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吡非尼酮联合乙酰半胱氨酸治疗 IPF 患者的疗效及机制分析 *

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摘要 目的:探讨吡非尼酮联合乙酰半胱氨酸治疗特发性肺纤维化(idiopathic pulmonary fibrosis, IPF)患者的疗效及可能机制。**方法:**选择 2018 年 1 月至 2020 年 1 月我院收治的 78 例 IPF 患者,根据随机数字表法将其分为观察组(38 例)及对照组(40 例)。对照组患者给予吡非尼酮,观察组给予吡非尼酮联合乙酰半胱氨酸,对比两组患者的治疗效果、治疗前及治疗后 1 d 的肺功能指标、血清肺纤维化指标、肿瘤坏死因子、转移生长因子 β -1 水平的变化及不良反应的发生情况。**结果:**治疗后,与对照组相比,观察组治疗有效率明显升高($P<0.05$)。治疗后,两组弥散量、用力肺活量、第一秒用力呼气容积均较治疗前明显升高,且观察组以上指标均明显高于对照组高($P<0.05$)。治疗后,两组的透明质酸、层粘连蛋白、III型胶原、III型前胶原、尿素氮、血清肿瘤坏死因子、转移生长因子 β -1 及基质金属蛋白酶-9 水平均较治疗前明显降低,观察组以上指标均明显低于对照组低($P<0.05$)。观察组不良反应发生率为 26.32%,对照组为 30.00%,组间对比差异无统计学意义($P>0.05$)。**结论:**与单独应用吡非尼酮相比,吡非尼酮联合乙酰半胱氨酸可提高 IPF 患者的治疗效果,可能与其可改善患者的炎症因子水平有关。

关键词:吡非尼酮;乙酰半胱氨酸;特发性肺纤维化(IPF);疗效;作用机制

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Efficacy and Mechanism of Pirfenidone Combined with Acetylcysteine in the Treatment of Patients with IPF*

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ABSTRACT Objective: To investigate the efficacy and possible mechanism of pirfenidone combined with acetylcysteine in the treatment of patients with idiopathic pulmonary fibrosis (IPF). **Methods:** Seventy-eight IPF patients from January 2018 to January 2020 in our hospital were chosen and divided into the observation group (38 cases) and control group (40 cases) according to the random number table method. The control group was given pirfenidone, and the observation group was given pirfenidone combined with acetylcysteine. The treatment efficacy, lung function indexes, serum pulmonary fibrosis indexes, serum tumor necrosis factors, metastatic growth factor β -1, cytokine level and adverse reactions incidence were compared between two groups before and after treatment. **Results:** After treatment, compared with the control group, the treatment efficiency of observation group was significantly increased ($P<0.05$), the diffusion volume, forced vital capacity, and forced expiratory volume in the first second of the two groups were significantly higher than before treatment, and the above indicators in the observation group were significantly higher than those in the control group($P<0.05$). After treatment, the levels of hyaluronic acid, laminin, type III collagen, type III procollagen, urea nitrogen, serum tumor necrosis factor, metastatic growth factor β -1 and matrix metalloproteinase-9 of the two groups were significantly lower than before treatment, and the above indicators in the observation group was significantly higher than that of the control group ($P<0.05$). The incidence of adverse reactions was 26.32% in the observation group, and 30.00% in the control group. There was no statistically significant difference between the groups ($P>0.05$). **Conclusion:** Compared with pirfenidone alone, pirfenidone combined with acetylcysteine could improve the treatment effect of IPF patients, which may be related to the improvement of the level of inflammatory factors in patients.

Key words: Pirfenidone; Acetylcysteine; Idiopathic pulmonary fibrosis (IPF); Curative effect; Mechanism

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前言

特发性肺纤维化(IPF)多发发于中老年男性患者中,是一种慢性进展性纤维化间质性肺炎^[1,2],临床表现为干咳、呼吸困难

等症状,随着疾病进展,晚期会出现双下肺爆裂音及杵状指。氧化/抗氧化失衡在纤维化中起到关键作用,氧化应激会使得患者上皮细胞坏死,多种纤维化细胞因子表达上调,抗蛋白酶与肺组织蛋白酶失衡,从而使得患者大量细胞外基质出现沉积,

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出现了肺纤维化症状^[3-5]。近年来,随着环境污染的加重,粉尘暴露的增加,IPF 发病率逐渐升高,而该疾病早期其胸闷气短症状容易被忽视,导致多数患者就诊时疾病已较重,同时随着疾病进展,患者会进一步出现深静脉血栓、肺动脉高压、右心衰竭,对患者的生存质量产生严重影响,因此需给予积极治疗^[6-8]。

目前,IPF 常用的治疗方法为肺移植、免疫抑制剂及糖皮质激素疗法^[9,10]。吡非尼酮是一种常用的抗纤维化、抗炎、抗氧化药物,研究显示^[11,12]其可延缓肺纤维化患者的肺功能降低,延长患者的无进展生存期。乙酰半胱氨酸一种化痰药,具有抗氧化、抗炎等作用,也可用于 IPF 的治疗^[13,14],目前二者联合应用于 IPF 研究的研究较多,而机制分析方面的研究较少。本研究主要探讨了吡非尼酮联合乙酰半胱氨酸对 IPF 患者的疗效及作用机制,以期 IPF 选择合适的治疗方法提供临床依据。

1 资料与方法

表 1 两组患者一般资料对比

Table 1 Comparison of the general data between two groups

Groups	n	Gender		Average age (Year)	Smoking		Average duration(Year)
		Male	Female		Yes	No	
Observation group	38	34	4	65.81± 8.76	28	10	3.58± 0.89
Control group	40	3	5	66.45± 9.23	32	8	3.69± 0.95

1.2 治疗方法

本研究所有患者均给予对症支持治疗、抗感染治疗,若患者出现咳嗽、气短症状,对照组口服吡非尼酮胶囊(购自北京康蒂尼药业有限公司,批准文号:国药准字:H20133375,规格为 0.2 g/片),每次 0.2 mg,3 次/日,之后第 2 w 每次增加 0.2 mg,两周内每次服药剂量增加至 0.6 mg;观察组患者在对照组患者基础上加用乙酰半胱氨酸片(购自浙江金华康恩贝生物制药有限公司,批准文号:国药准字:H20057334,规格为 600 μg/片),每次 600 μg,每天 3 次,两组均治疗 6 个月。

1.3 分析指标

(1)疗效评价,疗效标准参照《特发性肺间质纤维化诊治循环指南》^[15],治疗后患者活动后无呼吸苦难,咳嗽显著改善,双肺、发绀无高调爆裂音为显效,治疗后患者在轻微活动下有发绀情况出现,安静状态下呼吸困哪,有阵发性咳嗽症状未有效,治疗后患者的临床症状无改善甚至加重为无效;(2)治疗前及治疗后 1 d,采用肺功能测定仪检测两组患者的肺功能指标,包括

1.1 临床资料

选择我院 2018 年 1 月至 2020 年 1 月收治的 78 例 IPF 患者,患者均符合《特发性肺间质纤维化诊断与治疗指南(草案)》中关于 IPF 的诊断标准^[15],病程≥ 3 个月,同时患者的治疗依从性较好,可完成随访;排除标准:排除近期内使用皮质类固醇药物者、近期使用免疫抑制剂者、凝血功能障碍者、有肺部手术者、患有精神疾病者、合并严重肝肾功能障碍者及对本研究所用药物过敏者等。78 例患者中,男 69 例,女 9 例,年龄范围为 49~79 岁,平均年龄为 66.12± 8.94 岁,吸烟者 60 例,病程范围为 1~5 年,平均病程为 3.67± 0.89 年。根据随机数字表法将患者分为两组,对照组共 40 例,观察组共 38 例。两组一般资料(性别、年龄、是否吸烟、病程)对比差异无统计学意义($P>0.05$),见表 1,具有可比性。本研究所有患者知情同意,且符合医学伦理。

弥散量、用力肺活量及第一秒用力呼气容积;(3)采用放射免疫法检测两组患者治疗前后的血清肺纤维化指标,包括透明质酸、层粘蛋白、III 型胶原、III 型前胶原、尿素氮水平;(4)采用 ELISA 法检测两组患者治疗前后的血清肿瘤坏死因子、转移生长因子 β -1 水平及基质金属蛋白酶-9 水平;(5)对比两组肝酶升高、胃肠道症状、光过敏、皮肤损伤等不良反应发生率。

1.4 统计学方法

采用 SPSS 23.0 软件进行统计学分析,计数资料用百分数(%)表示,组间比较采用卡方检验分析,计量资料用 $\bar{x} \pm s$ 表示,组间比较采用 t 检验,以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 对比两组临床疗效的比较

与对照组相比,观察组治疗后总有效率明显升高(92.11 % vs. 70 %, $P<0.05$),见表 2。

表 2 两组患者的治疗效果比较[例(%)]

Table 2 Comparison of the efficacy between two groups[n(%)]

Groups	n	Significant efficacy	Efficacy	Invalid	Efficacy rate
Observation group	38	19	16	3	35(92.11)*
Control group	40	14	14	12	28(70.00)

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

2.2 两组治疗前后 1 d 的弥散量、用力肺活量、第一秒用力呼气容积水平的比较

治疗前,两组患者的弥散量、用力肺活量、第一秒用力呼

气容积对比差异无统计学意义($P>0.05$);治疗后,两组弥散量、用力肺活量、第一秒用力呼气容积均较治疗前明显升高,且观察组以上指标均明显高于对照组($P<0.05$),见表 3。

表 3 两组治疗前及治疗后 1 d 的肺功能指标的比较($\bar{x} \pm s$)

Table 3 Comparison of the lung function index before and at 1 d after treatment between two groups($\bar{x} \pm s$)

Groups	Time	Dispersion amount(%)	Hard lung capacity(L)	Forced expiratory volume in the first second(L)
Observation group(n=38)	Before treatment	61.25± 4.15**	2.43± 0.15**	1.54± 0.31**
	After treatment	76.89± 5.16	2.90± 0.29	2.35± 0.52
Control group(n=40)	Before treatment	61.30± 4.36 [#]	2.46± 0.19 [#]	1.53± 0.28 [#]
	After treatment	72.85± 5.66	2.69± 0.25	2.06± 0.48

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

2.3 两组治疗前后的肺纤维化指标的比较

治疗前,两组患者的透明质酸、层粘蛋白、III型胶原、III型前胶原、尿素氮水平均较治疗前明显降低,且观察组以上指标均明显低于对照组前胶原、尿素氮水平对比差异无统计学意义($P>0.05$);治疗后,两组透明质酸、层粘蛋白、III型胶原、III型前胶原、尿素氮水平对比差异均无统计学意义($P>0.05$),见表 4。

表 4 两组患者治疗前后的血清肺纤维化指标的比较($\bar{x} \pm s$)

Table 4 Comparison of the Serum pulmonary fibrosis index before and after treatment between two groups ($\bar{x} \pm s$)

Groups	Time	Hyaluronic acid (μg/L)	Mucin layer(μg/L)	Collagen type III (mg/L)	Before collagen type III(μg/L)	Urea nitrogen level (mmol/L)
Observation group (n=38)	Before treatment	135.71± 29.78	147.89± 28.56	106.45± 26.79	106.78± 26.15	15.41± 3.12
	After treatment	90.46± 15.63**	112.89± 31.46**	84.23± 14.23**	84.99± 21.46**	10.78± 2.15**
Control group (n=40)	Before treatment	135.41± 28.44	148.02± 29.05	107.02± 27.16	107.81± 30.25	15.69± 3.56
	After treatment	120.12± 18.74 [#]	131.79± 28.76 [#]	90.56± 16.89 [#]	92.16± 22.43 [#]	12.89± 2.78 [#]

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

2.4 两组患者治疗前后的血清肿瘤坏死因子、转移生长因子 β-1 及基质金属蛋白酶 -9 水平的比较

治疗前,两组患者的血清肿瘤坏死因子、转移生长因子 β-1 及基质金属蛋白酶 -9 水平对比差异均无统计学意义($P>0.05$);治疗后,两组以上指标均较治疗前明显降低,且观察组以上指标均明显低于对照组($P<0.05$),见表 5。

表 5 两组患者治疗前后的血清肿瘤坏死因子、转移生长因子 β-1 及基质金属蛋白酶 -9 水平的比较($\bar{x} \pm s$)

Table 5 Comparison of the Tumor necrosis factor, transfer growth factorβ-1 and Matrix metalloproteinase -9 level before and after treatment between two groups($\bar{x} \pm s$)

Groups	n	Tumor necrosis factor(pg/L)		Transfer growth factorβ-1(pg/L)		Matrix metalloproteinase -9(ng/mL)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Observation group	38	39.51± 5.68	26.78± 4.89**	19.52± 4.25	12.16± 2.89**	448.71± 48.72	175.41± 31.66
Control group	40	39.87± 6.02	32.45± 5.02 [#]	19.83± 4.56	16.99± 3.05 [#]	448.12± 50.13	251.77± 45.23

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

2.5 两组治疗期间的不良反应发生情况的对比

观察组不良反应发生率为 26.32%, 对照组为 30.00%, 组

间对比差异无统计学意义($P>0.05$),见表 6。

表 6 两组治疗期间的不良反应发生情况[例(%)]

Table 6 Comparison of the incidence of adverse reactions between two groups[n(%)]

Groups	n	Elevated liver enzymes	Gastrointestinal symptoms	Light allergic	Skin lesions	Total efficacy
Observation group	38	4	5	1	0	10(26.32)*
Control group	40	4	6	1	1	12(30.00)

3 讨论

IPF 的病理发展与患者的凝血级联反应有一定相关性,其

肺泡上皮出现损伤,患者的机体血管血液成分会出现外渗,导致止血机制出现重建^[17-19],而机体内的纤溶酶原激活因子抑制因子与组织因子在肺泡上皮细胞中出现过度表达,从而进一步

诱发凝血级联反应,导致肿瘤坏死因子及转移生长因子 β -1 等因子表达上升,出现肺泡壁水中及上皮细胞坏死,降低肺顺应性,减少肺总量,限制性的弥散功能障碍及通气功能障碍,该疾病的 5 年生存率低于 50%,其病情发展具有不可逆性,除肺移植外治疗均不能对患者的病情进展进行逆转,药物治疗的目的是延缓病情进展^[20-22],因为 IPF 的疾病发病原因与炎症反应、凝血功能密切相关,因此其治疗需以抗凝、控制炎症反应为主,同时降低肺泡上皮细胞损伤、延缓成纤维细胞异常增殖肺纤维重塑阶段^[23,24]。

吡非尼酮是抗纤维化的小分子化合物,具有吸收迅速、口服方便等优点,其可通过降低转化生长因子- β 水平、纤维细胞生长因子水平来降低胶原 III mRNA 的表达,抑制成纤维细胞增殖,最终达到减少细胞外基质异常沉积,起到抗纤维化的作用,同时其具有一定的抗氧化、抗炎作用^[25,26]。在日本进行的吡非尼酮 52 周 III 期临床试验中,与安慰剂相比,吡非尼酮可显著减少 IPF 患者的肺活量下降速度(-160 mL/年 vs -90 mL/年)^[27]。因此,在吡非尼酮的多中心、多项国际权威、随机对照研究中,吡非尼酮已成为 IPF 推荐用药之一。乙酰半胱氨酸是一种强效的抗氧化剂,有研究显示^[28]IPF、慢性阻塞性肺病等于氧化应激反应密切相关,而乙酰半胱氨酸可在患者体内转化为还原型谷胱甘肽,对细胞膜中的巯基免受氧化剂产生破坏作用,对白三烯、肿瘤坏死因子等释放产生抑制作用;同时,基质金属蛋白-9 可促进患者的气道平滑肌内细胞外基质的降解,对炎性细胞趋化聚集产生诱导作用,从而加重肺损伤程度,进一步加大细胞外基质沉积及组织异常修复,增加肺纤维化范围。

本研究结果显示与对照组相比,观察组治疗后弥散量、用力肺活量、第一秒用力呼气容积均明显高于对照组,而透明质酸、层粘蛋白、III 型胶原、III 型前胶原、尿素氮水平、肿瘤坏死因子、转移生长因子 β -1 及基质金属蛋白-9 水平明显低于对照组,与国内学者赵承杰^[29]等学者的研究类似,表明乙酰半胱氨酸联合吡非尼酮可显著改善 IPF 患者肺功能,降低 MMP 的含量,具有显著的抗纤维化的作用。国外学者还没有乙酰半胱氨酸联合吡非尼酮治疗 IPF,主要联合酪氨酸激酶抑制剂 nintedanib 治疗 TPF 且探究其治疗机制^[30]。本研究结果表明吡非尼酮联合乙酰半胱氨酸可较单独应用吡非尼酮可更显著,提示吡非尼酮基础上加入乙酰半胱氨酸后,可显著降低患者血清中的肿瘤坏死因子、转移生长因子 β -1 及基质金属蛋白酶-9 水平,通过以上因子水平的降低,改善 IPF 患者的肺纤维化情况、肺功能,提高治疗效果^[31,32]。此外,在吡非尼酮基础上加用乙酰半胱氨酸,不增加患者并发症发生率,提示用药安全。

综上所述,与单独应用吡非尼酮相比,吡非尼酮联合乙酰半胱氨酸可提高 IPF 患者的治疗效果,可能与其可改善患者的炎症因子水平有关。但本研究仍存在一定不足,样本量不足,未分析远期疗效,有待进一步扩大样本量、延长随访时间进行深入分析。

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