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雷公藤多苷联合甲氨蝶呤治疗类风湿关节炎活动期患者的疗效及对血清 CD62p、CD41 的影响 *

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摘要 目的:探讨雷公藤多苷联合甲氨蝶呤治疗类风湿关节炎(RA)活动期患者的疗效及对血清释放黏附分子 CD62p、CD41 的影响。**方法**:选择 2015 年 6 月至 2017 年 6 月我院接诊的 90 例类 RA 活动期患者作为研究对象,通过随机数表法分为观察组(n=45)和对照组(n=45),对照组口服甲氨蝶呤治疗,观察组联合雷公藤多苷片治疗,均连续用药 12 周。比较两组临床疗效、治疗前后临床症状评分、实验室指标[红细胞沉降率(ESR)、C 反应蛋白(CRP)、血小板计数(PLT)]及血清 CD62p、CD41 的变化,并比较治疗期间不良反应。**结果**:观察组临床疗效总有效率为 91.11%(41/45),明显高于对照组的 66.67%(30/45)(*P<0.05*);治疗后,两组临床症状评分及实验室指标较治疗前均显著降低(*P<0.05*),观察组晨僵时间、关节疼痛、关节肿胀、关节压痛评分及 ESR、CRP、PLT 均明显比对照组，比较均具有显著差异（*P<0.05*）；治疗后，两组血清 CD62p、CD41 较治疗前均显著降低（*P<0.05*），观察组血清 CD62p、CD41 均明显低于对照组[(16.58± 2.10)%vs(25.46± 2.58)%,(67.83± 11.03)%vs(76.40± 13.45)%](*P<0.05*);两组治疗期间肝肾功能均未发生异常,两组头痛、皮疹、胃肠道反应、感染、脱发发生率均无显著差异(*P>0.05*)。**结论**:在 RA 活动期患者中使用雷公藤多苷联合甲氨蝶呤效果显著,可有效改善临床症状及实验室指标,其内在机制可能和降低血清 CD62p、CD41 的表达相关,且联合用药安全性高,值得应用推广。

关键词:类风湿关节炎;活动期;雷公藤多苷;甲氨蝶呤;释放黏附分子

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Curative Efficacy of Tripterygium Glycosides Combined with Methotrexate in Treatment of Rheumatoid Arthritis Active Stage and Its Effects on Serum CD62p and CD41 Levels*

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ABSTRACT Objective: To study surative efficacy of tripterygium glycosides combined with methotrexate in treatment of rheumatoid arthritis (RA) active stage and its effects on serum release of adhesion molecules CD62p and CD41 levels. **Methods:** 90 patients of RA active stage who received therapy from June 2015 to June 2017 in our hospital were selected as research objects. According to random number table, those patients were divided into the observation group (n=45) and the control group (n=45), the control group was treated with oral methotrexate, while the observation group was combined with tripterygium glycosides, they were used for 12 weeks. The clinical efficacy, clinical symptom score, laboratory index [Erythrocyte sedimentation rate (ESR), C reactive protein (CRP), platelet count (PLT)], and serum CD62p and CD41 before and after treatmentof two groups were changed, and the adverse reactions was compared. **Results:** The total effective rate of clinical efficacy in the observation group was 91.11% (41/45), which was significantly higher than that of the control group 66.67% (30/45) (*P<0.05*); after treatment, the clinical symptom scores and laboratory indexes of two groups were significantly lower than those before treatment (*P<0.05*), the morning stiffen, joint pain, joint swelling, joint pressure pain and ESR, CRP and PLT in the observation group were significantly lower than that of control group, there are significant differences in comparison (*P<0.05*); after treatment, the serum CD62p and CD41 levels in the two groups were significantly lower than those before the treatment (*P<0.05*), the serum CD62p and CD41 in the observation group were significantly lower that of the control group[(16.58± 2.10)% vs(25.46± 2.58)%, (67.83± 11.03)%vs(76.40± 13.45)%](*P<0.05*); there was no abnormal liver and kidney function during the treatment of the two groups. there was no significant difference in the incidence of headache, rash, gastrointestinal reaction, infection and alopecia in the two groups (*P>0.05*). **Conclusion:** Tripterygium glycosides combined with methotrexate is well for RA active stage, which can effectively improve clinical symptoms and laboratory indicators, its

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intrinsic mechanism may be associated with the reduction of the expression of serum CD62p and CD41, and the combination of drug safety is high, its worthy of application and promotion.

Key words: Rheumatoid arthritis; Active stage; Tripterygium glycosides; Methotrexate; Release of adhesion molecules

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前言

类风湿关节炎(RA)是种以慢性进行性、对称性关节病变为主的自身免疫性疾病,患者可出现晨僵、关节疼痛、肿胀等临床症状,相关数据显示,全世界大约 16 亿 RA 患者,我国 RA 的发病率大约在 0.35%左右,多见于中年女性[1,2]。若得不到及时的治疗,极易对关节馆软骨、关节囊等造成破坏,严重的甚至引发关节畸形、关节功能丧失等,影响着生活质量[3]。该病的发病机制较为复杂,随着学者的不断研究发现,由于该病的主要病理改变是以全身炎症改变为主,而在 RA 活动期血小板活化功能异常,可释放大量的粘附分子 CD62p、CD41,参与着疾病进展[4]。甲氨蝶呤是该病中的首选治疗药物,也是联合治疗方案的基础用药,已有较多报道显示,联合用药效果明显优于单一治疗疗效[5-6]。近年来也有学者发现,雷公藤多苷具有类固醇样效应,具有抑制免疫、抗炎等作用,且不会对类固醇的正常分泌产生影响,也为 RA 活动期患者的联合治疗方案提供了新思路[7]。因此,本研究旨在探讨在 RA 患者活动期应用雷公藤多苷联合甲氨蝶呤的治疗优势,并观察其对血清 CD62p、CD41 的影响。

1 资料与方法

1.1 一般资料

选择 2015 年 6 月至 2017 年 6 月我院接诊的 90 例 RA 活动期患者进行研究,研究已获得我院伦理委员会批准实施。诊断标准参照文献,符合下列其中 4 项则可确诊:① 休息时疼痛关节≥ 4 个;② 晨间持续时间≥ 1h;③ 关节肿胀≥ 5 个;④ 关节压痛数量≥ 5 个;⑤ 红细胞沉降率(ESR)女性>30 mm/h,男性>25 mm/h。纳入标准[8]:① 符合 RA 活动期诊断标准;② 年龄 18~60 岁;③ 对本研究知情同意。排除标准[9]:① 合并其余风湿性疾病;② 合并心肺功能障碍、高血压、血液系统、中枢神经系统损伤等;③ 合并胃、十二指肠溃疡史;④ 妊娠期哺乳期;⑤ 对研究药物过敏。通过随机数表法分为 2 组,各 45 例。观察组男 18 例,女 27 例;年龄 23~58 岁,平均(40.75± 8.29)岁;病程 3 个月 ~23 个月,平均(14.85± 3.12)月。对照组胺 20 例,女 25 例;年龄 21~59 岁,平均(41.62± 8.04)岁;病程 4 个月 ~24 个月,平均(15.03± 3.04)月。

1.2 方法

对照组给予甲氨蝶呤片(规格 2.5 mg,厂家:上海上药信谊药厂有限公司,国药准字 H31020644)的口服,10 mg/ 次,1 次 / 周。观察组甲氨蝶呤片用法同对照组,再给予雷公藤多苷片(规格 10 mg,厂家:浙江得恩德制药有限公司,国药准字 Z33020422)的口服,20 mg/ 次,3 次 /d。

两组治疗前 1 个月均使用非甾体抗炎药或 10 mg 以下的泼尼松治疗,并辅以钙剂、叶酸、胃黏膜保护剂等对症治疗措施,若患者出现难以忍受的疼痛时,可酌情给予止痛药治疗。均连续用药 12 周。

1.3 观察指标

1.3.1 临床症状评分 参照文献[10],晨僵时间:1h 之内记 0 分,1~3h 记 3 分,3~5h 记 6 分,>5h 记 9 分;关节疼痛:主要指休息时关节疼痛感,无疼痛记 0 分,轻度疼痛可忍受记 3 分,中度疼痛失常影响睡眠记 6 分,重度疼痛日夜均难以忍受记 9 分;关节肿胀:无关节肿胀记 0 分,肿胀轻度、可见附近骨突记 3 分,肿胀和骨突平行记 6 分,肿胀比骨突高、对功能活动有严重影响记 9 分;关节压痛:无压痛记 0 分,于关节边缘或接触到韧带重压时自觉有压痛感记 3 分,被动活动时、重压时有压痛感且患者表情痛苦记 6 分,重压时患者自述十分疼痛且退缩记 9 分。

1.3.2 实验室指标 采集所有患者 5 mL 空腹静脉血,使用日本 Sysmex XT-2000i 对 ESR、C 反应蛋白(CRP)、血小板计数(PLT)进行检测。

1.3.3 血清 CD62p、CD41 使用 Beckman-coulter XL-ES-PICMC 型流式细胞仪分析检测血清 CD62p、CD41,试剂盒均购于美国 Immuno tech 公司,操作严格按照仪器及试剂盒说明书进行。

1.4 疗效平均标准

参照文献[11],显效:晨僵、疼痛等临床症状体征得到显著改善,实验室指标得到正常恢复;有效:晨僵、疼痛等临床症状体征得到部分改善,实验室指标至少有 1 项得到正常恢复;无效:晨僵、疼及实验室指标等均无明显改善,甚至加重。总有效率 = (显效 + 有效)/ 总例数× 100%。

1.5 统计学分析

以 spss18.0 软件包处理实验数据,计量资料为正态分布,用均数± 标准差($\bar{x}\pm s$)表示,组间比较采用独立样本 t 检验,计数资料组间比较采用 x^2 检验,以 $P<0.05$ 表示差异具有统计学意义。

2 结果

2.1 两组临床疗效比较

观察组临床疗效总有效率为 91.11%,明显比对照组的 66.67%高($P<0.05$),见表 1。

2.2 两组临床症状评分比较

治疗前,两组各症状评分比较无显著差异($P>0.05$);治疗后,两组晨僵时间、关节疼痛、关节肿胀、关节压痛评分较治疗前均显著降低($P<0.05$),观察组晨僵时间、关节疼痛、关节肿胀、关节压痛评分均明显比对照组($P<0.05$),见表 2。

2.3 两组实验室指标比较

治疗前,两组 ESR、CRP、PLT 比较无显著差异($P>0.05$);治疗后,两组 ESR、CRP、PLT 较治疗前均显著降低($P<0.05$),

观察组 ESR、CRP、PLT 均明显比对照组低（*P<0.05*），见表 3。

表 1 两组临床疗效比较[n(%)]

Table 1 Comparison of the clinical efficacy between two groups[n(%)]

Groups	Effective	Valid	Invalid	Total effective rate
Observation group(n=45)	22(48.89)	19(42.22)	4(8.89)	41(91.11)*
Control group(n=45)	16(35.56)	14(31.11)	15(33.33)	30(66.67)

Note: Vs the control group, **P<0.05*.

表 2 两组临床症状评分比较($\bar{x}\pm s$，分)

Table 2 Comparison of the clinical symptom score between two groups ($\bar{x}\pm s$, scores)

Groups		Morning stiffne	Joint pain	Joint swelling	Joint pressure pain
Observation group(n=45)	Before treatment	4.23± 1.06	6.43± 1.35	4.75± 0.73	5.09± 1.07
	After treatment	2.11± 0.32*#	2.50± 0.37*#	2.04± 0.35*#	2.31± 0.38*#
Control group(n=45)	Before treatment	4.31± 1.01	6.36± 1.42	4.81± 0.79	5.14± 1.03
	After treatment	3.26± 0.62*	3.72± 0.51*	3.12± 0.42*	3.59± 0.53*

Note: Vs the before treatment, **P<0.05*; vs the control group, #*P<0.05*.

表 3 两组实验室指标比较($\bar{x}\pm s$)

Table 3 Comparison of the laboratory index between two groups ($\bar{x}\pm s$)

Groups		ESR(mm/h)	CRP(mg/L)	PLT(× 10^9/L)
Observation group(n=45)	Before treatment	46.73± 5.91	38.45± 4.72	267.23± 35.08
	After treatment	18.75± 2.30*#	13.30± 2.40*#	189.64± 27.51*#
Control group(n=45)	Before treatment	45.96± 6.14	39.12± 4.50	265.18± 36.23
	After treatment	27.65± 3.05*	24.84± 3.10*	221.25± 32.94*

Note: Vs the before treatment, **P<0.05*; vs the control group, #*P<0.05*.

2.4 两组血清 CD62p、CD41 比较

治疗前，两组血清 CD62p、CD41 比较无显著差异（*P>0.05*）；治疗后，两组血清 CD62p、CD41 较治疗前均显著降低（*P<0.05*），观察组血清 CD62p、CD41 均明显比对照组低（*P<0.05*），见表 4。

表 4 两组血清 CD62p、CD41 比较($\bar{x}\pm s$，%)

Table 4 Comparison of the serum CD62p and CD41 between two groups ($\bar{x}\pm s$, %)

Groups		CD62p	CD41
Observation group(n=45)	Before treatment	32.74± 3.85	89.45± 15.86
	After treatment	16.58± 2.10*#	67.83± 11.03*#
Control group(n=45)	Before treatment	33.51± 3.62	88.95± 16.30
	After treatment	25.46± 2.58*	76.40± 13.45*

Note: Vs the before treatment, **P<0.05*; vs the control group, #*P<0.05*.

2.5 两组不良反应比较

两组治疗期间肝肾功能均未发生异常，两组头痛、皮疹、胃肠道反应、感染、脱发发生率均无显著差异（*P>0.05*），见表 5。

表 5 两组不良反应比较[n(%)]

Table 5 Comparison of the adverse reaction between two groups[n(%)]

Groups	Headache	Rash	Gastrointestinal reaction	Infected	Alopecia
Observation group(n=45)	3(6.67)	0(0.00)	2(4.44)	1(2.22)	0(0.00)
Control group(n=45)	2(4.44)	1(2.22)	3(6.67)	2(4.44)	1(2.22)

3 讨论

RA 的是以进行性、持续性的外周动关节滑膜炎为主要临床临床表现的疾病，在 RA 活动期患者可出现进一步的全身性

关节疼痛和肿胀,而若得不到及时的治疗,则容易引发关节畸形、关节活动功能丧失等。有报道指出,若 RA 病程>10 年,则至少有 50%的患者出现明显关节功能障碍,严重影响着生活质量。因此,早期给予患者有效的治疗显得极为重要[12]。

目前对于该病的治疗原则主要是控制关节和其余组织的炎症反应、缓解临床症状、维持关节功能、并修复损伤的关节等为主。甲氨蝶呤是 RA 治疗中的有效免疫抑制剂,可通过对腺苷诱导的免疫抑制作用,继而抑制炎症细胞及单核细胞的增值和凋亡等,降低关节滑膜组织金属蛋白酶的表达,具有较为满意免疫抑制、抗炎作用。但也有较多报道指出,单独使用该药临床疗效仅在 60%~70%左右, 而联合用药方案在提高临床疗效中具有积极意义[13,14]。

雷公藤多苷主要提取中药自卫矛科雷公藤根的多苷类药物,其活性成分具有细胞免疫、体液免疫抑制作用及镇痛、抗炎作用。Chen F 等[15]研究也指出,雷公藤多苷对 T 淋巴细胞的增值具有抑制作用, 可诱导活化的淋巴细胞凋亡, 抑制白介素(IL)-2 等释放。Li H 等[16]将雷公藤多苷用于骨性关节炎患者中后显示,其可明显缓解患者临床症状,有助于提高生活质量。

本研究结果显示, 联合雷公藤多苷临床疗效总有效率为 91.11%,明显高于对照组的 66.67%,且晨僵时间、关节疼痛、关节肿胀、关节压痛评分及实验室指标 ESR、CRP、PLT 的降低程度更明显,分析是由于雷公藤多苷中的雷公藤内酯醇对多种炎症介质具有抑制作用,有利于降低 ESR、CRP、PLT 等实验室指标的表达,而通过这种机制,可抑制 RA 骨侵蚀,促进缓解临床症状的缓解,而加上甲氨蝶呤的免疫抑制作用,两药相互协同,进一步提高临床疗效。Yang CL 等[17]研究也得出相似结论。且本研究还显示,联合用药并未增加药物不良反应,提示用药安全性高。

由于 RA 的发病机制和 T 细胞、B 细胞、滑膜细胞免疫反应所产生的自身抗体和细胞因子网络之间存在着密切关系,近年来相继有学者报道,CD62P、CD41 在其中发挥的作用十分关节 [18,19]。CD62P 则是以 P 选择素为粘附分子的整合素家族成员,其可由血小板表面脱落至血液,变为可溶性 CD62P,继而对淋巴细胞、中性粒细胞、单核细胞产生诱导作用。而 CD41 又被称作是αⅡb 整合素,可和 CD61 之间发挥作用,产生血小板糖蛋白复合物,当机体血小板活化时,血小板糖蛋白复合物又可和纤维蛋白原之间产生交联,促使血小板聚集。Gazitt T 等[20]报道也指出,降低 RA 患者血清 CD62p、CD41 的表达,在改善临床症状,延缓疾病进展中具有积极意义。

本研究结果显示, 联合雷公藤多苷的患者血清 CD62p、CD41 的降低程度明显更佳, 通过分析是由于雷公藤多苷对 T 淋巴细胞增值具有抑制作用,可降低 CD62P 的表达,且雷公藤多苷本身便具有活血化瘀、抗菌等中药作用,现代药理学中也指出,雷公藤多苷可令血小板扩张,降低血液粘稠度并改善血小板的异常粘附和聚集,有助于改善"血瘀"症状[21,22],继而明显降低 CD41 的表达,这也可能是联合用药患者临床疗效更显著的内在机制之一。但本研究时间较短, 对于联合用药在 RA 活动期患者中的远期疗效上仍需进一步深入研究。

综上所述,在 RA 活动期患者中使用雷公藤多苷联合甲氨蝶呤效果显著,可有效改善临床症状及实验室指标,其内在机制可能和降低血清 CD62p、CD41 的表达相关, 且联合用药安全性高,值得应用推广。

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(下转第 3921 页)

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