· 临床研究 ·

比伐芦定用于急性冠状动脉综合征合并慢性肾脏疾病 4 期患者经皮冠状动脉介入治疗术中抗凝疗效与安全性的评价

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【摘 要】 **目的** 评价比伐芦定用于急性冠状动脉综合征(ACS)合并慢性肾脏疾病(CKD)4 期患者经皮冠状动脉介入治疗术(PCI)中抗凝疗效与安全性。**方法** 回顾性分析 2017 年 4 月至 2019 年 10 月在武汉市汉口医院接受 PCI 治疗的 39 例 ACS 合并 CKD 2~4 期患者的临床资料,根据 CKD 临床分期标准分为对照组(CKD 2~3 期)和观察组(CKD 4 期)。比较 2 组患者围手术期活化凝血时间(ACT),术后 24 h 活化部分凝血活酶时间(APTT)、凝血酶时间(TT)、凝血酶原时间(PT),术后 30 d 出血情况及主要不良心脑血管事件(MACCE)。采用 SPSS 20.0 统计软件对数据进行分析。组间比较采用 t 检验或 χ^2 检验。**结果** 对照组和观察组给药后 10 min ACT 值[(438.38±76.79) 和(413.61±66.49) s]、术后即刻 ACT 值[(457.38±73.13)和(425.28±60.96)s]及停药后 2 h ACT 值[(184.21±48.15)和(171.39±38.86)s]比较,差异均无统计学意义(均 P>0.05)。对照组和观察组术后 24 h APTT[(37.67±5.51)和(39.50±9.04)s]、TT[(37.52±8.21)和(38.44±7.04)s]及 PT[(14.76±3.13)和(15.00±3.01)s]比较,差异均无统计学意义(均 P>0.05)。30 d 随访结果显示,对照组和观察组出血学术研究会(BARC) 1 型出血事件发生率[14.29%(3/21)和 11.11%(2/18)]及 BARC 2 型出血事件发生率[4.76%(1/21)和 5.56%(1/18)]比较,差异均无统计学意义(均 P>0.05),均未发生 BRAC 3~5 型出血事件。对照组和观察组 MACCE 发生率[9.52%(2/21)和 11.11%(2/18)]比较,差异无统计学意义(P>0.05)。**结论** 比伐芦定用于 ACS 合并 CKD4 期患者 PCI 术中抗凝具有较好的疗效及安全性。

【关键词】 急性冠脉综合征;慢性肾脏疾病;比伐芦定
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Evaluation of anticoagulant efficacy and safety of bivalirudin in treatment of acute coronary syndrome with stage 4 chronic kidney disease during percutaneous coronary intervention

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【**Abstract**】 **Objective** To evaluate the anticoagulant efficacy and safety of bivalirudin in patients with acute coronary syndrome (ACS) and stage 4 chronic kidney disease (CKD) during percutaneous coronary intervention (PCI). **Methods** A retrospective analysis was made of the clinical data of 39 ACS patients with CKD stages 2 to 4 who underwent PCI in Hankou Hospital of Wuhan from April 2017 to October 2019. The patients were divided into control group (CKD stages 2 to 3) and observation group (CKD stage 4) according to the CKD clinical staging criteria. The two groups were compared for the activated clotting time (ACT) in the perioperative period, activated partial thromboplastin time (APTT), thrombin time (TT) and prothrombin time (PT) at 24 h after operation, bleeding at 30 d after operation, and major adverse cardiac and cerebrovascular events (MACCE). Data were analyzed using SPSS statistics 20.0. Comparisons between groups were performed using t tests or χ^2 tests. **Results** There were no significant differences between the control and observation groups in ACT at 10 min after drug administration[(438.38±76.79) *vs* (413.61±66.49) s], at immediate postoperative period [(457.38±73.13) *vs* (425.28±60.96) s], and at 2 h after drug withdrawal [(184.21±48.15) *vs* (171.39±38.86) s] (P>0.05 for all). Control and observation groups did not have significant differences in APTT [(37.67±5.51) *vs* (39.50±9.04) s], TT [(37.52±8.21) *vs* (38.44±7.04) s], and PT [(14.76±3.13) *vs* (15.00±3.01) s] at 24 h postoperatively (P>0.05 for all). At 30-d follow-up, there was no significant difference between control and observation groups in the incidence of BARC type 1 bleeding events [14.29% (3/21) *vs* 11.11% (2/18)] and BARC type 2 bleeding events [4.76% (1/21) *vs* 5.56% (1/18)] (P>0.05

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for both), and no patients had a BARC type 3 to 5 bleeding event. There was no significant difference between the two groups in the incidence of MACCE [9.52% (2/21) *vs* 11.11% (2/18)] ($P>0.05$). **Conclusion** Bivalirudin had good efficacy and safety in anticoagulation in patients with ACS and CKD4 during PCI.

【Key words】 acute coronary syndrome; chronic kidney disease; bivalirudin

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慢性肾脏疾病(chronic kidney disease, CKD)是急性冠状动脉综合征(acute coronary syndrome, ACS)常见的合并症[1]。ACS合并CKD患者同时属于缺血高危和出血高危人群,一方面由于促血栓性因子增加、各种抗凝物质减少及抗凝活性降低、慢性炎症、内皮细胞损伤等因素导致患者处于高凝状态,易发生缺血事件;另一方面由于血小板功能受损,黏附、聚集能力降低、与血管壁之间相互作用减弱及贫血等因素使机体止血功能受损,可能导致经皮冠状动脉介入治疗(percutaneous coronary intervention, PCI)术中及术后出血风险增加[2-4]。研究显示随着肾小球滤过率(glomerular filtration rate, GFR)降低,患者出血风险明显增加[5,6],导致ACS合并CKD患者行PCI术中出血事件发生率及死亡率明显高于无CKD患者,特别是合并CKD 4期患者[1,7]。尽管如此,与保守治疗相比,PCI治疗ACS合并CKD4期患者仍能有效降低患者死亡风险,改善患者预后[6]。对于此类患者,在现有手术条件下,为提升PCI治疗效果及安全性,围手术期抗凝药物的选择成为了我们的关注点之一。

比伐芦定是一种新型的直接凝血酶抑制剂,具有抗凝效果稳定、出血风险较低等优势,被推荐用于ACS合并CKD1~3期患者PCI围手术期抗凝[8,9]。比伐芦定清除半衰期与GFR密切相关,在肾功能正常患者体内清除半衰期为25 min,随着患者GFR下降,其半衰期逐渐增加,CKD 4期患者[GFR 15~29 ml/(min·1.73 m^2)]半衰期延长至57 min,此时比伐芦定需调整静脉滴注剂量[10]。目前关于比伐芦定用于ACS合并CKD 4期患者PCI术中抗凝的药物代谢问题是否会影响其疗效及安全性的文献较少。本研究拟评价比伐芦定用于ACS合并CKD 4患者PCI围手术期抗凝疗效及安全性,以期为临床实践提供借鉴。

1 对象与方法

1.1 研究对象

回顾性分析2017年4月至2019年10月在武汉市汉口医院行PCI治疗的39例ACS合并CKD 2~4期患者的临床资料,其中男性24例,女性15例,年龄(73.46±7.14)岁。纳入标准:(1) ACS诊断符合《非ST段抬高型急性冠状动脉综合征诊断和治疗指南(2016)》或2015年《急性ST段抬高型心肌梗死诊断和治疗指南》中诊断标准;(2)以改良简化的肾脏病饮食调整方程计算GFR[11],GFR [ml/(min·1.73 m^2)] = 175×血肌酐(mg/ml)$^{-1.234}$×年龄(岁)$^{-0.179}$×(0.79女性)。CKD临床分期标准参照2017年《慢性肾脏病筛查、诊断及防治指南》,CKD 2期:GFR 60~89 ml/(min·1.73 m^2);CKD 3期:GFR 30~59 ml/(min·1.73 m^2);CKD 4期:GFR 15~29 ml/(min·1.73 m^2)。排除标准:(1)随访资料不全;(2)合并房颤,服用其他抗凝药物;(3)近期有出血史,包括消化道出血、脑出血等;(4)近期有外科手术史。

1.2 分组及治疗方法

根据CKD临床分期标准,将患者分为对照组[GFR 30~89 ml/(min·1.73 m^2),CKD 2~3期]和观察组[GFR 15~29 ml/(min·1.73 m^2),CKD 4期]。所有患者PCI术前给予180 mg替格瑞洛和300 mg阿司匹林抗血小板治疗。对照组21例:术前10 min比伐卢定以0.75 mg/kg静脉推注,即刻以1.75 mg/(kg·h)进行静脉泵入,并维持给药至术后3~4 h;观察组18例:术前10 min比伐卢定以0.75 mg/kg静脉推注,即刻以1.0 mg/(kg·h)进行静脉泵入,并维持给药至术后3~4 h。静脉推注给药10 min后,测定活化凝血时间(activated clotting time, ACT)以评估机体抗接触性血栓能力,若低于225 s,则以0.3 mg/kg追加静脉推注剂量至ACT值达标。非ST段抬高型ACS患者于术前6 h进行水化治疗:0.9%NaCl以1 ml/(kg·h)静脉滴注,至术后6 h;ST段抬高型心肌梗死患者,水化治疗至术后12 h。

1.3 观察指标

1.3.1 抗凝疗效指标 记录2组患者给药后10 min、术后即刻及停药后2 h ACT值,术后24 h活化部分凝血活酶时间(activated partial thromboplastin time, APTT)、凝血酶时间(thrombin time, TT)、凝血酶原时间(prothrombin time, PT)。

1.3.2 安全性指标 记录2组患者术后30 d全部出血事件及主要不良心脑血管事件(major adverse

cardiac and cerebrovascular events, MACCE)。出血事件分型参照出血学术研究会(Bleeding Academic Research Consortium, BARC)制定的出血标准[6]。MACCE 包括全因死亡、心肌梗死、脑卒中及心律失常。

1.4 统计学处理

采用 SPSS 20.0 统计软件对数据进行分析。计量资料以均数±标准差($\bar{x}\pm s$)表示,组间比较采用独立样本 t 检验;计数资料以例数(百分率)表示,组间比较采用 χ^2 检验。$P<0.05$ 为差异有统计学意义。

2 结 果

2.1 2 组患者基线资料比较

2 组患者在性别、年龄、体质量、吸烟、高血压、糖尿病、中风史、外周血管病、既往 PCI 史、血小板计数、左心室射血分数、ACS 分类及血管病变数量方面比较,差异均无统计学意义($P>0.05$;表 1),具有可比性。

2.2 2 组患者围手术期 ACT 值比较

2 组患者给药后 10 min, ACT 值均快速达标(ACT>225 s),差异无统计学意义($P>0.05$);术后即刻 ACT 值比较,差异无统计学意义($P>0.05$);停药后 2 h ACT 值快速回落,差异无统计学意义($P>0.05$;表 2)。

2.3 2 组患者术后 24 h 凝血指标比较

2 组患者术后 24 h APTT、TT 及 PT 比较,差异均无统计学意义($P>0.05$;表 3)。

2.4 2 组患者术后 30 d 出血情况比较

2 组患者 BACR1 型、BACR2 型出血发生率比较,差异均无统计学意义($P>0.05$)。2 组患者均无 BARC 3~5 型出血事件发生,详见表 4。

表 1 2 组患者基线治疗比较

Table1 Comparison of baseline data between two groups

Item	Control group(n=21)	Observation group (n=18)	t/χ^2	P value
Gender(male/female, n)	12/9	12/6	0.371	0.542
Age(years, $\bar{x}\pm s$)	74.43±7.12	74.67±7.17	0.976	0.791
Body mass(kg, $\bar{x}\pm s$)	66.43±9.03	64.22±8.27	0.791	0.434
Smoking[n(%)]	12(57.14)	7(38.89)	1.293	0.256
Hypertension[n(%)]	17(80.95)	14(77.78)	0.060	0.807
Diabetes mellitus[n(%)]	14(66.67)	13(72.22)	0.140	0.708
Strock history[n(%)]	6(28.57)	6(33.33)	0.103	0.748
Peripheral vascular disease[n(%)]	11(52.38)	11(61.11)	0.300	0.584
PCI history[n(%)]	3(14.29)	4(22.22)	0.042	0.837
Platelet($\times10^9$/L, $\bar{x}\pm s$)	140.86±23.31	128.50±31.77	1.398	0.370
LVEF(%, $\bar{x}\pm s$)	54.86±5.65	52.72±6.61	1.087	0.284
Distribution of ACS[n(%)]				
UA	16(76.19)	13(72.22)	0.080	0.777
NSTEMI	3(14.29)	3(16.67)	0.042	0.837
STEMI	2(9.52)	2(11.11)	0.027	0.871
Number of vascular lesions[n(%)]			1.146	0.284
1	8(38.10)	4(22.22)		
≥2	13(61.90)	14(77.78)		

PCI: percutaneous coronary intervention; LVEF: left ventricular ejection fraction; ACS: acute coronary syndrome; UA: unstable angina; NSTEMI: non-ST-segment elevation myocardial infarction; STEMI: ST-segment elevation myocardial infarction.

表 2 2 组患者围手术期 ACT 值比较

Table 2 Comparison of perioperative ACT values between two groups (s, $\bar{x}\pm s$)

Group	n	10 minutes after administration	Immediately after operation	2 hours after drug withdrawal
Control	21	438.38±76.79	457.38±73.13	184.21±48.15
Observation	18	413.61±66.49	425.28±60.96	171.39±38.86
t		1.067	1.474	0.907
P value		0.293	0.149	0.370

ACT: activated clotting time.

表3 2组患者术后24 h凝血指标比较

Table 3 Comparison of coagulation indices at 24 hours after surgery between two groups (s, $\bar{x}\pm s$)

Group	n	APTT	TT	PT
Control	21	37.67±5.51	37.52±8.21	14.76±3.13
Observation	18	39.50±9.04	38.44±7.04	15.00±3.01
t		0.777	0.372	0.241
P value		0.442	0.712	0.811

APTT: activated partial thromboplastin time; TT: thrombin time; PT: prothrombin time.

表4 2组患者术后30 d出血情况比较

Table 4 Comparison of bleeding within 30 days after operationg between two groups [n(%)]

Group	n	BARC1	BARC2	BARC3-5
Control	21	3 (14.29)	1 (4.76)	0(0.00)
Observation	18	2 (11.11)	1 (5.56)	0(0.00)
χ^2		0.870	0.013	-
P value		0.768	0.911	-

BARC: Bleeding Academic Research Consortium.

2.5 2组患者术后30 d MACCE比较

2组患者术后30 d MACCE比较,差异无统计学意义(P>0.05)。对照组发生1例心肌梗死及1例心律失常,观察组发生1例卒中及1例心律失常。详见表5。

3 讨 论

随着PCI技术经验的累积及新型抗栓药物的使用,ACS患者缺血事件得到显著改善,但出血事件如消化道出血、脑出血等非穿刺部位出血并未显著减少。因此《中国经皮冠状动脉介入治疗指南(2016)》强调,需评估患者的缺血风险和出血风险以制定ACS患者PCI治疗策略,避免因抗凝不足或出血等不良事件影响PCI治疗获益。

ACS合并CKD 4期患者属于缺血高危。研究表明,多种病理生理途径共同参与ACS合并CKD患者血栓的形成[12]:(1)凝血级联反应受CKD影响,使纤维蛋白原、组织因子及炎症标记物等促血栓性因子浓度增加,凝血酶活性增加;(2)纤溶酶原激活抑制剂水平升高抑制纤溶系统活性;(3)内皮损伤导致其抗血栓特性丧失。有研究表明GFR下降是引起CKD患者高缺血风险的独立危险因素,且随着GFR的下降缺血风险显著增加[5]。比伐芦定是一种特异性的直接凝血酶抑制剂,鉴于其在ACS合并CKD4期患者体内半衰期延长至57 min,参照相关报道,本研究调整比伐芦定静脉泵入剂量至1.0 mg/(kg·h),并持续至术后3~4 h[10,13]。比伐芦定用于ACS伴轻中度肾功能不全患者,具有良好的抗凝效果[14,15]。本研究中2组患者围手术期ACT值显示,尽管ACS合并CKD 4期缺血风险高于CKD 2~3期,调整剂量后,比伐芦定仍具有充分且平稳的抗接触性血栓能力。术后24 h APTT、TT及PT结果显示,比伐芦定用于ACS合并CKD 4期患者,停药后会被快速代谢,无体内蓄积毒性。

ACS合并CKD4期患者属于出血高危。可能与CKD患者体内尿毒素浓度增加,导致血小板功能受损、红细胞数量减少等因素有关[12]。研究显示ACS合并CKD4期患者PCI术后的主要出血风险是无CKD患者2~8倍[12,13],降低患者出血风险以增加患者获益尤为重要。陈存芳等[15]研究纳入GFR 15~89 ml/(min·1.73 m^2)的患者,结果显示,与肝素相比,比伐芦定显著降低ACS合并CKD患者PCI术后30 d内轻度出血及总体出血量,且不随肾功能下降而显著增加出血风险。本研究结果显示,2组患者BARC 1~2型出血事件比较,差异无统计学意义。进一步证实调整剂量后比伐芦定用于合并CKD 4期患者不会导致出血事件增加,具有良好的安全性。2组间MACCE比较差异无统计学意义。提示调整计量后比伐芦定用于ACS合并CKD 4期患者PCI术中抗凝与其用于合并CKD 2~3期疗效相当。

综上,比伐芦定用于ACS合并CKD 4期患者术中抗凝,具有良好的抗凝效果及安全性。本研究采用回顾性分析方法,病例数较少,可能对研究结果造成一定的影响。后期我们将持续性收集此类病例,

表5 2组患者术后30 d MACCE比较

Table5 Comparison of MACCE within 30 days after operation between two groups [n(%)]

Group	n	All cause death	Myocardial infarction	Stroke	Arrhythmia	MACCE
Control	21	0(0.00)	1(4.76)	0(0.00)	1(4.76)	2(9.52)
Observation	18	0(0.00)	0(0.00)	1(5.56)	1(5.56)	2(11.11)
χ^2			0.880	1.197	0.013	0.027
P value			0.348	0.274	0.911	0.871

MACCE: major adverse cardiac and cerebrovascular events.

并设计随机对照试验以评价比伐芦定用于 ACS 合并 CKD4 期患者 PCI 术中抗凝疗效与安全性,以期为临床事件提供更多的借鉴。

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