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双嘧达莫辅助治疗川崎病患儿的疗效及对 T 淋巴细胞亚群、凝血功能影响 *

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摘要 目的：探讨双嘧达莫辅助治疗川崎病患儿的疗效及对 T 淋巴细胞亚群、凝血功能影响。**方法**：选择我院 2016 年 3 月至 2018 年 1 月接诊的 90 例川崎病患儿，通过随机数表法分为对照组 44 例和观察组 46 例，对照组给予常规治疗，观察组在对照组基础上联合双嘧达莫进行辅助治疗。两组患者均连续治疗 8 周。比较两组 T 淋巴细胞亚群、症状缓解情况、凝血功能的变化情况及并发症。**结果**：治疗后，观察组临床疗效总有效率高于对照组，差异均有统计学意义（$P<0.05$）；观察组 CD_3^+、CD_8^+ 均高于对照组，CD_4^+/CD_8^+ 低于对照组，差异均有统计学意义（$P<0.05$）；观察组发热、颈淋巴结肿胀、眼结膜充血、口腔黏膜充血、躯干红斑缓解时间均短于对照组（$P<0.05$），差异均有统计学意义（$P<0.05$）；观察组凝血酶原时间（PT）、活化部分凝血活酶时间（APTT）均长于对照组，纤维蛋白原（FIB）低于对照组，差异均有统计学意义（$P<0.05$）；两组不良反应、冠状动脉损害情况发生率比较差异无统计学意义（$P>0.05$）。**结论**：双嘧达莫辅助治疗川崎病患儿临床疗效显著，缩短患儿症状缓解时间，能有效调节 T 淋巴细胞亚群的表达及凝血功能，值得临床应用推广。

关键词：双嘧达莫；丙种球蛋白；川崎病；T 淋巴细胞亚群；凝血功能；辅助治疗

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Effect of Dipyridamole on T lymphocyte Subsets and Coagulation Function in Children with Kawasaki Disease*

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ABSTRACT Objective: To study effect of dipyridamole on T lymphocyte subsets and coagulation function in children with Kawasaki disease. **Methods:** 90 patients of Kawasaki disease in our hospital from March 2016 to January 2018 were selected and divided into control group 44 cases and observation group 46 cases by random number table. the control group was treated with conventional therapy, while the observation group was treated with dipyridamole on the basis of the control group. two groups of patients were treated continuously for 8 weeks. The T lymphocyte subsets, symptoms relief, changes of coagulation function and complications were compared between the two groups. **Results:** After treatment, the total effective rate of the observation group was higher than that of the control group, and the difference was statistically significant ($P<0.05$); the levels of serum CD_3^+ and CD_8^+ in the observation group were higher than those in the control group, and the levels of CD_4^+/CD_8^+ in the observation group were lower than those in the control group, and the difference was statistically significant ($P<0.05$); the remission time of clinical symptoms such as body fever, cervical lymph node swelling, conjunctival congestion, oral mucosal hyperemia and erythema of trunk in the observation group was shorter than that in the control group, and the difference was statistically significant ($P<0.05$); the prothrombin time (PT) and activated partial thromboplastin time (APTT) in the observation group were longer than those in the control group, while the fibrinogen(FIB) were lower than those in the control group, and the difference was statistically significant ($P<0.05$); there was no significant difference in the incidence of adverse reactions and coronary artery lesions between the two groups($P>0.05$). **Conclusion:** The clinical effect of dipyridamole in the adjuvant treatment of children with Kawasaki disease is remarkable. It can shorten the remission time of symptoms, effectively regulate the expression of T lymphocyte subsets and coagulation function. It is worthy of clinical application and promotion.

Key words: Dipyridamole; Gamma globulin; Kawasaki disease; T lymphocyte subsets; Coagulation function; Adjuvant therapy

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前言

川崎病是儿科中一种较为严重的疾病，又被称作是皮肤黏膜淋巴结综合征，好发于 5 岁以下的儿童，发病后可出现发热、皮疹、淋巴结肿大、眼结膜充血、口腔黏膜弥漫性充血、多形性红斑等症状，且可对患儿心血管系统产生影响，若得不到及时有效的治疗，极易出现冠状动脉损害，影响预后[1,2]。已有研究较多报道证实，T 淋巴细胞亚群紊乱、凝血功能异常等在川崎病发生、发展起重要作用，积极调解患儿免疫功能、凝血功能在提高预后中十分关键[3,4]。阿司匹林、丙种球蛋白是该病中常用的治疗药物，但疗效仍有可提升的空间[5,6]。双嘧达莫既往多用于抗血栓形成、扩张动脉等治疗，其具有抗血小板聚集的作用，近年来也有研究显示，其可通过改善血小板功能等机制治疗川崎病，但目前其疗效及机制仍处于探讨阶段[7,8]。本文旨在探讨双嘧达莫辅助治疗川崎病患儿的疗效及对 T 淋巴细胞亚群、凝血功能影响。

1 资料与方法

1.1 一般资料

选择我院 2016 年 3 月至 2018 年 1 月接诊的川崎病患儿 90 例，纳入标准[9]：① 符合川崎病诊断标准，发热时间≥ 5 d，出现颈淋巴结肿大（直径＞1.5 cm）、口腔黏膜、眼结膜有红肿充血、口唇干燥龟裂、躯干红斑丘疹、手足红肿等症状，并经过实验室检查等确诊；② 患儿年龄小于 7 岁；③ 患儿的家人签署知情同意书。排除标准[10]：① 患有先天性心脏病；② 合并严重内分泌系统和造血系统疾病、重要肾脏器官功能障碍；③ 身体营养不良；④ 精神状态异常。通过随机数表法分为对照组 44 例和观察组 46 例，两组一般资料见表 1，差异无统计学意义（P＞0.05）。本研究已通过我院伦理委员批准实施。

表 1 两组一般资料比较[$\bar{x}\pm s$，n(%)]

Table 1 Comparison of general information between two groups [$\bar{x}\pm s$, n(%)]

Groups	Sex(M/F)	Age(years)	Clinical stages(example)				Fever time(d)
			Ⅰ	Ⅱ	Ⅲ	Ⅳ	
Observation group(n=46)	24/22	2.56± 0.42	5(10.87)	18(39.13)	14(30.43)	9(19.57)	7.58± 1.40
Control group(n=44)	21/23	2.83± 0.59	7(15.91)	15(34.09)	12(27.27)	10(22.73)	7.67± 1.35

1.2 方法

两组入院后均进行常规处理，包括退热、保持水电解质平衡等，对照组在此基础上，给予丙种球蛋白（规格：1 瓶 / 盒，厂家：华兰生物工程重庆有限公司，国药准字 S20113011）冲击静脉输注治疗，剂量为 2 g/kg；阿司匹林（厂家：拜耳医药保健有限公司，国药准字 J20130078）口服治疗，剂量为 30~50 mg/kg/d，热退 3 天后剂量缩减为 3~5 mg/kg/d，疗程 6~8 周。观察组在对照组治疗基础上同时给予口服双嘧达莫片（规格：25 mg× 100 片 / 瓶，厂家：亚宝药业集团股份有限公司，国药准字 H14020968），一次 25～50 mg，一日 3 次口服。两组患者均连续治疗 8 周。

1.3 观察指标

① T 淋巴细胞亚群：采集治疗前、治疗后 5 mL 空腹静脉血，加入未放置抗凝剂的干燥管中，室温下静置 1 h，使用 3500 r/min 的速度离心，提取上层清液储存于零下 20℃的冰箱中保存备检，用免疫比浊法检测外周血 T 淋巴细胞亚群中 CD_3^+、CD_8^+、CD_4^+/CD_8^+；② 症状缓解情况：包括发热、颈淋巴结肿胀、眼结膜充血、口腔黏膜充血、躯干红斑；③ 凝血功能：将治疗前、治疗后采集的待检血液，用 Stago 全自动血液凝固分析仪进行检测凝血酶原时间（PT）、活化部分凝血活酶时间（APTT）和纤维蛋白原（FIB）；④ 不良反应；⑤ 对所有患儿随访 3 个月，记录冠状动脉损害情况，判定标准[11]：通过超声心动图显示冠状动脉扩张情况，其中冠状动脉直径 2.5~4m 为轻度损害，4~7 mm 为中度损害，＞7 mm 为重度损害。

临床疗效，显效：治疗 5 d 后，体温正常，粘膜充血、淋巴结肿胀等症状基本消失；改善：治疗 5 d 后，体温正常，粘膜充血、淋巴结肿胀等症状较治疗前部分改善；无效：未满足上述标准。总有效率 = 显效率 + 有效率。

1.4 统计学分析

以 spss20.0 软件包处理，正态分布计量资料用均数± 标准差（$\bar{x}\pm s$）表示，组间比较使用独立样本 t 检验，组内比较使用配对样本 t 检验，计数资料以率表示，x^2 检验，P＜0.05 表示差异具有统计学意义。

2 结果

2.1 两组临床疗效比较

观察组临床疗效高于对照组（P＜0.05），见表 2。

表 2 两组临床疗效比较[n(%)]

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

Groups	Effective	Improve	Invalid	Total effective rate
Observation group(n=46)	26(56.52)	18(39.13)	2(4.35)	44(95.65)*
Control group(n=44)	20(45.45)	15(34.09)	9(20.45)	35(79.55)

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

2.2 两组 T 淋巴细胞亚群比较

治疗后，两组 T 淋巴细胞亚群较治疗前均明显改善（$P<0.05$），观察组 CD_3^+、CD_8^+ 均高于对照组，CD_4^+/CD_8^+ 比对照组低（$P<0.05$），见表 3。

表 3 两组 T 淋巴细胞亚群比较（$\bar{x}\pm s$）

Table 3 Comparison of T-lymphocyte subsets between two groups（$\bar{x}\pm s$）

Groups		CD_3^+（%）	CD_8^+（%）	CD_4^+/CD_8^+
Observation group(n=46)	Before treatment	46.96± 4.40	33.48± 2.30	1.41± 0.31
	After treatment	60.45± 5.63*#	45.06± 4.16*#	1.03± 0.14*#
Control group(n=44)	Before treatment	47.07± 4.19	33.51± 2.24	1.38± 0.33
	After treatment	54.18± 5.04*	38.20± 3.35*	1.19± 0.17*

Note: Compared with before treatment, *$P<0.05$; Compared with the control group, #$P<0.05$.

2.3 两组症状缓解情况比较

观察组发热、颈淋巴结肿胀、眼结膜充血、口腔黏膜充血、躯干红斑缓解时间均短于对照组（$P<0.05$），见表 4。

表 4 两组症状缓解情况比较（$\bar{x}\pm s$，d）

Table 4 Comparison of symptom relief between the two groups（$\bar{x}\pm s$, d）

Groups	Body fever	Cervical lymph node swelling	Conjunctival congestion	Oral mucosal hyperemia	Erythema of trunk
Observation group（n=46）	2.30± 0.84*	3.75± 1.44*	4.08± 1.25*	2.84± 0.96*	3.41± 1.01*
Control group（n=44）	3.19± 0.92	5.16± 1.37	5.50± 1.61	3.54± 1.35	4.22± 1.17

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

2.4 两组凝血功能比较

治疗后，观察组 PT、APTT 均长于对照组，FIB 低于对照组（$P<0.05$），见表 5。

表 5 两组凝血功能比较（$\bar{x}\pm s$）

Table 5 Comparison of coagulation function between two groups（$\bar{x}\pm s$）

Groups		PT(s)	APTT(s)	FIB(g/L)
Observation group(n=46)	Before treatment	10.27± 1.73	29.18± 3.53	3.62± 0.74
	After treatment	12.27± 0.48*#	38.52± 2.16*#	2.23± 0.36*#
Control group(n=44)	Before treatment	10.22± 1.82	29.24± 3.29	3.64± 0.72
	After treatment	11.69± 0.59*	33.75± 2.08*	2.80± 0.53*

Note: Compared with before treatment, *$P<0.05$; Compared with the control group, #$P<0.05$.

2.5 安全性评价

治疗期间，观察组出现 2 例（4.35%）恶心呕吐，对照组出现 3 例（6.82%）头晕头痛，差异无统计学意义（$P>0.05$）；经 3 个月随访结果显示，两组冠状动脉损害情况发生率分别为 4 例（8.70%）和 7 例（15.91%），均为轻度损害，差异无统计学意义（$P>0.05$）。

3 讨论

川崎病是一种以全身性中小血管炎为主要表现特点的疾病，5 岁以下的婴幼儿是高发年龄，近年来该病在我国的发病率也有着增长趋势[12,13]。虽然大部分患儿的预后较好，但也有 5%~9%的川崎病患儿可继发冠状动脉瘤，可由于冠状动脉瘤破裂、血栓、心肌炎、心肌梗死等诱发死亡[14,15]。目前对于该病的发病机制仍不明确，但较多研究认为，川崎病患儿存在着明显的 T 淋巴细胞活化状态，此过程可加速血小管发生免疫炎症反应，出现免疫激活、内皮细胞活化、通透性增加、血栓前状态等一系列病理改变，而积极调节 T 淋巴细胞的失衡在阻碍病情进展中极为关键[16,17]。

临床上对于该病的治疗多采取阿司匹林、丙种球蛋白等药物治疗，其中阿司匹林作为非甾体类抗炎药，可发挥抗炎、退热、抗血小板聚集、退热等作用[18,19]。而免疫球蛋白则可通过对外周淋巴细胞产生抑制作用，缓解患儿免疫损伤，可对Ⅲ型变态反应具有抑制作用，减弱 B 淋巴细胞活性，但也有部分患儿在使用丙种球蛋白后治疗无反应，得不到满意的效果[20,21]。双嘧达莫是一种抗血栓、扩张冠状动脉的药物，目前多用于中风、缺血性心脏病的治疗，对血小板的聚集具有较好的抑制效果，且具有改善血管微循环、抗炎等作用[22,23]。随着临床医学者对双嘧达莫的不断研究也发现，双嘧达莫对 T 淋巴细胞的活化反应可产生抑制效果，适用于一些免疫性疾病的治疗[24]。并有报道显示，双嘧达莫在降低川崎病患儿血管损伤、提高临床疗效上有一定作用[25]。

本研究结果显示，联合双嘧达莫辅助治疗的患儿 T 淋巴细

胞亚群和凝血功能指标水平的调节方面均优于常规治疗的患者，通过分析是双嘧达莫可扩张冠脉血管，缓解冠状血管阻力，促进冠脉血流的增加，继而调节血管高凝状态，改善凝血功能，而在积极的调节凝血功能后，对血管的免疫激活也有抑制作用，缓解 T 淋巴细胞的活化状态[26]，且丙种球蛋白作为免疫球蛋白，对外周血淋巴 T 细胞的活性和生长具有较好的抑制作用，且可缓解补体结合所致的免疫炎症反应[27,28]，阿司匹林也具有抗血小板、抗炎效果[29,30]，双嘧达莫和阿司匹林、丙种球蛋白发挥相互协同作用，进一步改善患儿免疫功能和凝血功能。且本研究中，观察组临床疗效总有效率为 95.65%，均明显高于对照组 79.55%；观察组症状缓解的时间也明显短于对照组，显示出双嘧达莫辅助治疗可缩短临床症状缓解时间，提高临床疗效，可能是辅助双嘧达莫可进一步改善缓解 T 淋巴细胞、缓解血管免疫炎症反应等相关。此外，在本研究 3 个月随访结果中，两组冠状动脉损害情况差异无统计学意义，在改善预后方面未体现出双嘧达莫的明显优势，考虑和样本量过少相关，因此对于此部分结论有待联合多中心进一步长期的探讨。

综上所述，双嘧达莫辅助治疗川崎病患儿临床疗效显著，缩短患儿症状缓解时间，能有效调节 T 淋巴细胞亚群的表达及凝血功能，值得临床应用推广。

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