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利伐沙班用于急性肺栓塞的抗凝效果及对血清 Hcy、BNP、TnI 与 D-D 水平的影响 *

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摘要 目的:探讨利伐沙班用于急性肺栓塞的抗凝效果及对血清脑钠肽(Brain natriuretic peptide, BNP)、肌钙蛋白 I (Troponin I, TnI)、D-二聚体(D-Dimer, D-D)、同型半胱氨酸(homocysteine, Hcy)水平的影响。**方法:**选择 2014 年 2 月至 2017 年 12 月在我院进行治疗的(高)中危组急性肺栓塞患者 106 例,并将其随机分为观察组和对照组。对照组皮下注射低分子肝素钙搭配华法林治疗,观察组予以利伐沙班治疗,观察和比较两组患者的临床疗效、治疗前后血清 BNP、TnI、D-D、Hcy 水平的变化及不良反应的发生情况。**结果:**治疗后,观察组患者总有效率为 94.37%,显著高于对照组(42.10%, $P<0.05$);观察组患者血清 BNP、TnI、D-D、Hcy 及肺动脉收缩压水平均显著低于对照组($P<0.05$),而动脉收缩压、动脉血氧分压水平较对照组水平显著升高($P<0.05$)。**结论:**利伐沙班应用于治疗急性肺栓塞的抗凝效果显著优于低分子肝素钙搭配华法林治疗,其可有效降低患者血清 BNP、TnI、D-D、Hcy 水平以及肺动脉收缩压。

关键词:利伐沙班;急性肺栓塞;抗凝;同型半胱氨酸;脑钠肽;肌钙蛋白;D-二聚体

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The Anticoagulant Effect of Rivaroxaban on Acute Pulmonary Embolism and its Effects on the Serum Hcy, BNP, TnI and D-D Levels*

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ABSTRACT Objective: To study the anticoagulant effect of rivaroxaban on the acute pulmonary embolism and its effects on the serum Hcy, BNP, TnI and D-D levels. **Methods:** 106 patients with acute pulmonary embolism who were treated from February 2014 to December 2016 were selected as the research objects. The patients were randomly divided into the observation group and the control group, the control group was subcutaneously injected with low molecular heparin calcium, and the observation group was combined with rivaroxaban on the basis of control group. The changes of serum levels of BNP, TnI, D-D, Hcy before and after treatment and incidence of adverse events were compared between two groups. **Results:** After treatment, the total effective rate was 94.37% in the observation group, which was significantly higher than that of the control group (42.10%, $P<0.05$); the serum BNP, TnI, DD, Hcy and systolic blood pressure levels in the observation group were significantly lower than those in the control group ($P<0.05$), while the levels of arterial systolic and arterial oxygen pressure were significantly higher than those in the control group ($P<0.05$). **Conclusion:** The anticoagulant effect of rivaroxaban is significantly better than low molecular heparin calcium combined with warfarin in the treatment of acute pulmonary embolism, which can effectively reduce the serum BNP, TnI, d-d, Hcy levels and pulmonary artery systolic pressure of patients.

Key words: Rivaroxaban; Acute pulmonary embolism; Anticoagulation; Homocysteine; Brain natriuretic peptide; Troponin; D-dimer

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前言

急性肺栓塞由多种原因导致,发于 40-70 岁中老年人群,

致死率极高,仅次于冠心病,且目前国内外无统一及规范的治疗方法^[1]。急性肺栓塞患者的临床症状主要表现为血流动力学水平波动较大、血压低、胸痛等^[2,3]。研究表明脑钠肽(BNP)、心肌

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肌钙蛋白 I (TnI)、D-二聚体(D-D)、血同型半胱氨酸(Hcy)等标志物水平的变化有助于患者进行正确的早期诊断,为临床治疗提供重要依据^[4,5]。

目前,我国临床针对低危组(及低中危)常用低分子肝素等药物抗凝治疗,高危组予溶栓治疗,但对高中危后期多次回访调查结果显示该药物治疗效果不够理想,不良反应发生率及死亡率均较高。研究表明高中危患者采用利伐沙班治疗效果明显较传统治疗方法(低分子肝素搭配华法林抗凝),更适用于目前治疗的需要^[6,7]。因此,本研究主要探讨了利伐沙班用于急性肺栓塞(高中危组)的抗凝效果及对患者血清 Hcy、BNP、TnI 与 D-D 水平的影响,结果报道如下:

1 材料与方法

1.1 一般资料

表 1 两组一般临床资料的对比($\bar{x} \pm s$)

Table 1 Comparison of the general information between the two groups($\bar{x} \pm s$)

Groups	n	M/F	Age (years)	Weight (kg/m ²)	Hypertension (n)	Diabetes (n)	Lower limbs vein infarction (n)
Observation group	53	33/20	58.25± 8.14	26.11± 4.01	28(52.83)	15(28.31)	14(26.42)
Control group	53	31/22	59.33± 8.82	27.25± 4.66	25(47.17)	18(33.96)	18(33.96)

1.2 治疗方法

所有患者进行治疗前均行常规心电图及血气分析检查,对照组患者采用皮下注射低分子肝素(20140125,湖北巨胜科技有限公司,10 mL/支)0.01 mL/kg,每隔 12 小时注射 1 次,并应用华法林(20140112,北京嘉林药业股份有限公司,2.5 mg/片)2.5 mg 口服治疗,1 次/d(据 INR 调整用量)。观察组予以利伐沙班(20131224,Bayer Pharma AG,10mg/每片)治疗,15 mg/次,2 次/d,三周后改为 20 mg/次,1 次/d。治疗观察疗效为 6 个月。

1.3 观察指标

① 临床疗效;② 治疗后血清 BNP、TnI、D-D、Hcy 水平的变化;③ 不良反应的发生情况及死亡情况;④ 治疗前后肺动脉收缩压、动脉收缩压、动脉血氧分压变化。于治疗前后收集两组患者静脉血 3-5 mL,经离心处理后置于 -70℃ 环境中待检。采用酶联免疫法检测 BNP、D-D、Hcy 水平;金标单抗法测定 TnI 水平,试剂盒均为(上海博灿生物科技有限公司)生产,具体操作方

选择 2014 年 2 月至 2017 年 12 月在我院进行治疗的急性肺栓塞患者 106 例,纳入标准:符合我国急性肺栓塞相关诊断标准:(1) 出现心悸及呼吸困难等症状;(2) 对本研究知情并同意,同时按要求复诊。排除标准:(1)排除其他肾脏疾病;(2)排除不配合治疗患者;(3)排除近期已行外科手术患者。将患者随机分为观察组及对照组,观察组 53 例患者,包括男 33 例,女 20 例,年龄在 42-70 岁,平均年龄 (58.25± 8.14) 岁,平均体重 (26.11± 4.01)kg,高血压患者 28 例、糖尿病患者 15 例、下肢静脉栓塞患者 14 例;对照组 53 例患者,包括男 31 例,女 22 例,年龄在 39-68 岁,平均年龄 (59.33± 8.82) 岁,平均体重 (27.25± 4.66)kg,高血压患者 25 例、糖尿病患者 18 例、下肢静脉栓塞患者 18 例。两组一般临床资料比较差异均无统计学意义($P>0.05$),具有可比性。

法参照试剂盒说明。

根据 CT 肺动脉造影结果进行疗效判定,疗效判定标准^①:
① 痊愈:患者临床症状完全消失且生活质量恢复如初;② 显效:患者临床症状完全消失但有轻微呼吸困难等不良反应;③ 好转:患者有明显的呼吸困难及胸痛等症状;④ 无效:患者治疗后临床症状无任何变化。

1.4 统计学分析

本研究数据选择 SPSS18.0 进行统计学分析,计量资料组间比较采用 t 检验,计数资料组间比较采用 χ^2 检验,以 $P<0.05$ 时表示其差异具有统计学意义。

2 结果

2.1 两组患者临床疗效的比较

治疗后,观察组患者总有效率为 94.34%,显著高于对照组 (77.36%, $P<0.05$),详见表 2。

表 2 两组患者临床疗效比较[例(%)]

Table 2 Comparison of the clinical curative effect between the two groups [n(%)]

Groups	n	Recovery	Excellent	Effective	Invalid	Total effective rate
Observation group	53	13(24.53)	20(37.74)	17(32.08)	3(5.66)	50(94.34) ^a
Control group	53	6(11.32)	12(22.64)	23(43.40)	12(22.64)	41(77.36)

Note: Compared with the control group. ^a $P<0.05$.

2.2 两组患者治疗前后血清脑钠肽 (BNP)、心肌肌钙蛋白 I (TnI)、D-二聚体(D-D)、血同型半胱氨酸(Hcy)水平的比较

治疗后,观察组患者血清脑钠肽 (BNP)、心肌肌钙蛋白 I (TnI)、D-二聚体(D-D)、血同型半胱氨酸(Hcy)水平均显著低于对照组($P<0.05$),详见表 3。

2.3 两组患者治疗前后各项收缩压的对比

治疗前,两组肺动脉收缩压、动脉收缩压、动脉血氧分压比较无明显统计学差异($P>0.05$);治疗后,观察组肺动脉收缩压较对照组显著降低($P<0.05$),动脉收缩压、动脉血氧分压较对照组显著升高($P<0.05$),详见表 4。

表 3 两组患者治疗后血清 BNP、TnI、D-D、Hcy 水平的比较($\bar{x} \pm s$)Table 3 Comparison of the serum BNP, TnI, D-D, Hcy levels between the two groups after treatment($\bar{x} \pm s$)

Groups	n	BNP(pg/mL)	TnI(ng/mL)	D-D(mg/L)	Hcy(umol/L)
Observation group	53	140.11± 20.66 ^a	0.16± 0.01 ^a	5.26± 0.66 ^a	6.14± 0.81 ^a
Control group	53	192.74± 26.11	0.42± 0.07	9.22± 1.43	12.28± 1.62

Note: Compared with the control group, ^a $P < 0.05$.

表 4 两组治疗前后 PAsP、PSBP、PaO₂ 水平的比较($\bar{x} \pm s$, mmHg)Table 4 Comparison of the PAsP, PSBP, PaO₂ between the two groups before and after treatment($\bar{x} \pm s$, mmHg)

Groups	n	Time	PAsP	PSBP	PaO ₂
Observation group	53	Pre-operation	51.33± 7.68	81.36± 12.58	57.28± 9.03
		Postoperation	20.67± 3.10 ^{ab}	97.69± 12.55 ^{ab}	82.47± 12.72 ^{ab}
Control group	53	Pre-operation	51.87± 7.81	81.57± 12.17	56.88± 9.31
		Postoperation	26.14± 4.22 ^b	87.64± 10.47 ^b	70.57± 11.38 ^b

Note: Compared with the control group, ^a $P < 0.05$; Compared with pre-operation, ^b $P < 0.05$.

2.4 两组抗凝结果的比较

对照组有 5 例患者出现出血反应,其中 3 例为牙龈出血,2 例为泌尿系出血;观察组未发生出血反应,观察组抗凝结果明显由于对照组($P < 0.05$)。

3 讨论

急性肺栓塞是因血栓脱落及相关原因导致肺动脉阻塞而形成的合并症。随着我国人口逐步进入老龄化,急性肺栓塞发病数量急剧上升,该病多发于 40-70 岁的中老年人群,死亡率仅次于冠心病及高血压等疾病,主要临床症状表现为:咯血、胸痛及呼吸困难等。急性肺栓塞的发病原因较为复杂,大体可分为内源性和外源性两种,内源性原因如肺动脉主干被栓子堵塞,外源性原因如栓子分支导致肺部正常循环受到影响^[9-12]。由于过去该病未得到医疗领域的重视,出现大量误诊、漏诊等情况,导致患者病情加重。对于肺动脉血栓栓塞高危患者,治疗的关键在于争取时间,迅速减轻血栓负荷,挽救生命。药物溶栓、外科手术取栓和经导管取栓或碎栓 3 种治疗方式均可有效减轻血栓负荷。目前认为抗凝是高危患者的主要治疗方法,约有 90% 的高危患者可从抗凝治疗中获益,表现为血流动力学紊乱得以改善^[13]。

脑钠肽(Brain natriuretic peptide, BNP)主要来源于心室,具有多种的生物活性^[14]。现代药理学研究显示 BNP 被广泛应用于心律失常及心力衰竭等检测,并具有调节肾功能的作用,对肾素-血管紧张素 II-醛固酮系统以及交感神经系统具有抑制效果,可松弛血管平滑肌细胞,促进钠排泄,减轻心脏负荷,缓解病情^[15,16]。BNP 的分泌是机体进行自身调节的一种保护性机制,因此在急性肺栓塞的治疗中及时补充外源性 BNP 可有效缓解患者病情。肌钙蛋白 I (Troponin I, TnI)是一种在临床上应用多年的心肌损伤标志物,可根据其水平变化判断心肌受损程度,升高表示病情加重,降低表示病情得到缓解^[17,18]。D-二聚体(D-Dimer, D-D)是一种降解产物,可作为一种标志物判断人体内纤维蛋白浓度,且可反映血管内血栓形成情况,常用于临床急性肺栓塞测定^[19]。有研究报道^[20,21]D-D 水平升高表示浓度高

病情重,D-D 水平降低表示病情得到抑制,但是患者经过手术或者曾有外伤感染等情况也会导致 D-D 水平升高,因此单一检测 D-D 水平无法准确判断是否患有急性肺栓塞。血同型半胱氨酸(homocysteine, Hcy)作为一种含硫氨基酸,在健康人体中 Hcy 会被分解代谢且浓度较低,若患上冠心病、肺栓塞及各种心脑血管疾病时 Hcy 浓度将升高,因此可通过检测该标志物浓度变化判断人体健康与否^[22-25]。本研究采用利伐沙班治疗的患者血清 BNP、TnI、D-D、Hcy 水平均显著低于采用肝素搭配华法林治疗的患者,表示采用利伐沙班治疗的患者病情控制更好,疗效更佳。

利伐沙班可选择性的阻断 Xa 因子的活性位点,从而通过内源性以及外源性途径活化 X 因子为 Xa 因子,在凝血级联反应中发挥着重要的作用^[26,27]。有学者经研究^[28-30]发现利伐沙班有助于形成新的血栓、提高 ADP 酶活性并抑制 ADP 诱导的血小板聚集,对预防肺栓塞的形成有良好的效果且安全性更高。本研究采用利伐沙班治疗的患者总有效率为 94.37%,显著优于采用肝素搭配华法林治疗患者,且采用利伐沙班治疗后的患者肺动脉收缩压水平较采用肝素搭配华法林治疗患者水平显著降低。

综上所述,利伐沙班应用于治疗急性肺栓塞的抗凝效果显著优于低分子肝素钙搭配华法林治疗,其可有效降低患者血清 BNP、TnI、D-D、Hcy 水平以及肺动脉收缩压。

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