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金乌骨通胶囊联合塞来昔布胶囊治疗强直性脊柱炎的临床研究 *

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摘要 目的：观察金乌骨通胶囊联合塞来昔布胶囊治疗强直性脊柱炎（AS）的临床疗效。**方法：**选取天津中医药大学第一附属医院2017年4月~2020年4月期间收治的126例AS患者。采用双色球法（红色、绿色）将患者分为对照组（红色）和研究组（绿色），各63例。对照组接受塞来昔布胶囊治疗，研究组接受金乌骨通胶囊联合塞来昔布胶囊治疗，两组均治疗3个月。治疗3个月后，观察两组疗效，记录治疗期间不良反应发生率，对比两组治疗前、治疗3个月后的临床症状缓解情况、生存质量及实验室指标变化。**结果：**研究组的临床总有效率高于对照组（P<0.05）。治疗3个月后，研究组巴氏强直性脊柱炎疾病活动指数（BASDAI）、巴氏强直性脊柱炎功能指数（BASFI）评分低于对照组，枕墙距小于对照组，腰椎活动度、胸廓活动度大于对照组（P<0.05）。治疗3个月后，研究组世界卫生组织生存质量简表（WHOQOL-BRIEF）各维度评分高于对照组（P<0.05）。治疗3个月后，研究组血沉（ESR）、C-反应蛋白（CRP）、白介素-6（IL-6）、肿瘤坏死因子-α（TNF-α）低于对照组（P<0.05）。两组不良反应发生率组间比较无统计学差异（P>0.05）。**结论：**金乌骨通胶囊联合塞来昔布胶囊治疗AS患者，可促进其临床症状及生存质量改善，降低ESR及炎性因子水平，是一种安全有效的治疗方案。

关键词：金乌骨通胶囊；塞来昔布胶囊；强直性脊柱炎；临床研究

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Clinical Study of Jinwugutong Capsule Combined with Celecoxib Capsule in the Treatment of Ankylosing Spondylitis*

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ABSTRACT Objective: To observe the clinical efficacy of Jinwugutong capsule combined with celecoxib capsule in the treatment of ankylosing spondylitis (AS). **Methods:** 126 patients with AS who were treated in The First Affiliated Hospital of Tianjin University of traditional Chinese Medicine from April 2017 to April 2020 were selected. The patients were divided into control group (red) and study group (green) by two-color ball method (red and green), 63 cases in each group. The control group was treated with celecoxib capsule, and the study group was treated with Jinwugutong capsule combined with celecoxib capsule. Both groups were treated for 3 months. 3 months after treatment, the curative effect of the two groups was observed, the incidence of adverse reactions during the treatment was recorded, and the clinical symptom relief, quality of life and laboratory index changes of the two groups before and 3 months after treatment were compared. **Results:** The total effective rate of the study group was higher than that of the control group (P<0.05). 3 months after treatment, the scores of disease activity index of pasteurized ankylosing spondylitis (BASDAI), barthel Ankylosing Spondylitis Functional Index (BASFI) of the study group were lower than those of the control group, the occipital wall distance was less than that of the control group, and the lumbar mobility and thoracic mobility were greate than those of the control group (P<0.05). 3 months after treatment, the scores of WHO quality of life brief (WHOQOL-BRIEF) each dimension of the study group were higher than those of the control group (P<0.05). 3 months after treatment, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α) of the study group were lower than those of the control group (P<0.05). There was no significant difference in the incidence of adverse reactions between the two groups (P>0.05). **Conclusion:** Jinwugutong capsule combined with celecoxib

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capsule in the treatment of patients with AS can promote the improvement of clinical symptoms and quality of life, and reduce the levels of ESR and inflammatory factors, which is a safe and effective treatment plan.

Key words: Jinwugutong capsule; Celecoxib capsules; Ankylosing spondylitis; Clinical study

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前言

强直性脊柱炎(AS)是一种主要侵犯中轴关节和肌腱韧带骨附着点的炎性、慢性、全身性自身免疫性疾病[1]。本病多发于男性,若未能予以及时治疗,可导致关节强直、脊柱畸形,降低患者生存质量[2]。现临床尚无有关 AS 的特效治疗方案,多以慢作用药物、非甾体类抗炎药及激素治疗为主[3]。塞来昔布胶囊具有抗炎、镇痛及退热作用,既往用于 AS 治疗,可获得一定效果[4]。但由于 AS 属于慢性疾病,需长期用药,而长期使用塞来昔布胶囊等西药治疗会造成明显的毒副作用,部分患者无法耐受[5]。金乌骨通胶囊是临床常用的中成药,主要功效为活血通络、祛风除湿[6]。本研究选取天津中医药大学第一附属医院收治的 126 例 AS 患者作为研究对象,观察金乌骨通胶囊联合塞来昔布胶囊治疗 AS 的临床应用价值,旨在为临床应用提供数据参考。

1 资料与方法

1.1 一般资料

研究病例来自于天津中医药大学第一附属医院 2017 年 4 月 ~2020 年 4 月期间收治的 AS 患者,共 126 例。入选者均自愿签署知情同意书。纳入标准:(1)AS 诊断标准参考《强直性脊柱炎诊断及治疗指南》[7]:① 在前后和侧屈方向上腰椎活动受限,② 下腰背痛,且病程 >3 个月,③ 影像学提示单侧骶髂关节炎 III~IV 级或双侧骶髂关节炎 II~III 级,④ 胸廓扩展度低于同性别、同年龄的正常值;(2)对本次研究用药:金乌骨通胶囊或塞来昔布胶囊均耐受者。排除标准:(1)患者近 3 个月内服用过糖皮质激素、免疫抑制剂等药物;(2)伴有严重关节畸形;(3)合并精神疾病;(4)合并血液系统疾病;(5)合并恶性肿瘤;(6)合并免疫系统疾病。本次研究已获得我院伦理学委员会批准进行。采用双色球法(红色、绿色)将患者分为对照组(红色)和研究组(绿色),各为 63 例。两组患者一般资料如下:对照组中男 51 例,女 12 例,病程范围 4 个月 ~8 年,平均病程(4.26± 0.84)年;年龄范围 43~69 岁,平均年龄(54.82± 4.29)岁。研究组中男 50 例,女 13 例,病程范围 6 个月 ~7 年,平均病程(4.32± 0.79)年;年龄范围 41~68 岁,平均年龄(55.26± 3.83)岁。两组一般资料之间的差异无统计学意义(P>0.05),具有可比性。

1.2 方法

入院后,两组均接受止痛药物等对症处理,治疗期间常规饮食指导,同时指导患者进行相关的功能锻炼。对照组给予塞来昔布胶囊(生产单位:青岛百洋制药有限公司,规格:0.2 g,国药准字 H20203325)治疗,口服,1 粒 / 次,1 次 /d。研究组则在对照组的基础上联合金乌骨通胶囊(生产单位:贵州盛世龙方制药股份有限公司,规格:每粒装 0.5 g,国药准字 Z20043621)治疗,口服,3 粒 / 次,3 次 /d。两组均治疗 3 个月。

1.3 疗效判定标准

总有效率 =(治愈例数 + 好转例数)/ 总例数 *100%。治愈:治疗 3 个月后局部症状消失,全身情况良好,畸形矫正,功能基本恢复。好转:局部症状减轻,全身情况好转,关节功能有改善,血沉(ESR)下降。无效:未达到以上标准者[8]。

1.4 评价指标

(1)对比两组治疗前、治疗 3 个月后的巴氏强直性脊柱炎疾病活动指数(BASDAI)评分[9]、胸廓活动度、枕墙距、巴氏强直性脊柱炎功能指数(BASFI)评分[10]、腰椎活动度。其中 BASDAI 包含 6 条目,分别为局部触痛、脊柱痛、关节肿痛、时间、晨僵、疲乏,总分 10 分,分数越高疾病越严重。BASFI 包含 10 条目,分别为穿衣、取物、拾物、无辅助下站起、持续站立、走台阶、向后看、增加体力活动、做家务和工作,总分 10 分,分数越高疾病越严重。(2)对比两组治疗前、治疗 3 个月后的世界卫生组织生存质量简表(WHOQOL-BRIEF)各项评分[11],WHOQOL-BRIEF 包括心理领域、生理领域、环境领域、社会关系领域这 4 个维度,每个维度各为 100 分,分数越高,生存质量越好。(3)对比两组治疗前、治疗 3 个月后的 ESR 和血清炎症因子水平,分别抽取患者治疗前、治疗 3 个月后的清晨空腹肘静脉血 5 mL,采用免疫比浊法检测 C- 反应蛋白(CRP)水平,采用 Ves-matic 20 全自动血沉分析仪(深圳德夏科技发展有限公司)检测 ESR 水平,采用酶联免疫吸附法检测白介素 -6(IL-6)、肿瘤坏死因子 -α(TNF-α)水平。检测期间涉及的试剂盒均采购自上海江莱生物科技有限公司,实验步骤参考说明书进行。(4)观察并记录治疗过程中失眠、腹泻、皮疹、背痛、恶心等发生情况。

1.5 统计学方法

采用 SPSS 19.0 软件进行统计分析。经检验符合正态分布,以($\bar{x}\pm s$)表示 ESR、IL-6、CRP 等计量资料,比较采用 t 检验。采用率的方式表示疗效、不良反应等计数资料,比较采用 x^2 检验。P<0.05 为差异有统计学意义。

2 结果

2.1 两组疗效对比

治疗 3 个月后,对照组临床总有效率为 74.60%(47/63),低于研究组的 93.65%(59/63),差异有统计学意义(P<0.05)。详见表 1。

2.2 两组临床症状相关指标对比

治疗前,两组 BASDAI、枕墙距、BASFI、腰椎活动度、胸廓活动度组间对比无统计学差异(P>0.05)。治疗 3 个月后,两组 BASDAI、BASFI 评分下降,枕墙距缩小,且研究组 BASDAI、BASFI 评分低于对照组,枕墙距小于对照组(P<0.05)。治疗 3 个月后,两组腰椎活动度、胸廓活动度扩大,且研究组大于对照组(P<0.05)。详见表 2。

表 1 两组疗效对比[n(%)]

Table 1 Comparison of curative effect between the two groups [n(%)]

Groups	Cure	Become better	Invalid	Total effective rate
Control group(n=63)	18(28.57)	29(46.03)	16(25.40)	47(74.60)
Study group(n=63)	24(38.10)	35(55.56)	4(6.35)	59(93.65)
x^2				8.558
P				0.003

表 2 两组临床症状相关指标对比($\bar{x}\pm s$)

Table 2 Comparison of clinical symptoms related indexes between the two groups($\bar{x}\pm s$)

Groups	BASDAI(scores)		Occipital wall distance(cm)		BASFI(scores)		Lumbar mobility(cm)		Thoracic mobility(cm)	
	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment
Control group(n=63)	7.19± 0.61	4.62± 0.79*	10.28± 0.78	9.04± 0.62*	6.84± 0.67	4.93± 0.59*	3.74± 0.46	4.57± 0.68*	3.14± 0.21	3.89± 0.25*
Study group(n=63)	7.02± 0.58	3.18± 0.45*	10.07± 0.83	7.95± 0.69*	6.71± 0.74	3.24± 0.48*	3.82± 0.59	5.18± 0.73*	3.18± 0.24	4.56± 0.23*
t	1.603	12.571	1.455	9.327	1.034	17.636	-0.849	-4.853	-0.996	-15.655
P	0.111	0.000	0.148	0.000	0.303	0.000	0.398	0.000	0.321	0.000

Note: *compared with the same group before treatment, the difference was statistically significant.

2.3 两组 WHOQOL-BRIEF 各维度评分对比

治疗前,两组 WHOQOL-BRIEF 各维度评分组间对比无统计学差异(P>0.05)。治疗 3 个月后,两组 WHOQOL-BRIEF 各维度评分升高,且研究组高于对照组(P<0.05)。详见表 3。

表 3 两组 WHOQOL-BRIEF 各维度评分对比($\bar{x}\pm s$,分)

Table 3 Comparison of scores of WHOQOL-BRIEF each dimension of the two groups($\bar{x}\pm s$, scores)

Groups	Psychological field		Physiological field		Environmental field		Social relations field	
	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment
Control group(n=63)	58.36± 8.37	71.43± 9.46*	54.72± 7.38	68.45± 8.72*	63.26± 8.48	70.52± 8.27*	65.26± 8.41	74.93± 7.52*
Study group(n=63)	57.73± 10.46	84.47± 7.39*	53.92± 6.13	80.47± 7.64*	63.52± 7.59	84.63± 7.04*	64.31± 7.38	85.24± 6.49*
t	0.375	-8.622	0.662	-8.229	-0.181	-10.312	0.674	-8.238
P	0.708	0.000	0.509	0.000	0.856	0.000	0.502	0.000

Note: * compared with the same group before treatment, the difference was statistically significant.

2.4 两组实验室指标对比

治疗前, 两组 ESR、CRP、IL-6、TNF-α 组间对比无统计学差异(P>0.05)。治疗 3 个月后,两组 ESR、CRP、IL-6、TNF-α 下降,且研究组低于对照组(P<0.05)。详见表 4。

2.5 两组不良反应发生率对比

对照组出现失眠 2 例、皮疹 1 例、腹泻 2 例、背痛 1 例、恶心 2 例,研究组出现失眠 1 例、腹泻 1 例、背痛 2 例、恶心 1 例,对照组、研究组的不良反应发生率分别为 12.70%、7.94%,两组不良反应发生率组间比较无统计学差异(x^2=0.772,P=0.380)。

3 讨论

AS 是一种慢性的炎性疾病,可引起患者肢体功能、劳动能力及生存质量等诸多方面的损害[12]。以往相关的研究认为[13],多数 AS 患者在症状出现的第一个 10 年内, 脊柱绝大部分运动能力将会丧失。因 AS 发病机制尚未完全明确,目前尚无有效根治的特效药, 塞来昔布胶囊是治疗 AS 的传统对症药物之一, 可通过抑制环氧化酶活性来阻止前列腺素的大量分泌,发挥减轻关节疼痛、晨僵等症状及抗炎作用[14,15]。但长期应用易引

表 4 两组实验室指标对比($\bar{x}\pm s$)

Table 4 Comparison of laboratory indexes between the two groups($\bar{x}\pm s$)

Groups	ESR(mm/h)		CRP(mg/L)		IL-6(pg/mL)		TNF-α(pg/mL)	
	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment	Before treatment	3 months after treatment
Control group (n=63)	41.07± 4.34	28.93± 4.24*	19.81± 378	12.54± 3.49*	21.32± 4.26	14.35± 2.54*	29.78± 4.42	22.57± 3.43*
Study group (n=63)	41.13± 5.29	17.06± 2.19*	19.54± 3.63	7.88± 1.37*	21.71± 3.34	8.87± 2.39*	29.19± 3.47	15.43± 2.32*
t	-0.070	19.743	0.409	9.865	-0.572	12.471	0.833	13.686
P	0.945	0.000	0.683	0.000	0.568	0.000	0.406	0.000

Note: * compared with the same group before treatment, the difference was statistically significant.

发胃肠道毒副反应,且伴有肝损伤,常需联合其他药物辅助使用[16]。中医学认为 AS 的病机要点在于先天禀赋不足,或是后天失于养护,致使肾精亏虚、素体虚弱、督脉失荣、肝肾精血不足、筋骨失养,最终发为痹症,并可累及全身多个脏腑,故中医治疗主张以补肝肾为主,配以舒筋通络[17]。金乌骨通胶囊是一种苗药,主要成分为金毛狗脊、乌梢蛇、葛根、淫羊藿、木瓜、威灵、补骨脂,其中乌梢蛇通络止痉、祛风除湿;金毛狗脊补肝肾、祛风湿;葛根发散表邪;淫羊藿强筋骨、补肾壮阳;威灵通络止痛;木瓜舒筋活络;补骨脂固精纳气、补肾壮阳;以上药物合用具有温肾补阳、祛风除湿、活血通络之功效[18]。

本次研究结果显示,与单用塞来昔布胶囊相比,金乌骨通胶囊联合塞来昔布胶囊治疗 AS 患者,其临床症状缓解更为明显,且不良反应发生率较低,疗效显著。相关研究指出金乌骨通胶囊可明显改善寒湿痹阻型、肾虚督寒型 AS 患者的临床及实验室指标[19],佐证了本研究结果。细胞因子在 AS 的发病进程中占据重要作用,ESR 是指红细胞沉降的速度, 机体状态正常时其下沉较缓慢,病理情况可以使 ESR 明显增快,且 ESR 变化是多种因素互相作用的结果, 有助于推断病变的发展情况[20,21]。CRP 是反映机体炎症状态的标志因子,敏感性较高,对于评估疾病病情和预后具有较好的敏感性[22-24]。IL-6 可通过刺激破骨细胞活化、诱导滑膜细胞增殖等途径,在关节及软骨的破坏中发挥重要作用[25]。TNF-α 则可通过诱导炎性因子的产生,从而抑制软骨 II 型胶原、蛋白聚糖的合成,在关节软骨基质的降解及骨破坏中发挥重要作用[26]。本次研究结果显示:金乌骨通胶囊联合塞来昔布胶囊治疗在调节 ESR、CRP、IL-6、TNF-α 水平方面效果更为显著。这可能是因为金乌骨通胶囊具有减轻充血、改善血液循环、减少中性白细胞渗出及浆细胞与淋巴细胞浸润等作用,从而有效控制机体炎症,减轻炎症因子对骨关节的破坏,明显减缓骨化病理发展[27,28]。此外,金乌骨通胶囊联合塞来昔布胶囊治疗还可促进 AS 患者生存质量提高,这可能与联合治疗可促进患者临床症状改善,利于患者尽早恢复正常工作生活有关[29,30]。需注意的是,AS 属于反复发作的疾病,难以根治,除药物治疗外,临床还应考虑调动患者的治疗积极性、依从性和信心,加强对患者的健康教育,鼓励其适当运动,防止肢体废用性萎缩。如有必要的话,可给予一定的心理治疗,积极引导,减轻患者心理负担。

综上所述,与单独应用塞来昔布胶囊相比,塞来昔布胶囊联合金乌骨通胶囊治疗 AS 患者,患者临床症状及生存质量改善更为明显、ESR 降低及炎症反应缓解更显著,疗效进一步提高。

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