观察组治疗期间不良反应发生率显著低于对照组(P=0.012)。**结论:**霉酚酸酯联合糖皮质激素治疗小儿紫癜性肾炎的临床效果较泼尼松联合环磷酰胺治疗更好,安全性更高。

关键词:霉酚酸酯;紫癜性肾炎;糖皮质激素;免疫功能;临床疗效

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Observation on the Curative Effect of Mycophenolate Mofetil Combined with Glucocorticosteroid on the Children with Anaphylatic Purpura Nephritis

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ABSTRACT Objective: To explore the clinical effect of mycophenolate mofetil combined with glucocorticosteroid on the children with anaphylatic purpura nephritis. **Methods:** 70 cases of children treated and diagnosed as anaphylatic purpura nephritis in our hospital from March, 2012 to September, 2015 were enrolled in this study. They were randomly divided into the observation group and the control group. Conventional therapy was applied to both groups, the observation group was treated by mycophenolate mofetil combined with prednisone, the control group was given cyclophosphamide combined with prednisone. The total effective rate, disappearence time of clinical symptoms, biochemical indicators, immune function as well as the incidence of adverse reactions were compared between the two groups. **Results:** The total effective rate of observation group was 94.29%, which was 85.17% in the control group, no statistical difference was found between two groups(P>0.05). After therapy, the disappearence time of albuminuria, hematuria in observation group showed no significant difference compared with those of the control group, the level of 24 h urine protein quantitation and $CD19^+$ of both groups were significantly decreased, and the level of $CD19^+$ of observation group was significantly lower than that of the control group (P＜0.05), the level of albumin, total protein and $CD3^+$, $CD3^+CD4^+$ of both groups were significantly increased, and the level of $CD3^+$, $CD3^+CD4^+$ of observation group were significantly higher than those of the control group (P＜0.05). The incidence of adverse reactions in observation group was significantly lower than that of the control group (P＜0.05). **Conclusion:** Mycophenolate mofetil combined with glucocorticosteroid was more effective and safe on the children with anaphylatic purpura nephritis than that of cyclophosphamide combined with prednisone.

Key words: Mycophenolate mofetil; Anaphylatic purpura nephritis; Glucocorticosteroid; Immune function; Clinical effect

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前言

过敏性紫癜又称急性血管性紫癜,是由血管变态反应性炎症引起的血管壁通透性及脆性增加而导致出血的皮肤及粘膜病变,好发于 10 岁以下儿童。除下肢对称性皮肤出血以外,临床上多伴有关节炎、腹痛、肾炎等并发症[1-3]。紫癜性肾炎是过敏性紫癜累及肾脏的表现,也是过敏性紫癜最为严重的并发症,是儿童期慢性肾脏疾病的主要原因之一。临床资料表明约有

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25%～60%的过敏性紫癜儿童会并发紫癜性肾炎，其中 15%的患儿发展为慢性肾功能不全，8%的患儿发展为肾衰竭 [4-6]。目前，针对小儿紫癜性肾炎的首选治疗药物是糖皮质激素，然而临床上考虑到有相当一部分患者对糖皮质激素产生依赖或抵抗，且持续的糖皮质激素刺激会一定程度上影响儿童的生长发育，因此临床上多用糖皮质激素联合免疫抑制剂进行治疗[7,8]。环磷酰胺联合糖皮质激素是传统的治疗方案，但临床实践表明其不良反应较多。因此，本研究旨在探究新型免疫抑制剂霉酚酸酯联合小剂量糖皮质激素治疗小儿紫癜性肾炎的疗效观察及安全性，以期为优化临床用药方案提供参考依据。

1 资料与方法

1.1 一般资料

选择 2012 年 3 月～2015 年 9 月 70 例于我院就诊的紫癜性肾炎儿童，按照不同的治疗方法将患者分为观察组(35 例)和对照组(35 例)。观察组患者平均年龄为(6.4± 1.2)岁，包含男性 20 例，女性 15 例，平均病程(2.33± 0.46)个月；对照组患者平均年龄为(6.3± 1.5)岁，包含男性 21 例，女性 14 例，平均病程(2.39± 0.37)个月。观察组和对照组患儿的一般临床资料比较差异无统计学意义(P＞0.05)，具有可比性。纳入标准：① 经病理确诊为紫癜性肾炎；② 均存在血尿或蛋白尿等典型临床特征；排除标准：① 非过敏性紫癜造成的肾脏损害；② 其他严重脏器功能不全。

1.2 治疗方法

两组患者入院后均嘱咐家长给予清淡，低蛋白，低脂肪饮食，适当补充维生素 C，并接受双嘧达膜，抗过敏，抗感染等常规治疗。在此基础上观察组患者给予泼尼松(浙江仙琚制药股份有限公司，国药准字 H33021207)0.5～1 mg/(kg·d)，加服霉酚酸酯(上海罗氏制药有限公司，国药准字 H20031277)20～30mg/(kg·d)，每日分两次服用，治疗 6 个月后减量至 15 mg/(kg·d)，维持 2 个月停用。对照组给予观察组同等剂量的泼尼松治疗，并静脉滴注环磷酰胺(山西振东泰盛制药有限公司，国药准字 H14023566)8～12 mg/ (kg·d) 溶于 250 mL 生理盐水，2 天为 1 个治疗周期，每两周 1 个疗程，共治疗 6-8 个疗程。环磷酰胺总剂量小于 150 mg/kg。

1.3 疗效判断及观察指标

1.3.1 两组患者疗效对比 临床疗效判定如下：治愈：紫癜症状消失，24 h 尿蛋白少于 150 mg，尿沉渣镜检红细胞少于 3 个 /HP，肾功能正常；显效：紫癜症状或体征基本消失，24 h 尿蛋白定量及尿沉渣镜检红细胞数减少一半以上，肾功能恢复正常；有效：紫癜症状有所缓解，24 h 尿蛋白定量及尿沉渣镜检红细胞数降幅 25%～49%，肾功能接近正常；无效：紫癜症状未改善，24 h 尿蛋白定量及尿沉渣镜检红细胞数及肾功能均无变化。

1.3.2 两组患者临床症状消失时间比较 比较两组患儿蛋白尿、血尿等临床症状消失时间。

1.3.3 两组患者治疗前后生化指标的变化情况 比较两组患儿治疗前、治疗 6 个月后 24 h 尿蛋白定量、清蛋白、总蛋白、尿 β2-MG 水平的变化情况。

1.3.4 两组患者机体免疫水平对比 比较治疗前后两组患儿淋巴细胞免疫水平($CD3^+$、$CD3^+CD4^+$、$CD19^+$)。

1.3.5 不良反应发生情况 治疗期间记录两组患儿的不良反应发生情况。

1.4 统计学分析

使用 SPSS18.0 软件，分别采用卡方检验、t 检验对计数资料、计量资料进行统计学分析，以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组患者的疗效对比

观察组的临床有效率为 94.29%(33/35)，对照组的总有效率为 85.17%(30/35)，两组比较差异无统计学意义(P=0.232)。

表 1 两组患者的临床疗效比较(n)

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

Groups	Number	Cure	Excellence	Effective	Invalid	Total effective rate(%)
Observation group	35	16	10	7	2	94.29
Control group	35	10	9	11	5	85.71

2.2 两组患儿蛋白尿、血尿症状消失时间比较

观察组患者蛋白尿、血尿症状消失时间与对照组相比差异无统计学意义(P＞0.05)。

表 2 两组患者临床症状消失时间比较($\bar{x}\pm s$，d)

Table 2 Compare the disappearance time of clinical symptoms between the two groups ($\bar{x}\pm s$, d)

Groups	Group	Number	Albuminuria	Hematuria
Observation group	Observation	35	18.4± 8.3	34.5± 10.9
Control group	Control	35	19.3± 6.6	35.2± 6.8

Note: compared with before therapy, $^aP<0.05$;

2.3 两组患者治疗前后生化指标的比较

治疗前，两组患者 24 h 蛋白定量、血清白蛋白、总蛋白、尿 β2-MG 水平比较差异无统计学意义(P＞0.05)；治疗后，两组的 24 h 蛋白定量均较治疗前显著下降，血清白蛋白、总蛋白含量

均较治疗前明显上升(P＜0.05),但两组之间上述指标比较差异 无统计学意义(P＞0.05)。

表 3 两组患儿治疗前后生化指标的对比($\bar{x}\pm s$)

Table 3 Comparison of the biochemical indicators between the two groups before and after the therapy ($\bar{x}\pm s$)

Biochemicalindicators	Observation group		Control group	
	Before therapy	After 6 months therapy	Before therapy	After 6 months therapy
urine protein quantitation (g/24 h)	2.46± 0.9	0.35± 0.19[a]	2.39± 1.20	0.38± 0.22[a]
Albumin (g/L)	35.7± 7.21	45.6± 4.27[a]	36.3± 6.91	45.29± 5.12[a]
Total protein (g/L)	58.41± 9.33	74.22± 7.25[a]	58.51± 8.93	73.78± 7.07[a]
Urineβ2-MG(g/L)	2.27± 0.93	2.4± 1.3	2.32± 1.2	2.35± 1.03

2.4 两组患者治疗前后机体免疫功能比较

治疗前，两组患儿 T 淋巴细胞亚群 $CD3^+$、$CD3^+CD4^+$、$CD19^+$ 水平比较差异无统计学意义(P＞0.05)。治疗后,两组患者 $CD3^+$、$CD3^+CD4^+$ 水平均明显增加，且观察组涨幅显著大于对照组(p＜0.05);两组患者的 $CD19^+$ 水平均显著降低,观察组显著低于对照组(p＜0.05)。

表 4 两组患者治疗前后机体免疫水平比较($\bar{x}\pm s$)

Table 4 Comparison of the immune function between the two groups before and after the therapy ($\bar{x}\pm s$)

Items	Observation group		Control group	
	Before therapy	After therapy	Before therapy	After therapy
$CD3^+$	56.42± 1.96	59.35± 2.19[a]	56.39± 2.20	57.98± 2.24[ab]
$CD3^+/CD4^+$	26.40± 3.27	37.02± 3.67a	26.3± 3.91	34.29± 3.82[ab]
$CD19^+$	22.11± 2.33	13.87± 2.25[a]	22.15± 1.93	18.58± 2.07[ab]

Note: compared with before therapy, [a]P<0.05; compared with observation group, [b]P<0.05.

2.5 两组患者不良反应发生情况比较

治疗期间，观察组出现 2 例并发呼吸道感染,1 例并发带状疱疹,1 例出现肠胃不适,不良反应发生率为 11.4%(4/35);对照组有 4 例发生明显的恶心、呕吐,3 例并发呼吸道感染,2 例出现带状疱疹,2 例并发肝损伤,2 例脱发，不良反应发生率为 37.14%(13/35)。观察组不良反应发生率显著低于对照组(P=0.012)。

3 讨论

紫癜性肾炎(HSPN)是小儿常见的肾脏疾病,大多数预后良好,但仍有 8%的患儿发展为慢性肾衰竭。机体免疫功能紊乱被认为是 HSPN 发病的主要机制,因此正向调节免疫功能,修复肾脏损伤是控制病情的关键点[9]。糖皮质激素联合环磷酰胺等免疫抑制剂治疗 HSPN 已取得一定成效,然而大量的文献报道及自身临床实践证实该治疗方案副作用明显,导致一部分患儿不耐受,影响疗效。因此,探究积极有效且副反应小的临床方案对提高治愈率有重大意义。

霉酚酸酯(MMF)是一种新型免疫抑制剂,在同种肾移植、狼疮性肾炎、难治性肾病综合征中已经有广泛的应用且取得肯定的疗效[10-12]。在机体内,霉酚酸酯代谢产物 - 霉酚酸可抑制次黄嘌呤单磷酸脱氢酶(IMPDH)的活性而阻断 DNA 及 RNA 的合成。患者体内的 T 淋巴细胞和 B 淋巴细胞高度依赖 IMPDH 来合成鸟嘌呤核苷酸，因此霉酚酸选择性抑制 T、B 淋巴细胞的活化,起免疫抑制作用[13-16]。糖皮质激素是一种使用最为广泛的免疫抑制剂,对 T 细胞的作用强于 B 细胞,还具有很强的抗炎作用,临床实践表明其单用时免疫抑制作用较弱与其他免疫抑制剂联用时具有明显的协同作用[17-19]。本研究结果显示霉酚酸酯联合小剂量糖皮质激素治疗小儿紫癜性肾炎的临床效果与泼尼松联合环磷酰胺治疗相当。治疗后,两组患者的尿蛋白含量明显降低,血清白蛋白、总蛋白含量明显上升。另外,研究结果显示霉酚酸酯联合小剂量糖皮质激素在免疫调节方面更具优势,这可能与霉酚酸酯较强的淋巴细胞靶向作用有关。在安全性方面,霉酚酸酯联合小剂量糖皮质激素治疗期间患者也存在肠胃不适、带状疱疹等的不良反应,但与对照组相比不良反应发生率显著降低,患者更为耐受,安全性更高。一项 Meta 分析结果也证实在临床实践中霉酚酸酯治疗 HSPN,无论是单用还是与糖皮质激素联用,安全性更高[20]。

综上所述,霉酚酸酯联合糖皮质激素治疗小儿紫癜性肾炎的临床效果较泼尼松联合环磷酰胺治疗更好,安全性更高。

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(上接第 5130 页)

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