世界华人消化杂志
https://www.wjgnet.com
二零二二年五月八日
第三十卷
第九期

ISSN 1009-3079 (print)
ISSN 2219-2859 (online)

世界华人消化杂志®

WORLD CHINESE JOURNAL OF DIGESTOLOGY

Shijie Huaren Xiaohua Zazhi

2022年5月8日 第30卷 第9期 (Volume 30 Number 9)

9/2022

《世界华人消化杂志》是一本高质量的同行评议, 开放获取和在线出版的学术刊物. 本刊被国际检索系统《化学文摘(Chemical Abstracts, CA)》、《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》、《文摘杂志(Abstract Journal, AJ)》、Scopus、中国知网《中国期刊全文数据库(CNKI)》、《中文科技期刊数据库(CSTJ)》和《超星期刊域出版平台(Superstar Journals Database)》数据库收录.

ISSN 1009-3079
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WCJD 世界华人消化杂志®

目　　次　　2022年5月8日 第30卷 第9期 (总第701期)

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消　息

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形式规范审核编辑部主任 李香; 最终清样审核总编辑 马连生

世界华人消化杂志

Shijie Huaren Xiaohua Zazhi

吴阶平　题写封面刊名
陈可冀　题写版权刊名
(半月刊)
创　刊 1993-01-15
改　刊 1998-01-25
出　版 2022-05-08
原刊名 新消化病学杂志

期刊名称
世界华人消化杂志

国际标准连续出版物号
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

编辑部
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《世界华人消化杂志》编辑部
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7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: wcjd@wjgnet.com
http://www.wjgnet.com

出版
百世登出版集团有限公司
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

制作
北京百世登生物医学科技有限公司
100025, 北京市朝阳区东四环中路62号, 远洋国际中心D座903室
电话: +86-10-85381901

《世界华人消化杂志》是一本高质量的同行评议, 开放获取和在线出版的学术刊物. 本刊被国际检索系统《化学文摘(Chemical Abstracts, CA)》、《医学文摘库/医学文摘(EMBASE/Excerpta Medica, EM)》、《文摘杂志(Abstract Journal, AJ)》、Scopus、中国知网《中国期刊全文数据库(CNKI)》、《中文科技期刊数据库(CSTJ)》和《超星期刊域出版平台(Superstar Journals Database)》数据库收录.

《世界华人消化杂志》正式开通了在线办公系统(https://www.baishideng.com), 所有办公流程一律可以在线进行, 包括投稿、审稿、编辑、审读, 以及作者、读者和编者之间的信息反馈交流.

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定价
每期136.00元 全年24期3264.00元

WCJD 世界华人消化杂志®

Volume 30 Number 9 May 8, 2022

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Indexed/Abstracted by

Chemical Abstracts, EMBASE/Excerpta Medica, Abstract Journals, Scopus, CNKI, CSTJ and Superstar Journals Database.

Shijie Huaren Xiaohua Zazhi

Founded on January 15, 1993
Renamed on January 25, 1998
Publication date May 8, 2022

NAME OF JOURNAL
World Chinese Journal of Digestology

ISSN
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

EDITORIAL OFFICE
Jin-Lei Wang, Director
World Chinese Journal of Digestology
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: wcjd@wjgnet.com
https://www.wjgnet.com

PUBLISHER
Baishideng Publishing Group Inc
7041 Koll Center Parkway, Suite 160, Pleasanton, CA 94566, USA
Telephone: +1-925-3991568
E-mail: bpgoffice@wjgnet.com
https://www.wjgnet.com

PRODUCTION CENTER
Beijing Baishideng BioMed Scientific Co., Limited Room 903, Building D,
Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
Telephone: +86-10-85381901

PRINT SUBSCRIPTION
RMB 136 Yuan for each issue
RMB 3264 Yuan for one year

INSTRUCTIONS TO AUTHORS
Full instructions are available online at https://www.wjgnet.com/1009-3079/Nav/36. If you do not have web access, please contact the editorial office.

WCJD 世界华人消化杂志®

在线投稿: https://www.baishideng.com
世界华人消化杂志 2022年5月8日; 30(9): 381-386

DOI: 10.11569/wcjd.v30.i9.381
ISSN 1009-3079 (print) ISSN 2219-2859 (online)

文献综述 *REVIEW*

肝素类药物防治肝硬化静脉血栓栓塞的研究进展

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收稿日期: 2022-02-09
修回日期: 2022-04-03
接受日期: 2022-04-18
在线出版日期: 2022-05-08

Heparins for prevention and treatment of venous thromboembolism in cirrhosis: Research advances

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Received: 2022-02-09
Revised: 2022-04-03
Accepted: 2022-04-18
Published online: 2022-05-08

Abstract
Current evidence suggests that liver cirrhosis may increase the risk of venous thromboembolism (VTE). In cirrhosis, common types of VTE include portal vein thrombosis (PVT), deep vein thrombosis, and pulmonary embolism (PE). Heparins are the most commonly prescribed anticoagulants for the prevention and treatment of VTE. However, the indications, choice, dosage, and monitoring of heparins in cirrhosis remain inconclusive. This paper aims to review the advances in the research of heparins for the prevention and treatment of VTE in cirrhosis to optimize the treatment strategy.

Key Words: Heparins; Low molecular weight heparin; Fondaparinux sodium; Cirrhosis; Portal vein thrombosis; Deep vein thrombosis; Pulmonary embolism

Citation: Li Z, Xu WT, Xu XB, Qi XS. Heparins for prevention and treatment of venous thromboembolism in cirrhosis: Research advances. Shijie Huaren Xiaohua Zazhi 2022; 30(9): 381-386
URL: https://www.wjgnet.com/1009-3079/full/v30/i9/381.htm
DOI: https://dx.doi.org/10.11569/wcjd.v30.i9.381

摘要
当前证据提示肝硬化可能增加静脉血栓栓塞风险. 肝硬化静脉血栓栓塞常见的类型包括门静脉血栓、深静脉血栓及肺栓塞. 作为临床最常用的抗凝药物, 肝素类药物是防治静脉血栓栓塞的重要手段. 然而, 肝硬化患者应用肝素类药物的适应症、药物种类、药物剂量及监测等问题尚无定论. 本文对肝素类药物防治肝硬化静脉血栓栓塞的研究进展作一综述, 为临床合理用药提供参考.

关键词: 肝素; 低分子肝素; 磺达肝癸钠; 肝硬化; 门静脉血栓; 深静脉血栓; 肺栓塞

核心提要: 肝素类药物可有效防治肝硬化门静脉血栓(portal vein thrombosis, PVT), 但对深静脉血栓(deep vein thrombosis, DVT)/肺栓塞(pulmonary embolism, PE)的防治效果尚有待进一步验证.

文献来源: 李喆, 许文涛, 许向波, 祁兴顺. 肝素类药物防治肝硬化静脉血栓栓塞的研究进展. 世界华人消化杂志 2022; 30(9): 381-386
URL: https://www.wjgnet.com/1009-3079/full/v30/i9/381.htm
DOI: https://dx.doi.org/10.11569/wcjd.v30.i9.381

0 引言

传统观点认为肝硬化患者处于低凝状态, 出血风险高[1]. 然而, 当前的证据提示肝硬化患者凝血系统处于“再平衡”状态, 不仅存在出血倾向, 而且常伴发多种静脉血栓栓塞性疾病(venous thromboembolism, VTE)[2,3]. 肝硬化患者中, 最常发生VTE的部位是门静脉[4]. 肝硬化患者发生门静脉血栓(portal vein thrombosis, PVT)的风险是普通人群的7倍[5], 其发病率为3%-17%, 患病率为5%-26%[6]. PVT可增加肝硬化患者消化道出血、腹水、急性肾损伤及肝移植术后死亡的风险[7,8]. 此外, 肝硬化患者发生其他部位VTE的风险是普通人群的1.7倍[9], 主要包括深静脉血栓(deep vein thrombosis, DVT)和肺栓塞(pulmonary embolism, PE). 肝硬化患者DVT或PE发病率为0.2%-6.3%[10,11], 患病率为0.4%-4.7%[10-12]. 肝硬化合并DVT患者30 d死亡率为7%, 为非肝硬化患者的2.17倍; 肝硬化合并PE患者30 d死亡率为35%, 为非肝硬化患者的1.3倍[13,14].

抗凝是预防及治疗肝硬化VTE的重要手段之一, 可显著减少肝硬化患者血栓发生率、增加血栓再通率, 甚至可以降低肝脏失代偿率并提高总体生存率[15-18]. 肝素类药物是目前临床最常用的抗凝药物[19], 主要包括普通肝素、低分子肝素(依诺肝素、那曲肝素、达肝素、达那肝素等)以及合成肝素(磺达肝癸钠等)[19]. 2020年美国重症医学会指南[18]推荐普通肝素及低分子肝素可用于预防及治疗肝硬化患者VTE, 但该推荐强度弱、证据质量低. 更值得一提的是, 肝硬化患者常合并食管胃底静脉曲张及血小板减少症, 故在临床实践中需考虑肝素类药物在肝硬化患者中应用的安全性[20,21]. 目前, 肝硬化患者应用肝素类药物的适应症、药物种类、药物剂量及监测等问题尚无定论. 为此, 本文通过回顾国内外相关文献, 总结肝素类药物防治肝硬化VTE的研究进展, 为临床合理用药提供参考.

1 肝素类药物的种类与特点

普通肝素是一种硫酸化的葡萄糖胺聚糖混合物, 平均分子量为12 kDa[22]. 其通过与抗凝血酶III(AT-III)特异性结合, 加速灭活血浆中凝血因子Ⅱa、Ⅸa、Ⅹa、Ⅺa和Ⅻa[23], 进而发挥抗凝作用. 普通肝素的生物利用度约为30%, 药物半衰期为30 min-60 min[24]. 出血是普通肝素主要的不良反应, 可表现为各种黏膜出血、关节腔积血和伤口出血等. 普通肝素也可导致免疫诱导性血小板减少症, 发生率达5%, 多发生在给药后7 d -10 d.

低分子肝素是从普通肝素中分离或由普通肝素降解后得到的短链制剂, 一般分子量低于7 kDa[24]. 由于分子链较短, 不能与AT-III和凝血因子Ⅱa同时结合形成复合物, 故主要对凝血因子Ⅹa发挥作用. 生物利用度约为90%. 药物半衰期为119 min-180 min, 约为普通肝素的2-4倍. 常见的不良反应有出血、免疫诱导性血小板减少症等. 临床常用的低分子肝素包括依诺肝素、那曲肝素、达肝素、达那肝素等.

磺达肝癸钠是一种以AT-III-肝素结合位点结构为基础人工合成的戊多糖. 仅对凝血因子Ⅹa发挥抑制作用. 与普通肝素和低分子肝素相比, 该药具有更高的生物利用度(100%)及更长的药物半衰期(17 h以上), 且基本上不会导致出血及免疫诱导性血小板减少症的不良反应[25].

2 肝素类药物的剂量与监测

通常情况下, 普通肝素预防剂量为首剂皮下注射5000 U, 之后每12 h注射5000 U[23], 治疗剂量为首剂静脉注射5000 U, 之后每1 h持续注射18 U/kg[26], 用药4 h后应监测抗Ⅹa因子活性, 参考范围为0.35 U/mL-0.7 U/mL[23]; 低分子肝素预防剂量为皮下注射4000 U-5000 U, 每日1次[27]. 治疗剂量为皮下注射100 U/kg, 每日2次[28], 用药4 h后同样应监测抗Ⅹa因子活性, 参考范围为0.6 U/mL-1.3 U/mL[29]; 磺达肝癸钠治疗剂量为皮下注射2.5 mg, 每日1次[19]. 然而, 目前研究不建议肝硬化患者根据抗Ⅹa因子活性调整剂量[30-32], 可使用总体止血试验作为补充监测[33-35]. Bechmann等[30]发现, 接受标准剂量依诺肝素的肝硬化患者未能达到推荐的预防性及治疗性抗Ⅹa因子活性. 该研究纳入了84例肝硬化患者, 分别给予预防剂量(4000 U, 每日1次)及治疗剂量(100 U/kg, 每日1次)依诺肝素, 给药4 h后, 接受预防及治疗剂量的肝硬化患者的平均抗Ⅹa因子活性分别为(0.169±0.122) U/mL及(0.432±0.173) U/mL, 均低于参考范围. 此外, 依诺肝素给药后发生出血的患者比未发生出血的患者抗Ⅹa因子活性更低[(0.088±0.038) U/mL *vs* (0.174±0.016 U/mL)]. 因此, 肝硬化患者根据抗Ⅹa因子活性调整剂量并不可靠. 相比于抗Ⅹa因子活性监测, 总体止血试验, 如凝血酶生成试验, 可能会更精确、更高效地反映肝素类药物在肝硬化患者中的抗凝活性[33-35]. Potze等[34]留取了30例肝硬化患者及30例健康对照者的血浆

表 1 肝素类药物防治肝硬化静脉血栓栓塞的文献回顾

参考文献	抗凝例数	血栓范围	血栓程度	药物剂量、频次	治疗周期	治疗应答(例数)	相关不良事件(例数)
预防性应用							
Shatzel[58](2015)	296	N/A	N/A	试验组: 普通肝素(5000 U, 每日1-2次)或依诺肝素(40 mg, 每日1次); 对照组: 无	N/A	试验组: DVT/PE或PVT(7); 对照组: DVT/PE或PVT(5)	试验组: 胃肠道出血(9), 非胃肠道出血(15), 死亡(5); 对照组: 胃肠道出血(10), 非胃肠道出血(7) 死亡(1)
Villa[37](2012)	70	N/A	N/A	试验组: 依诺肝素(4000 U, 每日1次); 对照组: 无	48 wk	试验组: 无PVT; 对照组: PVT(10)	N/A
Vivarelli[40](2010)	157	N/A	N/A	试验组: 那曲肝素(2850 U)或依诺肝素(4000 U); 对照组:无	7 d	试验组: PE(1); 对照组: PVT(1)	试验组: 总出血事件(5); 对照组: 总出血事件(1)
治疗性应用							
Senzolo[51](2021)	124	PVT(124)	N/A	磺达肝癸钠/低分子肝素(血小板减少症、严重肾功能障碍、胃肠道出血史、门脉高压胃病、行腹腔穿刺患者减量)	36 mo	磺达肝癸钠组: PVT完全(24)/部分(7)/无(10)再通; 低分子肝素组: PVT完全(32)/部分(10)/无(41)再通	磺达肝癸钠组: 总出血事件(11), 死亡(1); 低分子肝素组: 静脉曲张出血(3), 脑出血(2), 血小板减少症(3)
Summers[57](2019)	82	DVT/PE(59); PVT(23)	N/A	普通肝素/低分子肝素	N/A	N/A	普通肝素组: 大出血(10), 小出血(3); 低分子肝素组: 无
Rodriguez-Castro[47](2019)	65	PVT(65)	N/A	依诺肝素(PLT < 50 × 10^9/L或CC < 50 mL/min者减量)	3 mo-12 mo	PVT完全(25)/部分(6)/无(34)再通	大出血(2), 胃肠道出血(1), 脑出血(1)
Hayashi[43](2019)	52	PVT(52)	N/A	达那肝素(1250 U, 每日1次)或联合抗凝血酶III(1500 U)	14 d	PVT体积平均减少72%	无
Kwon[45](2018)	91	PVT(91)	N/A	依诺肝素(1 mg/kg, 每日2次)/达肝素(200 U/kg, 每日1次, 1月后转为150 U/kg, 每日1次)	6 mo	PVT完全(20)/部分(36)/无(35)再通	总出血事件(13), 死亡(2)
Zhang[50](2017)	7	PVT(7)	N/A	磺达肝癸钠(2.5 mg, 每日1次)	21 d	PVT完全(7)	无
Naeshiro[44](2015)	26	PVT(26)	N/A	达那肝素(2500 U, 每日1次)	14 d	PVT完全(4)/部分(16)/无(6)再通	无
Cui[48](2015)	65	PVT(65)	N/A	依诺肝素(1 mg/kg, 每日2次或1.5 mg/kg, 每日1次)	6 mo	PVT完全(17)/部分(34)/无(14)再通	注射部位出血(3), 鼻出血(5), 血尿(2)
Senzolo[49](2012)	33	PVT(31)	部分(24); 完全(7)	那曲肝素(95 U/kg, 每日1次)	10 mo	PVT完全(12)/部分(9)/无(12)再通	鼻出血(1), 血尿(1), 脑出血(1), 血小板减少(1)
Amitrano[46](2010)	28	PVT(28)	部分(23); 完全(5)	依诺肝素(200 U/kg, 每日1次)	6 mo-17 mo	PVT完全(21)/部分(2)/无(5)再通	无
García-Fuster[12](2008)	17	DVT/PE(17)	N/A	低分子肝素或联合华法林	N/A	N/A	总出血事件(16)

N/A: 文献中未提供相关信息; PVT: 门静脉血栓; DVT: 深静脉血栓; PE: 肺栓塞; PLT: 血小板计数; CCr: 肌酐清除率.

样本, 分别添加0.3 U/mL普通肝素、0.2 U/mL依诺肝素及0.5 μg/mL磺达肝癸钠. 结果显示, 肝硬化患者凝血酶生成曲线下面积的下降幅度较健康对照者更大, 这说明肝硬化患者对普通肝素及低分子肝素的反应增加[36], 抗凝效果增强, 建议减量使用[34]; 而磺达肝癸钠在肝硬化患者血浆中的反应降低, 抗凝效果减弱, 建议增加剂量[34]. 然而, 这一结论并未考虑到肝硬化患者体内血小板对凝血过程的影响. 尚不清楚调整剂量后的肝素类药物是否能在肝硬化患者体内最大限度地发挥药物疗效以及减少不良反应. 总之, 目前仍需更多的临床研究探讨凝血酶生成试验以及其他监测方法对指导肝素类药物剂量调整的临床实用价值.

3 肝素类药物在肝硬化VTE中的预防价值

低分子肝素可有效安全地预防肝硬化患者发生PVT(表1). 一项随机对照试验结果显示[37], 48 wk及96 wk时, 接受依

诺肝素预防的患者无一例发生PVT, 未接受依诺肝素的患者PVT发生率分别为16.6%及27.7%; 随访结束时, 接受依诺肝素预防的患者PVT发生率显著低于未接受依诺肝素的患者(8.8% *vs* 27.7%, P = 0.006); 两组间出血事件发生率无显著性差异(5.8% *vs* 2.7%, P = 0.521). 该研究也显示[37], 接受依诺肝素预防的患者肝脏失代偿率(38.2% *vs* 83.0%, P<0.0001)及死亡率(23.5% *vs* 36.1%, P = 0.251)均更低. 基于此, 2016年意大利肝病学会和意大利医学学会有关肝硬化止血平衡的共识建议将低分子肝素用于预防肝硬化PVT[38].

最近, 我国抗凝药物指南推荐低分子肝素可作为预防肝硬化患者DVT/PE的首选药物[39], 但证据尚不充分. 一项回顾性研究发现[40], 与未接受低分子肝素预防的患者相比, 接受低分子肝素预防的患者DVT/PE发生率更低(0.63% *vs* 1.38%, P = 0.530), 出血发生率更高(3.18% *vs* 1.38%, P = 0.380), 但两组间无显著差异(表1). 荟萃分析结果显示[41], 接受与未接受肝素类药物预防的肝硬化患者之间DVT/PE发生率也无显著性差异(OR = 1.65, 95%CI: 0.36-7.54, P>0.05). 因此, 肝素类药物预防肝硬化DVT/PE的确切疗效仍有待更为严格的随机对照试验加以验证.

4 肝素类药物在肝硬化VTE中的治疗价值

2020年, 我国《肝硬化门静脉血栓管理专家共识》建议[6], 肝硬化PVT抗凝治疗的主要适应证为急性症状性PVT、等待肝移植、合并肠系膜静脉血栓. 主要禁忌证为近期出血史、严重的食管胃静脉曲张、严重的血小板减少症. 近年的研究发现, 肝素类药物治疗肝硬化PVT具有重要作用, 但易引起出血事件及血小板减少症等不良反应[42](表1). 肝硬化PVT患者经达那肝素治疗2 wk后[43,44], PVT体积可平均缩小72%-77%, 完全再通率为15%, 部分再通率为62%, 未发生大出血、血小板减少、肝损伤等不良反应. 肝硬化PVT患者经达肝素或依诺肝素抗凝治疗6 mo后[45-48], 治疗应答率(包括完全再通及部分再通)为61%-78.5%, 无应答率为16.7%-30.8%, PVT进展率为4.4%, 总体出血率为4%-23.5%[45,47,48], 致死性出血率为2.1%[45]. 肝硬化PVT患者经那曲肝素治疗5.5 mo后[49], 治疗应答率(包括完全再通及部分再通)为63%, 总体出血率为8.5%. 肝硬化PVT患者经磺达肝癸钠治疗21 d后[50], 完全再通率为100%, 未发生出血或血小板减少等不良反应, 但该研究样本量小(仅7例患者), 且治疗时间较短(仅21 d). 最近, 一项回顾性研究比较了低分子肝素与磺达肝癸钠治疗肝硬化PVT患者36 mo后的疗效[51], 接受磺达肝癸钠治疗患者的治疗应答率(77% *vs* 51%, P = 0.001)及出血事件发生率(27% *vs* 13%, P = 0.06)均高于接受低分子肝素治疗患者. 荟萃分析结果显示[52], 低分子肝素及磺达肝癸钠治疗肝硬化PVT后, 治疗应答率分别为71.2%及71.6%, 完全再通率分别为41.0%及43.0%, 总体出血事件发生率分别为6.5%及15.1%. 尽管磺达肝癸钠给药剂量固定[53], 且无血小板减少等不良反应[54], 但该药在肝硬化患者中似乎有着较高的出血率. 因此, 低分子肝素被推荐作为治疗肝硬化PVT的首选肝素类药物[6,55,56], 疗程为6 mo或直至门静脉再通[56].

两项回顾性研究探讨了普通肝素及低分子肝素治疗肝硬化DVT/PE患者的安全性(表1); 2008年, García-Fuster等发现[12], 接受低分子肝素治疗的患者有着较高的出血率. 该研究纳入了1992-2007住院的17例肝硬化DVT/PE患者. 其中, 11例接受低分子肝素治疗, 6例接受低分子肝素序贯华法林治疗. 治疗期间, 16例发生出血, 6例需要输注血液制品, 14例因严重的出血事件不得不提前中止应用抗凝药物, 出血率达83%. 然而, 2020年, Summers等发现[57], 相比于普通肝素, 接受低分子肝素治疗的肝硬化DVT/PE及PVT患者有着较低的出血率. 该研究纳入了59例肝硬化DVT/PE患者及23例PVT患者, 其中接受普通肝素治疗52例, 大出血率为19.2%, 小出血率为5.8%; 低分子肝素治疗30例, 大、小出血率均为0%. 因此, 普通肝素及低分子肝素在肝硬化DVT/PE患者中的安全性仍存在争议.

5 结论

肝硬化患者使用肝素类药物时, 不推荐通过监测抗Ⅹa因子活性调整用药剂量; 相比之下, 总体止血试验可能会更好地评估肝素类药物的抗凝效果及安全性. 肝素类药物可有效防治肝硬化PVT, 但对DVT/PE的防治效果尚有待进一步验证.

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科学编辑: 张砚梁 制作编辑: 张砚梁

Published by **Baishideng Publishing Group Inc**
7041 Koll Center Parkway, Suite 160, Pleasanton,
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ISSN 1009-3079