

· 临床研究 ·

利伐沙班在老年全膝关节置换术后预防下肢深静脉血栓的效果

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【摘要】目的 探讨老年患者行膝关节置换术后应用利伐沙班预防下肢深静脉血栓的有效性及其安全性。**方法** 入选2017年3月至2018年3月初次在我院行全膝关节置换的患者356例,随机分为对照组和观察组,每组178例。对照组给予低分子肝素预防下肢深静脉血栓,观察组给予利伐沙班预防下肢深静脉血栓。比较2组患者术后1年内出现下肢深静脉血栓、出血及死亡的发生情况;同时比较2组患者治疗前后炎症因子(TNF- α 、IL-6、IL-1 β)和凝血指标(D-Dimer、FIB、APTT、PT、TT、PLT)的变化。采用GraphPad Prism 5.0软件进行数据分析。2组间比较采用 t 检验或 χ^2 检验,并进行Kaplan-Meier生存分析和Log-rank检验。**结果** 与治疗前相比,治疗后2组患者的TNF- α 、IL-6、IL-1 β 、PLT、D-Dimer和FIB均明显降低($P<0.05$),而APTT、PT和TT明显升高($P<0.05$)。治疗后,观察组D-Dimer明显低于对照组($P<0.05$)。1年内,观察组下肢深静脉血栓的发生率明显低于对照组($\chi^2=5.838, P=0.016$);观察组和对照组分别有2例(1.12%)和19例(10.67%)患者出现了不良反应,2组间比较差异有统计学意义($\chi^2=8.865, P=0.003$);观察组患者1年生存率明显高于对照组($\chi^2=4.614, P=0.032$)。**结论** 利伐沙班在老年全膝关节置换术后预防下肢深静脉血栓的效果和安全性优于低分子肝素,其机制可能与抑制炎症反应有关。

【关键词】 老年人;利伐沙班;全膝关节置换术;下肢静脉血栓;炎症反应

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Rivaroxaban in prevention of deep venous thrombosis in lower limbs after total knee arthroplasty in the elderly

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【Abstract】Objective To investigate the efficacy and safety of rivaroxaban in prevention of lower limb venous thrombosis after total knee arthroplasty in the elderly. **Methods** A total of 356 patients undergoing total knee arthroplasty in Liaocheng Second People's Hospital from March 2017 to March 2018 were randomly divided into the control group and study group ($n=178$ each). The control group were given low-molecular-weight heparin to prevent venous thrombosis, and the study group were given rivaroxaban to prevent lower limb venous thrombosis. The two groups were compared in the incidence of deep venous thrombosis in the lower limbs, hemorrhage, and death within one year after operation. Changes of inflammatory factors [tumor necrosis factor α (TNF- α), interleukin-6 (IL-6), IL-1 β] and coagulation parameters [(D-Dimer, fibrinogen (FIB), activated partial thromboplastin (APTT), prothrombin time (PT), thrombin time (TT), platelet (PLT)] were also compared between two groups before and after treatment. Data analysis was performed using GraphPad Prism 5.0. The t test or χ^2 test was used for comparison between the two groups. Survival analysis was estimated by Kaplan-Meier method and Log-rank test. **Results** Compared with before treatment, TNF- α , IL-6, IL-1 β , PLT, D-Dimer and FIB were significantly decreased in the elderly patients after knee arthroplasty ($P<0.05$), while APTT, PT and TT were significantly increased ($P<0.05$). The D-Dimer of the study group was significantly lower than that of the control group ($P<0.05$). After 1 year, the incidence of deep venous thrombosis in the lower limbs was significantly lower in the study group than in the control group ($\chi^2=5.838, P=0.016$). Adverse reaction occurred in 2 cases (1.12%) of the study group and 19 cases (10.67%) of the control group with statistically significant difference ($\chi^2=8.865, P=0.003$). The 1-year survival rate of the study group was significantly higher than that of the control group ($\chi^2=4.614, P=0.032$). **Conclusion** Rivaroxaban outperformed low-molecular-weight heparin in the efficacy and safety in the prevention of lower limb venous thrombosis after total knee arthroplasty in the elderly, and its mechanism may be related to the inhibition of inflammatory response.

【Key words】 aged; rivaroxaban; total knee arthroplasty; lower limb venous thrombosis; inflammatory response

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骨性关节炎又称老年性膝关节炎,是一种以关节软骨的变性、破坏及骨质增生为特征的慢性关节病。目前,对于病情严重患者的治疗手段以全膝关节置换术(total knee arthroplasty,TKA)为主,但术后易出现下肢深静脉血栓(deep venous thrombosis,DVT)等并发症,若不及时干预,会继发肺栓塞或者脑梗死,严重者会导致患者死亡,且并发症随着年龄的增加而增加^[1]。临床常规采用注射低分子肝素或者口服华法林等抗凝药物预防和治疗患者TKA术后下肢DVT发生,但其效果并不是很理想^[2]。利伐沙班是一种新型抗凝药物,主要通过抑制凝血因子Xa的活性、减少凝血酶(凝血因子IIa)生成等发挥抗凝作用。利伐沙班已广泛用于静脉血栓栓塞性疾病的预防和治疗,以及非瓣膜性房颤的卒中预防。目前研究报道,针对不同年龄段的患者,利伐沙班的药代动力学和药效学具有显著差异^[3]。本研究旨在探讨老年患者行TKA术后使用利伐沙班预防下肢DVT的有效性及其安全性,并探讨其作用机制。

1 对象与方法

1.1 研究对象

入选2017年3月至2018年3月初次在我院行全膝关节置换的患者356例,随机分为对照组和观察组,每组各178例。对照组中男性91例,女性87例;年龄62~87(71.4±5.9)岁;体质量45~79(63.5±9.8)kg。观察组中男性85例,女性93例;年龄67~86(72.4±8.9)岁;体质量44~82(62.7±7.9)kg。2组患者一般资料差异无统计学意义($P>0.05$),具有可比性。

纳入标准:(1)年龄60~85岁;(2)术前无DVT;(3)术前凝血功能指标正常。排除标准:(1)合并严重心肝肾等器官衰竭或肺功能障碍;(2)凝血功能紊乱;(3)既往血栓病史。

1.2 方法

观察组术后12h给予利伐沙班(德国拜耳公司,德国),10mg/d,口服。对照组术后12h于皮下注射低分子肝素[赛诺菲安万特(中国)投资有限公司,北京],4000IU/d。2组疗程均为12d。

1.3 观察指标

(1)观察2组患者治疗前后凝血指标,包括血小板计数(platelet,PLT)、凝血酶原时间(prothrombin time,PT)、活化部分凝血活酶时间(activated partial thromboplastin time,APTT)、D-二聚体、凝血酶时间(thrombin time,TT)、纤维蛋白原(fibrinogen,FIB)等。采用全自动凝血监测仪检测凝血指标,检验试

剂盒均购自南京比迪生物科技有限公司。(2)血清肿瘤坏死因子 α (tumor necrosis factor α ,TNF- α)、白细胞介素(interleukin-6,IL-6)、IL-1 β 均应用酶联免疫吸附法检测[KHC3011、KHC0061、KHC0011赛默飞世尔科技(中国)有限公司]。(3)随访记录2组患者术后下肢DVT发生和血肿、胃肠道出血等不良反应发生情况,并记录2组患者生存情况。通过电话、探访、门诊复查等方式对2组患者进行随访(2017年4月至2019年3月),每月1次,无失访病例。DVT诊断标准见文献^[4]。

1.4 统计学处理

采用GraphPad Prism 5.0对数据进行分析。计数资料以例数(百分率)表示,组间比较采用 χ^2 检验,计量资料以均数±标准差表示,组间比较采用 t 检验。采用Kaplan-Meier法进行生存分析,并行Log-rank检验。以 $P<0.05$ 为差异有统计学意义。

2 结果

2.1 2组患者炎症因子比较

治疗前2组患者炎症因子对比差异无统计学意义($P>0.05$)。与本组治疗前相比,治疗后2组患者TNF- α 、IL-6、IL-1 β 均明显降低($P<0.05$)。与对照组比较,观察组TNF- α 、IL-6、IL-1 β 显著降低($P<0.05$;表1)。

表1 观察组与对照组患者炎症因子比较

Table 1 Comparison of inflammatory indices between two groups
($n=178$, ng/L, $\bar{x}\pm s$)

Index	Control group		Observation group	
	Before	After	Before	After
	treatment	treatment	treatment	treatment
IL-6	24.31±1.69	16.23±2.34 [*]	24.52±1.52	10.48±1.26 ^{*#}
TNF- α	34.16±5.84	31.05±5.12 [*]	34.21±5.26	29.12±3.94 ^{*#}
IL-1 β	55.21±5.16	46.15±3.46 [*]	55.27±5.21	41.63±5.18 ^{*#}

IL: interleukin; TNF- α : tumor necrosis factor α . Compared with before treatment, ^{*} $P<0.001$;compared with control group, [#] $P<0.001$.

2.2 2组患者凝血指标相关变化

治疗前2组患者凝血指标比较差异无统计学意义($P>0.05$)。与治疗前相比,治疗后2组患者PLT、D-二聚体和FIB均明显降低,而APTT、PT和TT明显升高。与对照组比较,观察组D-二聚体显著降低($P<0.05$;表2)。

2.3 2组患者治疗有效性和安全性比较

随访观察期间,观察组6个月时发生DVT3例,肺栓塞1例;12个月时发生下肢DVT2例;共发生5例(2.81%)下肢DVT,1例肺栓塞。对照组

3个月时发生下肢DVT 3例、肺栓塞2例;6个月时发生下肢DVT 12例、肺栓塞4例;12个月时发生下肢DVT 7例;共发生21例(11.80%)下肢DVT,6例肺栓塞。观察组3个月时发生血肿1例;12个月时发生胃肠道出血1例;共有2例(1.12%)出现不良反应。对照组3个月时发生血肿2例,颅内出血2例,胃肠道出血4例;6个月时发生胃肠道出血6例;12个月时发生血肿2例,胃肠道出血3例;共有19例(10.67%)出现不良反应。观察组的疗效和安全性高于对照组($P<0.05$;表3)。

2.4 生存分析

整个随访期间,观察组治疗后6个月继发肺栓塞死亡1例;对照组治疗后1个月时死亡3例、3个月时死亡3例、6个月时死亡1例,共计死亡7例。2组患者Kaplan-Meier生存曲线如图1所示。Log-rank检验表明2组差异有统计学意义($\chi^2=4.614, P=0.032$)。

3 讨论

TKA是骨科大手术,老年人因身体机能下降,易导致下肢DVT的发生,继发肺栓塞、残疾,甚至发展至死亡。对于这类下肢DVT形成风险较高的TKA手术,临床上推荐使用注射低分子肝素或者口服华法林来预防下肢DVT形成^[2]。但皮下注射低分子肝素可能出现皮下淤血或者硬结等并发症,口

服华法林的药代动力学易受食物、药物及遗传因素的影响,起效速度慢、稳定性差,且用药期间需监测国际标准化比值(international normalized ratio, INR)^[5]。因此,研发新型的抗凝药物是目前预防和治疗下肢DVT的热点和难点。

利伐沙班是一种新型口服抗凝药物,主要通过抑制凝血因子Xa的活性、减少凝血酶(凝血因子IIa)生成而发挥抗凝作用。杨霞等^[1]研究表明,利伐沙班治疗DVT的疗效优于传统的抗凝治疗方式,且不会增加大出血、死亡等风险。但是,Burgazli等^[6]和左丽等^[7]研究表明,利伐沙班更容易引起高龄患者胃肠道出血,造成患者死亡。本研究使用低剂量利伐沙班预防老年TKA术后下肢DVT的发生,利伐沙班观察组与低分子肝素对照组相比,D-二聚体明显降低。利伐沙班观察组下肢DVT的发生率明显低于对照组,提示利伐沙班可改善患者体内高凝状态,降低下肢DVT的发生率。这与崔建双等^[5]和黄承^[8]的研究一致,提示使用低剂量利伐沙班可有效预防老年TKA术后下肢DVT的发生。除此之外,本研究结果还显示,观察组出血性并发症发生率和45d的死亡率明显低于对照组,且对照组发现2例严重出血并死亡的患者,而利伐沙班观察组中未出现严重出血并死亡患者。这与刘蕾等^[9]的研究一致,提示老年患者使用低剂量利伐沙班是安全可行的。

表2 2组患者凝血指标比较

Table 2 Comparison of coagulation parameters between two groups (n=178, $\bar{x}\pm s$)

Parameter	Control group		Study group	
	Before treatment	After treatment	Before treatment	After treatment
PLT($\times 10^9/L$)	415.23 $\pm$ 24.16	256.31 $\pm$ 12.94*	416.28 $\pm$ 21.49	254.00 $\pm$ 11.36*
D-Dimer($\mu g/ml$)	1.18 $\pm$ 0.05	0.67 $\pm$ 0.03*	1.19 $\pm$ 0.06	0.45 $\pm$ 0.04**
FIB(g/L)	5.36 $\pm$ 0.11	3.22 $\pm$ 0.06*	5.29 $\pm$ 0.14	3.22 $\pm$ 0.13**
PT(s)	10.93 $\pm$ 1.58	17.45 $\pm$ 1.21*	10.86 $\pm$ 1.34	17.52 $\pm$ 1.27*
APTT(s)	25.52 $\pm$ 2.36	39.92 $\pm$ 1.25*	25.19 $\pm$ 1.07	40.01 $\pm$ 1.92*
TT(s)	11.72 $\pm$ 1.94	18.42 $\pm$ 1.61*	11.75 $\pm$ 1.43	18.26 $\pm$ 1.74*

PLT: platelet; FIB: fibrinogen; PT: prothrombin time; APTT: activated partial thromboplastin time; TT: thrombin time. Compared with before treatment, * $P<0.001$; compared with control group, ** $P<0.001$.

表3 2组患者治疗有效性和安全性比较

Table 3 Comparison of efficiency and safety between two groups [n=178, n(%)]

Group	Efficiency		Safety		
	Lower limber DVT	Pulmonary embolism	Hematoma	Gastrointestinal bleeding	Intracranial bleeding
Study	5(2.81)	1(0.56)	1(0.56)	1(0.56)	0(0.00)
Control	21(11.80)	6(3.37)	4(2.25)	13(7.30)	2(1.12)
χ^2	5.838		8.865		
P value	0.016		0.003		

DVT: deep venous thrombosis.

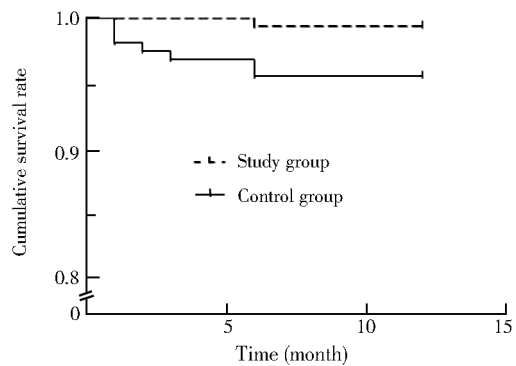


图1 2组患者TKA术后的生存曲线

Figure 1 Survival curves for the subjects after total knee arthroplasty

下肢DVT的形成是多种因素共同作用的结果。近年来临床研究表明下肢DVT的形成也与炎症有关。患者接受手术受到创伤时,血清中的炎症因子显著升高,损伤血管内皮功能,聚集血小板,加重高凝状态,促进血栓形成,血栓的形成又可刺激静脉壁发生更显著炎症反应。因此,炎症因子是评估术后是否发生血栓的关键性指标之一。本研究结果表明,利伐沙班观察组与低分子肝素对照组比较,炎症因子TNF- α 、IL-6、IL-1 β 明显降低。这与魏明等^[10]和彭远程等^[11]的研究结果一致,提示术后使用低剂量利伐沙班可以改善患者体内炎症因子水平,从而有效预防患者术后下肢DVT的形成。

综上所述,利伐沙班在老年膝关节置换术后预防DVT的效果和安全性优于低分子肝素,其机制可能与抑制炎症反应有关。

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