

APTT 监测对达比加群酯治疗 VTE 病人不良事件发生的影响

崔文军 安乾 司江涛 王颖 吴斐 李阳 王兵

(郑州大学第五附属医院血管外科, 河南 郑州 450001)

[摘要] **目的** 探讨监测活化部分凝血活酶时间(APTT)对达比加群酯治疗静脉血栓栓塞症(VTE)病人不良事件发生的影响。**方法** 回顾性分析 2015 年 1 月—2017 年 12 月我院采用达比加群酯抗凝治疗的 589 例 VTE 病人的临床资料,根据半年内 APTT 监测次数分为 3 组,未进行监测的病人 151 例(A 组),仅进行 1 次监测的病人 255 例(B 组),监测 ≥ 2 次的病人 183 例(C 组)。对比分析 3 组病人的临床资料及随访结果。**结果** 半年内 3 组病人不良事件发生及停用药物比例比较差异无统计学意义($P>0.05$),随访中监测 APTT 值几乎没有超出正常值上限 2 倍。**结论** 达比加群酯治疗 VTE 病人期间监测 APTT 并不能有效减少临床不良事件的发生,应该寻找更加有效的监测指标,以减少病人不良事件的发生。

[关键词] 部分促凝血酶原时间;达比加群;静脉血栓栓塞;出血

[中图分类号] R619.2;R972.7;R969.1 **[文献标志码]** A

EFFECT OF ACTIVATED PARTIAL THROMBOPLASTIN TIME MEASUREMENT ON ADVERSE EVENTS IN PATIENTS WITH VENOUS THROMBOEMBOLISM TREATED WITH DABIGATRAN ETEXILATE CUI Wenjun, AN Qian, SI Jiangtao, WANG Ying, WU Fei, LI Yang, WANG Bing (Department of Vascular Surgery, The Fifth Affiliated Hospital of Zhengzhou University, Zhengzhou 450001, China)

[ABSTRACT] **Objective** To investigate the effect of activated partial thromboplastin time (APTT) measurement on adverse events in patients with venous thromboembolism (VTE) treated with dabigatran etexilate. **Methods** The clinical data of 589 eligible VTE patients were retrospectively analyzed, who underwent anticoagulant therapy with dabigatran etexilate in the Fifth Affiliated Hospital of Zhengzhou University from January 2015 to December 2017. The patients were divided into three groups based on the number of APTT measurements during the first 6 months after drug prescription, namely group A with 151 cases who did not receive any APTT measurement, group B with 255 cases who underwent measurement once, and group C with 183 cases who received two or more measurements. Then the clinical data and follow-up outcomes were compared between these groups. **Results** There were no significant differences in the rates of adverse events and drug discontinuation between the three groups during the six-month follow-up period ($P>0.05$). Meanwhile, the APTT value during the follow-up period barely exceeded twice the upper limit of the normal value. **Conclusion** APTT measurements in the treatment of VTE patients with dabigatran etexilate cannot effectively reduce the incidence of clinical adverse events. Therefore, more effective indicators should be found to reduce the incidence of adverse events.

[KEY WORDS] Partial thromboplastin time; Dabigatran; Venous thromboembolism; Hemorrhage

口服抗凝剂达比加群酯是直接凝血酶抑制剂,其抗凝效果稳定可靠,应用于围手术期及治疗房颤、静脉血栓栓塞症(VTE)等疾病安全有效^[1-4]。VTE 包括深静脉血栓形成(DVT)和肺栓塞(PE),是临床常见的疾病之一^[5-8],血栓后遗症时间漫长且复发率高^[9-11],给社会和家庭带来沉重经济负担^[12-13]。很多研究表明达比加群酯和华法林抗凝效果相当,但比华法林更安全,出血风险更低^[14-17]。之前研究证实口服达比加群酯后部分病人会出现活化部分凝血活酶时间(APTT)延长,APTT 延长可以增加出血

风险^[18-20]。同时药物最佳浓度及药物敏感性存在个体差异,所以通过检测口服抗凝药物的抗凝强度,可为临床用药提供参考,并有助于预防临床不良事件的发生。有关的机构和组织已经考虑制定一些细则来检测新型口服抗凝剂的剂量,寻找在合适的时间采用恰当的方法实时检测抗凝强度的有效举措^[21]。临床工作中由于病人的病情变化或担心抗凝强度的变化,也可能会进行重复的血凝检测来确保药物抗凝治疗的安全性,从而可能导致过度检测,为病人增加经济负担和增加病人精神、身体的痛苦。本研究旨在探讨达比加群酯治疗 VTE 病人期间通过检测 APTT 能否及时发现临床不良事件的发生,为能在合适的时间采用恰当方法实时监测抗凝强度提供数据支持,有助于临床决策。

[收稿日期] 2019-01-19; **[修订日期]** 2019-02-10

[基金项目] 河南省医学科技攻关计划联合共建项目(2018-020242)

[通讯作者] 王兵, Email: wangbing222111@sina.com

1 资料与方法

1.1 一般资料

选取 2015 年 1 月—2017 年 12 月于我院口服达比加群酯治疗的 VTE 病人。纳入标准:病人年龄 ≥ 18 岁,明确诊断急性有症状的下肢近心端静脉血栓(包括腘静脉、股静脉、髂静脉)及有症状的肺栓塞(合并有或无深静脉血栓)。排除标准:存在活动性出血;出血风险较高;存在抗凝禁忌证;合并恶性肿瘤计划长期使用低分子肝素治疗;深静脉血栓或肺栓塞已被完全处理不存在 VTE 复发的持续危险因素;口服抗凝治疗计划小于半年;正在口服抗血小板的药物。符合条件者共有 589 例病人,其中男 354 例,女 235 例;平均年龄 57.6 岁。根据病人半年内 APTT 监测次数分为 3 组,未进行监测 151 例(A 组),仅仅监测 1 次 255 例(B 组),监测 ≥ 2 次 183 例(C 组)。3 组病人的基本情况见表 1,3 组病人的基本特征比较差异无统计学意义。

1.2 研究方法

对采用达比加群酯抗凝治疗的 589 例 VTE 病人的临床资料进行回顾性分析。所有病人急性期 VTE 均卧床休息,并给予低分子肝素或普通肝素抗凝(首次负荷量 80 U/kg,每小时 18 U/kg 输注维持,使 APTT 保持在正常对照值 1.5~2.5 倍)治疗 2 周^[22]。急性期后口服达比加群酯 110 mg,每天 2 次抗凝治疗^[23]。所有病人随访半年平均每个月电话随访一次,详细记录从口服药物开始到半年随访结束病人发生的与 VTE 或服用药物相关的不良事件,主要不良事件包括 VTE 复发、严重出血(需要住院输血治疗或血红蛋白降低 ≥ 20 g/L)及任何原因的死亡^[24];次要不良事件主要包括不严重出血(有明显出血尚未达到严重出血标准,需要暂停抗凝药物治疗)及消化道症状(如烧心、反酸、恶心、厌食等)^[25]。

1.3 统计学处理

采用 SPSS 16.0 软件进行统计学处理,计数资料以百分比表示,组间比较采用卡方检验或 Fisher 确切概率法,以 $P < 0.05$ 为差异有统计学意义。

2 结 果

3 组病人主要不良事件及次要不良事件发生率比较差异均无统计学意义 ($P > 0.05$)。

3 组病人不良事件(主要不良事件+次要不良事件)发生率比较差异均无统计学意义 ($P > 0.05$)。

半年随访中 3 组病人是否停止服药差异无统计学意义 ($P > 0.05$)。见表 1。

表 1 3 组病人的基本情况及随访结果比较

参数	A 组	B 组	C 组
年龄($\bar{x} \pm s$, 岁)	54.6 \pm 11.6	56.7 \pm 13.7	61.3 \pm 12.2
性别(例,男/女)	90/61	156/99	108/75
肌酐清除率(q_v /mL \cdot min ⁻¹)	80.2 \pm 30.2	84.8 \pm 32.6	78.3 \pm 31.7
前期华法林治疗(例(χ /%)	33(21.9)	58(22.7)	46(25.1)
恶性肿瘤(例(χ /%)	15(10.0)	33(12.9)	31(16.9)
APTT 明显延长(例(χ /%)	—	3(1.2)	5(2.7)
主要不良事件(例(χ /%)	5(3.3)	8(3.1)	6(3.3)
VTE 复发(例(χ /%)	3(2.0)	4(1.6)	3(1.6)
死亡(例(χ /%)	0(0)	1(0.4)	0(0)
严重出血(例(χ /%)	2(1.3)	3(1.2)	3(1.6)
次要不良事件(例(χ /%)	9(6.0)	19(7.5)	15(8.2)
不严重出血(例(χ /%)	7(4.6)	10(3.9)	8(4.4)
消化道症状(例(χ /%)	2(1.3)	9(3.5)	7(3.8)
停止服药(例(χ /%)	2(1.3)	4 (1.6)	3(1.6)

3 讨 论

本研究结果显示,部分口服达比加群酯抗凝治疗病人血凝指标 APTT 延长,这和之前多项观察研究结果相同^[26-30],但 APTT 指标和达比加群酯剂量及抗凝强度关系并不清楚。VAN 等^[31]通过监测达比加群酯血药浓度及血凝指标,并对比分析其相关性,结果提示当达比加群酯血药浓度较低时血凝指标 APTT 较为敏感;SAMAMA 等^[32]通过对比监测正常成人血凝指标与口服达比加群酯病人血凝指标认为,APTT 是监测达比加群酯的一个敏感指标;很多研究认为 APTT 可作为达比加群酯抗凝治疗的监测指标^[33-35]。但本观察研究结果显示,并非所有口服达比加群酯治疗的病人血凝指标 APTT 均延长,所以 APTT 并不是监测达比加群酯治疗的一个可靠指标。ANTOVIC 等^[36]采用液相色谱-串联质谱(LC-MS/MS)法对血浆达比加群酯进行定量检测,并以此为基准评价血凝指标检测的效度,结果显示 APTT 对血浆中达比加群酯药物浓度变化并不敏感。KAWABATA 等^[20]研究发现,口服达比加群酯可引起 APTT 延长,但 APTT 延长个体差异性较大,并且 APTT 延长与临床出血等不良事件发生无关联性。TESTA 等^[37]利用稀释的凝血酶时间(dTT)作为基准,对比分析发现 APTT 与 dTT 关联性差,认为 APTT 并不能很好体现达比加群酯抗凝强度。CHANG 等^[38]研究发现,口服达比加群酯治疗后 APTT 改变存在较大个体差异,血清达比加群酯的浓度和 APTT 值关联并不密切,更不是单

纯线性关系,观察到的临床不良事件与检测 APTT 并无明显的关联性。本研究随访结果显示检测 APTT 与不良事件的发生及是否停止服药之间并无明确关联,即检测 APTT 并不能很好地评估达比加群酯的抗凝强度。

本研究发现 3 组病人不良事件(主要不良事件、次要不良事件、主要不良事件+次要不良事件)的发生率以及是否停药差异无统计学意义,即多次的 APTT 检测并不能减少病人临床不良事件的发生。CUKER 等^[39] 回顾性分析关于检测达比加群酯抗凝强度的血凝指标的文献,共有 17 项研究纳入分析,17 项研究中均以血浆中达比加群酯含量(采用 LC-MS/MS 法检测)为基准评价相关血凝指标的效应。分析结果认为 APTT 对达比加群酯浓度变化敏感性差。虽然 APTT 检测参考价值有限,但临床检测方便、迅速、成本低廉。临床实际工作中采用 LC-MS/MS 检测达比加群酯血药浓度不仅耗时并且成本高昂,再由于个体对达比加群酯耐受不同,单纯检测达比加群酯血药浓度并不能完全代表出血风险。尽管检测 APTT 并不能完全代表达比加群酯的抗凝强度及血药浓度,但是检测 APTT 可以对一些特定病人提供有价值的信息,例如刚服药后高出血病人的评估、需要进行侵入性诊疗操作的病人、临床有出血表现的病人等。

口服达比加群酯后有较好的生物利用度,受食物因素干扰较小,这与华法林不同^[2,14-17]。在本随访研究中半年内大约 1/4 的病人未进行检测,大约 40% 的病人仅监测 1 次,不到 1/3 的病人进行多次监测,这个监测频率总体是合理的。监测目的是核查是否有系统性出血风险而不是监测达比加群酯抗凝强度。监测随访半年内多次血凝指标监测并未发现 APTT 超出正常值上限 2 倍。口服达比加群酯治疗期间,APTT 监测可以帮助核查口服达比加群酯后是否有系统性出血风险,当 APTT 明显增高时要引起临床重视。基于本次半年的临床研究观察,服用药物后的采集血标本的时间,每天的药物吸收变化及肾脏代谢功能的变化,均可能会对 APTT 造成影响^[23],但一般对 APTT 值影响较小。所以当服用达比加群酯治疗后,一次监测 APTT 延长但未超出正常值上限 2 倍时应当考虑为正常的生理波动,是否需进行重复监测应根据临床病情变化来确定。短期内重复监测 APTT 意义不大。当然,当病人身体状况突然出现重大变化时,是否行 APTT 监测应由临床医师根据具体情况而定。

总之,在达比加群酯治疗 VTE 病人期间监测 APTT 并不能有效减少临床不良事件的发生,应该寻找更加有效的监测指标,以减少病人不良事件的发生。

[参考文献]

- [1] CHAN Y H, KUO C T, YEH Y H, et al. Thromboembolic, bleeding, and mortality risks of rivaroxaban and dabigatran in asians with nonvalvular atrial fibrillation[J]. J Am Coll Cardiol, 2016,68(13):1389-1401.
- [2] CALKINS H, WILLEMS S, GERSTENFELD E P, et al. Uninterrupted dabigatran versus warfarin for ablation in atrial fibrillation[J]. N Engl J Med, 2017,376(17):1627-1636.
- [3] SHAW J, DE WIT C, LE GAL G, et al. Thrombotic and bleeding outcomes following perioperative interruption of direct oral anticoagulants in patients with venous thromboembolic disease[J]. J Thromb Haemost, 2017,15(5):925-930.
- [4] CANNON C P, LIP G Y H, OLDGREN J. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation[J]. N Engl J Med, 2018,378(5):485-486.
- [5] SOGAARD K K, SCHMIDT M, PEDERSEN L, et al. 30-year mortality after venous thromboembolism: A population-based cohort study[J]. Circulation, 2014,130(10):829-836.
- [6] ROBBINS I M, PUGH M E, HEMNES A R. Update on chronic thromboembolic pulmonary hypertension[J]. Trends Cardiovasc Med, 2017,27(1):29-37.
- [7] CARRIER M, LE GAL G, WELLS P S, et al. Systematic review: Case-fatality rates of recurrent venous thromboembolism and major bleeding events among patients treated for venous thromboembolism[J]. Ann Intern Med, 2010,152(9):578-589.
- [8] YUSUF H R, REYES N, ZHANG Q C, et al. Hospitalizations of adults ≥ 60 years of age with venous thromboembolism[J]. Clin Appl Thromb Hemost, 2014,20(2):136-142.
- [9] MARTINEZ C, COHEN A T, BAMBER L, et al. Epidemiology of first and recurrent venous thromboembolism: A population-based cohort study in patients without active cancer[J]. Thromb Haemost, 2014,112(2):255-263.
- [10] TAGALAKIS V, PATENAUDE V, KAHN S R, et al. Incidence of and mortality from venous thromboembolism in a real-world population: The Q-VTE Study Cohort[J]. Am J Med, 2013,126(9):832.e13-21.
- [11] KAHN S R, COMEROTA A J, CUSHMAN M, et al. The postthrombotic syndrome: Evidence-based prevention, diagnosis, and treatment strategies: A scientific statement from the American Heart Association[J]. Circulation, 2014,130(18):1636-1661.
- [12] KRÖGER K, KÜPPER-NYBELEN J, MOERCHER C, et al. Prevalence and economic burden of pulmonary embolism in Germany[J]. Vasc Med, 2012,17(5):303-309.
- [13] LAMORI J C, SHOHEIBER O, MODY S H, et al. Inpatient

- resource use and cost burden of deep vein thrombosis and pulmonary embolism in the United States[J]. *Clin Ther*, 2015,37(1):62-70.
- [14] SCHULMAN S, KAKKAR A K, GOLDBERGER S Z, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis[J]. *Circulation*, 2014,129(7):764-772.
- [15] ROETKER N S, LUTSEY P L, ZAKAI N A, et al. All-cause mortality risk with direct oral anticoagulants and warfarin in the primary treatment of venous thromboembolism [J]. *Thromb Haemost*, 2018,118(9):1637-1645.
- [16] HUISMAN M V, FERREIRA M, FEURING M, et al. Less abnormal uterine bleeding with dabigatran than warfarin in women treated for acute venous thromboembolism [J]. *J Thromb Haemost*, 2018,16(9):1775-1778.
- [17] BASTO A N, FEWEL N P, VO K, et al. Initiation of direct oral anticoagulants versus warfarin for venous thromboembolism: Impact on time to hospital discharge[J]. *J Thromb Thrombolysis*, 2018,45(1):51-55.
- [18] WOLFE Z, KHAN S U, NASIR F, et al. A systematic review and Bayesian network meta-analysis of risk of intracranial hemorrhage with direct oral anticoagulants[J]. *J Thromb Haemost*, 2018,16(7):1296-1306.
- [19] TSUTSUMI Y, SHIMONO J, OHHIGASHI H, et al. Analysis of the influence of dabigatran on coagulation factors and inhibitors[J]. *Int J Lab Hematol*, 2015,37(2):225-230.
- [20] KAWABATA M, YOKOYAMA Y, SASANO T, et al. Bleeding events and activated partial thromboplastin time with dabigatran in clinical practice[J]. *J Cardiol*, 2013,62(2):121-126.
- [21] GOSSELIN R C, ADCOCK D M, BATES S M, et al. International council for standardization in haematology (ICSH) recommendations for laboratory measurement of direct oral anticoagulants[J]. *Thromb Haemost*, 2018,118(3):437-450.
- [22] 中华医学会外科学分会血管外科学组. 深静脉血栓形成的诊断和治疗指南(第三版)[J]. *中华普通外科杂志*, 2017,32(9):807-812.
- [23] DALE B J, CHAN N C, EIKELBOOM J W. Laboratory measurement of the direct oral anticoagulants[J]. *Br J Haematol*, 2016,172(3):315-336.
- [24] SCHULMAN S, ANGERAS U, BERGQVIST D, et al. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in surgical patients[J]. *J Thromb Haemost*, 2010,8(1):202-204.
- [25] HOFFMAN A, GALLE P R. Gastrointestinal disorders and dabigatran[J]. *Scand J Gastroenterol*, 2013,48(1):9-16.
- [26] MANI H. Interpretation of coagulation test results under direct oral anticoagulants[J]. *Int J Lab Hematol*, 2014,36(3):261-268.
- [27] EHRENSCHWENDER M, KOESSLER J, BRUNNER K, et al. A 77-year-old man with a prolonged activated partial thromboplastin time[J]. *Clin Chem*, 2012,58(10):1402-1405.
- [28] KITCHEN S, GRAY E, MACKIE I, et al. Measurement of non-coumarin anticoagulants and their effects on tests of Haemostasis: Guidance from the British Committee for Standards in Haematology[J]. *Br J Haematol*, 2014,166(6):830-841.
- [29] DOUXFELS J, MULLIER F, ROBERT S, et al. Impact of dabigatran on a large panel of routine or specific coagulation assays. Laboratory recommendations for monitoring of dabigatran etexilate[J]. *Thromb Haemost*, 2012,107(5):985-997.
- [30] GOSSELIN R C, ADCOCK D M. The laboratory's 2015 perspective on direct oral anticoagulant testing [J]. *J Thromb Haemost*, 2016,14(5):886-893.
- [31] VAN RYN J, STANGIER J, HAERTTER S, et al. Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: Interpretation of coagulation assays and reversal of anticoagulant activity [J]. *Thromb Haemost*, 2010, 103 (6):1116-1127.
- [32] SAMAMA M M, GUINET C, LE FLEM L, et al. Measurement of dabigatran and rivaroxaban in primary prevention of venous thromboembolism in 106 patients, who have undergone major orthopedic surgery: An observational study [J]. *J Thromb Thrombolysis*, 2013,35(2):140-146.
- [33] GOSSELIN R C, DWYRE D M, DAGER W E. Measuring dabigatran concentrations using a chromogenic ecarin clotting time assay[J]. *Ann Pharmacother*, 2013,47(12):1635-1640.
- [34] AVECILLA S T, FERRELL C, CHANDLER W L, et al. Plasma-diluted thrombin time to measure dabigatran concentrations during dabigatran etexilate therapy[J]. *Am J Clin Pathol*, 2012,137(4):572-574.
- [35] VAN BLERK M, BAILLEUL E, CHATELAIN B, et al. Influence of dabigatran and rivaroxaban on routine coagulation assays. A nationwide Belgian survey[J]. *Thromb Haemost*, 2015,113(1):154-164.
- [36] ANTOVIC J P, SKEPPHOLM M, EINTREIJ, et al. Evaluation of coagulation assays versus LC-MS/MS for determinations of dabigatran concentrations in plasma[J]. *Eur J Clin Pharmacol*, 2013,69(11):1875-1881.
- [37] TESTA S, LEGNANI C, TRIPODI A, et al. Poor comparability of coagulation screening test with specific measurement in patients receiving direct oral anticoagulants: Results from a multicenter/multiplatform study [J]. *J Thromb Haemost*, 2016,14(11):2194-2201.
- [38] CHANG Y T, HU Y F, LIAO J N, et al. The assessment of anticoagulant activity to predict bleeding outcome in atrial fibrillation patients receiving dabigatran etexilate[J]. *Blood Coagul Fibrinolysis*, 2016,27(4):389-395.
- [39] CUKER A, SIEGAL D M, CROWTHER M A, et al. Laboratory measurement of the anticoagulant activity of the non-vitamin K oral anticoagulants [J]. *J Am Coll Cardiol*, 2014, 64 (11):1128-1139.