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槐杞黄颗粒治疗原发免疫性血小板减少症患儿疗效及对血小板参数、外周血 Treg/Th17 和 CD4/CD8 的影响*

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摘要 目的:探讨槐杞黄颗粒治疗原发免疫性血小板减少症(ITP)患儿疗效及对血小板参数、外周血 Treg/Th17 和 CD4/CD8 的影响。**方法:**2019 年 8 月到 2021 年 5 月选择在本院诊治的免疫性血小板减少症患儿 60 例作为研究对象,根据 1:1 简单分配原则把患儿分为槐杞黄颗粒组与对照组各 30 例。对照组给予常规药物-注射用人免疫球蛋白治疗,槐杞黄颗粒组以对照组为基础,给予槐杞黄颗粒治疗,两组都治疗观察 3 个月,观察患儿治疗疗效与血小板参数、外周血 Treg/Th17 和 CD4/CD8 的变化情况。**结果:**治疗后槐杞黄颗粒组的总有效率为 96.7%,明显高于对照组的 80.0%($P<0.05$)。槐杞黄颗粒组的起效时间少于对照组,疗效维持时间多于对照组,两两对比有明显差异($P<0.05$)。两组治疗后的血小板计数、血小板参数都明显高于治疗前,槐杞黄颗粒组也明显高于对照组($P<0.05$)。两组治疗后的外周血 Treg/Th17 和 CD4/CD8 比值都明显高于治疗前,槐杞黄颗粒组明显高于对照组($P<0.05$)。**结论:**槐杞黄颗粒治疗原发免疫性血小板减少症患儿能有效提高治疗效果,可缩短起效时间,延长疗效持续时间,还能有效改善患儿血小板计数、血小板参数,提高外周血 Treg/Th17 和 CD4/CD8 水平。

关键词:槐杞黄颗粒;原发免疫性血小板减少症;血小板参数;Treg/Th17;CD4/CD8

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Curative Effect of Huaiqihuang Granule in The Treatment of Children with Primary Immune Thrombocytopenia and Its Effect on Platelet Parameters, Peripheral Blood Treg/Th17 and CD4/CD8*

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ABSTRACT Objective: To investigate the efficacy of Huaiqihuang granule in the treatment of children with idiopathic thrombocytopenic purpura (ITP) and its effect on platelet parameters, peripheral blood Treg/Th17 and CD4/CD8. **Methods:** From August 2019 to May 2021, 60 children with immune thrombocytopenia treated in our hospital were selected as research subjects. Children were divided into Huaiqi Huang granule group according to the 1:1 simple distribution principle and the matched group. The matched group was given conventional drug-injection human immunoglobulin treatment, and the group was treated on the basis of the matched group. Both groups were treated for 3 months to observe the efficacy of treatment, platelet parameters, peripheral blood Treg / Th17 and CD4 / CD8. **Results:** Post-treatment, the total effective rates of Huaiqihuang granule group were 96.7 %, which were higher than 80.0 % of matched group ($P<0.05$). The onset time of Huaiqihuang granule group were shorter than that of the matched group, and the duration of the curative effect were longer than that of the matched group. there were difference compared between the two groups ($P<0.05$). The platelet count and platelet parameters in the two groups Post-treatment were higher than those pretherapy, and the Huaiqihuang granule group were also higher than that in the matched group ($P<0.05$). The Peripheral blood Treg/Th17 and CD4/CD8 in both groups post-treatment were higher than that pretherapy, and the Huaiqihuang granule group were higher than that in the matched group ($P<0.05$). **Conclusion:** Huaiqihuang granules in the treatment of children with primary immune thrombocytopenia can effectively improve the therapeutic effect, shorten the onset time and prolong the duration of the effect, and can also effectively improve the platelet count and platelet parameters in children, increase Peripheral blood Treg/Th17 and CD4/CD8.

Key words: Huaiqihuang granules; Primary immune thrombocytopenia; Platelet parameters; Treg/Th17; CD4/CD8

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前言

原发性免疫性血小板减少症 (Immune thrombocytopenia, ITP) 在临床上比较常见, 其是因患者失去对自身血小板抗原的免疫耐受, 产生细胞免疫、体液免疫所介导产生的血小板破坏增多和血小板产生不足, 两者皆主要由 IgG 抗血小板抗体介导, 部分患者伴有皮肤黏膜出血特征, 在临床上可表现为血小板破坏增多、出血风险升高、骨髓巨核细胞数目正常或升高等^[1-2]。ITP 的治疗原则是阻止血小板的破坏和促进血小板的生成, 对患者身心健康产生严重影响^[3,4]。当前治疗 ITP 主要为糖皮质激素、静脉注射丙种球蛋白, 还可包括长春碱类、利妥昔单抗等药物, 当前应用注射用人免疫球蛋白治疗也比较多见^[5,6]。外周血 Treg/Th17、CD4/CD8 可反映机体的免疫功能, 可介导 ITP 的发生与发展^[7]。ITP 患者往往伴随血小板形态及功能的异常, 为此进行血小板参数的测定可反映机体的血小板形态及功能^[8]。槐杞黄颗粒是一种以真菌为主的中药成药新药, 主要由黄精、槐耳菌质、枸杞子等加工组成^[9,10]。槐耳菌质、枸杞子、黄精

等含有多种有机成分、矿物质元素, 能提高机体的免疫功能^[11]。本文具体探讨与分析了槐杞黄颗粒治疗 ITP 患儿疗效及对血小板参数、外周血 Treg/Th17 和 CD4/CD8 的影响, 以促进槐杞黄颗粒的临床应用。现报道如下。

1 资料与方法

1.1 研究对象

2019 年 8 月到 2021 年 5 月选择在本院诊治的免疫性血小板减少症患儿 60 例作为研究对象。

纳入标准: 年龄 1-12 岁; 符合 ITP 的诊断标准; 所有患儿均有不同程度出血症状; 无其他系统严重疾病者; 血小板 $< 30 \times 10^9/L$; 本次研究得到了医院伦理委员会的批准; 患儿家长依从性好; 心电图正常者; 患儿家长签署知情同意书。

排除标准: 研究者认为不宜参加本试验的患儿; 乙肝表面抗原阳性者; 有严重免疫缺陷者。

根据 1:1 简单分配原则把患儿分为槐杞黄颗粒组与对照组各 30 例, 两组患儿一般资料对比无差异 ($P > 0.05$)。见表 1。

表 1 一般资料对比

Table 1 The comparison of the general data

Groups	n	Clinical stage (phase / phase / period)	Disease course (month)	Gender (male / female)	Age (year)	Weight (kg)	Stature (cm)
Huai Qi Huang granule group	30	11/16/3	5.64± 0.25	16/14	6.23± 0.33	21.10± 1.33	121.09± 13.83
Matched group	30	10/15/5	5.69± 0.34	15/15	6.29± 0.14	21.48± 0.88	121.58± 12.68

1.2 治疗方法

对照组: 给予常规药物治疗, 采用注射用人免疫球蛋白 (国药准字 s20113011, 华兰生物工程重庆有限公司) 给予 1 g/kg·d 静脉注射, 连续应用 2 d, 间隔 3-4 周行下一周期治疗。

槐杞黄颗粒组: 以对照组治疗为基础, 给予槐杞黄颗粒治疗, 每次口服槐杞黄颗粒 (国药准字 B20020074, 启东盖天力药业公司) 5-10 g, 2 次/d。

两组都治疗观察 3 个月。

1.3 观察指标

(1) 疗效标准: 完全缓解: 血小板计数 $> 100 \times 10^9/L$, 且无出血症状; 缓解: 治疗后血小板计数 $\geq 30 \times 10^9/L$, 且无出血症状; 无效: 未达到上述标准甚或恶化。(完全缓解 + 缓解)/组内例数 $\times 100.0\%$ = 总有效率。

(2) 测定与记录两组的起效时间与疗效维持时间, 起效时间为从治疗开始, 至血小板水平达至 $30 \times 10^9/L$ 水平, 且无出血

症状; 疗效维持时间: 从治疗开始至复发或随访结束。

(3) 所有患儿在治疗前后抽取患儿的空腹外周静脉血 2-3 mL, 采用全自动生化分析仪检测血小板计数、血小板参数等指标。

(4) 所有患儿在治疗前后抽取骨髓, 送检验科室测定与记录外周血 Treg/Th17 和 CD4/CD8 比值。

1.4 统计方法

本次研究统计软件为 SPSS22.00 进行分析, $P < 0.05$ 表示差异有统计学意义。计量数据与计数数据均以均数 \pm 标准差、率表示, 两两对比方法为 t 检验与卡方 χ^2 检验等。

2 结果

2.1 总有效率对比

治疗后槐杞黄颗粒组的总有效率为 96.7%, 明显高于对照组的 80.0% ($P < 0.05$)。见表 2。

表 2 两组治疗后总有效率对比(n)

Table 2 Comparison of total effective rate between the two groups after treatment(n)

Groups	n	Complete remission	Remission	Invalid	Total effective rate
Huai Qi Huang granule group	30	26	3	1	29(96.7%) [#]
Matched group	30	20	4	6	24(80.0%)

Note: compared with the Matched group, [#] $P < 0.05$, the same below.

2.2 起效时间与疗效维持时间对比

对照组,两两对比有明显差异($P<0.05$)。见表3。

枸杞黄颗粒组的起效时间少于对照组,疗效维持时间多于

表3 两组起效时间与疗效维持时间对比(均数±标准差)

Table 3 Comparison of onset time and efficacy maintenance time of the two groups (mean ± standard deviation)

Groups	n	Effective time (d)	Efficacy maintenance time (month)
Huai Qi Huang granule group	30	28.14± 3.22 [#]	15.03± 1.48 [#]
Matched group	30	34.39± 2.58	22.48± 2.17

2.3 血小板计数、血小板参数变化对比

前,枸杞黄颗粒组也明显高于对照组($P<0.05$)。见表4。

两组治疗后的血小板计数、血小板参数都明显高于治疗

表4 两组治疗前后血小板计数、血小板参数变化对比(均数±标准差)

Table 4 Comparison of platelet count and platelet parameters before and post-treatment (mean ± standard deviation)

Groups	n	Platelet count ($\times 10^{12}/L$)		Platelet parameters	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Huai Qi Huang granule group	30	0.21± 0.03	1.76± 0.24 ^{*#}	21.38± 4.20	71.73± 3.33 ^{*#}
Matched group	30	0.21± 0.03	0.62± 0.09 [*]	21.48± 3.02	45.29± 5.19 [*]

Note: compared with the pretherapy, ^{*} $P<0.05$, the same below.

2.4 外周血 Treg/Th17 和 CD4/CD8 比值变化对比

疗前,枸杞黄颗粒组高于对照组($P<0.05$)。见表5。

两组治疗后的外周血 Treg/Th17 和 CD4/CD8 比值高于治

表5 两组治疗前后外周血 Treg/Th17 和 CD4/CD8 比值变化对比(均数±标准差)

Table 5 Comparison of Peripheral blood Treg/Th17 and CD4/CD8 ratio before and post-treatment (mean ± standard deviation)

Groups	n	Treg/Th17		CD4/CD8	
		Pretherapy	Post-treatment	Pretherapy	Post-treatment
Huai Qi Huang granule group	30	1.33± 0.24	4.58± 0.24 ^{*#}	1.01± 0.23	3.28± 0.26 ^{*#}
Matched group	30	1.33± 0.18	2.48± 0.27 [*]	1.09± 0.21	2.11± 0.17 [*]

3 讨论

ITP 被发现是一种血液系统疾病,患有该疾病的患者临床表现主要为皮肤、粘膜出血等,发病机制主要涉及机体内大量血小板破坏以及大幅度减少的血小板生成量^[12,13]。ITP 推荐一线治疗方式为糖皮质激素,该治疗方法可有效作用于脾脏单核-巨噬细胞对包被有抗体血小板的吞噬作用,进而使得毛细血管通透性降低,并抵抗血小板抗体产生具有抑制作用,缓解出血症状,减少出血倾向^[14-16]。采用注射人免疫球蛋白治疗 ITP 是当前较现代与成熟的治疗方案,其主要成分是 IgG,是人体血浆中含量最高免疫球蛋白,从大量健康人群混合血浆中分离浓缩而成,在体液免疫、细胞免疫中均发挥着重要的作用。人免疫球蛋白治疗原发免疫性血小板可能是通过 B 细胞来调节 IL-10 和 TGF- β 1 的水平而发挥治疗作用^[17,18]。

本研究显示治疗后枸杞黄颗粒组的总有效率为 96.7%,明显高于对照组的 80.0%;枸杞黄颗粒组的起效时间少于对照组,疗效维持时间多于对照组,两两对比有明显差异,表明枸杞黄颗粒治疗 ITP 患儿能提高治疗效果,起效时间有所减少,疗

效持续时间有所延长。该结果与戴静等人^[9]的报道具有相似性。分析可知,枸杞黄颗粒的安全性高,对症治疗无不良反应。槐耳为君药味苦辛性平,功擅益气强壮;枸杞子补肝明目、滋肾润肺;黄精补气而兼润养,上述药物的联合使用可益气又滋阴平补气阴,平中寓奇,补气而不致滞气^[20,21]。尤其是槐耳菌质富含多种氨基酸、矿物质元素、蛋白质,达到温煦"少火"、清退"壮火"的目的,可缓入肺、脾、肾经,调度水液平衡,使病不复、疾无来矣^[22]。因此联合使用枸杞黄颗粒可提高患者疗效;两组治疗后的血小板计数、血小板参数都明显高于治疗前,枸杞黄颗粒组也明显高于对照组,表明枸杞黄颗粒治疗 ITP 患儿能有效改善患儿的血小板计数、血小板参数。分析可知,ITP 患儿多伴随有巨核细胞的损害,表现为巨核细胞数目正常或增加,血小板更新率降低,缺乏形成血小板的胞浆颗粒表现,直接影响巨核细胞的成熟,同时细胞核与胞浆都有退行性改变,造成血小板生成减少^[23]。常规西药治疗 ITP 有一定的效果,但是持续效应不强^[24]。枸杞黄颗粒包含多种微量元素和生物活性化合物,可以抑制相关酶和信号传导途径,可以抑制相关酶和信号传导途径,还可抑制炎症因子的表达,阻止氧化反应的传播,增

强细胞的抗氧化能力,进而改善患者血小板水平,有利于恢复^[25];两组治疗后的外周血 Treg/Th17 和 CD4/CD8 比值都明显高于治疗前,枸杞黄颗粒组明显高于对照组,表明枸杞黄颗粒治疗 ITP 患儿能有效提高 Treg/Th17 和 CD4/CD8 比值。分析可知:Treg/Th17、CD4/CD8 失衡在 ITP 的发生中发挥重要作用,也可反映机体的免疫状况。比如 Treg 细胞可介导免疫耐受,而 Th17 细胞可作为机体免疫炎症的效应细胞^[26,27]。Treg/Th17、CD4/CD8 比值增加表明机体逐渐恢复免疫功能,可用来反映 ITP 患儿症状变化情况^[28,29]。枸杞黄颗粒是活性很强的生物反应调节剂,能激发机体免疫系统中诸多环节,调节机体的淋巴细胞及吞噬细胞免疫应答反应,从而调节免疫细胞的平衡失调,增强机体免疫功能,可提高免疫细胞的活性^[30]。但本研究未进行动物实验分析,纳入患儿数量比较少,也未选择成人进行调查分析,将在后续研究中探讨。

总之,枸杞黄颗粒治疗 ITP 患儿能有效提高治疗效果,可缩短起效时间,延长疗效持续时间,还能有效改善患儿的小血小板计数、血小板参数,提高外周血 Treg/Th17 和 CD4/CD8 水平。

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