

doi: 10.13241/j.cnki.pmb.2017.32.019

利伐沙班与华法林对高龄非瓣膜性房颤患者 D- 二聚体、NT-proBNP 水平的影响 *

哈斯高娃 曹中朝 刘东华 张 勇 乌吉斯古楞

(内蒙古医科大学附属医院 干部保健病房 A 区 内蒙古 呼和浩特 010059)

摘要 目的:探讨利伐沙班与华法林对高龄非瓣膜性房颤(NVAF)患者血浆 D- 二聚体(D-D)、N 末端 B 型利钠肽原(NT-proBNP)水平的影响及其临床疗效。**方法:**选取我院 2015 年 1 月~2016 年 11 月收治的 146 例高龄 NVAF 患者,采取随机数字表法均分为两组。华法林组予以华法林抗栓治疗,利伐沙班组采取利伐沙班抗栓治疗。记录比较两组治疗期间栓塞、出血情况及不良反应,以及治疗前后血浆 D- 二聚体(D-D)、N 末端 B 型利钠肽原(NT-proBNP)水平的变化情况。**结果:**两组治疗后栓塞发生率比较,差异无统计学意义($P>0.05$)。利伐沙班组出血发生率(4.1%)低于华法林组(15.1%),差异具有统计学意义($P<0.05$)。与治疗前相比,两组治疗后血浆 D-D 和 NT-proBNP 水平均降低,差异具有统计学意义($P<0.01$);治疗后,两组血浆 D-D 和 NT-proBNP 水平比较,差异无统计学意义($P>0.05$)。两组不良反应发生率对比,差异无统计学意义($P>0.05$)。**结论:**与华法林相比,高龄非瓣膜性房颤应用利伐沙班抗栓治疗在患者耐受性与预防血栓栓塞方面优势相当,但利伐沙班更能有效降低患者出血风险。

关键词:非瓣膜性房颤;高龄患者;利伐沙班;华法林;D- 二聚体;N 末端 B 型利钠肽原

中图分类号:R541.75 **文献标识码:**A **文章编号:**1673-6273(2017)32-6291-04

Effects of Rivaroxaban and Warfarin on D-dimer and NT-proBNP Levels in Elderly Patients with NVAF*

Hasigaowa, CAO Zhong-chao, LIU Dong-hua, ZHANG Yong, Wujisiguleng

(District A of the Cadre Health Care Ward, the Affiliated Hospital of Inner Mongolia Medical University, Hohhot, Inner Mongolia, 010059, China)

ABSTRACT Objective: To investigate the clinical effect of rivaroxaban and warfarin on the serum levels of D-dimer (D-D) and N-terminal pro-brain natriuretic peptide (NT-proBNP) in elderly patients with non-valvular atrial fibrillation (NVAF). **Methods:** 146 cases with NVAF who were treated in our hospital from January 2015 to November 2016 were selected and randomly divided into two groups. The warfarin group was treated with warfarin, while the rivaroxaban group was treated with rivaroxaban. Then the occurrence of embolism, the hemorrhage, the adverse reactions and the changes of plasma D-D and NT-proBNP of patients in the two groups were observed and compared before and after the treatment. **Results:** After treatment, there was no statistically significant difference about the incidence of embolism in the two groups ($P>0.05$). The incidence of hemorrhage in the rivaroxaban group was 4.1%, which was lower than 15.1% of the warfarin group, and the difference was statistically significant ($P<0.01$). After treatment, the plasma D-D and NT-proBNP levels in the two groups were lower than before ($P<0.01$); There was no statistically significant difference about the changes of plasma D-D and NT-proBNP levels in the two groups ($P>0.05$). There was no statistically significant difference about the incidence of adverse reactions between the two groups ($P>0.05$). **Conclusion:** The clinical effect of rivaroxaban and warfarin are equal in terms of the tolerance and thromboembolism prevention of elderly patients with nonvalvular atrial fibrillation, while rivaroxaban is more effective in reducing bleeding risk.

Key words: Non-valvular atrial fibrillation; Elderly patient; Rivaroxaban; Warfarin; D-dimer; N-terminal pro-brain natriuretic peptide

Chinese Library Classification(CLC): R541.75 **Document code:** A

Article ID:1673-6273(2017)32-6291-04

前言

心房颤动(房颤)是一种快速心律失常。非瓣膜性房颤(non-valvular atrial fibrillation, NVAF)是指一类与心室无关的心房快而无序的搏动^[1]。年龄是引发房颤的独立危险因素,年龄 ≥ 75 岁人群的 NVAF 特称为高龄 NVAF^[2]。心脏输出量降低是房

颤引起的主要危害,极易诱发血栓形成。故而抗栓治疗是其整个治疗过程的关键^[3]。华法林属香豆素类抗凝剂,是临床预防血栓的经典药物^[4]。利伐沙班为新型口服抗凝药(new oral anticoagulants, NOACs),近年来因其具有颅内出血并发症少、半衰期短、起效快、不需实验室监测及与其他药物相互作用少等优势而受到广泛关注^[5,6]。D- 二聚体(D-dimer, D-D)可作为反映机体

* 基金项目:内蒙古自治区自然科学基金项目(2012MS121)

作者简介:哈斯高娃(1976-),女,本科,主治医师,研究方向:心内科

(收稿日期:2017-06-12 接受日期:2017-07-10)

血栓形成与血栓前状态的敏感指标,房颤患者血浆 D-D 水平升高与血栓形成密切相关^[7]。N 末端 B 型利钠肽原(N-terminal pro-brain natriuretic peptide, NT-proBNP)是影响 NVAf 的相关因素,在房颤的发生发展中发挥了一定作用^[8]。本研究以我院 2015 年 1 月~2016 年 11 月收治的高龄 NVAf 患者为研究对象,探讨高龄 NVAf 患者分别应用利伐沙班与华法林治疗的安全性及其对 D-D、NT-proBNP 水平的影响,以期指导临床抗 NVAf 用药。现报道如下。

1 资料与方法

1.1 一般资料

选取我院 2015 年 1 月~2016 年 11 月收治的 146 例高龄 NVAf 患者,入选标准:①符合《老年人非瓣膜性心房颤动诊治中国专家建议(2016)》(以下简称《建议》)中制定的 NVAf 诊断标准^[9],并经临床表现及心脏超声、24 h 动态心电图等检查确诊;②75 岁≤年龄≤85 岁;③男性 CHA2DS2-VASc 评分≥2 分、女性 CHA2DS2-VASc 评分≥3 分^[9];④HAS-BLED 评分<3 分^[9];⑤用药依从性好,能接受长期随访,积极配合相关治疗与检查;⑥自愿受试,签署知情同意书;⑦身体质量指数(BMI)<30 kg/m²;⑧入组前合并的基础疾病(如糖尿病、高血压等)均已获得有效控制;⑨无抗凝禁忌证[如伴有严重肝肾功能不全、严重高血压(≥180/110 mmHg)、血液病或消化道溃疡史等]。排除标准:①近 3 个月内有缺血性脑卒中、手术、外伤史或有非甾体类抗炎药、抗血小板药物联用史者;②过敏体质或对本研究所用药物过敏者;③有酗酒、人工心脏瓣膜置换术史或有深静脉血栓、脑出血、肺栓塞、风湿性心脏病史者;④合并恶性肿瘤、血小板减少或出血性疾病者;⑤近 1 年内有泌尿或消化系统出血史者;⑥未遵医嘱用药或失访者。

本研究经我院医学伦理委员会审核通过。采取随机数字表法均分为两组。利伐沙班组 73 例,男 39 例,女 34 例;年龄(80.3±1.7)岁;房颤类型:阵发性 17 例,持续性 21 例,永久性 35 例;CHA2DS2-VASc 评分(3.79±0.15)分;HAS-BLED 评分(0.91±0.23)分;BMI(23.3±1.2)kg/m²;合并基础疾病:冠心病 23 例,糖尿病 18 例,高血压 31 例。华法林组 73 例,男 41 例,女 32 例;年龄(80.1±1.8)岁;房颤类型:阵发性 16 例,持续性 19 例,永久性 38 例;CHA2DS2-VASc 评分(3.76±0.16)分;HAS-BLED 评分(0.93±0.22)分;BMI(23.5±1.1)kg/m²;合并基础疾病:冠心病 24 例,糖尿病 17 例,高血压 29 例。两组基线资料对比差异均无统计学意义(P>0.05),具有临床可比性。

1.2 方法

所有患者均采取相同的室率与节律控制治疗,具体用药方案可参照《建议》^[9]。主要包括:1)室率控制:常用药物有胺碘酮、洋地黄类(如地高辛、毛花苷 C)、β 受体阻滞剂(如美托洛尔、阿替洛尔、比索洛尔)等;2)节律控制:①快速房颤的复律:常用药物有胺碘酮、伊布利特、普罗帕酮;②维持窦律的长期治疗:有稳心颗粒、决奈达隆、索他洛尔、胺碘酮、参松养心胶囊等药物。

华法林组:在此基础上,予以华法林(上海信谊药厂,国药准字 H31022123)抗栓治疗;具体为①起始剂量:2.5 mg/d,且于用药前监测 1 次凝血指标,测定国际标准化比率(INR)值;②再

于治疗第 3、6、9 d 后,各复查 1 次 INR 值,并对华法林剂量依据复查时 INR 值进行及时调整;③若连续 2 次 INR 值均达 1.6~2.5,则 INR 值复查频率可调整为 1 次/周,再稳定 1~2 周时,可调整为 1 次/月;④但若 INR 值连续 2 次均处于目标范围之外时,应及时调整华法林剂量,并加强凝血指标监测;⑤用药期间出血并发症与 INR 值升高的具体处理方式参照《建议》^[9]。利伐沙班组:在以上室率与节律控制治疗基础上,采取利伐沙班(德国拜耳先灵制药,批准文号 H20140132)抗栓治疗;具体是①口服,15 mg/次,于每天固定时间段顿服;②治疗期间针对病人出血并发症的具体处理方案亦参照《建议》^[9]。两组均连服 6 个月。同时为有效提高每位患者长期用药的依从性应于治疗前加强 NVAf 相关知识教育及评估病人认知功能。

1.3 观察指标

1)栓塞事件:详细记录两组治疗期间下肢静脉栓塞、肺栓塞及脑栓塞等发生情况。2)出血事件^[10,11]:详细记录所有患者用药期间自发性出血事件,包括①轻微出血:如有镜下血尿、结膜或皮肤出血点、鼻衄、痰中带血、淤斑、牙龈出血等情况,或红细胞比容(HCT)下降<9%,或血红蛋白(Hb)下降<30 g/L;②少量出血:如有黑便或血便、少量呕血或咯血、肉眼血尿等情况,或 10%≤HCT 下降<15%,或 30 g/L≤Hb 下降<50 g/L;③严重出血:如有脑出血,或输血>400 mL、1 次出血量≥300 mL,或有大咳血、消化道大出血等颅外大出血,或 HCT 下降≥15%,或 Hb 下降≥50 g/L。3)血浆指标检测:①于治疗前和治疗 3、6 个月清晨对每位患者各抽取 1 次空腹肘静脉血,3 mL/次,离心分离血浆,并于-20℃冰箱中保存,待测;②仪器选用全自动酶标仪(山东博科,型号 BIOBASE-EL10A),D-D、NT-proBNP 均运用酶联免疫法测定;③试剂盒均购自上海江莱生物,且以上指标检测步骤均严格依据其配套说明书执行。4)不良反应:详细记录用药期间两组患者因药物而引发的,如头晕头痛、转氨酶升高、腹泻等不良反应/事件。

1.4 统计学分析

应用统计软件 SPSS19.0 处理数据,计数资料以(%)表示,运用 χ^2 检验,计量资料以($\bar{x} \pm s$)表示,采取 t 检验,以 P<0.05 为差异有统计学意义。

2 结果

2.1 两组栓塞情况的比较

利伐沙班组栓塞发生率为 5.5%(4/73),较华法林组的 6.8%(5/73)相比,差异无统计学意义(P=0.731),见表 1。

2.2 两组出血情况的比较

利伐沙班组出血发生率为 4.1%(3/73),较华法林组明显降低[15.1%(11/73),P<0.05],见表 2。

2.3 两组治疗前后血浆指标的比较

与治疗前相比,两组治疗 3、6 个月后血浆 D-D 和 NT-proBNP 水平,均逐渐改善(P<0.01);但与华法林组同期对比,利伐沙班组治疗 3、6 个月后以上血浆指标水平,均无明显差异(P>0.05)。见表 3。

2.4 两组不良反应发生情况的比较

两组随访期间均无死亡病例。观察组有 5 例头晕头痛,2 例转氨酶升高,3 例谷氨酰转氨酶升高,2 例腹泻,3 例恶心呕

表 1 两组栓塞情况的比较

Table 1 Comparison of the embolization between two groups

Groups	n	Vein embolism of lower extremity	Pulmonary embolism	Cerebral embolism	The total incidence(%)
Rivaroxaban group	73	1	1	2	5.5
Warfarin group	73	2	1	2	6.8
P					0.731

表 2 两组出血情况的比较

Table 2 Comparison of the bleeding between two groups

Groups	n	Slight bleeding	Moderate bleeding	Severe bleeding	The total incidence(%)
Rivaroxaban group	73	2	1	0	4.1
Warfarin group	73	5	3	3	15.1
P					0.025

表 3 两组治疗前后血浆指标的比较($\bar{x} \pm s$)Table 3 Comparison of the plasma indexes between two groups before and after treatment($\bar{x} \pm s$)

Groups	n	D-D(ng/mL)				NT-proBNP(pg/mL)			
		Before treatment	3 months after treatment	6 months after treatment	P	Before treatment	3 months after treatment	6 months after treatment	P
Rivaroxaban group	73	367.5± 54.8	231.1± 43.5	123.6± 31.3	0.000	3165.3± 452.8	1954.9± 358.3	768.5± 183.4	0.000
Warfarin group	73	361.9± 55.7	236.8± 42.5	129.7± 32.4	0.000	3087.2± 461.5	2018.5± 352.9	802.3± 178.5	0.000
P		0.541	0.425	0.249		0.304	0.282	0.261	

吐,总发生率为 20.5%(15/73);对照组出现 4 例头晕头痛,1 例皮肤坏死,4 例皮疹,5 例腹泻,4 例恶心呕吐,总发生率为 24.7%(18/73)。两组不良反应率对比差异无统计学意义($P=0.553$)。

3 讨论

现代医学认为 NVAf 的发生发展与心脏因素(如心脏病、心脏瓣膜病、冠状动脉疾病、充血性心衰、缺血性心脏病、高血压等)及非心脏因素[如年龄、迷走神经刺激、糖尿病、甲状腺疾病、慢性阻塞性肺疾病(COPD)、嗜酒、肥胖、电解质紊乱、睡眠呼吸暂停综合征(SAS)、肺栓塞等]密切相关^[12-13]。华法林属中效抗凝剂,其用于治疗 NVAf 的作用机制与优势为①通过对维生素 K(Vit K)产生竞争性对抗作用,阻断肝细胞合成凝血因子 II~X,进而发挥抗凝作用;②还能通过抑制凝血酶(Thr)活性,降低血小板聚集率(PAR),继而起到抗血小板聚集(PA)的作用;③生物利用度高;④能有效抑制栓塞的发生与血栓脱落、阻止血栓的延展与扩大、抑制新的血栓形成等优势^[14]。但在临床使用中仍存在诸多局限性,如易与多种药物及食物发生相互作用、有时需肝素矫接治疗、治疗窗窄、存在代谢的基因多态性、需要实验室监测凝血指标调整用药剂量、起效慢等^[9]。Yang 等^[15]报道显示在中国急性缺血性卒中(AIS)合并 NVAf 的患者中出院后使用华法林抗凝治疗的比例较低,仅为 19.4%。由此可见,临床

上 NVAf 患者若只依赖于华法林进行抗凝治疗是远远不够的。

利伐沙班属凝血因子 Xa(FXa)抑制剂,其用于抗凝的作用机制主要是通过直接、高选择性地抑制 FXa,致使凝血瀑布的外源性与内源性途径中断,进而抑制 Thr 的形成,并可阻断由 Thr 介导的级联放大效应,起到抗凝作用^[16]。利伐沙班的优势在于①分子量小、几乎不溶于水;②口服吸收不受食物影响、起效快;③对机体已有 Thr 活性影响较小,从而对生理性止血功能的影响不大;④以单个凝血因子为靶点,因此能影响其药效的药物种类较少;⑤同时治疗期间无需频繁监测 INR。Enomoto 等^[17]研究显示 NVAf 电复律患者采取利伐沙班抗凝治疗是安全、有效的,能明显缩短电复律时间。一项国外荟萃分析^[18]亦显示房颤患者采用利伐沙班抗凝治疗具有较高有效性与安全性,能显著减少患者中风、降低颅内出血与死亡率,是一种不错的选择。ROCKET AF 试验^[19]显示在 NVAf 患者全身性栓塞与卒中的预防上利伐沙班具有替代华法林的潜在优势。2016 年《建议》^[9]也推荐针对 INR 不稳定、以往使用华法林发生出血、不愿意或不能接受华法林治疗的老年房颤患者可优先考虑使用 NOACs(如利伐沙班、达比加群)。

资料^[20]显示多数高龄 NVAf 患者均合并血栓倾向疾病。本研究中高龄 NVAf 患者分别采用利伐沙班与华法林进行抗凝治疗 6 个月期间栓塞发生率依次仅为 5.5%和 6.8%,且两组差异无统计学意义;提示以上两种药物在预防高龄 NVAf 患者血

栓栓塞事件方面效果相近;这与国内外相关报道^[21,22]的结果是一致的。本研究显示与华法林组(15.1%)相比,利伐沙班组治疗6个月内出血发生率为4.1%,明显降低;说明高龄 NVAf 患者采用利伐沙班抗栓治疗更有助于减少出血事件与降低出血程度;这与有关研究^[23,24]结果相似。从药物不良反应的角度分析,两组不良反应主要集中于神经系统和胃肠道反应,但症状均较轻微、未见其他严重事件,且两组不良反应总发生率相比差异无统计学意义;可见高龄 NVAf 患者对以上两种药物的耐受性均较高。

D-D 是一种特异性降解产物,能有效反映纤维蛋白溶解功能。当机体血管内有纤维溶解活动与活化的血栓形成,D-D 含量就会明显增加。同时病人在弥漫性血管内凝血(DIC)、肺栓塞(PE)、深静脉血栓(DVT)等病理状态下,亦均可引起 D-D 水平的升高^[25]。文献^[26]显示 NVAf 患者机体存在一定程度的高凝状态,D-D 含量可作为评估 NVAf 患者栓塞风险的重要参考指标。NT-proBNP 是当前临床评估心功能的客观标志物^[27]。当患者发生房颤时,可引发心室容量改变、心房压力增加,使得 NT-proBNP 大量合成与分泌,此外心房肌细胞在持续房颤发作状态下又极易引起变性纤维化,进一步促使心肌细胞(CMC)释放 NT-proBNP,继而损伤机体内皮功能、增加血液浓度与粘稠度,从而间接导致血栓形成。因此监测 NT-proBNP 水平对判断房颤患者血栓前状态具有重要意义^[28]。本研究结果显示与治疗前相比,两组治疗 3、6 个月后血浆 D-D 和 NT-proBNP 水平,均逐渐改善;但与华法林组同期对比,利伐沙班组治疗 3、6 个月后以上血浆指标水平,均无明显差异。说明高龄 NVAf 采取上述两种药物进行抗栓治疗均能有效改善患者血液高凝状态、降低栓塞风险;这与本研究两组血栓栓塞事件的控制效果是一致的。

综上所述,与华法林相比,高龄 NVAf 应用利伐沙班抗栓治疗在患者耐受性与预防血栓栓塞方面优势相当,但利伐沙班更能有效降低患者出血风险。但本研究仍存在诸如观察指标不够全面、随访时间较短、样本量有限等局限性,故有待临床更多前瞻性、大样本、多中心的随机对照研究进一步论证与分析。

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