

· 临床研究 ·

替罗非班对冠心病支架术后行非心脏手术患者围手术期抗栓治疗的观察

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【摘要】目的 探讨冠心病药物洗脱支架(DES)植入患者行非心脏手术围手术期的抗栓治疗方法。**方法** 选择1年内曾因冠心病植入DES服用双联抗血小板药物期间因外科疾病需手术治疗的48例患者, 随机分为低分子肝素(依诺肝素)组及替罗非班组, 两组患者均于术前5d停用双联抗血小板药物, 低分子肝素组应用依诺肝素皮下注射(1mg/kg, 1次/12h), 替罗非班组应用替罗非班0.1μg/(kg·min)持续泵入, 两组患者均于术前12h停用依诺肝素或替罗非班, 术后根据外科情况, 尽早恢复双联抗血小板药物使用。观察围术期新发心血管事件以及出血事件。**结果** 两组患者桥接时间及手术方式无明显区别, 围术期两组患者未发生心脏事件, 肝素组发生2例牙龈出血, 1例鼻出血; 替罗非班组发生1例牙龈出血, 1例便潜血阳性, 两组患者出血发生率差异无统计学意义。3个月随访, 肝素组于术后2个月发生心肌梗死1例, 心绞痛再发2例, 替罗非班组心绞痛再发1例, 两组心脏事件发生率差异无统计学意义。**结论** DES植入术后近期行非心脏手术患者围术期可以考虑应用依诺肝素或Ⅱb/Ⅲa受体拮抗剂替罗非班替代双联抗血小板药物。

【关键词】 药物涂层支架; 支架内血栓; 非心脏手术; Ⅱb/Ⅲa受体拮抗剂; 低分子肝素

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Peri-operative anti-thrombotic efficiency of tirofiban for patients undergoing noncardiac surgery within 1 year after implantation of drug-eluting stent

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【Abstract】 Objective To evaluate the peri-operative anti-thrombotic strategy for the patients undergoing noncardiac surgery within 1 year after implantation of drug-eluting stent (DES). **Methods** A total of 48 patients who having taken dual antiplatelet therapy (DAPT) drugs (clopidogrel and aspirin) within 1 year after DES implantation and now undergoing operative treatment for the surgical diseases in our department from January 2010 to August 2013 were recruited in this study. They were randomly divided into heparin (enoxaparin) group and tirofiban group. In 5d before surgery, oral DAPT was stopped in both groups, and continuous intravenous infusion of 0.1μg/(kg·min) tirofiban or subcutaneous injection of enoxaparin (1mg/kg) twice per day, were performed respectively. In 12h before surgery, tirofiban or enoxaparin was stopped, and oral DAPT was returned as soon as possible after surgery according to the patients' condition. Peri-operative cardiovascular events and bleeding were observed. **Results** There was no statistical significance in bridge time and surgery method between the 2 groups. No major adverse cardiac event (MACE) was observed in neither the enoxaparin nor the tirofiban group in perioperation. There were 2 cases of gingival bleeding and 1 of epistaxis in the enoxaparin group, and 1 of gingival bleeding and 1 positive occult test in the tirofiban group. But no difference was found in bleeding incidence between the 2 groups. During the 3 months' follow-up, 1 case of myocardial infarction and 2 of angina occurred in the enoxaparin group, and 1 of angina in the tirofiban group, with no difference in MACE in the 2 groups. **Conclusion** Low molecular weight heparin enoxaparin and Ⅱb/Ⅲa receptor antagonist tirofiban may be substitute for oral DAPT in the patients undergoing noncardiac

surgery recently after implantation of DES.

【Key words】 drug-eluting stent; stent thrombosis; noncardiac surgery; II b/III a receptor antagonist; low molecular weight heparin

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目前,介入治疗已成为冠心病的主要治疗方法之一,药物洗脱支架(drug-eluting stents, DES)也被广泛地应用于冠心病的治疗^[1],但增加了支架血栓形成风险^[2],因此,指南推荐植入DES后,双联抗血小板治疗(dual antiplatelet therapy, DAPT)应至少持续12个月^[3],但临床上植入DES后1年内如必须行外科手术,此时采取何种抗栓策略是医师及患者共同关心的问题^[4]。本研究旨在探讨GP II b/III a受体拮抗剂在非心脏外科手术围手术期中的有效性及安全性。

1 对象与方法

1.1 对象

该研究通过北京军区总医院伦理委员会批准,入选2010年1月至2013年8月冠心病植入DES一年内需要服用双联抗血小板药物、同时需近期行非心脏手术的患者,所有入组患者签署知情同意书。排除标准:(1)年龄>75岁;(2)心功能纽约分级为NYHA 3、4级;(3)高血压未控制;(4)血红蛋白<100g/L,血小板<100×10⁹/L;(5)严重的肝、肾功能不全、严重感染等。

1.2 方法

入选患者随机分为低分子肝素组及替罗非班(tirofiban)组,两组患者均于术前5d停用双联抗血小板药物,低分子肝素组用依诺肝素(enoxaparin)1mg/kg,皮下注射,1次/12h,替罗非班组应用II b/III a受体拮抗剂替罗非班(欣维宁,武汉远大制药有限公司)0.1μg/(kg·min)持续泵入,两组患者均于术前12h停用肝素或替罗非班,手术后根据外科情况,如无明显出血,可予24~48h后恢复氯吡格雷、阿司匹林治疗。

1.3 观察指标

1.3.1 心血管事件 围术期及3个月随访期主要心脏不良事件(major adverse cardiac events, MACE)包括任何原因死亡、新近出现心肌梗死或心肌缺血

或靶血管重建术等。次要心血管事件包括心绞痛发作或因心绞痛入院。

1.3.2 并发症发生情况 出血事件按心肌梗死溶栓TIMI试验协作组的定义分为主要出血[颅内出血或显著出血征象伴有血红蛋白(Hb)下降>50g/L]、次要出血(临床明显出血征象且Hb下降30~50g/L)和轻微出血(临床明显出血征象且Hb下降<30g/L)。支架内血栓形成定义为冠脉支架植入术后造影证实的支架内血栓性闭塞且TIMI血流0~1级。血小板减少症:血小板计数<100×10⁹/L;轻度者定义为50×10⁹~100×10⁹/L;严重者定义为<50×10⁹/L。

1.4 统计学处理

采用SPSS13.0软件包进行数据分析。所有计量数据以均数±标准差表示,组间均数比较采用t检验,计数资料比较采用χ²检验。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组患者临床情况

两组患者临床特征差异无统计学意义($P > 0.05$;表1)。植入支架到手术的时间,最短为1周(1人次),1个月内3人次,1~2个月8人次,2~3个月13人次,其他均>3个月,最长的11个月。肝素组平均(6.4±2.9)个月,替罗非班组平均(5.9±2.7)个月,植入支架到手术的时间两组差异无统计学意义($P > 0.05$)。

2.2 两组患者预后情况

两组患者桥接时间及手术方式无明显区别,围术期两组患者未发生心脏事件,肝素组2例发生牙龈出血,1例发生鼻出血;替罗非班组1例发生牙龈出血,1例便潜血阳性,未发生肝素及替罗非班的药物不良反应,两组患者围术期出血发生率差异无统计学意义($P > 0.05$)。3个月随访肝素组于术后2个月发生心肌梗死1例,心绞痛再发2例,替罗非班组心绞痛再发1例,两组心脏事件发生率差异无统计学意义($P > 0.05$;表2)。

表1 两组患者临床情况
Table 1 General clinical characteristics of subjects in two groups

Group	Male [n(%)]	Age (years, $\bar{x} \pm s$)	Hypertension [n(%)]	HLP [n(%)]	T2DM [n(%)]	Smoking [n(%)]	Post-PCI time (months, $\bar{x} \pm s$)
Enoxaparin	17 (70.1)	52.6 ± 10.6	16 (66.7)	15 (62.5)	13 (54.2)	10 (41.7)	6.4 ± 2.9
Tirofiban	18 (75.0)	53.1 ± 11.7	17 (70.1)	17 (70.1)	14 (58.3)	11 (45.8)	5.9 ± 2.7

HLP: hyperlipidemia; T2DM: type 2 diabetes mellitus; PCI: percutaneous coronary intervention

表2 两组患者外科手术情况、心血管事件发生情况比较
Table 2 Comparison of surgical situations and cardiovascular events between two groups (n = 24)

Group	Bridge-time (h, $\bar{x} \pm s$)	Surgical option(n)		Cardiac event(n)			TIMI bleeding(n)		
		Endoscopy	Non-endoscopy	Major	Minor	Total	Major	Minor	Total
Enoxaparin	82 ± 19	11	13	1	2	3	0	3	3
Tirofiban	86 ± 20	9	15	0	1	1	0	2	2

3 讨 论

介入治疗是冠心病的常规治疗手段,已有研究证明了DES在冠心病介入治疗中的安全性和近、远期疗效^[6],但与金属裸支架(bare-metal stent, BMS)相比,DES在更好地防止支架再狭窄的同时延迟了支架的内皮化进程^[7],增加了支架血栓形成的整体风险^[2],过早停用DAPT是导致植入DES后支架血栓形成的重要因素^[8]。因此,指南^[9]强烈建议DES植入患者应用双抗至少1年时间。但近期植入DES且需要外科手术治疗的患者不断增多。对于出血风险较小的手术,如拔牙、常规皮肤手术等,可以采用局部有效止血措施,术前可不停用DAPT^[10];但出血风险较大的手术,如不停止DAPT,外科手术出血的风险就会增加,停用DAPT,支架内血栓发生率就会增加,而且手术期间的高凝状态更易促发血栓形成。此时多用肝素进行桥接,然而肝素并不能充分抗血小板,因此临床工作中仍会担心围术期出现支架内血栓的问题。

盐酸替罗非班是非肽类血小板GP II b/III a受体拮抗剂,可竞争性地抑制血小板聚集,阻止血栓形成。替罗非班具有起效快、半衰期长的特点,给药5min对血小板的作用达96%,血浆半衰期2h,停药后4~10h血小板的活性就可快速逆转,停药后4h内50%的血小板功能均可恢复,因此适合反复给药^[11]。其在急性心肌梗死患者的介入治疗中有较大的应用价值,可改善预后而不增加出血风险^[12,13]。《替罗非班在冠心病抗血小板治疗的中国专家共识》及美国心脏联合会/美国心脏病学会(AHA/ACC)非心脏手术围术期心血管评估和管理均认为在接受DAPT的患者,如面临外科手术,应采取替罗非班“桥接”治疗。本研究选择支架术后近期拟行外科手术患者应用肝素或替罗非班替代口服DAPT,并于术前12h停药,术后尽早恢复DAPT,以观察其临床有效性及安全性。结果发现,两组患者围术期及3个月时心脏事件发生率均较低,差异无统计学意义;两组患者围术期出血发生率差异亦无统计学意义。提示替罗非班的有效性及安全性不劣于肝素。

总之,支架术后行非心脏手术患者要平衡血

栓与出血之间的风险,恰当把握抗血小板的强度及时间,防止血栓形成和术后出血。原则上应考虑疾病种类、部位及手术缓急等,综合平衡血栓及出血风险。对于确需手术的患者桥接治疗是适宜的。既往围术期多用低分子肝素替代DAPT,结合本研究结果,可以考虑应用替罗非班作为桥接治疗预防支架内血栓。但是,本研究存在一定的局限性,如随访时间短、观察例数少等,替罗非班用于桥接治疗是否真正安全、有效,仍然需要进一步大规模的临床研究。

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