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利伐沙班与低分子肝素对老年 AECOPD 患者症状缓解、 血气分析指标及凝血功能的影响 *

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摘要 目的:探讨利伐沙班与低分子肝素对老年慢性阻塞性肺疾病急性加重期(AECOPD)患者症状缓解、血气分析指标及凝血功能的影响。**方法:**选取 2016 年 8 月~2019 年 11 月期间我院收治的老年 AECOPD 患者 72 例,按照抽签法分为对照组(n=36,低分子肝素治疗)和研究组(n=36,利伐沙班治疗),对比两组疗效、症状缓解、血气分析指标及凝血功能,记录治疗期间不良反应情况。**结果:**研究组治疗 10d 后总有效率较对照组高($P<0.05$)。两组咳嗽、咳痰、发热、呼吸困难症状缓解时间对比差异无统计学意义($P>0.05$)。治疗 10d 后两组氧分压(PaO_2)、氧饱和度(SaO_2)升高,二氧化碳分压(PaCO_2)降低($P<0.05$),研究组治疗 10d 后 PaO_2 、 SaO_2 较对照组高, PaCO_2 低于对照组($P<0.05$)。治疗 10d 后两组纤维蛋白原(Fib)升高,D-二聚体(D-D)、活化部分凝血活酶时间(APTT)、血浆凝血酶原时间(PT)、凝血酶时间(TT)均降低($P<0.05$),治疗 10d 后研究组 D-D 低于对照组($P<0.05$),治疗 10d 后两组 Fib、APTT、TT、PT 组间比较无差异($P>0.05$)。两组不良反应发生率比较无差异($P>0.05$)。**结论:**老年 AECOPD 患者采用利伐沙班与低分子肝素治疗,均可改善患者临床症状且安全性较好,但采用利伐沙班治疗者疗效更好,血气分析指标及凝血功能改善更佳。

关键词:利伐沙班;低分子肝素;老年;慢性阻塞性肺疾病急性加重期;症状缓解;血气分析;凝血功能

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Effects of Rivaroxaban and Low Molecular Weight Heparin on Symptom Relief, Blood Gas Analysis Indexes and Coagulation Function in Elderly Patients with AECOPD*

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ABSTRACT Objective: To investigate the effects of rivaroxaban and low molecular weight heparin on the symptom relief, blood gas analysis indexes and coagulation function in elderly patients with acute exacerbation of chronic obstructive pulmonary disease (AECOPD). **Methods:** A total of 72 elderly patients with AECOPD admitted to our hospital from August 2016 to November 2019 were selected, and were randomly divided into control group (n=36, low molecular weight heparin treatment) and study group (n=36, rivaroxaban treatment) by lottery. The efficacy, symptom relief, blood gas analysis index and coagulation function of the two groups were compared, and adverse reactions during the treatment were recorded. **Results:** The total effective rate of the study group 10 days after treatment was higher than the control group ($P<0.05$). There were no significant differences in the relief time of cough, sputum, fever and dyspnea between the two groups ($P>0.05$). 10 days after treatment, the oxygen partial pressure (PaO_2), oxygen saturation (SaO_2) of the two groups increased, while the partial pressure of carbon dioxide (PaCO_2) of the two groups decreased ($P<0.05$). 10 days after treatment, PaO_2 and SaO_2 of the study group were higher than the control group, while PaCO_2 was lower than those of the control group ($P<0.05$). 10 days after treatment, fibrinogen (Fib) of the two groups increased, D-Dimer (D-D), activated partial thromboplastin time (APTT), plasma prothrombin time (PT) and thrombin time (TT) decreased ($P<0.05$). 10 days after treatment, D-D of the study group was lower than the control group ($P<0.05$). There were no significant differences between Fib, APTT, TT and PT of the two groups ($P>0.05$). There was no significant difference in the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** Elderly patients with AECOPD treated with rivaroxaban and low molecular weight heparin can improved their clinical symptoms and showed better safety, but those treated with rivaroxaban had better efficacy, and better improvement in blood gas analysis indicators and coagulation function.

Key words: Rivaroxaban; Low molecular weight heparin; Elderly; Acute exacerbation of chronic obstructive pulmonary disease;

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前言

慢性阻塞性肺疾病急性加重期(AECOPD)是呼吸系统的常见疾病,典型表现是持续进展,气流受限不完全可逆,严重影响患者生命质量^[1,2]。据统计^[3],截止到目前,AECOPD在全球肺部疾病死因中居第4位。现临床有关AECOPD的治疗尚无统一方案,多以抗感染、扩张支气管、止咳及化痰等治疗为主,低分子肝素具有抗凝血、抗血栓、保护动脉内皮等多种药理作用^[4,5]。但该药物在临床使用中常伴有局部疼痛、皮肤瘀点和皮下血肿等不良反应,临床应用受限^[6]。AECOPD患者由于缺氧、感染等原因,凝血功能可出现异常,导致AECOPD患者发生血栓的概率将显著增加,加剧病情恶化^[7,8]。利伐沙班是一种新型口服Xa因子直接抑制剂,具有较好的抗凝效果^[9]。本研究通过探讨利伐沙班与低分子肝素对老年AECOPD患者症状缓解、血气分析指标及凝血功能的影响,以期为临床治疗该病提供参考。

表1 两组一般资料比较

Table 1 Comparison of general data between the two groups

Groups	Male/female	Age(years)	Disease course(years)	Body mass index(kg/m ²)
Control group(n=36)	21/15	69.38±3.52	3.19±0.62	23.74±0.83
Study group(n=36)	23/13	69.51±4.16	3.24±0.69	23.92±0.99
χ^2/t	0.234	0.143	0.323	0.836
P	0.649	0.887	0.747	0.406

1.2 方法

入院后均给予常规对症治疗,如抗感染、吸氧、止咳、化痰、维持水电解质平衡及营养支持等,对照组给予低分子肝素钙注射液(河北常山生化药业股份有限公司,国药准字H20063909,规格:0.4 mL: 4100AXa单位)治疗,4100单位低分子肝素钙注射液腹部皮下注射,1次/d,连续治疗10d。研究组给予利伐沙班(拜耳医药公司,国药准字J20180076,规格:10 mg)治疗,10 mg/次,口服,1次/d。两组均治疗10d。

1.3 观察指标

(1)观察两组治疗10d后的临床总有效率。疗效标准如下:临床控制:咳嗽、咳痰等临床表现恢复为急性加重前的状态。减轻:咳嗽、咳痰等临床表现有所改善,但不及急性加重前的状态。无效:肺部哮鸣音和咳、痰、喘在1个月内仍不及急性加重前的状态。总有效率=临床控制率+减轻率^[10]。(2)于治疗前、治疗10d后采用SYSMEX N9000型血气分析仪检测氧分压(PaO₂)、氧饱和度(SaO₂)、二氧化碳分压(PaCO₂)。(3)采用治疗前、治疗10d后的清晨空腹静脉血5 mL,采用西森美康5100型全自动凝血分析仪检测凝血功能指标:纤维蛋白原(Fib)、D-二聚体(D-D)、活化部分凝血活酶时间(APTT)、血浆凝血酶原时间(PT)、凝血酶时间(TT)。(4)记录两组不良反应。(5)记录两组患者咳嗽、咳痰、发热、呼吸困难症状缓解时间。

1.4 统计学方法

采用SPSS20.0进行数据分析。计数资料以率表示,行卡方

1 资料与方法

1.1 一般资料

选取2016年8月~2019年11月期间我院收治的老年AECOPD患者72例,纳入标准:(1)AECOPD诊断标准参考《慢性阻塞性肺疾病诊治指南》^[10];(2)均属于急性加重期,短期内出现喘息、咳嗽、咳痰加重的情况,痰液呈脓性;(3)患者及其家属知情本研究且签署了同意书;(4)年龄≥60岁;(5)对本次研究用药无禁忌者。排除标准:(1)近期内服用过抗凝药物者;(2)合并有自身免疫性疾病者;(3)合并精神疾病不能配合本次研究者;(4)患有严重心脑血管等原发性疾病者;(5)合并感染性疾病、恶性肿瘤者;(6)合并器质性病变和严重的造血系统疾病者;(7)依从性较差,不配合治疗者。本次研究经医院伦理学委员会批准进行。按照抽签法分为对照组(n=36)和研究组(n=36),两组一般资料行组间比较,无差异(P>0.05),见表1。

检验。计量资料均为正态资料,以($\bar{x} \pm s$)表示,行t检验。 $\alpha=0.05$ 为检验标准。

2 结果

2.1 两组疗效比较

治疗10d后,研究组总有效率明显高于对照组(P<0.05),见表2。

2.2 两组症状缓解时间比较

两组咳嗽、咳痰、发热、呼吸困难症状缓解时间对比差异无统计学意义(P>0.05),见表3。

2.3 两组血气分析指标比较

治疗前两组血气分析指标比较无差异(P>0.05),两组治疗10d后PaO₂、SaO₂升高,PaCO₂降低(P<0.05),治疗10d后研究组PaO₂、SaO₂较对照组高,PaCO₂较对照组低(P<0.05),详见表4。

2.4 两组凝血功能指标比较

治疗前两组凝血功能指标比较无差异(P>0.05),治疗10d后两组Fib升高,D-D、APTT、TT、PT均降低(P<0.05),治疗10d后研究组D-D低于对照组(P<0.05),治疗10d后两组Fib、APTT、TT、PT组间比较差异无统计学意义(P>0.05),见表5。

2.5 两组不良反应比较

两组不良反应发生率比较无差异(P>0.05),见表6。

表 2 两组疗效比较【例(%)】

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

Groups	Clinical control	Alleviate	Invalid	Total effective rate
Control group(n=36)	6(16.67)	18(50.00)	12(33.33)	24(66.67)
Study group(n=36)	9(25.00)	24(66.67)	3(8.33)	33(91.67)
χ^2				6.821
<i>P</i>				0.009

表 3 两组症状缓解时间比较($\bar{x} \pm s, d$)

Table 3 Comparison of symptom relief time between the two groups($\bar{x} \pm s, d$)

Groups	Cough	Sputum	Fever	Dyspnea relieved
Control group(n=36)	5.52±1.13	6.76±0.93	4.22±0.84	3.12±0.65
Study group(n=36)	5.55±1.04	6.53±0.72	4.19±0.76	3.29±0.54
<i>t</i>	0.117	1.173	0.159	1.207
<i>P</i>	0.907	0.245	0.874	0.231

表 4 两组血气分析指标比较($\bar{x} \pm s$)

Table 4 Comparison of blood gas analysis indicators between the two groups($\bar{x} \pm s$)

Groups	PaO ₂ (mmHg)		SaO ₂ (%)		PaCO ₂ (mmHg)	
	Before treatment	10 days after treatment	Before treatment	10 days after treatment	Before treatment	10 days after treatment
Control group(n=36)	61.62±5.91	69.53±7.16*	81.34±7.39	89.47±6.25*	69.86±6.65	61.80±6.67*
Study group(n=36)	61.29±6.87	78.21±6.82*	80.91±8.26	96.93±7.04*	69.27±7.49	52.34±7.19*
<i>t</i>	0.218	5.267	0.233	4.755	0.353	5.787
<i>P</i>	0.828	0.000	0.817	0.000	0.725	0.000

Note: Comparison with before treatment, **P*<0.05.

表 5 两组凝血功能指标比较($\bar{x} \pm s$)

Table 5 Comparison of coagulation function indexes between the two groups($\bar{x} \pm s$)

Groups	Fib(g/L)		D-D(μg/mL)		APTT(s)		TT(s)		PT(s)	
	Before treatment	10 days after treatment	Before treatment	10 days after treatment	Before treatment	10 days after treatment	Before treatment	10 days after treatment	Before treatment	10 days after treatment
Control group(n=36)	2.73±0.41	4.07±0.52*	3.56±0.35	2.43±0.28*	44.90±5.13	32.13±3.14*	18.29±3.47	13.83±2.24*	15.03±2.68	10.27±2.01*
Study group(n=36)	2.76±0.37	4.09±0.46*	3.51±0.39	1.98±0.36*	44.72±6.25	32.08±4.13*	18.32±2.52	13.62±2.51*	14.96±2.25	10.19±2.29*
<i>t</i>	0.326	0.173	0.572	12.418	0.134	0.058	0.042	0.375	0.120	0.158
<i>P</i>	0.745	0.863	0.569	0.000	0.894	0.954	0.967	0.709	0.905	0.875

Note: Compared with before treatment, **P*<0.05.

表 6 不良反应发生率比较【例(%)】

Table 6 Comparison of adverse reactions [n(%)]

Groups	Gastrointestinal discomfort	Nausea and vomiting	Rash	Insomnia	Total incidence rate
Control group(n=36)	2(5.56)	1(2.78)	1(2.78)	1(2.78)	5(13.89)
Study group(n=36)	2(5.56)	2(5.56)	1(2.78)	2(5.56)	7(19.44)
χ^2					0.400
<i>P</i>					0.527

3 讨论

近年来随着环境污染的加重,人们生活方式的改变,AECOPD的发病率逐年增高,近9年来AECOPD的发病率已经上升了将近50%^[12]。AECOPD患者机体长期处于低氧状态,为了适应长期的缺氧状态,会增加红细胞,而红细胞受缺氧的影响,能量代谢方式发生改变,聚集能力增加,顺应性和变形能力降低,导致全血黏稠度增高^[13,14]。同时长期的低氧还可引起血管内皮细胞受损,胶原组织暴露,激活凝血反应,血液呈高凝状态或肺微血栓形成^[15,16]。而老年AECOPD患者在临床并不少见,我国40岁以上人群中AECOPD发病率已高达9.9%~12.0%^[17]。老年患者多伴有高血压、高血脂和糖尿病等基础性疾病,长期的血液高凝或微血栓可引起动脉粥样硬化,增加心血管疾病的发生风险^[18,19]。既往就有研究证实^[20],凝血状态异常和血栓形成可加速AECOPD进展,加速肺动脉高压形成。因此,针对AECOPD的治疗,仅进行常规的对症支持治疗,虽对病情控制有一定的作用,但远期治疗效果存在明显的不足。

低分子肝素钙属于一种新型抗凝血酶依赖性药物,其抗凝的具体机制为与抗凝血酶结合从而抑制凝血酶的活性^[21,22]。既往研究指出^[23],AECOPD患者在常规治疗基础上联合低分子肝素钙治疗,疗效肯定,且相对安全,肯定了低分子肝素钙在AECOPD治疗中的应用成效与价值。但由于老年患者体质特殊,长期应用低分子肝素钙的效果并不十分理想。故本研究尝试采用利伐沙班治疗老年AECOPD患者,利伐沙班是噁烷酮类选择性Xa因子抑制剂,对Xa因子选择性较高,且治疗窗宽,用药后无需进行常规检测,与药物、食物相互作用小,使用相对安全^[24,25]。研究结果显示,利伐沙班与低分子肝素治疗者的症状缓解更快,疗效优于单用低分子肝素钙治疗。利伐沙班进入人体后可选择性地阻断Xa因子的活性位点,通过外源性、内源性等多种途径活化X因子为Xa因子,参与着机体的凝血级联反应,有效阻止AECOPD的疾病进展^[26]。AECOPD患者由于细胞因子大量释放,肺损伤加剧,导致肺功能呈进行性下降^[27]。本研究中利伐沙班与低分子肝素治疗均可有效改善机体血气分析指标,但利伐沙班治疗者的改善效果更佳,分析其原因,利伐沙班可竞争性结合P-选择素和L-选择素,组织白细胞黏附活化,调节炎症级联反应,发挥良好的抗炎效果,从而减轻炎症对肺组织的损伤,保护肺功能,维持良好的肺通气^[28],加上利伐沙班除抗凝以外还具有其他的药理活性,利伐沙班可增加外周组织对氧的摄取及利用能力,改善微循环,减轻气道压力,阻止血管平滑肌增生,降低肺动脉高压,从而改善机体低氧状态和肺通气^[29]。D-D是由交联纤维蛋白产生的可溶性降解产物,正常人体血中含量很低,当机体存在血管内形成活化的血栓时和纤维溶解时则明显增高。Fib是血小板凝聚的重要递质,可影响血液的凝滞度。APTT、PT、TT均是临床反映凝血功能的常见指标,其数值升高预示着机体凝血功能障碍。本研究中治疗10d后研究组D-D低于对照组,提示利伐沙班改善机体凝血功能的效果略优于低分子肝素钙,可能是因为低分子肝素不能直接对Xa因子产生作用,需与抗凝血酶III结合后才能产生抗Xa因子的活性。而利伐沙班可直接拮抗游离和结合的Xa因子,克服了低分子肝素需长期服药以维持疗效,出血风险大,且需要

密切监测凝血功能指标等的局限性^[30]。另利伐沙班治疗者较低分子肝素治疗者并未增加不良反应发生率,可见其安全性较好,取决于利伐沙班具有口服吸收快、生物利用度高、受体重、性别、进食和药物的影响小等优势。

综上所述,老年AECOPD患者采用利伐沙班与低分子肝素治疗,均可改善患者临床症状且安全性较好,但采用利伐沙班治疗者的疗效更好,血气分析指标及凝血功能改善更佳。

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