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老年类风湿关节炎患者应用 MTX 或 LEF 联合糖皮质激素治疗的效果观察 *

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摘要 目的:探讨甲氨蝶呤(MTX)或来氟米特(LEF)联合泼尼松(PDN)对老年类风湿关节炎的疗效。方法:选取 112 例老年 RA 患者,按随机数表法将患者分为 LEF 组(n=28)、MTX 组(n=28)、LET+PDN 组(n=28)、MTX+PDN 组(n=28),治疗 3 个月后统计四组关节肿胀数、关节压痛数、DAS28 评分、VAS 评分、RF、晨僵时间,并记录不良反应事件。结果:MTX 组和 LEF 组治疗后各项指标均低于治疗前($P<0.05$);MTX+PDN 组与 LEF+PDN 组治疗后各项指标均明显低于治疗前($P<0.001$);MTX+PDN 组治疗效果明显优于 MTX 组 ($P<0.001$);LEF+PDN 组治疗效果明显优于 LEF 组 ($P<0.001$);MTX+PDN 组治疗总有效率为 53.57%,高于 LEF+PDN 组的 42.86%,但差异无统计学意义($\chi^2=2.426$, $P=0.119$)。结论:四组对 RA 均有治疗效果,联合使用效果更佳,且服药后无严重不良反应,安全性较高。

关键词: 类风湿关节炎;泼尼松;甲氨蝶呤;来氟米特

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Observation on the Effect of MTX or LEF Combined with Glucocorticoid in the Treatment of Elderly Patients with Rheumatoid Arthritis*

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ABSTRACT Objective: To investigate the curative effect of methotrexate (MTX) or leflunomide (LEF) in combination with prednisone (PDN) in the treatment of senile rheumatoid arthritis (RA). **Methods:** 112 elderly patients with RA in our hospital between May 2013 and November 2015 were selected. All patients were divided into LEF group (n=28), MTX group (n=28), LET+PDN group (n=28), MTX+PDN group (n=28) according to the random number table method. After 3 months of treatment, calculate the swollen joints, joint tenderness, DAS28 score, VAS score, RF, morning stiffness time and record the adverse events. **Results:** The indexes of MTX group and LEF group after treatment were significantly lower than before treatment ($P<0.05$). The indexes of MTX+PDN group and LEF+PDN group were also significantly lower after treatment than before treatment, and the difference was statistically significant ($P<0.001$). MTX+PDN group showed significantly better effect than MTX group ($P<0.001$), and LEF+PDN group also showed significantly better effect than LEF group ($P<0.001$). The total effective rate of MTX+PDN group was 53.57%, higher than that of 42.86% in LEF+PDN group, but the difference was not statistically significant ($\chi^2=2.426$, $P=0.119$). **Conclusion:** The four groups all had curative effect, but the combination of two had better effect, and there were no serious adverse reactions after treatment. The efficacy difference between MTX+PDN group and LEF+PDN group was not distinct, so they can be selected according to the actual situation.

Key words: Rheumatoid arthritis; Prednisone; Methotrexate; Leflunomide

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前言

风湿性关节炎(rheumatic arthritis, RA)是一种常见的急性/慢性结缔组织炎症,可反复发作并累及心脏。临床症状主要包

括关节和肌肉游走性酸楚、重著、疼痛,是风湿热的主要表现之一,起病原因常有急性发热及关节疼痛^[1]。其发病机制目前尚未清楚,目前治疗方法较多,但均不能有效治愈^[2]。常见的治疗药物包括糖皮质激素、非甾体抗炎药及各种抗风湿药,而老年风

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湿病因常常多种,临床选择联合多种药物一起治疗,希望获得更好的疗效。本研究分析比较氟米特(leflunomide, LEF)、甲氨蝶呤(methotrexate, MTX)和泼尼松(prednison, PDN)三种药物单独和联合使用的疗效差异。

1 资料与方法

1.1 一般资料

选取我院 2013 年 5 月至 2015 年 11 月期间收治的老年 RA 患者 112 例,其中男性 25 例,女性 87 例,年龄为 58~77 岁,平均年龄为(63.87± 3.92)岁,病程为 6 个月~4 年,平均病程为(1.74± 0.62)年。根据随机数表法将所有患者分为 LEF 组(n=28)、MTX 组(n=28)、LET+PDN 组(n=28)、MTX+PDN 组(n=28)。四组患者年龄分部、性别比例及病程等差异无统计学意义(P<0.05)。本研究为前瞻性实验,经院伦理协会批准,并或者患者自愿签署知情同意书。

1.2 纳入与排除标准

纳入标准^[3]:1)有 3 个或 3 个以上的关节部位的软组织肿胀(关节炎);2)早晨起来关节僵硬,持续至少 1 小时;3)掌指关节、近端指间关节或腕关节肿胀超过 6 周;4)皮下类风湿结节;5)对称性肿胀(关节炎);6)X 线片显示手和(或)腕关节软骨面呈糜烂样和(或)关节周围骨质稀疏改变;7)类风湿因子阳性。诊断条件满足以上 3 点即可。排除标准^[4,5]:1)合并严重心肝肾疾病或其他内分泌系统疾病;2)伴有严重肠胃功能不全或消化疾病;3)3 个月内曾接受糖皮质激素或抗风湿药物的治疗;4)对 LEF、MTX 或 PDN 敏感;5)身体严重虚弱或怀孕患者。

1.3 方法^[6]

LEF 组:给予 LEF 20 mg,1 次/天,口服;MTX 组:给予 MTX 15 mg,1 次/天,口服;MTX 联合 PDN 组:MTX 15 mg+

PDN 10 mg,1 次/天,口服;LEF 联合 PDN 组:LEF 20 mg+PDN 10 mg,1 次/天,口服,四组均连续服用 3 个月。

1.4 观察及评价指标

统计四组治疗前后关节肿胀数、关节压痛数、DAS28 评分、视觉模拟评分法(VAS)评分、类风湿因子(Rheumatoid factor, RF)、晨僵时间^[7]。并记录四组是否有恶心腹泻、发热和皮疹等药物不良反应症状。设置各项评价指标均改善程度在 40%以下为中,各项指标均有改善,评分及时间改善程度在 30%~70%为良,各项指标均有显著改善,评分及时间改善程度在 70%以上为优。

1.5 统计学方法

将本组关节肿胀数、关节压痛数、DAS28 评分、VAS 评分、RF、晨僵时间录入 SPSS 21.0 行数据分析,计数资料行 χ^2 检验或确切概率法,计量资料用($\bar{x} \pm s$)表示,组间比较采用两样本 t 检验,如结果提示 P<0.05,差异存在统计学意义。

2 结果

2.1 对比 MTX 组与 MTX 联合 PDN 组各项指标

MTX 组治疗后关节压痛数、关节肿胀数、VAS 评分、DAS28 评分、晨僵时间和 RF 均明显低于治疗前(P<0.05);MTX+PDN 组治疗后关节压痛数、关节肿胀数、VAS 评分、DAS28 评分、晨僵时间和 RF 均明显低于治疗前(P<0.05);同期治疗后,与 MTX 组相比,MTX+PDN 组的关节压痛数($t=21.239, P<0.001$),关节肿胀数($t=7.348, P<0.001$),VAS 评分($t=12.379, P<0.001$),DAS28 评分($t=5.714, P<0.001$),晨僵时间($t=9.565, P<0.001$)与 RF($t=12.637, P<0.001$)等指标均明显要低,差异均有统计学意义(P<0.001)(表 1)。

表 1 MTX 组与 MTX 联合 PDN 组各项指标比较

Table 1 Comparison of the indexes between MTX group and MTX plus PDN group

Groups		Joint tenderness counts	Swollen joint counts	VAS scores	DAS28 scores	Morning stiffness time(min)	RF(IU/min)
MTX	Prior treatment	4.48± 0.32	2.76± 0.52	55.28± 3.90	5.11± 1.19	120.17± 5.86	495.33± 10.54
	Posttreatment	3.36± 0.20 [°]	1.33± 0.34 [°]	28.20± 4.40 [°]	3.31± 0.74 [°]	57.70± 4.87 [°]	210.70± 11.81 [°]
MTX+PDN	Prior treatment	4.86± 0.28	2.85± 0.41	56.32± 4.00	6.08± 0.98	125.74± 3.98	501.31± 12.36
	Posttreatment	2.28± 0.18 ^{°°}	0.76± 0.23 ^{°°}	17.53± 1.20 ^{°°}	2.21± 0.70 ^{°°}	46.72± 3.63 ^{°°}	170.71± 11.87 ^{°°}

Note: ° compared with prior treatment, P<0.05; °° compared with the MTX group at the same period, P<0.001.

2.2 LEF 组与 LEF 联合 PDN 组患者各项指标比较

LEF 组治疗后关节压痛数、关节肿胀数、VAS 评分、DAS28 评分、晨僵时间和 RF 均明显低于治疗前(P<0.05);LEF+PDN 组治疗后关节压痛数、关节肿胀数、VAS 评分、DAS28 评分、晨僵时间和 RF 明显低于治疗前义(P<0.05)。同期治疗后,与 LEF 组相比,LEF+PDN 组的关节压痛数($t=4.2629, P=0.001$),关节肿胀数($t=6.721, P<0.001$),VAS 评分($t=11.261, P<0.001$),DAS28 评分($t=5.213, P<0.001$),晨僵时间($t=8.912, P<0.001$)与 RF($t=12.091, P<0.001$)等指标均明显要低,差异均有统计学意义(P<0.001)(表 2)。

2.3 MTX+PDN 组与 LEF+PDN 组疗效分析

MTX+PDN 组疗效为中和良的比例与 LEF+PDN 组差异无统计学意义(P>0.05);MTX+PDN 组疗效为优的比例显著高于 LEF+PDN 组,差异有统计学意义($\chi^2=8.139, P=0.004$);MTX+PDN 组总有效率为 53.57%,高于 LEF+PDN 组的 42.86%,差异无统计学意义($\chi^2=2.426, P=0.119$ (表 3)。

2.4 四组患者不良反应对比

服药期间 MTX 产生 2 例恶心呕吐,LEF 产生 1 例恶心呕吐,经过治疗后均无不适,对实验结果无影响。

表 2 LEF 组与 LEF 联合 PDN 组患者各项指标对比

Table 2 Comparison of the indexes between LEF group and LEF plus PDN group

Groups		Joint tenderness counts	Swollen joint counts	VAS score	DAS28 score	Morning stiffness time(min)	RF(IU/min)
LEF	prior treatment	4.51± 1.12	2.55± 0.49	56.32± 4.24	5.61± 0.87	121.30± 7.32	480.30± 10.38
	posttreatment	3.19± 0.91 [°]	1.21± 0.30 [°]	29.86± 3.56 [°]	2.84± 0.73 [°]	52.26± 6.28 [°]	220.51± 9.40 [°]
LEF+PDN	prior treatment	5.01± 1.24	3.02± 0.44	56.27± 5.30	5.56± 0.52	125.38± 8.29	498.48± 8.52
	posttreatment	2.24± 0.75 ^{° °}	0.73± 1.15 ^{° °}	18.48± 4.89 ^{° °}	1.33± 0.44 ^{° °}	43.21± 7.19 ^{° °}	170.53± 7.20 ^{° °}

Note: [°] compared with prior treatment, P<0.05; ^{° °} compared with the LET group at the same period, P<0.001.

表 3 MTX+PDN 组与 LEF+PDN 组疗效比较

Table 3 Comparison of the curative effect between MTX + PDN group and LEF + PDN group

Groups	N	Medium	Good	Excellent	Total effective rate
MTX+PDN	28	13(46.43)	9(32.14)	6(21.43)	15(53.57)
LEF+PDN	28	16(57.14)	10(35.71)	2(7.15)	12(42.86)
χ^2		2.422	0.202	8.139	2.426
P		0.119	0.653	0.004	0.119

3 讨论

RA 为慢性炎症病变的自身免疫疾病,其表现部位包括全身关节,发病率随着年龄增长不断递增,老年发病率为较高,通常早 50 岁左右达到高峰值^[8]。RA 发病过程缓慢,随着天气及机体自身因素而出现发作与缓解的交替现象,对患者的生活及身心健康均造成极大的影响,延治的患者可导致疾病缠绵难愈,严重者可出现关节变形甚至肢体残疾。临床研究对 RA 的发病机制未完全了解,国外研究表明 RA 的结局包括残疾、死亡、经济负担、药物毒发反应和痛苦^[9],药物能够缓解患者疼痛,控制和防止关节受损,现研究不同药物组合对 RA 的治疗效果。

根据实验结果可知 MTX、LEF 对 RA 均有治疗效果,治疗后关节压痛数、关节肿胀数、VAS 评分、DAS28 评分、晨僵时间和 RF 均低于治疗前,差异有统计学意义(P<0.05)。MTX 联合 PDN 组治疗效果与 LEF 联合 PDN 组的疗效均高于纯 MTX 组和纯 LEF 组,差异有统计学意义(P<0.05)。表明 PDN 能对提高 MTX 和 LEF 对 RA 的治疗效果,联合使用更加理想。MTX+PDN 组总有效率为 53.57%,高于 LEF+PDN 组的 42.86%,但差异无统计学意义($\chi^2=2.426$, P=0.119),证明两种药物治疗效果并未有显著差异,但从结果可知 MTX 联合 PDN 组的疗效较 LEF 联合 PDN 组更好一些。在不良反应中,MTX 产生 2 例恶心呕吐,LEF 产生 1 例恶心呕吐,差异并不明显,猜测与例数过少有关。在国内临床试验中,LEF 组不良反应发生率和严重不良反应均显著低于 MTX 组^[10]。

MTX 和 LEF 均属于典型的治疗风湿类药物,其本身并不具备抗炎作用,但对疾病的缓解有一定作用。其中 MTX 为抗风湿药物首选,非甾体类抗炎镇痛药只能够控制患者的疼痛症状,抑制病情发展,但无法根治疾病,且每日服用会引起骨髓抑制,产生毒副作用^[11],国外研究表明长期使用 MTX 会导致淋巴瘤等恶性肿瘤的发生率升高^[12]。LEF 主要通过抑制嘌呤的从头合成途径和酪氨酸激酶的活性发挥作用,对多种自身免疫性疾

病和免疫介导性疾病有确切的疗效和良好的安全性,现运用于类风湿疾病^[13-15]。LEF 治疗 RA 的不良反映较为少见,且症状轻微。PDN 自身对类风湿也有一定治疗效果,作为一种肾上腺皮质激素类药,具有抗炎、抗过敏、抗风湿、免疫抑制作用,作用机理为抗炎作用,但剂量过大会导致严重不良反应,所以通常使用最小有效剂量治疗 RA^[16-18]。临床上将两种药物协同使用,不仅能提高疗效,同时并未提高不良反应的发生率。实验结果表明 MTX 联合 PDN 和 LEF 联合 PDN 药效差异不大,所以临床可根据不同患者对药效敏感度进行选择使用^[19,20]。

综上所述,MTX 联合 PDN 组较纯 MTX 组疗效更好,同时 LEF 联合 PDN 较纯 LEF 组疗效更好,药物联合使用在提高疗效的同时也保证了药效的安全性,但两种组合疗效差异并不明显,临床可根据不同疾病类型选用不同组合药物。

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