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不同剂量利伐沙班对老年髋关节置换术患者凝血功能及下肢深静脉血栓的影响

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摘要 目的:探讨不同剂量利伐沙班对老年髋关节置换术患者凝血功能及下肢深静脉血栓(DVT)的影响。**方法:**选择 2013 年 6 月~2016 年 6 月期间我院收治的 200 例老年髋关节置换术患者,按随机数字表法分为两组各 100 例,术后分别予利伐沙班 5 mg、10 mg 口服以预防 DVT。术前及术后 1d、7d 检测纤维蛋白原(Fbg)、凝血酶原时间(PT)、凝血酶时间(TT)、活化部分凝血酶原时间(APTT)及 D-二聚体(D-D),同时行下肢彩色多普勒超声检查判断 DVT 发生情况,观察临床出血事件。**结果:**术后 1d 两组 Fbg 水平明显降低,PT 明显延长(均 $P<0.05$);术后 7d 两组 Fbg 水平与术后 1d 相比明显回升,PT 明显缩短(均 $P<0.05$)。两组各时期的 Fbg 与 PT 均无明显差异($P>0.05$)。术后 1d 两组 D-D 水平均明显升高($P<0.05$),且利伐沙班 5 mg 组明显高于利伐沙班 10 mg 组($P<0.05$);术后 7d 两组 D-D 水平均较术后 1d 明显降低($P<0.05$),且利伐沙班 10 mg 组明显低于利伐沙班 5 mg 组($P<0.05$)。利伐沙班 10 mg 组术后早期 DVT 发生率明显低于利伐沙班 5 mg 组($P<0.05$)。两组预防性抗凝后临床出血事件的发生率比较无统计学差异($P>0.05$)。**结论:**老年髋关节置换术后口服大剂量(10 mg)利伐沙班,可有效改善血液高凝状态,降低 DVT 发生率,且不会明显增加临床出血事件,值得推广。

关键词:利伐沙班;髋关节置换术;凝血功能;下肢深静脉血栓;老年

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Hip Replacement: Effects of Different Doses of Rivaroxaban on Coagulation Function and Deep Venous Thrombosis in Elderly Patients

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ABSTRACT Objective: To investigate the effects of different doses of rivaroxaban on coagulation function and deep venous thrombosis (DVT) in elderly patients undergoing hip replacement. **Methods:** A total of 200 patients, who underwent hip replacement in Jingzhou Central Hospital of Hubei Province from June 2013 to June 2016, were selected and randomly divided into group I ($n=100$) and group II ($n=100$). After surgery, group I and group II were treated with 5 mg and 10 mg rivaroxaban orally to prevent DVT. Fibrinogen (Fbg), prothrombin time (PT), thrombin time (TT), activated partial thromboplastin time (APTT) and D-dimer (D-D) were detected before surgery and 1d and 7d after surgery. At the same time, lower extremity color Doppler ultrasound was used to determine the occurrence of DVT, the clinical bleeding events were observed. **Results:** The levels of Fbg in the two groups were decreased significantly 1d after surgery, and PT was significantly prolonged (all $P<0.05$). 7d after surgery, the levels of Fbg in the two groups were significantly higher than those of 1d after surgery, and PT was significantly shortened (all $P<0.05$). There were no significant differences in Fbg and PT between the two groups in each period ($P>0.05$). The levels of D-D were significantly increased in the two groups 1d after surgery ($P<0.05$), and group I was higher than group II ($P<0.05$). The levels of D-D in the two groups 7d after surgery were significantly lower than those 1d after operation ($P<0.05$), and group II was lower than that group I ($P<0.05$). The incidence of early DVT in group II was significantly lower than that in group I ($P<0.05$). There was no significant difference in the incidence of clinical bleeding events after prophylactic anticoagulation between the two groups ($P>0.05$). **Conclusion:** Oral high dose (10 mg) rivaroxaban after hip arthroplasty in elderly patients can effectively improve the hypercoagulable state and reduce the incidence of DVT, and will not significantly increase the clinical bleeding events, which is worth popularizing.

Key words: Rivaroxaban; Hip replacement; Coagulation function; Deep venous thrombosis; Elderly

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前言

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在骨科临床上,人工髋关节置换术是治疗股骨头坏死与股骨颈骨折的常用手段,但术后常见并发下肢深静脉血栓形成(Deep Venous Thrombosis, DVT),尤其是老年患者术后出现血栓栓塞事件的可能性更高^[1-3]。流行病学研究表明,年龄大于 65 岁是 DVT 的独立危险因素之一^[4]。因此,做好老年髋关节置换

术患者术后 DVT 的预防工作, 确保患者顺利渡过围手术期是临床医疗工作与护理工作的重要内容。目前术后常规抗凝的效果与临床期望值仍有一定的差距^[5,6]。利伐沙班是一种新型抗凝药物, 能够对凝血瀑布中的共同通路起始环节的 Xa 因子产生抑制作用而达到抗凝的目的^[7,8]。研究显示, 利伐沙班对关节置换术后的普通患者可起到较好的 DVT 预防作用, 且对 65 岁以上的老年患者亦可获得与常规抗凝相当的 DVT 预防效果^[9]。但目前尚鲜有研究报道不同剂量利伐沙班对老年髋关节置换术患者的影响, 为此, 本研究对 200 例分别予利伐沙班 5 mg、10 mg 进行临床对照研究, 以期临床用药剂量的选择提供一定的参考, 现报道如下。

1 资料和方法

1.1 临床资料

选择 2013 年 6 月~2016 年 6 月期间我院收治的 200 例老年髋关节置换术患者。纳入标准: ① 年龄 ≥ 65 岁; ② 初次单侧行髋关节置换术; ③ 术前双下肢血管彩超检查无 DVT; ④ 术前无凝血功能异常; ⑤ 签署知情同意书; 排除标准: ① 合并血液系统疾病, 心脑血管疾病, 糖尿病及恶性肿瘤等; ② 术前双下肢血管彩超提示已存在 DVT; ③ 存在肝、肾、心脏功能异常; ④ 近期服用过对血液流变学指标有影响的药物。按照随机数字表法分为两组, 每组各 100 例, 其中利伐沙班 5 mg 组男 37 例, 女 63 例; 年龄 65~84 岁, 平均 (69.6 ± 3.1) 岁, 平均体质指数 (BMI) (25.2 ± 4.2) kg/m²; 利伐沙班 10 mg 组男 39 例, 女 61 例; 年龄 65~82 岁, 平均 (70.1 ± 4.3) 岁, 平均 BMI (24.7 ± 3.9) kg/m²; 两组的一般资料比较无统计学差异 ($P > 0.05$), 具有可比性。

1.2 方法

两组的标准化治疗方案相同, 入院后 3~5d 接受手术, 由同一组医师主刀, 换髋术式相同, 术毕回病房治疗。两组的抗凝方案均采用利伐沙班 (德国 Bayer Schering Pharma AG, 注册证号 H20140132, 规格 10 mg), 利伐沙班 5 mg 组 5 mg/次, 利伐沙班 10 mg 组 10 mg/次, 首剂于术后 8 h 给药, 1 次/d, 连续 2 周。两组定期行血常规及凝血功能检查, 对于血小板计数持续

小于 10×10^{12} 及国际标准化比值 (INR) 延长大于 3 的患者, 及时停药。

1.3 观察指标

1.3.1 实验室检查 采用贝克曼库尔特自动凝血仪检测术前及术后 1d、7d 的纤维蛋白原 (Fbg)、凝血酶原时间 (PT)、凝血酶时间 (TT)、活化部分凝血酶原时间 (APTT) 及 D-二聚体 (D-D)。D-D 测定方法为免疫比浊法, 试剂由法国 Stago 公司生产。INR = PTtest/PTnormal。

1.3.2 双下肢血管彩超检查 使用 Philip IU-22 型彩色多普勒超声仪, 探头频率 5~13 MHz, 检查术后早期 (14d 内) 的 DVT 发生情况。超声诊断标准: 管腔内存在实性回声; 管腔用探头加压无法压瘪; 管腔内无彩色血流信号。仅局限于位于腘静脉以上的深静脉血栓为近端 DVT, 以下为远端 DVT, 近远均有深静脉血栓为全静脉血栓。

1.3.3 主要临床出血事件观察 包括切口持续渗血或切口内血肿形成, 肉眼可见的血尿、便血或咯血, 牙龈、鼻衄出血, 皮下瘀斑等。

1.4 统计学方法

数据采用 SPSS16.0 分析软件进行统计学分析, 计量资料均以 $(\bar{x} \pm s)$ 表示, t 检验, 计数资料以率 (%) 表示, χ^2 检验, $P < 0.05$ 表示差异有统计学意义。

2 结果

2.1 两组术前术后凝血功能指标及 D-D 水平比较

两组术前凝血功能指标及 D-D 水平比较差异无统计学意义 ($P > 0.05$)。术后两组 TT、APTT 均无明显变化 ($P > 0.05$)。术后 1d 两组 Fbg 水平明显降低, PT 明显延长 (均 $P < 0.05$); 术后 7d 两组 Fbg 水平与术后 1d 相比明显回升, PT 明显缩短 (均 $P < 0.05$)。两组各时期的 Fbg 与 PT 均无明显差异 ($P > 0.05$)。术后 1d 两组 D-D 水平均明显升高 ($P < 0.05$), 且利伐沙班 5 mg 组明显高于利伐沙班 10 mg 组 ($P < 0.05$); 术后 7d 两组 D-D 水平均较术后 1d 明显降低 ($P < 0.05$), 且利伐沙班 10 mg 组明显低于利伐沙班 5 mg 组 ($P < 0.05$), 见表 1。

表 1 两组术前术后凝血功能指标及 D-D 水平比较 ($\bar{x} \pm s$)

Table 1 Comparison of coagulation function and D-D level between two groups before and after surgery ($\bar{x} \pm s$)

Groups	Periods	Fbg(g/L)	TT(s)	PT(s)	APTT(s)	D-D(μ g/L)
5mg rivaroxaban group (n=100)	Before surgery	4.43 $\pm$ 0.71	16.93 $\pm$ 5.74	14.23 $\pm$ 2.59	33.49 $\pm$ 5.74	377.93 $\pm$ 69.45
	1d after surgery	2.95 $\pm$ 0.87*	17.53 $\pm$ 4.61	15.72 $\pm$ 1.39*	34.50 $\pm$ 4.69	549.56 $\pm$ 115.25*
	7d after surgery	3.73 $\pm$ 0.51 [#]	17.66 $\pm$ 5.77	14.51 $\pm$ 1.54 [#]	35.09 $\pm$ 6.09	316.34 $\pm$ 99.76**
10mg rivaroxaban group (n=100)	Before surgery	4.55 $\pm$ 0.47	16.97 $\pm$ 3.61	13.92 $\pm$ 2.39	33.57 $\pm$ 5.69	394.61 $\pm$ 71.97
	1d after surgery	2.73 $\pm$ 0.11*	17.72 $\pm$ 4.79	15.69 $\pm$ 2.79*	34.49 $\pm$ 4.74	458.63 $\pm$ 104.55* [△]
	7d after surgery	3.62 $\pm$ 0.25 [#]	17.44 $\pm$ 3.24	14.42 $\pm$ 1.38 [#]	35.20 $\pm$ 4.65	287.54 $\pm$ 67.28** ^{△△}

Note: Compared with before surgery, * $P < 0.05$; compared with 1d after surgery, [#] $P < 0.05$; compared with group I, [△] $P < 0.05$.

2.2 两组预防性抗凝后早期 DVT 发生率比较

利伐沙班 5 mg 组术后早期 DVT 发生率为 21.00%, 利伐沙班 10 mg 组为 4.00%, 组间比较有统计学差异 ($\chi^2=13.211$, $P=0.000$)。见表 2。

2.3 两组预防性抗凝后临床出血事件比较

两组术后均无切口持续渗血或切口内血肿形成, 无肉眼血尿、便血或咯血, 利伐沙班 5 mg 组中皮下瘀斑 ≥ 50 cm² 有 9 例, 鼻衄或齿龈出血 ≥ 5 min 有 3 例, 利伐沙班 10 mg 组分别有 10 例、6 例, 组间比较无统计学差异 ($\chi^2=0.664$, $P=0.415$)。

表 2 两组预防性抗凝后早期 DVT 发生率比较[n(%)]

Table 2 Incidence of early DVT after prophylactic anticoagulation in the two groups [n(%)]

Groups	近端	远端	全静脉	合计
5 mg rivaroxaban group (n=100)	2(2.00)	12(12.00)	7(7.00)	21(21.00)
10 mg rivaroxaban group (n=100)	0(0.00)	1(1.00)	3(3.00)	4(4.00)*

Note: Compared with group I, *P<0.05.

3 讨论

据了解,在不进行抗凝治疗的情况下,关节置换术患者发生 DVT 的可能性高达 43.2%,其中 1%~5%的患者存在肺栓塞的风险^[10],对患者的生命安全构成了严重威胁。当前预防 DVT 常规使用低分子肝素进行抗凝,但效果并不令人满意,DVT 的发生率仍达到了 10%左右^[11,12]。因此研究出新的药物及治疗策略显得十分有临床意义。过去临床主要是通过皮下注射低分子肝素来预防术后 DVT,但容易导致患者注射痛、注射部位血肿、血小板减少症等情况发生^[13-15],目前则越来越倾向于使用口服抗凝药物治疗。新型口服抗凝药物利伐沙班是一种 Xa 因子抑制剂,可影响凝血瀑布的内、外源性途径,对凝血酶的生成产生抑制,从而预防血栓形成,与传统的抗凝药物相比,其不需要抗凝血酶Ⅲ的介导也可实现抗凝的效果^[16]。研究证实,利伐沙班预防 DVT 及出血事件的临床效应要优于依诺肝素^[17,18]。但是对于老年人来说,由于其药物代谢特点有一定的特殊性,不仅肝代谢率及肾脏清除率比较低下,而且多合并多种基础病^[19],故在选药及治疗方面相对麻烦。目前不少研究均已证实利伐沙班适用于术后老年患者。周健等^[20]对老年全膝关节置换患者围手术期分别采用口服利伐沙班与皮下注射低分子量肝素的方法进行抗凝治疗,结果显示,前者可有效预防 DVT,疗效与后者相当,而且安全性良好。Loganathan L 等^[21]研究表明,口服利伐沙班与皮下注射低分子肝素均对全膝关节置换术后的老年糖尿病患者有一定的 DVT 预防作用,但口服利伐沙班的疗效更优,安全性更高。但利伐沙班的剂量的不同是否对关节置换术后老年患者的影响有所差异目前尚鲜有研究报道。

本研究中利伐沙班 5 mg 组与 10 mg 组术后 1dFbg 水平明显降低,PT 明显延长,术后 7d 两组 Fbg 水平与术后 1d 相比明显回升,PT 明显缩短。Fbg 是一种应急期蛋白,手术和创伤均可使患者产生一定程度的应激反应,从而促使肝脏合成 Fbg^[22-24]。血液中 Fbg 增加时,PT 降低,并导致高凝血状态的发生,而高凝血状态又将导致形成血栓的危险性大大增加^[25,26]。本研究结果表明两种剂量的利伐沙班均能有效改善患者术后的高凝血状态,促进血液循环,降低 DVT 发生。D-D 是临床中常用的可定量反映药物溶栓效果及诊断、筛选新形成的血栓的指标。本研究术后 1d 两组 D-D 水平均明显升高,且利伐沙班 5 mg 组明显高于利伐沙班 10 mg 组;术后 7d 两组 D-D 水平均较术后 1d 明显降低,且利伐沙班 10 mg 组明显低于利伐沙班 5 mg 组,提示大剂量利伐沙班对预防 DVT 的效果更佳。推测其与利伐沙班的药代动力学随剂量的增加而提高有关,研究表明,利伐沙班口服 10 mg 的绝对生物利用度可达到 80%~100%,其药代动力学在理想的范围内(最高 15mg/次·d)基本呈线性,而若再增加剂量就会出现溶出限制性吸收,剂量越大,生物利用度与吸收越差,特别是在空腹时表现更为明显^[27,28]。大剂量利伐沙

班可发挥更好的抗凝作用,但用药过量可能导致出血并发症^[29]。本研究结果显示,利伐沙班 10 mg 组临床出血事件的发生率高于利伐沙班 5 mg 组,但无差异无统计学意义,说明口服利伐沙班 10 mg 并不会明显增加临床出血事件的风险。陈德强等人^[30]采用 10 mg 利伐沙班预防骨科大手术术后深静脉血栓形成,出血事件的发生率为 2.1%,与本研究基本一致。

综上所述,髌关节置换术后口服利伐沙班 10mg 可有效改善血液高凝状态,降低 DVT 发生率,且不会明显增加临床出血事件,值得在临床上推广。

参考文献(References)

- [1] Wu PK, Chen CF, Chung LH, et al. Population-based epidemiology of postoperative venous thromboembolism in Taiwanese patients receiving hip or knee arthroplasty without pharmacological thromboprophylaxis[J]. Thromb Res, 2014, 133(5): 719-724
- [2] Łęgosz P, Krawczak K, Szczęśny G. Outcomes of treatment of periprosthetic femoral fractures after total hip replacement - experience of department of orthopedics and traumatology, medical university of Warsaw [J]. Ortop Traumatol Rehabil, 2014, 16 (3): 265-274
- [3] 尹星华,周一新,唐杞衡,等.人工髌膝关节置换术后症状性静脉血栓栓塞性疾病的危险因素分析[J].中国矫形外科杂志, 2016, 24(19): 1765-1769
Yin Xing-hua, Zhou Yi-xin, Tang Qi-heng, et al. Analysis of risk factors for symptomatic venous thromboembolism after total hip and knee arthroplasty [J]. Orthopedic Journal of China, 2016, 24 (19): 1765-1769
- [4] Li F, Wang X, Huang W, et al. Risk factors associated with the occurrence of silent pulmonary embolism in patients with deep venous thrombosis of the lower limb [J]. Phlebology, 2014, 29 (7): 442-446
- [5] 吴国强,邹灵.短期和延长抗凝在髌关节置换手术患者中预防下肢深静脉血栓的作用比较[J].医学综述, 2015, 21(24): 4575-4577
Wu Guo-qiang, Zou Ling. Curative Effect of Short-term and Prolonged Thromboprophylaxis in Patients with Total Hip Replacement[J]. Medical Recapitulate, 2015, 21(24): 4575-4577
- [6] 徐祎骏,肖军,张洋,等.关节置换术后抗凝药物预防深静脉血栓及相关并发症的临床研究进展 [J]. 现代生物医学进展, 2016, 16(12): 2376-2379, 2383
Xu Yi-jun, Xiao Jun, Zhang Yang, et al. Clinical Research Progress of Anticoagulants for Prophylaxis of Deep Vein Thrombosis and Complications after Arthroplasty [J]. Progress in Modern Biomedicine, 2016, 16(12): 2376-2379, 2383
- [7] Antoniou S. Rivaroxaban for the treatment and prevention of thromboembolic disease[J]. J Pharm Pharmacol, 2015, 67(8): 1119-1132
- [8] Hashikata T, Yamaoka-Tojo M, Namba S, et al. Rivaroxaban Inhibits

- Angiotensin II-Induced Activation in Cultured Mouse Cardiac Fibroblasts Through the Modulation of NF- κ B Pathway [J]. *Int Heart J*, 2015, 56(5): 544-550
- [9] Burness CB, Perry CM. Rivaroxaban: a review of its use in the treatment of deep vein thrombosis or pulmonary embolism and the prevention of recurrent venous thromboembolism[J]. *Drugs*, 2014, 74 (2): 243-262
- [10] 周筠,毕方刚,陈聚伍.利伐沙班与低分子肝素对骨折患者下肢深静脉血栓预防的疗效比较 [J]. *中华实验外科杂志*, 2015, 32(12): 3187-3189
- Zhou Yun, Bi Fang-gang, Chen Ju-wu. A comparative study of efficacy between rivaroxaban and low molecular weight heparin on preventing deep vein thrombosis in patients with lower limb fractures [J]. *Chinese Journal of Experimental Surgery*, 2015, 32(12): 3187-3189
- [11] Beitland S, Sandven I, Kjærvi LK, et al. Thromboprophylaxis with low molecular weight heparin versus unfractionated heparin in intensive care patients: a systematic review with meta-analysis and trial sequential analysis [J]. *Intensive Care Med*, 2015, 41 (7): 1209-1219
- [12] Dooley C, Kaur R, Sobieraj DM. Comparison of the efficacy and safety of low molecular weight heparins for venous thromboembolism prophylaxis in medically ill patients[J]. *Curr Med Res Opin*, 2014, 30 (3): 367-380
- [13] Wan B, Fu HY, Yin JT, et al. Low-molecular-weight heparin and intermittent pneumatic compression for thromboprophylaxis in critical patients[J]. *Exp Ther Med*, 2015, 10(6): 2331-2336
- [14] 王燕娇,苏靖,王新.注射低分子肝素致皮下出血的原因分析与护理进展[J].*中国医学创新*, 2016, 13(26): 135-139
- Wang Yan-jiao, Su Jing, Wang Xin. The Reason Analysis and Nursing Progress for Injection of Low Molecular Heparin to Subcutaneous Hemorrhage[J]. *Medical Innovation of China*, 2016, 13 (26): 135-139
- [15] 张菊霞,马玉霞,温玉洁,等.皮下注射低分子肝素时不同推注时间对皮下出血的影响[J].*中华护理杂志*, 2014, 49(2): 233-235
- Zhang Ju-xia, Ma Yu-xia, Wen Yu-jie, et al. Effect of injection duration on bruising associated with subcutaneous low molecular weight heparin[J]. *Chinese Journal of Nursing*, 2014, 49(2): 233-235
- [16] Özler T, Uluçay Ç, Önal A, et al. Comparison of switch-therapy modalities (enoxaparin to rivaroxaban/dabigatran) and enoxaparin monotherapy after hip and knee replacement [J]. *Acta Orthop Traumatol Turc*, 2015, 49(3): 255-259
- [17] Bookhart BK, Haskell L, Bamber L, et al. Length of stay and economic consequences with rivaroxaban vs enoxaparin/vitamin K antagonist in patients with DVT and PE: findings from the North American EINSTEIN clinical trial program[J]. *J Med Econ*, 2014, 17 (10): 691-695
- [18] Charters MA, Frisch NB, Wessell NM, et al. Rivaroxaban Versus Enoxaparin for Venous Thromboembolism Prophylaxis after Hip and Knee Arthroplasty[J]. *J Arthroplasty*, 2015, 30(7): 1277-1280
- [19] 鲁义,屠伟峰,卿朝晖,等.静脉与硬膜外自控镇痛对老年髋关节置换术患者术后镇静、舒适度及并发症影响的比较[J].*临床麻醉学杂志*, 2015, 31(2): 109-112
- Lu Yi, Tu Wei-feng, Qing Zhao-hui, et al. Comparison of sedation effect, comfort degree and incidence of complications by PCIA and PCEA in elderly patients after hip replacement surgery [J]. *Journal of Clinical Anesthesiology*, 2015, 31(2): 109-112
- [20] 周健,刘忠达,林伟龙.髋关节置换术后利伐沙班预防下肢深静脉血栓的疗效与安全性 [J]. *中国临床药理学杂志*, 2015, (12): 1106-1108
- Zhou Jian, Liu Zhong-da, Lin Wei-long. Efficacy and safety of rivaroxaban on anti-deep venous thrombosis for patients undergoing hip arthroplasty [J]. *The Chinese Journal of Clinical Pharmacology*, 2015, (12): 1106-1108
- [21] Loganathan L, Hua A, Patel S, et al. Efficacy and safety of rivaroxaban thromboprophylaxis after arthroplasty of the hip or knee: retrospective cohort study [J]. *Ann R Coll Surg Engl*, 2016, 98(7): 507-515
- [22] 张培根,衡孝来,吴文涛,等.不同年龄段多发性创伤骨折患者围术期凝血及血小板功能的变化 [J]. *血栓与止血学*, 2016, 22(3): 303-306
- Zhang Pei-gen, Heng Xiao-lai, Wu Wen-tao, et al. Changes of Blood Coagulation and Platelet Function During the Perioperative Period in Different age Paragraph Patients with Multiple Traumatic Fractures [J]. *Chinese Journal of Thrombosis and Hemostasis*, 2016, 22 (3): 303-306
- [23] Levy JH, Welsby I, Goodnough LT. Fibrinogen as a therapeutic target for bleeding: a review of critical levels and replacement therapy[J]. *Transfusion*, 2014, 54(5): 1389-1405
- [24] Collins PW, Solomon C, Sutor K, et al. Theoretical modelling of fibrinogen supplementation with therapeutic plasma, cryoprecipitate, or fibrinogen concentrate[J]. *Br J Anaesth*, 2014, 113(4): 585-595
- [25] Kell DB, Pretorius E. The simultaneous occurrence of both hypercoagulability and hypofibrinolysis in blood and serum during systemic inflammation, and the roles of iron and fibrin (ogen) [J]. *Integr Biol (Camb)*, 2015, 7(1): 24-52
- [26] 赵玥.急性脑梗死的颈动脉内膜厚度与血清高敏C反应蛋白、纤维蛋白原和同型半胱氨酸关系 [J]. *临床荟萃*, 2014, 29(2): 168-170
- Zhao Yue. Correlation of high-sensitive C-reactive protein, fibrinogen, homocysteine and intima-media thickness in patients with acute cerebral infarction[J]. *Clinical Focus*, 2014, 29(2): 168-170
- [27] 周沁,吴艳,蒋鑫,等.利伐沙班治疗静脉血栓栓塞症的初步临床观察[J].*中华心血管病杂志*, 2015, 43(9): 782-784
- Zhou Qin, Wu Yan, Jiang Xin, et al. Efficacy comparison of 3 rivaroxaban regimen in patients with venous thromboembolism [J]. *Chinese Journal of Cardiology*, 2015, 43(9): 782-784
- [28] Kreutz R. Pharmacokinetics and pharmacodynamics of rivaroxaban-an oral, direct factor Xa inhibitor [J]. *Curr Clin Pharmacol*, 2014, 9 (1): 75-83
- [29] Sharifi M, Bay C, Schwartz F, et al. Safe-dose thrombolysis plus rivaroxaban for moderate and severe pulmonary embolism: drip, drug, and discharge[J]. *Clin Cardiol*, 2014, 37(2): 78-82
- [30] 陈德强,贾世孔,王泓.利伐沙班预防骨科大手术后深静脉血栓形成的有效性及安全性评价[J].*天津医药*, 2014, 42(2): 176-178
- Chen De-qiang, Jia Shi-kong, Wang Hong. Effectiveness and Safety of Rivaroxaban in Prevention of Deep Vein Thrombosis after Major Orthopedic Surgery[J]. *Tianjin Medical Journal*, 2014, 42(2): 176-178