

doi: 10.13241/j.cnki.pmb.2019.01.033

磺达肝癸钠治疗急性冠脉综合症的临床疗效及安全性研究*

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摘要 目的:探讨磺达肝癸钠对急性非 ST 段抬高心肌梗死(NSTEMI)患者经皮冠状动脉介入治疗(PCI)的临床疗效及安全性。**方法:**入选 164 例接受 PCI 治疗的 NSTEMI 患者,将其随机分为观察组(82 例)和对照组(80 例)。观察组患者给予磺达肝癸钠治疗;对照组患者给予那曲肝素治疗。观察和比较两组治疗第 10 天的心脏事件(死亡、再梗死)及不良反应(出血)的发生率、凝血酶原时间(PT)及活化部分凝血活酶时间(APTT)、心脏功能(LVEDV、EF)及第 30 天的死亡率。**结果:**观察组与对照组第 10 天的死亡率[2.4% (2/82) vs. 3.7%(3/80), $P=0.630$]、新发梗死率[3.6%(3/82) vs. 5.0%(4/80), $P=0.724$], 第 30 天的死亡率[1.2%(1/80) vs. .6%(2/77), $P=0.538$], 严重出血发生率[1.2%(1/82) vs. 2.5%(2/80), $P=0.546$]比较差异均无统计学意义。磺达肝癸钠组轻微出血发生率显著低于对照组[3.6%(3/82) vs. 12.5%(10/80), $P=0.038$], 差异有统计学意义。与对照组比较, 观察组的凝血时间显著延长[APTT(30.02 ± 2.10) vs. (29.24 ± 1.84), $t=2.512$, $P=0.013$; PT(13.62 ± 1.34) vs. (12.24 ± 1.20), $t=6.89$, $P=0.000$], 心功能明显改善[LVEDV(35.80 ± 1.62) vs. (36.25 ± 1.22), $t=1.993$, $P=0.048$; EF(42.25 ± 0.34) vs. (42.15 ± 0.26), $t=2.099$, $P=0.037$]。**结论:**磺达肝癸钠在急性冠脉综合征行 PCI 治疗中的抗凝效果优于那曲肝素, 其改善心功能的效果更好, 且出血发生率低。

关键词:磺达肝癸钠;经皮冠状动脉介入治疗;急性心肌梗死

中图分类号:R542.22 文献标识码:A 文章编号:1673-6273(2019)01-150-04

Efficacy and Safety of Fondaparinux in the Treatment of Patients with Acute Coronary Syndrome*

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ABSTRACT Objective: To observe the clinical efficacy and safety of Fondaparinux in the treatment of patients with non-ST-elevation myocardial infarction (NSTEMI) undergoing percutaneous coronary intervention(PCI). **Methods:** 164 cases of patients with NSTEMI were randomly divided into the study group (82 cases) and the control group (80 cases). Patients in the study group were treated with Fondaparinux and patients in the control group were treated with Nadroparin. The incidence of cardiac events (death, reinfarction) and adverse reactions (bleeding), changes of prothrombin time (PT) and activated partial thromboplastin (APTT) time, heart function (LVEDV, EF) on the 10th day of treatment, the mortality on the 30th day were compared between two groups. **Results:** The mortality on the 10th day (2.4% (2/82) vs. 3.7% (3/80), $P=0.630$), the incidence of reinfarction [3.6% (3/82) vs. 5.0% (4/80), $P=0.724$], the mortality on the 30th day [1.2% (1/80) vs. 2.6% (2/77), $P=0.538$], the incidence of severe bleeding [1.2% (1/82) vs. 2.5% (2/80), $P=0.546$] showed no significant difference between the two groups. The incidence of mild hemorrhage in the group of Fondaparinux was significantly lower than that of the control group [3.6% (3/82) vs. 12.5% (10/80), $P=0.038$], the coagulation time was prolonged [APTT (30.02 ± 2.10) vs. (29.24 ± 1.84), $P=0.013$; PT (13.62 ± 1.34) vs. (12.24 ± 1.20), $P=0.000$] and; the heart function was obviously improved in the observation group [LVEDV (35.80 ± 1.62) vs. (36.25 ± 1.22), $P=0.048$, EF (42.25 ± 0.34) vs. (42.15 ± 0.26), $P=0.037$]($P<0.05$). **Conclusion:** Compared with Nadroparin alone, Fondaparinux has excellent anticoagulant effect, it can better improve the heart function and lower incidence of bleeding in the treatment of patients with acute coronary syndrome undergoing PCI.

Key words: Fondaparinux; Percutaneous coronary intervention; Acute myocardial infarction

Chinese Library Classification(CLC): R542.22 **Document code:** A

Article ID: 1673-6273(2019)01-150-04

前言

急性冠脉综合征(acute coronary syndrome, ACS)是全球致死及致病的重要原因之一^[1], 包括不稳定型心绞痛(unstable

angina, UA)、急性 ST 段抬高心肌梗死(ST-elevation myocardial infarction, STEMI)及急性非 ST 段抬高心肌梗死(non-ST-elevation myocardial infarction, NSTEMI)。经皮冠状动脉介入治疗(percutaneous coronary intervention, PCI) 是治疗冠心病的主要

* 基金项目:黑龙江省教育厅科研基金项目(11551259)

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(收稿日期:2018-09-30 接受日期:2018-10-24)

手段之一。ACS 发生时,保证介入手术成功与安全的关键环节是合理规范并尽早启动抗凝治疗^[2]。尽管直接 PCI 联合多种抗血小板和抗凝药物改善了患者的预后,但出血并发症给临床带来新的问题。

磺达肝癸钠是一种新型抗凝剂,在国外已广泛使用。研究显示亚裔人群抗凝治疗后颅内出血的风险高于欧美人群^[3]。本研究主要通过对比磺达肝癸钠与那曲肝素在急性非 ST 段抬高心肌梗死行 PCI 治疗中的应用情况,评价了磺达肝癸钠的有效性与安全性。

1 资料与方法

1.1 一般资料

选取 2011 年 1 月至 2013 年 12 月在哈尔滨医科大学附属第四医院心内科住院的急性非 ST 段抬高心肌梗死接受 PCI 治疗的患者 162 人,将其随机分为两组。观察组 82 例,男 44 人,女 38 人,平均年龄(62.3 ± 7.2)岁,病程 3~26 个月,平均病程(12.3 ± 4.2)个月。对照组 80 例,男 43 人,女 37 人,平均年龄(61.2 ± 6.3)岁,病程 4~27 个月,平均病程(11.2 ± 4.3)。两组患者性别、年龄、病程比较均无统计学差异($p > 0.05$),具有可比性。

按照美国心脏病学会(ACC)/美国心脏协会(AHA)指南^[4]诊断标准入选患者。患者 48 小时内心肌缺血发作持续 10 分钟以上,同时满足至少下列条件之一,(1)肌钙蛋白 I 或肌钙蛋白 T 升高;(2)心电图提示缺血性改变(至少两个连续导联出现 ST 段压低,短暂性 ST 段抬高或者 T 波改变);(3)既往心肌梗死、典型心绞痛或血运重建史。排除标准:(1)年龄 > 80 岁;(2)血压 $> 180/110$ mmHg;(3)严重的肝肾功能障碍;(4)一年内出现出血性卒中;(5)出血性疾病者;(6)抗凝药物禁忌者。

1.2 治疗方法

所有患者入院后均给予常规药物治疗,包括硝酸酯类、他汀类、 β 受体阻滞剂及血管紧张素抑制剂(angiotensin converting enzyme inhibitor, ACEI)。行急诊 PCI 术前给予患者口服负荷量阿司匹林 300 mg、氯吡格雷 300~600 mg。术后长期口服阿司匹林 100 mg 一日一次;氯吡格雷 75 mg 一日一次共 12 个月。观察组患者给予磺达肝癸钠 2.5 mg,每日一次皮下注射,对照组患者给予那曲肝素 0.1 mL/10 kg,每 12 小时 1 次皮下注射;两组均连用 7 天。

1.3 观察指标

PCI 术后第 10 天的观察指标:(1)临床事件包括心源性死亡、新发心肌梗死。(2)出血发生情况包括严重出血(脑出血、腹膜后血肿及消化道出血);轻微出血^[5](皮下瘀斑、牙龈出血及便潜血);(3)活化部分凝血酶原时间(activated partial thromboplastin time, APTT)、凝血酶原时间(prothrombin time, PT);(4)心功能包括左心室舒张末内径(left ventricular end diastolic diameter, LVEDV)值及心室射血分数(ejection fraction, EF)值。

1.4 统计学方法

使用 SPSS22.0 统计软件进行数据处理,所有计量数据以均数 $\pm$ 标准差($\bar{x} \pm s$)表示,组间比较采用 t 检验,计数资料数据以率表示,组间比较采用 χ^2 检验,以 $P < 0.05$ 时表示差异有统计学意义。

2 结果

2.1 两组临床事件发生情况的比较

两组心源性死亡率、再发心肌梗死率及第 30 天随访的死亡率比较均无统计学差异($p > 0.05$),见表 1。

表 1 两组患者临床事件发生情况的比较[例(%)]

Table 1 Comparison of the incidence of clinical event between two groups[n(%)]

Groups	Control group	Study group	P
Number	80	82	
Cardiac death (10d)	3(3.7)	2(2.4)	0.630
Recurrent AMI(10d)	4(5.0)	3(3.6)	0.724
Follow-up Number	77	80	
Cardiac death (30d)	2(2.6)	1(1.2)	0.538

2.2 两组出血情况比较

两组大出血发生率均较低,组间相比无统计学差异($p > 0.05$);磺达肝癸钠组轻微出血发生率显著低于对照组($p < 0.05$),见表 2。

2.3 两组治疗前后 APTT、PT 比较

与对照组相比,磺达肝癸钠组 APTT 与 PT 时间明显延长,差别有统计学意义($p < 0.05$),见表 3。

2.4 两组治疗前后心功能比较

与对照组相比,磺达肝癸钠组左心室舒张末内径(LVEDV)减小,心室射血分数(EF)增加($p < 0.05$),见表 4。

表 2 两组患者出血情况比较[例(%)]

Table 2 Comparison of the incidence of bleeding between two groups[n(%)]

Group	Control group	Study group	P
Number	80	82	
Severe bleeding	2(2.5)	1(1.2)	0.546
Minor bleeding	10(12.5)	3(3.6)	0.038

表 3 两组患者治疗前后 APTT、PT 比较($\bar{x} \pm s$)

Table 3 Comparison of the APTT and PT before and after treatment between two groups($\bar{x} \pm s$)

Groups	Control group	Study group	t	P
Number	80	82		
Before treatment				
APTT	29.10± 1.92	29.24± 1.84	0.474	0.636
PT	12.16± 0.84	12.24± 1.20	0.490	0.624
After treatment				
APTT	29.24± 1.84	30.02± 2.10	2.512	0.013
PT	12.24± 1.20	13.62± 1.34	6.899	0.000

表 4 两组患者治疗前后心脏功能比较($\bar{x} \pm s$)

Table 4 Comparison of the heart function between two groups before and after treatment($\bar{x} \pm s$)

Group	Control group	Study group	t	P
Number	80	82		
Before treatment				
LVEDV(mm)	44.92± 1.26	44.86± 1.24	0.305	0.760
EF(%)	36.04± 0.21	35.96± 0.58	1.452	0.148
After treatment				
LVEDV(mm)	36.25± 1.22	35.80± 1.62	1.993	0.048
EF(%)	42.15± 0.26	42.25± 0.34	2.099	0.037

3 讨论

急性冠脉综合征(ACS)是以冠状动脉粥样硬化斑块破溃、继发完全或不完全闭塞性血栓为病理基础的一组临床综合征,其发生率和程度随年龄的增加而上升。ACS 患者中,由于出血和缺血事件的双重风险同时存在,因此临床 PCI 及抗栓治疗面临极大的挑战^[6]。一项汇入 4 个研究的 meta 分析纳入了 37241 例 ACS 患者,结果显示颅内出血死亡率为 33%,而且年龄每增加 10 岁,颅内出血风险增加 61%^[7]。尽管经皮冠脉介入术不断发展,PCI 联合抗血小板与抗凝治疗使心脏事件明显下降,但 PCI 围手术期出血患者的远期心血管事件发病率及死亡率明显升高^[8,9]。PCI 围术期出血不仅使患者满意度下降,出院延迟,医疗费用增加,而且一年的死亡、心肌梗死和卒中的风险也相应增加^[10]。急性心肌梗死发作时,血小板活化,白细胞升高,机体处于应激状态^[11],并且血小板活性增高的状态可持续一年^[12],故而指南推荐急性心机更死发生后双联抗血小板药物至少服用一年^[13]。

普通肝素作为临床常用抗凝剂具有较强的抗凝作用,常规用于 PCI。由于其自身结构及成分的缺陷,不良反应多见,血小板减少症的发生率是低分子肝素的 10 倍^[14],使用期间需要监测活化部分凝血激酶时间(activated clotting time, ACT)以调整剂量。低分子肝素因其快速、持续的抗血栓形成作用、无需监测 ACT 的特性已在临床广泛应用。但低分子肝素只抑制流动相凝血酶,不抑制纤维蛋白降解产物,无法抑制与活化的血小板表面结合的 Xa 因子,最终致使血小板减少^[15]。为了降低出血风险,临床迫切需要新型抗凝药。磺达肝癸钠作为新型抗凝剂,对

血小板无影响,国外多项大型试验均证明了其用于急性冠脉综合征是安全有效的^[16,17]。基于多项亚裔人群抗凝治疗后易出现致命大出血的研究^[18,19],磺达肝癸钠是否对国人安全有效尚需要进一步临床证实。

磺达肝癸钠选择性与抗凝血酶(antithrombin, AT)结合,增强 Xa 因子的中和,抑制凝血酶及血栓形成。磺达肝癸钠不经过肝脏 P450 酶代谢,主要以原型由肾脏清除。由于其具有低变性及高再生性等线性动力学特点,皮下注射可被快速吸收,起效快,无剂量依赖性;不会灭活凝血酶(活化因子 II),对血小板无影响,不引起肝素诱导的血小板减少症(heparin-induced thrombocytopenia, HIT),有效降低患者的出血风险,安全性较高^[20,21]。OASIS-5 和 6 是两个著名的大型试验,共入选了超过 32000 例 ACS 患者,OASIS-5 随机入选了 20078 例非 ST 段抬高型 ACS 患者,随机分为依诺肝素组和磺达肝癸钠组,结果表明两种药物在降低心脏事件的有效性方面相似,但磺达肝癸钠组的出血并发症显著降低。在更为复杂的 OASIS-6 中,入选 12092 例 ST 段抬高心肌梗死患者,在溶栓、PCI 或非再灌注治疗的不同患者中比较磺达肝癸钠与常规治疗(安慰剂或普通肝素),结果磺达肝癸钠组在第 9 天、30 天和试验结束的 3 至 6 个月,死亡、再梗死显著减低,而出血无显著增加。这两个试验联合分析表明,在不同类型的 ACS 患者中,新型抗凝药物磺达肝癸钠都要优于普通肝素或者依诺肝素,且能显著降低出血并发症^[22]。美国 AHA/ACC 指推荐 NSTEMI 患者可应用磺达肝癸钠进行抗凝治疗(Ib 类推荐)^[23]。国内有报道^[24,25]磺达肝癸钠对急性 ST 段抬高型心肌梗死行 PCI 是安全的;在 80 岁以上老年急性心肌梗死中应用磺达肝癸钠出血事件小,安全有效。

本研究结果显示急性非 ST 段抬高型心肌梗死应用磺达肝癸钠与那曲肝素后病情均得到改善, 两组患者心源性死亡率、再次新发心肌梗死率均较低, 均无明显大出血。磺达肝癸钠组 1 人出现牙龈出血, 2 人出现便潜血, 轻微出血发生率较对照组低, 有潜在优势。磺达肝癸钠组的抗凝效果强于对照组。磺达肝癸钠组患者的心功能强于对照组。

综上所述, 磺达肝癸钠在急性冠脉综合征行 PCI 治疗中的抗凝效果优于那曲肝素, 改善心功能的效果更好, 且出血发生率降低。

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显著提升。通常而言,发明专利较之于实用新型有着较高的法律稳定性和技术价值,其审查过程也相对漫长,一旦确权,发明专利的社会认可度和市场价值往往比较高,在中国当前实施专利质量提升工程的背景下,应继续强化产业专利政策导向,为战略性新兴产业发展提供更多高质量发明专利及其专利组合。

(2)技术与产业发展应考虑不同区域的专利技术优劣势

中国 3D 生物打印专利(含申请)在各省区的分布前十位由高到低依次为广东、北京、浙江、上海、江苏、山东、陕西、四川、湖北、天津。其中,广东在各技术领域的优势均较为明显,具有良好的产业化基础,北京在 A61F、A61L 两个技术领域优势较大,浙江则在 B29C 领域具有一定优势,广东、北京、江苏在各技术领域均有所涉及,产业化基础比较全面,不同区域之间可以通过技术合作发挥各自在产业链上的优势、弥补不足、共赢发展,在培育 3D 生物打印产业中心时,也应充分参考各区域的技术优势特征,建立特色化、差异化的技术和产业发展模式。

(3)来自企业的专利申请有待提升

从专利申请人视角来看,中国专利(含申请)的申请主体可划分为大专院校、企业、个人、机关团体、科研单位五类,大专院校的专利占比达到 34.23%,高于企业占比的 32.79%,个人申请专利占比接近 20%。企业占比不到三分之一的现状意味着专利技术的产业化程度不高,存在一定的技术和市场脱节的情况,大专院校和个人申请专利的动机大部分并不是专利的直接产业化,但在技术发展初期由大专院校申请的一系列专利往往构成了本领域的一系列原理性技术方案,即基础专利,这类专利可以以技术投资为目的进行前瞻性的专利运营与收购,重点培育具有技术优势的 3D 生物打印企业是实现产业发展的关键。

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