·临床研究·

经皮冠状动脉介入治疗中比伐芦定与肝素钠的抗凝效果和安全性比较

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【摘 要】 **目的** 比较经皮冠状动脉介入(PCI)治疗中应用比伐芦定与肝素钠抗凝的有效性和安全性。**方法** 连续纳入100例择期PCI患者作为研究对象,随机数表法将患者分为比伐芦定组(50例)和肝素钠组(50例),分别于给药后15、30、60 min及手术结束时监测活化凝血时间(ACT),观察围术期出血事件及主要不良心血管事件(MACE)发生情况。应用SPSS 20.0统计软件进行数据分析。**结果** 给药15 min后2组患者ACT值均达标。术中比伐芦定组ACT水平基本稳定维持在较高水平[15 min:(280.5±12.5) s;30 min:(279.5±5.5)s;60 min:(282.1±6.8)s;手术结束时:(275.3±9.9)s],而肝素钠组ACT水平持续下降[15 min:(276.6±6.1)s;30 min:(258.1±3.0)s;60 min:(241.8±8.6)s;手术结束时:(234.9±7.9)s],给药30 min后2组ACT值的差异均具有统计学意义($P<0.001$)。2组术中及术后24 h内出血事件及血栓性事件的发生率无统计学差异($P>0.05$)。**结论** 比伐芦定与肝素钠在PCI术中均安全有效。应用比伐芦定ACT数值较为稳定;而应用肝素钠时ACT数值波动较为明显,建议间隔15 min复测ACT为宜。

【关键词】 经皮冠状动脉介入;活化凝血时间;比伐芦定;肝素钠
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Comparison on anticoagulant efficacy and safety between bivalirudin and heparin during percutaneous coronary intervention

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【**Abstract**】 **Objective** To compare the anticoagulant efficacy and safety of bivalirudin and heparin during percutaneous coronary intervention (PCI). **Methods** A total of 100 consecutive patients hospitalized in our center due to unstable angina from December 1st to 31st, 2018, and undergoing elective PCI were enrolled in this study. They were randomly divided into bivalirudin group ($n=50$) and heparin group ($n=50$). Their activated coagulation time (ACT) was monitored at 15, 30, 60 min after administration and at the end of the operation, and the occurrence of perioperative bleeding events and major adverse cardiovascular events (MACE) were observed. SPSS statistics 20.0 was used for data analysis. **Results** After 15 min of administration, the ACT were up to the standard time in both groups. The ACT levels remained stable in the bivalirudin group [15 min: (280.5±12.5)s; 30 min: (279.5±5.5)s; 60 min: (282.1±6.8)s; end of operation: (275.3±9.9)s], while those of heparin group continued to decline [15 min: (276.6±6.1)s; 30 min: (258.1±3.0)s; 60 min: (241.8±8.6)s; end of operation: (234.9±7.9)s]. Significant difference was seen in ACT between the 2 groups from 30 min after administration ($P<0.001$). There were no obvious differences in the prevalence of hemorrhagic events and thrombotic events between the 2 groups ($P>0.05$). **Conclusion** Both bivalirudin and heparin are efficient and safe anticoagulants during PCI, and the former can obtain more stable ACT. While, for the latter, ACT should be monitored every 15 min due to its obvious fluctuation during the whole operation.

【**Key words**】 percutaneous coronary intervention; activated coagulation time; bivalirudin; heparin

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经皮冠状动脉介入(percutaneous coronary intervention,PCI)治疗是冠心病重要的血运重建技术,术中常会因内源性与外源性凝血途径激活而导致血栓形成,因此,规范、有效的抗栓治疗对于预防血栓性事件至关重要。同时,抗栓治疗也必须权衡缺血与出血风险,兼顾有效性与安全性,避免出血和缺血事

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件发生[1,2]。比伐芦定与肝素钠是目前 PCI 术中最常用的抗凝药物,但二者的药理学机制不同,故术中对活化凝血时间(activated coagulation time,ACT)进行针对性监测更有利于保证其维持在安全范围内[3]。本研究旨在观察择期 PCI 术中应用比伐芦定和肝素钠后的 ACT 值,并比较各自围术期的有效性与安全性。

1 对象与方法

1.1 研究对象

连续纳入 2018 年 12 月 1 日至 2018 年 12 月 31 日因不稳定型心绞痛入解放军总医院、计划行择期 PCI 术的患者 100 例作为研究对象,以随机数表法将上述患者随机分为 2 组:比伐芦定组(50 例)和肝素钠组(50 例),并由科室相同手术组医师经桡动脉入路行冠状动脉造影检查并决定是否需 PCI 治疗。纳入标准:(1)年龄 40~60 岁;(2)诊断为不稳定型心绞痛;(3)患者及家属同意药物及手术治疗方案,并签署知情同意书。排除标准:(1)急性 ST 段抬高型心肌梗死或急性非 ST 段抬高型心肌梗死;(2)CRUSADE 出血风险评分处于极高危分层(CRUSADE≥50 分);(3)术前 4 h 经静脉注射肝素钠注射液、12 h 内经皮下注射低分子肝素纳注射液或长期使用口服抗凝药物;(4)有肝素钠注射液过敏史或有肝素诱导的血小板减少症病史;(5)合并肝肾功能不全;(6)合并其他 PCI 术禁忌证。

1.2 方法

1.2.1 药物使用 2 组患者均术前给予双联抗血小板药物阿司匹林(300 mg)、氯吡格雷(300 mg)或替格瑞洛(180 mg)负荷。比伐芦定组(注射用比伐芦定,深圳信立泰药业股份有限公司,国药准字:H20110095)术前经静脉注射 0.75 mg/kg 负荷量,随后以 1.75 mg/(kg·h)持续泵入维持至术后 4 h,术中根据 ACT 调整泵入剂量,若给予负荷剂量比伐芦定 15 min 后监测 ACT<250 s,则继续追加 0.3 mg/kg 负荷量。肝素钠组(肝素钠注射液,上海上药第一生化药业有限公司,国药准字:H31022052)术前经静脉注射 100 IU/kg,若给药 15 min 后监测 ACT<250 s 则继续追加 3 000 IU,若手术时间超过 1 h,则继续追加 1 000 IU[4]。

1.2.2 ACT 监测 2 组患者分别于给药后 15、30、60 min 及手术结束时监测 ACT。ACT 检测使用凝血时间监测仪(Hemochron Jr. Signature),具体步骤如下:(1)将室温下放置的测试片插入仪器;(2)仪器自检、加热;(3)当仪器显示“Add Sample”后采血样 0.2 ml;(4)将血液样本 50 μl 注入血样池内,按开始键检测开始。

1.2.3 出血性事件与血栓性事件 出血性事件:小出血包括皮肤黏膜出血、肉眼血尿、呕吐物带血且隐血试验阳性、黑便且隐血试验阳性等;大出血或危及生命的出血包括血红蛋白降低超过 30 g/L、需输血超过 2 个单位、颅内出血或出血需要外科手术干预等[5]。血栓性事件:急性支架内血栓为发生在介入治疗 24 h 内、经冠状动脉造影或病理学证实的支架段部分性或完全性血栓栓塞[5]。

1.3 统计学处理

所有数据均采用 SPSS 20.0 软件进行统计分析。计量资料以均数±标准差($\bar{x}\pm s$)表示,计数资料以例数(百分率)表示。计量资料比较使用独立样本 t 检验或方差分析,计数资料比较则使用卡方检验。以 $P<0.05$ 为差异具有统计学意义。

2 结 果

2.1 纳入患者一般资料

2 组患者在性别、年龄、生命体征等一般临床情况,合并冠心病危险因素,基本检查、检验结果,以及双联抗血小板药物使用、出血风险 CRUSADE 评分方面的差异均无统计学意义($P>0.05$;表 1)。

表 1 2 组患者一般资料比较

Table 1 Comparison of baseline data between 2 groups

($n=50$)

Item	Bivalirudin group	Heparin group	P value
Male[n(%)]	36(72)	34(68)	0.663
Age(years, $\bar{x}\pm s$)	50.60±3.78	49.20±4.10	0.438
BMI(kg/m^2, $\bar{x}\pm s$)	26.05±1.89	25.46±1.87	0.494
Heart rate(times/min, $\bar{x}\pm s$)	66.40±4.11	65.90±3.67	0.774
SBP(mmHg, $\bar{x}\pm s$)	136.60±6.52	134.90±7.01	0.584
DBP(mmHg, $\bar{x}\pm s$)	80.20±4.24	82.61±6.38	0.335
Smoking[n(%)]	18(36)	16(32)	0.673
Hypertension[n(%)]	21(42)	17(34)	0.410
Hyperlipidemia[n(%)]	11(22)	11(22)	1.000
T2DM[n(%)]	13(26)	14(28)	0.822
LVEF(%, $\bar{x}\pm s$)	56.32±3.53	54.40±2.86	0.203
SCr(μmol/L, $\bar{x}\pm s$)	66.28±6.93	67.52±8.85	0.731
Aspirin & clopidogrel [n(%)]	17(34)	13(26)	0.383
Aspirin & ticagrelor [n(%)]	33(66)	37(74)	0.383
CRUSADE score($\bar{x}\pm s$)	11.20±4.47	13.90±4.56	0.198

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; T2DM: type 2 diabetes mellitus; LVEF: left ventricular ejection fraction; SCr: serum creatinine. 1 mmHg=0.133 kPa.

2.2 纳入患者冠状动脉造影及PCI治疗情况

2组患者均成功接受冠状动脉造影检查，结果提示2组患者病变情况的差异无统计学意义（$P>0.05$）。比伐芦定组中32例患者与肝素钠组中29例患者进一步接受PCI治疗，该比例的差异同样无统计学意义（$P=0.539$）。2组中接受PCI治疗患者的植入支架数量、直径、长度与手术时间的差异亦不具有统计学意义（$P>0.05$；表2）。

表2 2组患者冠状动脉造影与介入治疗情况比较

Table 2 Comparison of cardiac angiography and percutaneous coronary intervention data between two groups ($n=50$)

Item	Bivalirudin group	Heparin group	P value
Number of stenosed coronary vessel[n(%)]			0.749
Single	7(14)	9(18)	-
Double	27(54)	28(56)	-
Multiple	16(32)	13(26)	-
Number of stent($\bar{x}\pm s$)	1.60±0.70	1.80±0.79	0.556
Stent diameter(mm, $\bar{x}\pm s$)	2.81±0.27	2.76±0.30	0.704
Stent length(mm, $\bar{x}\pm s$)	24.50±4.93	27.50±7.28	0.295
Operation time(min, $\bar{x}\pm s$)	74.00±11.50	70.00±12.91	0.474

2.3 纳入患者ACT监测情况

比伐芦定组患者给药15 min后ACT值（280.5±12.5）s，至手术结束时基本稳定在（275.3±9.9）s。肝素钠组患者15 min后ACT值（276.5±6.1）s，至手术结束时达到最低（234.9±7.9）s。2组患者给药15 min时ACT的差异不具有统计学意义（$P>0.05$）；自给药30 min后多次监测，比伐芦定组ACT值均高于肝素钠组[30 min：（279.5±5.5）和（258.1±3.0）s；60 min：（282.1±6.8）和（241.8±8.6）s；手术结束时：（275.3±9.9）和（234.9±7.9）s]，差异具有统计学意义（$P<0.05$；图1）。

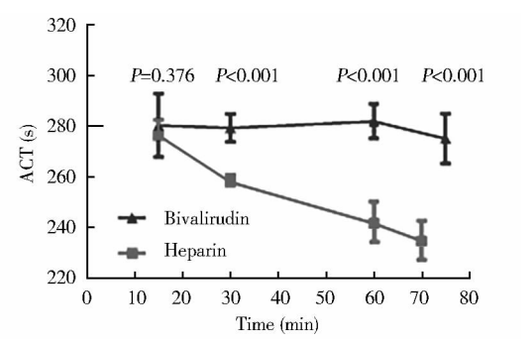

图1 比伐芦定组与肝素钠组ACT监测变化曲线

Figure 1 Differences of ACT values between bivalirudin group and heparin group

ACT: activated coagulation time.

2.4 纳入患者出血事件及血栓事件情况

2组患者围术期无大出血事件及血栓性事件发生。比伐芦定组及肝素钠组患者分别有1例（2%）及3例（6%）出现小出血事件，差异无统计学意义（$P=0.307$）。

3 讨 论

抗凝治疗是PCI围术期抗栓治疗的重要环节，《中国经皮冠状动脉介入治疗指南2016》推荐PCI术中抗凝药物使用比伐芦定或肝素钠，并建议术前采用CRUSADE评分评估出血风险。本研究纳入的患者CRUSADE评分均属于出血低危风险人群，该分层下发生出血事件的风险大约为1.5%，术中使用抗凝药物较为安全合理，但是在一定程度上会造成选择偏倚。

术中监测ACT有助于评估抗凝药物是否达到理想抗凝效果[6]。曾有国内研究者对比伐芦定及肝素钠给药后ACT变化情况做过统计调查，发现事实上并非所有患者在给药后均能达到理想抗凝水平或术中ACT稳定维持在理想水平，这种情况在应用肝素钠时更为常见[4,7]。本研究中比伐芦定组患者给予负荷量药物15 min后ACT可满足PCI手术要求，同时术中持续稳定在较高水平；肝素钠组患者虽给药15 min后ACT亦可达标，但术中持续下降，至1 h左右已降至介入手术要求的ACT下限临界值，该动态变化趋势与既往研究基本一致[8]。上述现象与比伐芦定和肝素钠的药理学机制有关[9]。比伐芦定属水蛭素衍生物，为合成肽类物质，直接作用于凝血酶，即刻起效、半衰期短，且不会诱导激活血小板；肝素纳为硫酸氨基葡萄糖的钠盐，属黏多糖类物质，通过催化抗凝血酶发挥抗自身性血栓和接触性血栓的双重抗凝作用，但其血浆蛋白结合率高，生物利用率低，半衰期不稳定。

比伐芦定相比肝素钠对血小板功能影响更显著，抗凝效果更佳，不良反应发生率低[10,11]，且比伐芦定较肝素钠发生死亡、出血性事件及血栓性事件的风险也更低[12-14]。本研究中出血性事件与血栓性事件发生率较低，并未得出药物安全性方面显著差异性结论，但可以说明在充分评估缺血与出血风险后，使用这2种抗凝药物是相对安全的。需要补充的是，在急诊冠状动脉PCI术的情况下或针对出血高危风险人群，比伐芦定与肝素钠的有效性与安全性比较尚存在争议[15-18]。

综上所述，比伐芦定及肝素钠在择期冠状动脉PCI术中均是有效且安全的抗凝药物，但使用比伐

芦定效果更稳定。PCI 术中应注意:(1)应用比伐芦定确保 ACT 达标后,术中按需复测 ACT;(2)应用肝素钠在给药后除监测 ACT 以确保达标外,术中以间隔 15 min 复测 ACT 为宜。

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