

重组人 II 型肿瘤坏死因子受体-抗体融合蛋白 关节腔注射联合中药熏洗治疗膝骨关节炎的临床研究

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摘要 目的: 观察注射用重组人 II 型肿瘤坏死因子受体-抗体融合蛋白(recombinant human tumor necrosis factor receptor - Fc fusion protein, rhTNFR:Fc) 关节腔注射联合中药熏洗治疗膝骨关节炎的临床疗效。方法: 将 60 例膝骨关节炎患者随机分为 2 组, 每组 30 例。分别采用关节腔注射 rhTNFR:Fc 联合中药熏洗和关节腔注射玻璃酸钠联合中药熏洗治疗。比较治疗前后 2 组膝关节疼痛视觉模拟评分(visual analogue score, VAS) 及西安大略和麦克马斯特大学(Western Ontario and McMaster Universities, WOMAC) 骨关节炎评分, 并于治疗结束后 3 个月比较 2 组患者的综合疗效。结果: 治疗前 2 组患者的膝关节 VAS 评分及 WOMAC 评分比较, 组间差异均无统计学意义[(7.15 ± 1.09) 分, (6.90 ± 1.52) 分, $t = 1.045$, $P = 0.309$; (54.75 ± 3.23) 分, (55.45 ± 3.11) 分, $t = 0.700$, $P = 0.493$]。治疗结束后 3 个月, 2 组患者的膝关节 VAS 评分[(3.05 ± 0.76) 分, (4.10 ± 0.97) 分] 及 WOMAC 评分[(16.55 ± 2.65) 分, (27.20 ± 3.17) 分] 均较治疗前下降($t = 14.173$, $P = 0.000$; $t = 10.101$, $P = 0.000$; $t = 34.451$, $P = 0.000$; $t = 39.161$, $P = 0.000$)。rhTNFR:Fc 组的膝关节 VAS 评分及 WOMAC 评分下降幅度均大于玻璃酸钠组[(4.10 ± 1.29) 分, (2.80 ± 1.31) 分, $t = 3.771$, $P = 0.001$; (38.20 ± 4.96) 分, (28.25 ± 3.23) 分, $t = 8.132$, $P = 0.000$]。治疗结束后 3 个月, rhTNFR:Fc 组治愈 10 例、显效 12 例、有效 7 例、无效 1 例, 玻璃酸钠组治愈 6 例、显效 8 例、有效 13 例、无效 3 例, rhTNFR:Fc 组疗效优于玻璃酸钠组($Z = -1.987$, $P = 0.047$)。结论: 采用关节腔注射 rhTNFR:Fc 联合中药熏洗治疗膝骨关节炎, 可以有效缓解膝关节疼痛, 促进膝关节运动功能恢复, 疗效优于关节腔注射玻璃酸钠联合中药熏洗治疗, 值得临床推广应用。

关键词 骨关节炎, 膝; 受体, 肿瘤坏死因子, II 型; 透明质酸; 熏洗; 治疗, 临床研究性

Clinical study on intra-articular injection of Type II recombinant human tumor necrosis factor receptor - Fc fusion protein combined with Chinese herbal steaming and washing therapy for treatment of knee osteoarthritis

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ABSTRACT Objective: To observe the clinical curative effects of intra-articular injection of Type II recombinant human tumor necrosis factor receptor - Fc fusion protein (rhTNFR:Fc) combined with Chinese herbal steaming and washing therapy for treatment of knee osteoarthritis (KOA). **Methods:** Sixty patients with KOA were randomly divided into 2 groups, 30 cases in each group. The patients were treated with combination therapy of intra-articular injection of rhTNFR:Fc with Chinese herbal steaming and washing (rhTNFR:Fc group) and combination therapy of intra-articular injection of sodium hyaluronate (SH) with Chinese herbal steaming and washing (SH group) respectively. The knee visual analogue score (VAS) and Western Ontario and McMaster Universities (WOMAC) osteoarthritis score were compared between the 2 groups before and after the treatment, and the total clinical curative effects were also compared between the 2 groups at 3 months after the end of the treatment. **Results:** There was no statistical difference in the knee VAS scores and WOMAC scores between the 2 groups before the treatment (7.15 ± 1.09 vs 6.90 ± 1.52 points, $t = 1.045$, $P = 0.309$; 54.75 ± 3.23 vs 55.45 ± 3.11 points, $t = 0.700$, $P = 0.493$). The knee VAS scores (3.05 ± 0.76, 4.10 ± 0.97 points) and WOMAC scores (16.55 ± 2.65, 27.20 ± 3.17 points) of all patients decreased at 3 months after the end of the treatment ($t = 14.173$, $P = 0.000$; $t = 10.101$, $P = 0.000$; $t = 34.451$, $P = 0.000$; $t = 39.161$, $P = 0.000$). The decreased degree of knee VAS scores and WOMAC scores of rhTNFR:Fc group were greater than those of SH group (4.10 ± 1.29 vs 2.80 ± 1.31 points, $t = 3.771$, $P = 0.001$; 38.20 ± 4.96 vs 28.25 ± 3.23 points, $t = 8.132$, $P = 0.000$). At 3 months after the end of the treatment, 10 patients were cured, 12 got a good result, 7 fair and 1 poor in the rhTNFR:Fc group; while 6 patients were cured, 8 got a good result, 13 fair and 3 poor in the SH group. The rhTNFR:Fc group surpassed the SH group in the curative

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effect ($Z = -1.987, P = 0.047$). **Conclusion:** The therapy of intra-articular injection of rhTNFR:Fc combined with Chinese herbal steaming and washing can effectively relieve the knee pain and promote the knee function recovery in the treatment of KOA, and its curative effect is better than that of intra-articular injection of SH combined with Chinese herbal steaming and washing, so it is worthy of popularizing in clinic.

Key words osteoarthritis, knee; receptors, tumor necrosis factor, type II; hyaluronic acid; steaming washing therapy; therapies, investigational

膝骨关节炎 (knee osteoarthritis, KOA) 属于常见病、多发病,多见于中老年人,临床常表现为膝关节疼痛及运动功能障碍^[1],可严重影响患者工作和生活。2013 年 1 月至 2014 年 12 月,我们分别采用关节腔注射重组人 II 型肿瘤坏死因子受体-抗体融合蛋白 (recombinant human tumor necrosis factor receptor-Fc fusion protein, rhTNFR:Fc) 联合中药熏洗和关节腔注射玻璃酸钠联合中药熏洗治疗 KOA 患者 60 例,并对 2 种方法的疗效进行比较,现报告如下。

1 临床资料

1.1 一般资料 纳入研究的患者 60 例,男 18 例,女 42 例。年龄 45~70 岁,中位数 65 岁。均为吉林省中医药科学院门诊患者,左膝 28 例,右膝 32 例。病程 3 个月至 12 年,中位数 8.4 年。试验方案经医学伦理委员会审核通过。

1.2 诊断标准

1.2.1 西医诊断标准 参照美国风湿病学会 2001 年制定的 KOA 标准^[2]:①年龄 ≥ 50 岁;②晨僵 < 30 min;③关节活动时骨摩擦音;④膝部检查示骨性肥大;⑤有骨压痛;⑥无明显滑膜升温;⑦放射学检查有骨赘形成。

1.2.2 中医诊断标准 采用《中药新药临床研究指导原则》中 KOA 诊断标准^[3]。

1.3 纳入标准 ①符合上述诊断标准;②年龄 45~70 岁;③近 1 周内未接受任何治疗;④同意参与本研究并签署知情同意书。

1.4 排除标准 ①合并心血管、肝、肾及造血系统等严重原发性疾病者;②合并急性感染性疾病者;③妊娠期或哺乳期妇女;④精神病患者;⑤局部皮肤有感染者。

1.5 剔除和脱落标准 ①不符合纳入标准而被误纳入者;②未按规定治疗或疗程不全影响疗效评价者;③未说明原因而失访者。

1.6 疗效评定标准 采用疼痛视觉模拟评分 (visual analogue score, VAS) 及西安大略和麦克马斯特大学 (Western Ontario and McMaster Universities, WOMAC) 骨关节炎评分评价膝关节疼痛及功能恢复情况,采用

《中药新药临床研究指导原则》中骨关节炎疗效标准^[3]评定综合疗效。

2 方法

2.1 分组方法 采用随机数字表将符合要求的 60 例患者随机分为 rhTNFR:Fc 组和玻璃酸钠组,每组 30 例。2 组患者的性别、年龄、病程比较,组间差异均无统计学意义,有可比性 (表 1)。

表 1 2 组膝骨关节炎患者基线资料的比较

组别	例数	性别 (例)		年龄 ($\bar{x} \pm s$, 岁)	病程 ($\bar{x} \pm s$, 年)
		男	女		
rhTNFR:Fc 组	30	8	22	64.50 \pm 2.88	8.30 \pm 0.26
玻璃酸钠组	30	10	20	65.30 \pm 2.50	8.40 \pm 0.31
检验统计量		$\chi^2 = 0.317$		$t = 0.593$	$t = 0.264$
P 值		0.573		0.568	0.798

2.2 治疗方法 rhTNFR:Fc 组采用关节腔注射 rhTNFR:Fc 联合中药熏洗治疗,玻璃酸钠组采用关节腔注射玻璃酸钠联合中药熏洗治疗。

2.2.1 关节腔注射 rhTNFR:Fc 患者坐于诊查床边,双腿自然下垂,于髌骨上缘与髌骨外缘交点处进针,抽出关节积液,注入 rhTNFR:Fc 0.5 mL (上海中信国健药业股份有限公司生产,批号 20130436)。每周 1 次,3 周为 1 个疗程,共治疗 1 个疗程。

2.2.2 关节腔注射玻璃酸钠 采用上述注射方法向关节腔内注入玻璃酸钠注射液 (昆明贝克诺顿制药有限公司生产,批号 4DD232),每次 2.5 mL。每周 1 次,5 周为 1 个疗程,共治疗 1 个疗程。

2.2.3 中药熏洗 于关节腔内注射药物 2 d 后,采用吉林省中医药科学院自制的熏洗方熏洗,药物组成:伸筋草、透骨草、香附、桃仁、红花、川芎、艾叶、乳香、没药、海桐皮、穿山龙、防风各 10 g。每次熏洗 20 min,每日 1 次,7 d 为 1 个疗程,连续治疗 3 个疗程。

2.3 统计学方法 采用 SPSS17.0 统计软件对所得数据进行统计学分析,2 组患者性别的组间比较采用 χ^2 检验,年龄、病程、VAS 评分及 WOMAC 评分的组间比较采用 t 检验,检验水准 $\alpha = 0.05$ 。

3 结果

治疗前 2 组患者的膝关节 VAS 评分及 WOMAC

评分比较,组间差异均无统计学意义(表 2、表 3)。治疗结束后 3 个月,2 组患者的膝关节 VAS 评分及 WOMAC 评分均较治疗前下降;rhTNFR:Fc 组的膝关节 VAS 评分及 WOMAC 评分下降幅度均大于玻璃酸

钠组(表 2、表 3)。rhTNFR:Fc 组的综合疗效优于玻璃酸钠组,差异有统计学意义($Z = -1.987, P = 0.047$),见表 4。

表 2 2 组膝关节炎患者治疗前后膝关节 VAS 评分的比较 $\bar{x} \pm s$, 分

组别	例数	治疗前	治疗结束后 3 个月	治疗前后差值	<i>t</i> 值	<i>P</i> 值
rhTNFR:Fc 组	30	7.15 ± 1.09	3.05 ± 0.76	4.10 ± 1.29	14.173	0.000
玻璃酸钠组	30	6.90 ± 1.52	4.10 ± 0.97	2.80 ± 1.31	10.101	0.000
<i>t</i> 值		1.045	3.804	3.771		
<i>P</i> 值		0.309	0.001	0.001		

表 3 2 组膝关节炎患者治疗前后膝关节 WOMAC 评分的比较 $\bar{x} \pm s$, 分

组别	例数	治疗前	治疗结束后 3 个月	治疗前后差值	<i>t</i> 值	<i>P</i> 值
rhTNFR:Fc 组	30	54.75 ± 3.23	16.55 ± 2.65	38.20 ± 4.96	34.451	0.000
玻璃酸钠组	30	55.45 ± 3.11	27.20 ± 3.17	28.25 ± 3.23	39.161	0.000
<i>t</i> 值		0.700	11.596	8.132		
<i>P</i> 值		0.493	0.000	0.000		

表 4 2 组膝关节炎患者综合疗效的比较 例

组别	治愈	显效	有效	无效	合计
rhTNFR:Fc 组	10	12	7	1	30
玻璃酸钠组	6	8	13	3	30
合计	16	20	20	4	60

4 讨 论

KOA 是由创伤、超负荷运动、肥胖等导致关节软骨出现原发性或继发性退行性改变,并伴有软骨下骨质增生、软骨剥脱,从而使关节逐渐破坏,最终发生膝关节功能障碍的一种疾病^[4-5]。该病属于中医“骨痹”范畴,多因年老体衰、筋脉失养或久卧湿地、感受风寒湿邪等,导致气血运行不畅所致。该病常用的中医药疗法包括口服或外用中药、穴位注射、针灸和推拿等,西医疗法包括口服非甾体类抗炎药或硫酸氨基葡萄糖、关节腔注射激素或玻璃酸钠、膝关节镜手术或膝关节置换术等,虽然均有效果,但疗效不一。

玻璃酸钠是膝关节软骨基质和关节滑液的主要成分,具有润滑和保护关节的作用,关节腔注射玻璃酸钠是治疗 KOA 的常用方法,可以有效缓解疼痛、改善运动功能,但是疗效并不持久^[6-8]。肿瘤坏死因子 α (tumor necrosis factor α , TNF- α) 是参与关节病变的主要细胞因子和炎性介质,在骨关节炎的发病过程中起着重要作用,不仅促进单核巨噬细胞与粒细胞吞噬趋化,释放溶酶体酶、氧自由基、组胺等,导致软骨基质降解,而且还诱导 T 细胞和 B 细胞活化,加重免疫损伤;其含量高低与关节病变程度密切相

关^[9-11]。膝关节腔注射 rhTNFR:Fc 可以降低关节液 TNF- α 水平,缓解疼痛症状,改善膝关节功能^[12-13]。中药熏洗治疗 KOA,能有效改善局部血液循环,促进炎性介质的吸收,有利于膝关节功能恢复^[14-15]。

本研究结果显示,采用关节腔注射 rhTNFR:Fc 联合中药熏洗治疗 KOA,可以有效缓解膝关节疼痛,促进膝关节运动功能恢复,疗效优于关节腔注射玻璃酸钠联合中药熏洗治疗,值得临床推广应用。

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