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针刺疗法联合塞来昔布对老年类风湿性关节炎患者血清 MMP-3, IL-6 及自身抗体水平的影响 *

陈 杰 刘江涛 杨举广 韩兆铭 葛文龙 韩复光

(湖北医药学院附属襄阳市第一人民医院 骨科 湖北 襄阳 441000)

摘要 目的:研究针刺疗法联合塞来昔布对老年类风湿性关节炎患者的临床疗效及其对患者血清基质金属蛋白酶-3(MMP-3)、白细胞介素-6(IL-6)及自身抗体水平的影响。**方法:**选取2014年10月至2015年9月本院收治的86例类风湿性关节炎患者,随机分为观察组(43例)和对照组(43例)。对照组使用塞来昔布胶囊治疗,观察组在对照组基础上联合针刺疗法。分析和比较两组患者临床疗效、治疗前后20m步行时间、晨僵时间、关节压痛数、治疗前后MMP-3、IL-6及自身抗体水平的变化。**结果:**观察组总有效率显著高于对照组[90.70%(39/43)比65.12%(28/43)]($P<0.05$)。治疗后,两组患者20m步行时间、晨僵时间、关节压痛数均较治疗前显著降低或缩短,其中观察组明显低于或短于对照组($P<0.05$)。治疗后,两组患者血清MMP-3、IL-6水平较治疗前显著降低,其中观察组显著低于对照组($P<0.05$)。治疗后,两组患者AFA、抗-CCP抗体、抗Sa抗体、AKA、ANA自身抗体阳性率较治疗前显著降低,其中观察组显著低于对照组($P<0.05$)。**结论:**针刺疗法联合塞来昔布治疗老年类风湿性关节炎的临床疗效良好,能有效降低患者血清MMP-3、IL-6水平及自身抗体阳性率。

关键词:针刺疗法;塞来昔布;类风湿性关节炎;基质金属蛋白酶-3;白细胞介素-6

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Effect of Acupuncture Combined with Celecoxib on the Serum Levels of MMP-3, IL-6 and Autoantibodies of Elderly Patients with Rheumatoid Arthritis*

CHEN Jie, LIU Jiang-tao, YANG Ju-guang, HAN Zhao-ming, GE Wen-long, HAN Fu-guang

(Department of orthopedics, Xiangyang first people's Hospital, Hubei Medical College, Xiangyang, Hubei, 441000, China)

ABSTRACT Objective: To study the effect of acupuncture combined with celecoxib on the elderly patients with rheumatoid arthritis and the serum levels of metalloproteinase-3 (MMP-3), interleukin-6 (IL-6) and autoantibodies. **Methods:** 86 elderly patients with rheumatoid arthritis who were treated in our hospital from October 2014 to September 2015 were selected and randomly divided into the observation group and the control group with 43 cases in each group. The patients in the control group were treated with celecoxib capsules, while the patients in the observation group were treated with acupuncture on the basis of the control group. Then the clinical efficacy, time of 20 m walking and morning stiffness, incidence of joint tenderness, and the levels of MMP-3, IL-6 and autoantibody were observed and compared between the two groups before and after the treatment. **Results:** After treatment, the total effective rate of the observation group was significantly higher than the control group ($P<0.05$), the time of 20 m walking, morning stiffness and joint tenderness of both groups were significantly lower than those before treatment and the observation group were lower than those of the control group ($P<0.05$), the serum levels of MMP-3 and IL-6 in both groups were significantly lower than before, treatment and the observation group were lower than those of the control group ($P<0.05$), the positive rate of AFA, anti-CCP, anti-Sa, AKA and ANA in both groups were significantly lower than those before, treatment and the observation group were lower than those of the control group ($P<0.05$). **Conclusion:** Acupuncture combined with celecoxib could decrease the serum levels of MMP-3 and IL-6 and the positive rate of autoantibody in the elderly patients with rheumatoid arthritis.

Key words: Acupuncture; Celecoxib; Rheumatoid arthritis; Matrix metalloproteinase-3; Interleukin-6

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前言

类风湿性关节炎主要是因为自身免疫所导致的骨状症关

节炎,发病早期主要表现为功能障碍、关节红肿热痛,晚期关节会表现出不同程度上的畸形、僵硬,是导致人群丧失劳动能力的主要因素之一,并且有着较高的致残率^[1-3]。类风湿性关节炎

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作者简介:陈杰,本科,主治医师,研究方向:创伤及关节骨科,电话:13986398369

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属于慢性骨质逐渐受损的退行性疾病,其病因较为复杂^[1]。非甾体抗炎药主要应用于退热、镇痛、抗炎,已在临床中得到广泛推广。塞来昔布具有较高的选择性和特异性,抗炎和镇痛效果显著,治疗类风湿性关节炎和传统 NSAIDs 的疗效相当,并且能有效降低患者不良反应的发生率^[5,6]。但长时间采取西医方式进行干预整体效果较差,近年来针灸、重要等中医疗法已在临床中得到推广和运用,且疗效较为显著^[7]。为给临床治疗类风湿性关节炎提供更多可借鉴之处,本研究就针刺疗法联合塞来昔布对老年类风湿性关节炎患者血清基质金属蛋白酶-3(MMP-3)、白细胞介素-6(IL-6)及自身抗体水平影响进行了探讨。

1 资料与方法

1.1 临床资料

选取 2014 年 10 月至 2015 年 9 月本院收治的 86 例类风湿性关节炎患者,纳入标准:① 患者临床诊断和美国风湿病协会类风湿性关节炎中的有关标准相符^[8];② 通过对血清中的类风湿因子检查呈现出阳性;③ 近端指间关节区、掌指、腕伴有肿胀现象;④ 至少超过 3 个的关节区软组织出现积液或肿胀。排除标准:① 肝、肾、心、脑、肺、消化性溃疡疾病;② 伴有结核、病毒性肝炎、梅毒、艾滋病等传染性疾病者;③ 白血病、脑癌、肾癌、肝癌、肺癌等恶性肿瘤者;④ 神志不清、精神异常者,难以配合医护人员完成本次研究。整个研究均在患者及其家属的知情同意下完成,并相应的获得了我院伦理委员会批准和实施。根据投硬币法将本次研究对象分为观察组(43 例)和对照组(43 例)。观察组中,男性 28 例,女性 15 例;年龄为 36~74 岁,平均(55.32±4.71)岁;病程为 4~18 个月,平均(11.23±2.01)个月。对照组中,男性 31 例,女性 12 例;年龄为 37~75 岁,平均(55.29±4.79)岁;病程为 3~19 个月,平均(11.41±2.04)个月。两组患者性别、年龄、病程临床资料比较无显著性差异($P>0.05$),具有可比性。

1.2 治疗方法

患者入院后,需对所有患者予以一般疗法,包括物理疗法、休息、急性期的关节制动、恢复期的关节功能锻炼,对照组患者在此基础上使用塞来昔布胶囊(生产厂家:辉瑞制药有限公司,规格:200 mg,生产批号:20140121)进行治疗,200 mg/次,2 次/天。观察组在对照组治疗基础上使用针刺疗法进行治疗,针刺选穴:足三里、肝俞、脾俞、肾俞、关元,根据患者症状选取内外膝眼、血海、阳陵泉、肩贞穴位、天宗、肩髃等穴位。针刺操作方

式:选取 30 mm 毫针,进针方式为指切进针法,配穴、主穴分别采取平补平泻法、插补法,留针时间为 30 min,1 次/天。所有患者均需连续治疗 2 个月。

1.3 观察指标

1.3.1 疗效评价 根据类风湿性关节炎分类标准医生对临床疗效予以评价^[9],显效:经治疗后,患者生化指标、体征、临床症状较治疗前改善程度 $\geq 70\%$;有效:经治疗后,患者生化指标、体征、临床症状较治疗前改善程度 $<70\%$, $\geq 50\%$;改善:经治疗后,患者生化指标、体征、临床症状较治疗前改善程度 $<50\%$, $\geq 30\%$;无效:经治疗后,患者生化指标、体征、临床症状较治疗前改善程度 $<30\%$ 。总有效=显效+有效+改善。

1.3.2 临床症状及体征 包括 20 m 步行时间、晨僵时间、关节压痛数。

1.3.3 MMP-3、IL-6 水平检测 分别在治疗前和治疗 24 h 后抽取两组患者 5 mL 的空腹静脉血,分离血清后放置在 -50°C 低温箱中待测,使用酶联免疫吸附法检测 MMP-3、IL-6 水平。

1.3.4 自身免疫性抗体阳性率 比较两组患者治疗前后抗聚角蛋白微丝蛋白抗体(AFA)、抗环瓜氨酸太抗体(抗-CCP 抗体)、抗 Sa 抗体、抗角蛋白抗体(AKA)、抗核抗体(ANA)阳性率。使用斑点法检测 AFA 抗体,在反应板中加入稀释标本,稀释血清中的抗原和抗体相结合,结合的抗体和酶标记的抗人抗体反应,将底物液加入其中,若呈现出蓝色条带则为阳性。使用酶联免疫法检测抗-CCP 抗体、抗 Sa 抗体,在包被孔中放置稀释的血清,包被在固相上的抗原和血清中的特异性抗体相结合,已结合的抗体和酶标记的抗人抗体反应,和底物液、标记抗体相结合,呈现出蓝色则为阳性。使用间接免疫荧光法检测抗 AKA 抗体、抗 ANA 抗体,稀释血清后和包被基质反应,抗体和抗原相互结合,将荧光素加入其中进行标记。按照荧光模式的不同对 ANA 阳性结果进行判断,在胶质层有板层状或线性状荧光出现则判断为 AKA 阳性。

1.4 统计学分析

本次实验数据处理选择 SPSS11.5 软件包进行,计量资料以 $(\bar{x}\pm s)$ 来表示,采用 t 检验,计数资料以[n(%)]表示,采取 χ^2 检验,以 $P<0.05$ 表明差异具有统计学意义。

2 结果

2.1 两组患者临床疗效比较

治疗后,观察组总有效率显著高于对照组[90.70%(39/43)比 65.12%(28/43)]($P<0.05$),见表 1。

表 1 两组患者的临床疗效比较[n 例(%)]

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

Groups	Markedly	Effective	Improvement	Invalid	Total effective
Observation group (n=43)	18(41.86)	15(34.88)	6(13.95)	4(9.30)	39(90.70)*
Control group(n=43)	11(25.58)	3(6.98)	14(32.56)	15(34.88)	28(65.12)

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

2.2 两组患者治疗前后临床症状体征比较

治疗前,两组患者 20 m 步行时间、晨僵时间、关节压痛数比较差异无统计学意义($P>0.05$)。治疗后,两组患者 20m 步行

时间、晨僵时间、关节压痛数均较治疗前显著降低或缩短($P<0.05$),观察组的 20 m 步行时间、晨僵时间、关节压痛数明显低于或短于对照组($P<0.05$),见表 2。

表 2 两组患者治疗前后临床症状体征的比较($\bar{x} \pm s$)Table 2 Comparison of the clinical symptoms and signs between two groups before and after treatment($\bar{x} \pm s$)

Items	Time	Observation group(n=43)	Control group(n=43)
20 m walking time(s)	Before treatment	25.43± 2.21	25.39± 2.18
	After treatment	14.87± 1.46* [#]	21.34± 1.97*
Morning stiff time(min)	Before treatment	48.21± 4.21	48.28± 4.24
	After treatment	19.45± 1.87* [#]	28.43± 2.45*
Joint tenderness(Piece)	Before treatment	11.23± 2.12	11.26± 2.11
	After treatment	3.87± 0.43* [#]	7.21± 0.97*

Note: Compared with before treatment,*P<0.05; Compared with control group after treatment,[#]P<0.05.

2.3 两组患者治疗前后血清 MMP-3、IL-6 水平的比较

疗前显著降低(P<0.05),观察组的血清 MMP-3、IL-6 水平显著低于对照组(P<0.05),见表 3。

治疗前,两组患者血清 MMP-3、IL-6 水平比较差异无统计学意义(P>0.05)。治疗后,两组患者血清 MMP-3、IL-6 水平较治

表 3 两组患者血清 MMP-3、IL-6 水平的比较($\bar{x} \pm s$)Table 3 Comparison of the serum levels of MMP-3 and IL-6 between two groups($\bar{x} \pm s$)

Items	Time	Observation group(n=43)	Control group(n=43)
MMP-3(ng/mL)	Before treatment	62.32± 5.21	62.11± 5.18
	After treatment	38.98± 3.21* [#]	49.54± 4.14*
IL-6(pg/mL)	Before treatment	18.16± 1.43	18.17± 1.46
	After treatment	6.34± 0.54* [#]	10.85± 1.32*

Note: Compared with before treatment,*P<0.05; Compared with control group after treatment,[#]P<0.05.

2.4 两组患者治疗前后自身抗体阳性情况比较

自身抗体阳性率均较治疗前显著降低(P<0.05),且观察组的血清 AFA、抗-CCP 抗体、抗 Sa 抗体、AKA、ANA 自身抗体阳性率显著低于对照组(P<0.05),见表 4。

治疗前,两组患者 AFA、抗-CCP 抗体、抗 Sa 抗体、AKA、ANA 自身抗体阳性率比较差异无统计学意义(P>0.05)。治疗后,两组患者血清 AFA、抗-CCP 抗体、抗 Sa 抗体、AKA、ANA

表 4 两组患者自身抗体阳性情况比较[例(%)]

Table 4 Comparison of the positive rates of autoantibodies between two groups[n(%)]

Items	Time	Observation group(n=43)	Control group(n=43)
AFA	Before treatment	16(37.21)	3(6.98)
	After treatment	17(39.53)* [#]	13(30.23)*
Anti-CCP antibody	Before treatment	24(55.81)	4(9.30)
	After treatment	26(60.47)* [#]	17(39.53)*
Anti-Sa antibody	Before treatment	17(39.53)	3(6.98)
	After treatment	18(41.86)* [#]	14(32.56)*
AKA	Before treatment	15(34.88)	1(2.33)
	After treatment	14(32.56)* [#]	7(16.28)*
ANA	Before treatment	19(44.19)	4(9.30)
	After treatment	20(46.51)* [#]	15(34.88)*

Note: Compared with before treatment,*P<0.05; Compared with control group after treatment,[#]P<0.05.

3 讨论

类风湿性关节炎是一种风湿科较为常见的自身免疫性疾病,患者会因此疾病的影响而丧失劳动能力甚至致残,类风湿性关节炎的病因目前尚不完全明确,大部分研究表明类风湿性

关节炎的主要发病机制和机体免疫紊乱有关^[1]。在治疗类风湿性关节炎中主要以非甾体类抗炎药为主,然而其会产生较为严重的胃肠道不良反应。

在关节炎早期形成阶段,大量的成纤维细胞存在于血管翳中,可释放出 MMP-3,并且在软骨和滑膜细胞中有着较高的

MMP-3 表达,不但可在血管生成时降解间质成分和微血管基底膜,还能对 IX 型胶原起着直接降解作用,不利于软骨稳定性的维持,导致代谢产物堆积和细胞缺氧,局部表现为酸性环境,MMP-3 在其中发挥作用,恶化程度进一步加重^[12,13]。IL-6 对软骨细胞增殖具有刺激性作用,增加滑膜组织的炎性细胞^[14]。在类风湿性关节炎患者中,AFA、抗-CCP 抗体、抗 Sa 抗体、AKA、ANA 阳性率显著高于正常人群,其中 AKA 抗体是在类风湿性关节炎患者血清中所发现的抗食管上皮角质层的自身抗体,CCP 在鉴别非侵蚀、侵蚀性类风湿性关节炎中的灵敏性较高^[15,16]。

塞来昔布属于非甾体抗炎药,作为特异性抑制环氧化酶具有较好的镇痛和消炎功效,相关研究显示塞来昔布作为环氧酶-2 高选择性抑制剂,对环氧酶-2 能发挥选择性抑制作用,对炎性前列腺素类物质的产生能发挥抑制作用,实现退热、镇痛的目的^[17]。在药物治疗基础上结合针刺疗法,上肢以合谷、阳池、曲池、大椎为主,下肢以昆仑、照海、梁邱、足三里、风市、阳陵泉为主,随之开展循经选穴及局部取穴,也被称之为经验取穴,能痹痛遂解,在临床治疗中应根据患者部位及症状进行局部穴位的选取^[18]。相关研究表明借助针体朝患者穴位中传导热量,此种热量能激发经气,并且有利于针感的加强,实现活血通络、益气逐瘀的目的^[19]。本研究对老年类风湿性关节炎患者予以针刺疗法联合塞来昔布治疗后,患者 20 m 步行时间、晨僵时间显著缩短,关节压痛数明显减少,提示针刺疗法联合塞来昔布有利于患者临床症状的改善,提高临床疗效,其改善效果优于单纯塞来昔布治疗者,符合上述研究者的观点^[20]。本研究对老年类风湿性关节炎患者予以针刺疗法联合塞来昔布治疗,患者的血清 MMP-3、IL-6 水平均显著降低,且降低的效果显著优于单纯塞来昔布治疗者,提示针刺疗法联合塞来昔布能有效降低类风湿性关节炎患者血清中导致免疫紊乱、组织受损、骨质破坏的生化物质,有利于患者临床症状的改善。此外,老年类风湿性关节炎患者经针刺疗法联合塞来昔布治疗后 AFA、抗-CCP 抗体、抗 Sa 抗体、AKA、ANA 的阳性率显著降低,并且明显低于单纯塞来昔布治疗者。

总之,针刺疗法联合塞来昔布治疗老年类风湿性关节炎的临床疗效良好,能有效降低患者血清 MMP-3、IL-6 水平及自身抗体阳性率,有利于患者临床症状的改善。

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