

· 临床研究 ·

## 比伐芦定在冠心病合并终末期肾病患者行经皮冠状动脉介入治疗术中的抗凝效果

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**【摘要】** 目的 回顾性分析比伐芦定与肝素用于冠心病(CHD)合并终末期肾病(ESRD)患者经皮冠状动脉介入治疗(PCI)术中的抗凝效果。方法 选择2015年10月至2018年12月在武汉市普仁医院接受PCI治疗的62例CHD合并ESRD患者为研究对象,根据术中给予抗凝药物的不同,将患者分为对照组(肝素)29例和观察组(比伐芦定)33例。比较2组住院期间造影剂肾病(CIN),术后30d及1年净临床不良事件(NACE)、主要不良心脑血管事件(MACCE)及全部出血事件发生情况;观察2组MACCE分项指标的差异。采用SPSS 25.0统计软件对数据进行分析,根据数据类型,分别采用 $t$ 检验或 $\chi^2$ 检验。结果 住院期间2组各发生CIN 3例,差异无统计学意义( $P>0.05$ )。术后30d,观察组NACE与全部出血事件发生率均低于对照组,差异有统计学意义( $P<0.05$ );2组MACCE发生率比较,差异无统计学意义( $P>0.05$ )。术后1年,观察组NACE发生率低于对照组,差异有统计学意义( $P<0.05$ );2组MACCE、全部出血事件发生率差异无统计学意义( $P>0.05$ )。结论 CHD合并ESRD患者行PCI治疗,与肝素相比,比伐芦定能显著减少术后30d NACE及全部出血事件,抗凝效果良好,且NACE减少优势持续至术后1年。比伐芦定更适合CHD合并ESRD患者PCI术中抗凝。

**【关键词】** 冠心病;终末期肾病;肾小球滤过率;比伐芦定;肝素

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## Anticoagulant effect of bivalirudin in patients with coronary heart disease and end-stage renal disease during percutaneous coronary intervention

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**【Abstract】 Objective** To retrospectively analyze anticoagulant effect of bivalirudin and heparin in the patients with coronary heart disease (CHD) and end-stage renal disease (ESRD) during percutaneous coronary intervention (PCI). **Methods** A total of 62 patients with CHD complicated with ESRD were selected for the study, who received PCI treatment in Wuhan Puren Hospital from October 2015 to December 2018. According to the different anticoagulants administered during operation, they were divided into control group (heparin,  $n=29$ ) and observation group (bivalirudin,  $n=33$ ). The two groups were compared in contrast-induced nephropathy (CIN) during hospitalization, net adverse clinical events (NACE) and major adverse cardiac and cerebrovascular events (MACCE) in 30 days and 1 year after operation. The difference of MACCE sub-indexes between the two groups was observed. SPSS statistics 25.0 was used for data analysis, and  $t$ -test or Chi-square test was used for comparison between groups. **Results** During hospitalization, 3 patients developed CIN in both groups without significant difference ( $P>0.05$ ). At 30 days after the operation, NACE and all bleeding events in the observation group were lower than those in the control group, and the differences were significant ( $P<0.05$ ). There was no significant difference in MACCE between the two groups ( $P>0.05$ ). At postoperative 1 year, NACE was significantly lower in the observation group than the control group ( $P<0.05$ ), and there was no significant difference in MACCE and all bleeding events between the two groups ( $P>0.05$ ). **Conclusion** Bivalirudin reduces the NACE and all bleeding events more significantly than heparin within 30 days after PCI in CHD patients with ESRD, showing better anticoagulant effect. The advantage of risk reduction of NACE may last till 1 year after PCI. Bivalirudin is more suitable for anticoagulation in patients with CHD and ESRD during PCI.

**【Key words】** coronary heart disease; end-stage renal disease; glomerular filtration rate; bivalirudin; heparin

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冠心病(coronary heart disease, CHD)合并终末期肾病(end-stage renal disease, ESRD)患者全因死

亡风险高达45%。数据显示,在过去25年里美国ESRD患者增长了8倍之多,同时介入导管室接受

治疗的CHD合并ESRD患者也明显增长<sup>[1]</sup>。经皮冠状动脉介入治疗(percutaneous coronary intervention, PCI)可用于开通此类患者罪犯血管,缓解患者心肌缺血症状,改善预后。目前PCI术中使用最多的抗凝药物为肝素或比伐芦定,肝素清除不依赖肾脏,但可能会导致出血风险增加,影响预后;以低出血风险优势著称的直接凝血酶抑制剂比伐芦定清除却部分依赖肾脏,用于ESRD患者是否会因为药物蓄积影响临床结局?关于肝素与比伐芦定用于PCI术中抗凝的临床研究基本都排除肾小球滤过率(glomerular filtration rate, GFR) < 30 mL/(min · 1.73 m<sup>2</sup>)患者。本研究回顾性分析比伐芦定与肝素用于CHD合并ESRD患者PCI术中抗凝的效果,以期为临床实践操作提供参考。

## 1 对象与方法

### 1.1 研究对象

回顾性分析2015年10月至2018年12月武汉市普仁医院收治的CHD合并ESRD行PCI治疗的62例患者的临床资料。年龄(67.94 ± 9.81)岁,其中男性36例,女性26例。纳入标准:(1)CHD诊断符合2015年欧洲心脏病学会(European Society of Cardiology, ESC)非ST段抬高急性冠脉综合征管理指南;(2)以简化的肾脏病饮食调整方程(modification of diet in renal disease, MERD)计算GFR < 15 mL/(min · 1.73 m<sup>2</sup>)且下降超过3个月。排除标准:(1)SYNTAX(synergy between percutaneous coronary intervention with taxus and cardiac surgery)评分>32分;(2)左主干病狭窄>50%;(3)近期有出血史,包括腹膜、消化道或近期有外科手术史等;(4)随访资料不完全,死亡除外。

### 1.2 方法

根据患者PCI术中使用抗凝药物不同,将其分为对照组和观察组。对照组29例,以75 U/kg静脉推注普通肝素,5 min后监测活化凝血酶时间(activated clotting time, ACT),若小于225 s,追加肝素25 U/kg,使ACT维持在250~300 s。

观察组33例,术前5 min以0.75 mg/kg快速静脉推注比伐芦定,推注完后立刻以0.25 mg/(kg · h)进行静脉泵入,并维持静脉泵入至术后3~4 h。推注给药5 min后,检测ACT,若小于225 s,以0.3 mg/kg追加静脉推注剂量至ACT达标。所有患者PCI术前24 h及术后48 h内行常规血液透析,术前6 h给予水化治疗:0.9% NaCl以1 mL/(kg · h)静脉滴注至术

后6 h,常规给予300 mg阿司匹林+300 mg氯吡格雷抗血小板治疗,术中使用非离子等渗型对比剂碘克沙醇注射液。

### 1.3 观察指标

住院期间造影剂肾病(contrast-induced nephropathy, CIN);术后30 d及1年净临床不良事件(net adverse clinical events, NACE),主要心脑血管事件(major adverse cardiocerebral events, MACCE)、参照出血学术研究会(Bleeding Academic Research Consortium, BARC)制定的出血分型标准诊断的BARC出血事件<sup>[2]</sup>。MACCE包括:全因死亡、心肌梗死(myocardial infarction, MI)、心力衰竭(heart failure, HF)、心律失常及卒中;CIN指在PCI术后72 h内出现急性肾功能损伤,在排除其他肾损伤因素的情况下,血清肌酐值较基础值升高25%或增加44.2 μmol/L。

### 1.4 统计学处理

采用SPSS 25.0统计软件进行处理。计量资料采用均数±标准差( $\bar{x} \pm s$ )表示,组间比较采用 $t$ 检验。计数资料以例数(百分率)表示,组间比较采用 $\chi^2$ 检验。 $P < 0.05$ 为差异有统计学意义。

## 2 结果

### 2.1 2组患者一般资料比较

2组患者性别、年龄、体质量、透析时间、血脂异常、高血压、糖尿病、血管病变数、造影剂用量及平均手术时间等差异均无统计学意义,具有可比性( $P > 0.05$ ;表1)。

### 2.2 2组患者住院期间及术后30 d主要观察指标比较

住院期间,2组患者分别发生3例CIN,差异无统计学意义( $P > 0.05$ )。术后30 d,2组患者MACCE发生率比较,差异无统计学意义( $P > 0.05$ );观察组NACE与全部出血事件发生率低于对照组,差异均有统计学意义( $P < 0.05$ ;表2)。

### 2.3 2组患者术后1年主要观察指标比较

术后1年,观察组NACE发生率低于对照组,差异有统计学意义( $P < 0.05$ );2组患者MACCE发生率与全部出血事件发生率比较,差异均无统计学意义( $P > 0.05$ ;表2)。

### 2.4 2组患者术后30 d及1年MACCE分项指标比较

2组患者术后30 d及1年MACCE分项指标全因死亡、心肌梗死、心力衰竭、心律失常和卒中比较,差异均无统计学意义( $P > 0.05$ ;表3)。

表 1 2组患者一般资料比较

Table 1 Comparison of baseline data between two groups (n = 62)

Item	Control group (n = 29)	Observation group (n = 33)	t/χ <sup>2</sup>	P value
Gender (male/female, n)	17/12	19/14	0.007	0.934
Age (years, $\bar{x} \pm s$ )	68.14 ± 11.53	67.75 ± 8.17	0.151	0.880
Body mass (kg, $\bar{x} \pm s$ )	66.69 ± 10.18	64.79 ± 8.07	0.819	0.416
Hemodialysis time (years, $\bar{x} \pm s$ )	3.47 ± 1.30	3.35 ± 1.05	0.393	0.696
Dyslipidemia [n (%)]	11 (37.93)	16 (48.48)	0.699	0.403
Hypertension [n (%)]	25 (86.21)	25 (75.76)	1.080	0.299
Diabetes mellitus [n (%)]	11 (37.93)	12 (36.36)	0.016	0.899
Number of vascular lesions [n (%)]			0.342	0.559
1	8 (27.59)	7 (21.21)		
≥ 2	21 (72.41)	26 (78.79)		
Contrast volume (ml, $\bar{x} \pm s$ )	83.28 ± 9.75	84.39 ± 9.66	0.041	0.840
Average operation time (min, $\bar{x} \pm s$ )	58.76 ± 13.49	57.39 ± 12.49	0.189	0.665

表 2 2组患者住院期间、术后 30 d 及 1 年主要观察指标比较

Table 2 Comparison of main observation indexes during hospitalization, 30 days and 1 year after operation between two groups [n (%)]

Group	n	Hospitalization		Postoperative 30 d			Postoperative 1 year		
		CIN	NACE	MACCE	All bleeding events	NACE	MACCE	All bleeding events	
Control	29	3 (10.34)	15 (51.72)	10 (34.48)	11 (37.93)	16 (55.17)	12 (41.38)	13 (44.83)	
Observation	33	3 (9.09)	9 (27.27)	7 (21.21)	5 (15.15)	10 (30.30)	8 (24.24)	8 (24.24)	
χ <sup>2</sup>		0.028	3.890	1.366	4.183	3.921	2.074	2.920	
P value		0.868	0.049	0.243	0.041	0.048	0.150	0.087	

CIN: contrast-induced nephropathy; NACE: net adverse clinical events; MACCE: major adverse cardiac or cerebrovascular events.

表 3 2组患者术后 30 d 及 1 年 MACCE 分项指标比较

Table 3 Comparison of MACCE sub indexes at 30 days and 1 year after operation between two groups [n (%)]

Group	n	Postoperative 30 d					Postoperative 1 year				
		All cause death	MI	HF	arrhythmia	stroke	All cause death	MI	HF	arrhythmia	stroke
Control	29	2 (6.90)	2 (6.90)	5 (17.24)	4 (13.79)	1 (3.45)	3 (10.34)	2 (6.90)	7 (24.14)	6 (20.69)	2 (6.90)
Observation	33	2 (6.06)	2 (6.06)	3 (9.09)	4 (12.12)	1 (3.03)	2 (6.06)	3 (9.09)	5 (15.15)	6 (18.18)	1 (3.03)
χ <sup>2</sup>		0.018	0.018	0.912	0.038	0.009	0.382	0.100	0.799	0.062	0.501
P value		0.894	0.894	0.339	0.845	0.926	0.536	0.752	0.372	0.803	0.479

MACCE: major adverse cardio-cerebrovascular events; MI: myocardial infarction; HF: heart failure.

### 3 讨论

研究显示,由于肾功能不全导致机体环境代谢紊乱,加速了 ESRD 患者的动脉粥样硬化进程,超过 50% 的 ESRD 患者合并 CHD<sup>[2,3]</sup>。目前关于改善此类患者心肌缺血症状的方法,哪种获益更多学术界尚无定论,积极血运重建似乎优于药物保守治疗,患者获益更多且预后更好<sup>[4]</sup>。ESRD 合并 CHD 患者并发症较多且血管钙化严重,采用心脏冠状动脉旁路移植术 (coronary artery bypass graft, CABG) 治疗时,围手术期并发症发生率较高<sup>[5]</sup>。近年来随着介入器械与技术的发展与进步,心内科介入医师积极

尝试通过 PCI 介入方式治疗此类患者,以减少围手术期并发症,并改善远期预后<sup>[6-8]</sup>。对于多支病变及无保护左主干病变,CABG 治疗效果及远期预后更有优势<sup>[9]</sup>,但单支、双支等没有良好搭桥靶点的 ESRD 合并 CHD 患者,PCI 是一种有利方法<sup>[10]</sup>。

ESRD 是不可逆的严重肾功能不全,患者依赖透析治疗。使用药物治疗时,应首先关注药物肾脏毒性、代谢途径及是否增加肾脏负担等,以免造成严重后果,因此 PCI 围手术抗凝药物选择尤其重要。比伐芦定是一种人工合成的多肽类、直接凝血酶抑制剂,与凝血酶作用具有可逆性,在体内不与血浆蛋白结合形成药物蓄积作用,无肾脏毒性<sup>[11]</sup>。研究显

示比伐芦定出血风险显著低于肝素<sup>[12,13]</sup>,临床实践中多被推荐用于 CRUSADE (Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early Implementation of the ACC/AHA guidelines) 评分>30 分的中高出血风险患者 PCI 术中抗凝<sup>[14]</sup>,以减少围手术期出血风险。ESRD 患者体内尿素氮浓度增加使血小板功能受损、红细胞数量减少等因素所导致的机体凝血功能障碍,从 CRUSADE 评分来看,仅 ESRD 一项就占 39 分,为降低患者 PCI 围手术期及术后出血风险,比伐芦定成为此类患者抗凝的一种选择。比伐芦定在一定程度上依赖肾脏功能代谢,在  $GFR \geq 60 \text{ ml}/(\text{min} \cdot 1.73 \text{ m}^2)$  患者体内,其药物清除率为  $3.4 \text{ ml}/(\text{min} \cdot \text{kg})$ ,对应药物代谢半衰期为 22~25 min;随着患者 GFR 下降,比伐芦定在体内清除减慢,半衰期延长;在依赖透析患者体内,其清除率下降至  $1.0 \text{ ml}/(\text{min} \cdot \text{kg})$ ,对应半衰期延长至 3.5 h,所以对于 CHD 合并 ESRD 患者,使用比伐芦定进行围手术期抗凝时需要调整用药剂量,以免血药浓度过高导致严重出血事件<sup>[15]</sup>。本研究中观察组使用比伐芦定维持滴注剂量为  $0.25 \text{ mg}/(\text{kg} \cdot \text{h})$ ,研究结果显示,2 组 CIN 发生率无显著差异,且与肝素相比,比伐芦定能减少 30 d 出血风险,与 Washam 等<sup>[1]</sup> 的回顾性研究报道类似,说明比伐芦定并未导致肾脏毒性或因代谢异常致使出血风险的增加。

与肝素相比,比伐芦定显著减少 30 d NACE 及 30 d 全部出血事件,而 30 d MACCE 无显著差异,表明比伐芦定降低 NACE 可能源于其减少围手术期出血风险。1 年随访结果显示,尽管比伐芦定显著减少 NACE,但对 MACCE、全部出血事件及各分项指标的改善却无统计学意义,结论与比伐芦定用于  $GFR > 30 \text{ ml}/(\text{min} \cdot 1.73 \text{ m}^2)$  的研究报道类似<sup>[16]</sup>。由于缺乏比伐芦定用于 ESRD 患者的随机对照研究,我们尚不能确定这种非显著差异是否与本研究样本量偏少有关。

综上所述,比伐芦定用于 CHD 合并 ESRD 患者 PCI 术中抗凝,能较好地平衡代谢与出血风险,增加患者临床获益,值得借鉴。

CHD 合并 ESRD 患者人群较少,收集病例耗时较长,本研究采用回顾性分析,且病例数偏少,可能导致研究结论的偏倚。对 CHD 合并 ESRD 患者开展 PCI 救治,对临床意义重大。为弥补本研究样本量不足的问题,后期我们还会持续收集病例,并设计相应的试验性研究以评估比伐芦定的疗效与安全性,以期为临床实践提供更多借鉴。

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## 致“一带一路”沿线国家和地区医学机构

《中华老年多器官疾病杂志》是由中国工程院院士、老年心脏学专家王士雯教授于2002年创办的全世界唯一一本以老年心脏病和老年心脏病合并其他器官疾病为主要内容的杂志,月刊,由中国人民解放军总医院老年心血管病研究所主办。杂志已被“中国科技论文统计源期刊”(中国科技核心期刊)收录。本杂志的摘要、图表和参考文献,均为中、英文双语对照,方便国外读者顺利阅读。为促进中国与“一带一路”沿线国家和地区的医学及文化交流,本刊将免费刊登其来稿,并赠送当期杂志。欢迎“一带一路”沿线国家和地区的老年心脏病和老年病学医生、学者踊跃投稿。

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