Original Article

Unfractionated Heparin with Sequential Enoxaparin in Patients with Complex Coronary Artery Lesions during Percutaneous Coronary Intervention

Zhi-Zhong Li, Ying Tao, Su Wang, Cheng-Qian Yin, Yu-Long Gao, Yu-Tong Cheng, Zhao Li, Chang-Sheng Ma

Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart Lung and Blood Vessel Diseases, Beijing 100029, China

Abstract

Background: Unfractionated heparin (UFH), despite its limitations, has been used as the primary anticoagulant alternative during the percutaneous coronary intervention (PCI). Some studies indicated that intravenous enoxaparin could be an effective and safe option. Our team used enoxaparin alone at one time according to the guidelines (Class IIA) and found a little catheter thrombosis during PCI. We recommend a new anticoagulation strategy using enoxaparin in combination with UFH. Enoxaparin has a more predictable anticoagulant response with no need of repeatedly monitoring anticoagulation during PCI. This retrospective study aimed to evaluate the efficacy and safety of using enoxaparin in combination with UFH in PCI patients with complex coronary artery disease.

Methods: Between January 2015 and April 2017, 600 PCI patients who received intravenous UFH at an initial dose of 3000 U plus intravenous enoxaparin at a dose of 0.75 mg/kg (observation group) and 600 PCI patients who received UFH at a dose of 100 U/kg (control group) were consecutively included in this retrospective study. The endpoints were postoperative 48-h thrombolysis in myocardial infarction (TIMI) bleeding and transfusion and 30-day and 1-year major adverse cardio-cerebrovascular events (MACCE).

Results: Baseline clinical, angiographic, and procedural characteristics were similar between groups, except there was less stent implantation per patient in the observation group (2.13 vs. 2.25 in the control group, $P = 0.002$). TIMI bleeding (3.3% vs. 4.7%) showed no significant difference between the observation group and control group. During the 30-day follow-up, the rate of MACCE was 0.9% in the observation group and 1.5% in the control group. There was no significant difference in the rates of MACCE, death, myocardial infarction, target vessel revascularization, cerebrovascular event, and angina within 30 days and 1 year after PCI between groups as well as in the subgroup analysis of transfemoral approach.

Conclusions: UFH with sequential enoxaparin has similar anticoagulant effect and safety as UFH in PCI of complex coronary artery disease.

Key words: Complex Coronary Heart Disease; Enoxaparin; Percutaneous Coronary Intervention; Unfractionated Heparin

Introduction

The application of percutaneous coronary intervention (PCI) as a treatment option is increasing in patients with unstable angina in China. During the procedure of PCI, intravenous unfractionated heparin (UFH) is mainly used as the standard anticoagulant in the catheterization laboratory, needing dose adjustment for activated clotting time (ACT).[1,2] Most domestic centers with interventional cardiology facilities would choose classical UFH at first. In fact, UFH sometimes has unstable and unpredictable effects on coagulation; the low therapeutic window of UFH leads to potential drug-induced thrombocytopenia and high risk of bleeding; the half-life is short (1 h), and the ACT should be closely observed in patients.[3] It is necessary to suggest a better anticoagulation drug or plan for PCI.

Enoxaparin, a low-molecular-weight heparin, has anticoagulant and antithrombotic effects during PCI with no need of repeatedly monitoring ACT due to its longer

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.4103/0366-6999.243559

Address for correspondence: Prof. Chang-Sheng Ma, Department of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing Institute of Heart Lung and Blood Vessel Diseases, Beijing 100029, China
E-Mail: chshma@vip.sina.com

Received: 13-07-2018 **Edited by:** Qiang Shi

How to cite this article: Li ZZ, Tao Y, Wang S, Yin CQ, Gao YL, Cheng YT, Li Z, Ma CS. Unfractionated Heparin with Sequential Enoxaparin in Patients with Complex Coronary Artery Lesions during Percutaneous Coronary Intervention. Chin Med J 2018;131:2417-23.

half-life (3.5–4.5 h). In the past, due to induction of thrombosis and even abrupt vessel closure, there were some limitations for intravenous enoxaparin alone applying to PCI patients. Recently, studies have shown that enoxaparin is able to reduce the risk of bleeding and it has similar safety and efficacy compared to UFH in PCI patients.[3-6] Although enoxaparin has been accepted as a guideline-recommended Class IIA and first-line therapy since many years ago,[7] there are still many concerns for doctors in China. In our ward, we once used enoxaparin alone according to the guidelines and found a little catheter thrombosis during PCI. Considering the above studies and clinical experiences of our team, we suggest a new anticoagulation strategy of UFH in combination with sequential enoxaparin, using UFH 3000 U plus enoxaparin 0.75 mg/kg per patient. In clinical practice, we observed that the strategy showed obvious advantages in PCI patients with transfemoral approach; it significantly shortened the bedridden time (at least 24 h) and potentially reduced the bleeding complications and medical consumption (for instance, nursing time). We have performed it in our center since 2003, and the low mortality and complications have probably confirmed its clinical safety and efficacy. This study evaluated the efficacy and safety of UFH with sequential enoxaparin, as compared with UFH, on PCI patients with complex coronary artery lesions.

Methods

Ethical approval

This study complied with the *Declaration of Helsinki* and local regulations, and it was authorized by the Ethics Committee of Beijing Anzhen Hospital. Informed consent was obtained from all individual participants included in the study.

Subjects

Between January 2015 and April 2017, we retrospectively consecutively identified the medical records of PCI patients who received UFH with sequential enoxaparin (600) or UFH alone (600) at the same time in our institution. Eligible participants were at least older than 18 years. Entry criteria also included: patients with a final diagnosis of unstable angina pectoris and having complex coronary artery lesions confirmed by coronary angiography. The diagnosis of unstable angina was based on clinical histories, physical examinations, and documentation of ischemia-like electrocardiogram (ECG) changes. The ECG changes were defined as ST-segment depression of at least 0.1 mV (including reciprocal changes) or T-wave inversion of at least 0.1 mV in ≥2 contiguous leads. Patients' vessel lesions were considered "complex" according to the previous studies[8,9] when any of the following symptoms were present: ostial lesion, unprotected left main coronary artery lesion, bifurcation lesion, more than two vessels treated, lesion length >27 mm, totally occluded lesion (defined as the thrombolysis in myocardial infarction [TIMI] grade 0 flow and lasting ≥3 months), any lesion with thrombus, in-stent restenosis lesion, saphenous vein graft lesion, arterial bypass graft lesion, etc. Patients were excluded when they had any of the following major criteria: acute myocardial infarction (MI), overt congestive heart failure, severe arrhythmia, pericarditis, symptoms of aortic dissection, pregnancy, severe renal or hepatic diseases, malignant disease, history of a cerebrovascular accident, neutropenia or thrombocytopenia, known allergy to the study drugs, recent major surgery, life-limiting major concomitant noncardiac diseases, etc.

Anticoagulation procedures

The included 1200 patients who need PCI after initial angiography would be treated with either UFH with sequential enoxaparin (n = 600) or UFH alone (n = 600) in the catheterization laboratory. The observation group was given an initial intravenous dose of 3000 U of UFH plus additional intravenous enoxaparin at a dose of 0.75 mg/kg. The control group was given intravenous UFH at a dose of 100 U/kg, with dose adjustment according to activated clotting time (ACT) during PCI. Before PCI, a total dose of aspirin (300 mg) and clopidogrel (600 mg) was administered for all patients if no contraindication was present, according to local practice.

PCI was performed according to the current standard techniques. The intraoperative device, pharmacotherapy use, and interventional strategy were decided by an operator. All patients had the second-generation drug-eluting stents. For the observation group, patients did not need ACT monitoring and the sheath could be removed immediately at the end of the procedure of PCI (no more than 2 h). For the control group, if the operation time lasted over 1 h, necessitating additional dose of UFH was at the discretion of the operator to achieve a target ACT of 300–350 s during PCI. For patients undergoing transfemoral approach, arterial closure devices were allowed according to the patients' willing but not free in China. After PCI, all patients were recommended lifelong aspirin and clopidogrel therapy for at least 12 months.

Measurements and endpoints

The measurements included baseline demographic, clinical, angiographic, and procedural characteristics. All patients were followed up at 30 days and 1 year by telephonic interview or office visits. Clinical data during hospitalization and events during follow-up were adjudicated by source documentation by independent physicians blinded to the objectives of the study. The safety endpoints were the occurrence of bleeding events and transfusion during hospitalization within 48 h after PCI. Bleeding was stratified according to the TIMI criteria from Chesebro *et al*.'s study.[10] The primary endpoints were major adverse cardio-cerebrovascular events (MACCE) and repeat angina within 30 days after PCI. MACCE included a composite of all-cause death, recurrent MI, cerebrovascular event, and urgent target vessel revascularization (TVR). All-cause death was defined as death from many causes, including cardiac and noncardiac events. MI was defined as an elevation of troponin over the upper range limit satisfying at least the following one: symptoms of cardiac ischemia, new

ischemic ECG changes, or ECG's development of pathologic Q-waves.[11] TVR was defined as repeat revascularization of the target lesion and target vessel proximal to the stent site. Cerebrovascular accident was defined as either a transient ischemic attack or a stroke, which would be diagnosed by a neurologist. The secondary endpoint was MACCE and repeat angina within 1 year after PCI.

Statistical analysis

All statistical analysis was performed with SPSS 18.0 (SPSS Inc., Chicago, IL, USA). Continuous variables were presented as mean ± standard deviation (SD) and analyzed by the Student's *t*-test or Wilcoxon rank-sum test if necessary. Data distribution of patients was tested for normality using the Kolmogorov–Smirnov test. Categorical variables were expressed as frequencies and percentages and analyzed by the Chi-square or Fisher's exact tests if necessary. For the safety endpoints, the multivariate logistic regression adjusted for covariates was used to compare the incidence of TIMI bleeding and transfusion between groups. The multivariate Cox proportional hazard model was used to analyze the 30-day and 1-year events, with adjustment for covariates. Patients were divided into subgroups by the transfemoral approach and transradial approach. All *P* values and 95% confidence intervals were two-sided. A value of $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

A total of 1200 eligible patients were finally included: 600 patients received 3000 U of UFH plus 0.75 mg of enoxaparin per kilogram intravenously and 600 patients received 100 U of UFH per kilogram intravenously. Follow-up was not available in all patients. During 30-day follow-up, 131 were not eligible for inclusion: 83 were lost to contact after several attempts, and 48 were unwilling or unknown to answer the questions, giving a follow-up rate of 89.1%. During 1-year follow-up, 179 were lost: 110 were lost to contact, and 69 were unwilling to reply, giving a follow-up rate of 85.1%.

Baseline characteristics of the patients are summarized in Table 1. The mean age was 59.5 years and 75.8% (909) of the patients were men. As shown in Table 1, patients in the observation group were older and they showed higher prevalence or level of hypercholesterolemia, familial history, peripheral vascular disease, serum lipids, and glucose compared with the control group; however, there was no significant difference between groups. The two groups had normal left ventricular ejection fractions. Overall, the baseline characteristics of the patients were similar in the two groups.

The angiographic and procedural characteristics of the two groups are shown in Table 2. The complexity of coronary artery lesions and number of vessel lesions per patient showed no difference between groups. Patients in the observation group had less stent implantation per patient than the control group (2.13 vs. 2.25, $P = 0.002$), and each patient in both groups was treated with at least two stents. A percentage of 11.5% of all patients underwent primary PCI via the transfemoral approach, which was obviously not used as the first option. Intraprocedural complications were low

Table 1: Baseline characteristics of the control and observation groups

Characteristics	Control group* ($n = 600$)	Observation group† ($n = 600$)	t or χ^2	P
Age (years), mean ± SD	59.41 ± 9.53	59.61 ± 9.35	0.36‡	0.286
Men, *n* (%)	467 (77.8)	442 (73.7)	2.84§	0.092
BMI (kg/m^2), mean ± SD	26.73 ± 3.35	26.34 ± 3.47	−2.00‡	0.109
Hypertension, *n* (%)	407 (67.8)	380 (63.3)	2.69§	0.101
Hypercholesterolemia, *n* (%)	86 (14.3)	100 (16.7)	1.25§	0.264
Diabetes mellitus, *n* (%)	221 (36.8)	193 (32.2)	2.89§	0.089
Familial history, *n* (%)	58 (9.7)	78 (13.0)	3.32§	0.069
Previous MI, *n* (%)	130 (21.7)	126 (21.0)	0.08§	0.778
Previous CABG, *n* (%)	21 (3.5)	15 (2.5)	1.03§	0.310
Previous PCI, *n* (%)	123 (20.5)	117 (19.5)	0.19§	0.665
Previous stroke, *n* (%)	75 (12.5)	64 (10.7)	0.99§	0.321
Peripheral vascular disease, *n* (%)	21 (3.5)	25 (4.2)	0.36§	0.548
Smokers, *n* (%)	262 (43.7)	240 (40.0)	1.66§	0.198
Drinkers, *n* (%)	163 (27.2)	140 (23.3)	2.34§	0.126
TG (mmol/L), mean ± SD	2.03 ± 1.51	2.16 ± 1.67	0.73‡	0.063
TC (mmol/L), mean ± SD	3.97 ± 1.10	4.14 ± 1.16	2.61‡	0.294
LDL-C (mmol/L), mean ± SD	2.51 ± 0.93	2.55 ± 0.96	0.76‡	0.558
HDL-C (mmol/L), mean ± SD	0.97 ± 0.37	0.99 ± 0.25	1.27‡	0.061
Glucose (mmol/L), mean ± SD	6.32 ± 2.13	6.55 ± 2.55	0.84‡	0.203
LVEF (%), mean ± SD	62.31 ± 7.18	63.56 ± 6.82	3.09‡	0.864

*UFH alone; †UFH with sequential enoxaparin; ‡*t* value; §χ^2 value. BMI: Body mass index; MI: Myocardial infarction; CABG: Coronary bypass surgery; PCI: Percutaneous coronary intervention; TG: Triglyceride; TC: Total cholesterol; LDL-C: Low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol; LVEF: Left ventricular ejection fraction; UFH: Unfractionated heparin; SD: Standard deviation.

and similar between groups. The PCI success was achieved in 94.8% of all patients with complex lesion morphology.

Clinical outcomes

The clinical outcomes of 48 h, 30 days, and 1 year are listed in Table 3. The major and minor TIMI bleeding during the first 48 h occurred in 3.3% of patients in the observation group and 4.7% of patients in the control group; no obvious difference was demonstrated between groups. No transfusion was found in the observation and control groups, respectively. In Table 3, we primarily paid attention to the endpoints in 30-day follow-up. The rate of MACCE was 0.9% in the observation group and 1.5% in the control group, and the difference was not significant between them. No significant difference was found in the incidences of all-cause death, MI, TVR, and cerebrovascular

Table 2: Angiographic and procedural characteristics of the control and observation groups

Characteristics	Control group* (n = 600)	Observation group† (n = 600)	t or χ^2	P
Lesion characteristics, n (%)				
Ostial lesion	9 (1.5)	8 (1.3)	0.06‡	0.807
Bifurcation lesion	69 (11.5)	67 (11.2)	0.03‡	0.855
Left main lesion	17 (2.8)	13 (2.2)	0.55‡	0.460
Multivessel lesion ($n \geq 2$)	272 (45.3)	258 (43.0)	0.66‡	0.416
Diffuse and long lesion	234 (39.0)	207 (34.5)	2.61‡	0.106
In-stent restenosis	60 (10.0)	65 (10.8)	0.22‡	0.637
Calcified lesion (with rotational atherectomy)	8 (1.3)	9 (1.5)	0.06‡	0.807
Total occlusion	155 (25.8)	176 (29.3)	1.84‡	0.175
Thrombus-containing lesion	12 (2.0)	6 (1.0)	2.03‡	0.154
Saphenous vein graft	21 (3.5)	15 (2.5)	1.03‡	0.310
Procedural characteristics				
Number of narrowed coronary vessels, mean ± SD	1.62 ± 0.75	1.58 ± 0.78	−0.87§	0.575
Number of stents per patient, mean ± SD	2.25 ± 1.45	2.13 ± 1.31	−1.43§	0.002
Stent length (mm), mean ± SD	22.58 ± 5.82	22.25 ± 5.58	−1.00§	0.288
Stent diameter (mm), mean ± SD	2.97 ± 0.45	2.92 ± 0.45	−1.61§	0.193
Catheter thrombosis, n (%)	0 (0.0)	0 (0.0)	–	–
Final TIMI 3 flow, n (%)	562 (93.7)	561 (93.5)	0.01‡	0.906
Transfemoral approach, n (%)	70 (11.7)	68 (11.3)	0.03‡	0.856
PCI success, n (%)	564 (94.0)	573 (95.5)	1.36‡	0.244

*UFH alone; †UFH with sequential enoxaparin; ‡χ^2 value; §t-value. –: Not applicable; TIMI: Thrombosis in myocardial infarction; PCI: Percutaneous coronary intervention; UFH: Unfractionated heparin; SD: Standard deviation.

Table 3: Clinical outcomes of the control and observation groups

Events	Control group* (n = 600)	Observation group† (n = 600)	P
48 h, n (%)	n = 600	n = 600	
TIMI bleeding	28 (4.7)	20 (3.3)	0.258‡
Major	10 (1.7)	5 (0.8)	0.199‡
Minor	18 (3.0)	15 (2.5)	0.606‡
Transfusion	0 (0.0)	0 (0.0)	–
30 days, n (%)	n = 538	n = 531	
All-cause death	0 (0.0)	0 (0.0)	–
Myocardial infarction	3 (0.6)	2 (0.4)	0.648§
TVR	5 (0.9)	3 (0.6)	0.481§
Cerebrovascular event	0 (0.0)	0 (0.0)	–
MACCE	8 (1.5)	5 (0.9)	0.406§
Angina	18 (3.3)	15 (2.8)	0.613§
1 year, n (%)	n = 513	n = 508	
All-cause death	2 (0.4)	3 (0.6)	0.659§
Myocardial infarction	6 (1.2)	4 (0.8)	0.528§
TVR	6 (1.2)	5 (1.0)	0.760§
Cerebrovascular event	0 (0.0)	1 (0.2)	0.312§
MACCE	14 (2.7)	13 (2.6)	0.846§
Angina	63 (12.3)	50 (9.8)	0.368§

*UFH alone; †UFH with sequential enoxaparin; ‡P value calculated from the logistic regression model; §P value calculated from the Cox regression model. –: Not applicable; TIMI: Thrombosis in myocardial infarction; TVR: Target vessel revascularization; MACCE: Major adverse cardio-cerebrovascular events; UFH: Unfractionated heparin.

event. Angina rate was 2.8% in the observation group and 3.3% in the control group, which still showed insignificant difference ($P = 0.613$).

During 1-year follow-up after PCI, total MACCE occurred in 2.6% of patients in the observation group and 2.7% in the control group; there was no significant difference between the two groups. The 1-year incidences of all-cause death, MI, TVR, and cerebrovascular event showed no significant difference between groups. Angina in the observation group was less frequent than that in the control group (9.8% vs. 12.3%, $P = 0.368$).

Due to the clinical experience that the operative approach has some influence on the rates of bleeding and MACCE, we finally performed a subgroup analysis between PCI patients with transfemoral approach and those with transradial approach. In this study, our data were unable to identify a significant difference in the above complications and events between the two subgroups (data not shown).

Discussion

In the current study, we compared the safety and efficacy of UFH with sequential enoxaparin intravenously with that of UFH intravenously in PCI patients with complex coronary artery disease. The wide range of lesion and clinical complexity were collected to best reflect the spectrum of patients in real-world practice. As the results, for the risk of bleeding, the benefit of UFH at a dose of 3000 U plus enoxaparin at a dose of 0.75 mg/kg was not significant, as compared with UFH at a dose of 100 U/kg. UFH with sequential enoxaparin showed similar results with UFH in terms of transfusion as well as the endpoints within 30 days and 1 year.

"UFH with sequential enoxaparin" had been implemented since 2003 in our center, and approximately 600 patients per year have been benefited from the treatment. Prior domestic studies only focused on UFH or enoxaparin alone.[12-14] This anticoagulation plan had been used for our patients with different severity of coronary artery lesions and operative approach. With many years' practice, we had observed that there were very low risks of in- and out-hospital complications. In this study, our team introduced the strategy's content to medical workers in the area of interventional cardiology, and we hoped that medical peers could take it into consideration for PCI patients in clinical practice. More high-quality clinical studies should be performed to verify the findings.

The negative results obtained between the two groups, to some extent, were not surprising and several potential explanations may account for them in the following section. The transradial approach for patients undergoing coronary catheterization is used as the first option according to local practice, and the transfemoral access is chosen when contraindications to the former are present. In our study, 88.5% of the PCI patients chose transradial approach, which is associated with lower incidence of clinical complications in comparison with transfemoral approach.[15] In addition, the low-risk populations, physicians with improved coronary stent technology, standardized adjunctive pharmacotherapy, and routine use of potent antiplatelet therapy were all able to reduce the rates of clinical complications related to PCI. Our anticoagulation plan was originally designed to ease complications in patients undergoing transfemoral access. In the subgroup analysis regarding this approach, we identified no significant difference in the risk of bleeding and MACCE. However, the results should be interpreted with caution, and owing to the small number of patients between groups (68 vs. 70), the statistical power of the subgroup might be limited to detecting differences.

Compared with UFH, enoxaparin has the advantages of a more predictable anticoagulant dose response without repetitive ACT monitoring during PCI, a longer half-life (3.5–4.5 h), as well as a greater ratio of anti-factor Xa to anti-factor IIa activity, inhibiting the downstream production of many thrombin molecules.[14,16,17] Enoxaparin can decrease activation of the platelet, release of the von Willebrand factor, and inflammation.[18-20] Due to a longer half-life of enoxaparin, when using our anticoagulation plan, no additional dose of anticoagulant is needed during PCI (no more than 2 h), especially for patients with complex coronary artery lesions whose operation time generally lasts long. For such patients receiving UFH alone, additional dose is usually necessary when PCI performs over 1 h, and neglecting this step probably results in in-stent thrombosis and even serious complications. Our plan can bring about the best advantage for PCI patients via the transfemoral approach. In fact, the transfemoral approach remains the most common vascular access for PCI in many countries and patients with complex coronary artery disease, especially with totally occluded lesion. For these patients, failing or being unwilling to apply arterial closure devices, when receiving UFH alone, the femoral artery sheath cannot be immediately removed after PCI. Patients have to keep the sheath for at least 4–6 h, and sheath removal should meet the criteria that ACT is less than 180 s. The puncture point is manually pressed for 1 h and then restricted with the use of pressure bandaging for 48 h. After 72 h, the patients can leave the bed. For patients receiving our plan, the femoral artery sheath can be immediately removed after PCI. The puncture point is manually pressed for 30 min and then only restricted with the use of pressure bandaging for 24 h. The bedridden time is 48 h after PCI. These potentially reduced the bleeding complications and discomfort due to long bedridden time, such as back pain. These also decrease the clinical stress for doctors and nurses. Guidelines at abroad recommended intravenous enoxaparin alone during PCI, but we observed a little catheter thrombosis and substandard testing results of anti-Xa factor and ACT in some patients undergoing this anticoagulant scheme. In our new plan, when 3000 U UFH is used before PCI, these two indicators can reach the standard and catheter thrombosis does not appear. Finally, the effect of enoxaparin on the risk of bleeding was handled by a simpler treatment protocol than that typically used for

UFH. Taken together, "UFH with sequential enoxaparin" plan should be encouraged for PCI patients. Although our study did not report significant clinical benefits over UFH using the novel strategy, it should be useful for PCI patients undergoing transfemoral approach.

Some clinical studies in PCI patients found that cross-anticoagulation might increase the bleeding risk and it is not well recommended.[21,22] In these studies, the PCI patients received different anticoagulation before operation, during operation and after operation at the time of hospitalization, which was not consistent with the anticoagulation option in the present study and might affect the bleeding risk. For our study, preoperative, intraoperative, and postoperative options related to anticoagulation were always enoxaparin. Receiving UFH at a dose of 3000 U before angiography during PCI was designed to reduce the catheter thrombosis.

Several limitations need to be showed in our study. First, this study was only performed at a single center. Second, we had a relatively small number of PCI patients in the overall and subgroup analysis, possibly resulting in insufficient power to detect significant differences between groups. The sample size of male patients in our study was approximately three times than that of female, probably restricting extrapolation of our results to female. Third, our analysis was restricted to patients with unstable angina pectoris. Larger scale studies and other patients such as acute ST-segment elevation MI should be needed in the future. Last but not least, another key limitation was that 179 patients were lost finally. Full data of MACCE were not collected during the study and the incompleteness of follow-up data availability may cause the loss of statistical power and bias of the final results.

In conclusion, our limited clinical evidence suggests that the strategy (UFH with sequential enoxaparin) may be at least as effective and safe as UFH. UFH with sequential enoxaparin has a predictable anticoagulant effect, and patients may not need repetitive ACT monitoring and no additional dose of UFH during a long time operation. When PCI patients use the transfemoral approach, we suggest that the operator take it into consideration, and the femoral artery sheath can be immediately removed after the procedure. We also recommend large-scale randomized controlled trials to verify our findings.

Financial support and sponsorship

This work was supported by a grant from the Capital Characteristic Clinic Project of Beijing (No. Z131107002213042).

Conflicts of interest

There are no conflicts of interest.

References

1. Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, *et al.* 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the society for cardiovascular angiography and interventions. Catheter Cardiovasc Interv 2013;82:E266-355. doi: 10.1002/ccd.23390.
2. American College of Emergency Physicians, Society for Cardiovascular Angiography and Interventions, O'Gara PT, Kushner FG, Ascheim DD, Casey DE Jr., *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: A report of the American College of Cardiology Foundation/American Heart Association task force on practice guidelines. J Am Coll Cardiol 2013;61:e78-140. doi: 10.1016/j.jacc.2012.11.019.
3. Cohen M. The role of low-molecular weight heparin in the management of acute coronary syndromes. J Am Coll Cardiol 2013;41:55S-61S. doi: 10.1097/00001573-200111000-00012.
4. Montalescot G, White HD, Gallo R, Cohen M, Steg PG, Aylward PE, *et al.* Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. N Engl J Med 2006;355:1006-17. doi: 10.1056/NEJMoa052711.
5. Montalescot G, Gallo R, White HD, Cohen M, Steg PG, Aylward PE, *et al.* Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention 1-year results from the STEEPLE (SafeTy and efficacy of enoxaparin in percutaneous coronary intervention patients, an international randomized evaluation) trial. JACC Cardiovasc Interv 2009;2:1083-91. doi: 10.1016/j.jcin.2009.08.016.
6. Silvain J, Beygui F, Barthélémy O, Pollack C Jr., Cohen M, Zeymer U, *et al.* Efficacy and safety of enoxaparin versus unfractionated heparin during percutaneous coronary intervention: Systematic review and meta-analysis. BMJ 2012;344:e553. doi: 10.1136/bmj.e553.
7. Braunwald E, Antman EM, Beasley JW, Califf RM, Cheitlin MD, Hochman JS, *et al.* ACC/AHA 2002 guideline update for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction – Summary article: A report of the American College of Cardiology/American Heart Association Task Force on practice guidelines (Committee on the management of patients with unstable angina). J Am Coll Cardiol 2002;40:1366-74. doi: 10.1161/01.CIR.0000037106.76139.53.
8. Stefanini GG, Serruys PW, Silber S, Khattab AA, van Geuns RJ, Richardt G, *et al.* The impact of patient and lesion complexity on clinical and angiographic outcomes after revascularization with zotarolimus- and everolimus-eluting stents: A substudy of the RESOLUTE all comers trial (a randomized comparison of a zotarolimus-eluting stent with an everolimus-eluting stent for percutaneous coronary intervention). J Am Coll Cardiol 2011;57:2221-32. doi: 10.1016/j.jacc.2011.01.036.
9. Sen H, Lam MK, Tandjung K, Löwik MM, Stoel MG, de Man FH, *et al.* Complex patients treated with zotarolimus-eluting resolute and everolimus-eluting xience V stents in the randomized TWENTE trial: Comparison of 2-year clinical outcome. Catheter Cardiovasc Interv 2015;85:74-81. doi: 10.1002/ccd.25464.
10. Chesebro JH, Knatterud G, Roberts R, Borer J, Cohen LS, Dalen J, *et al.* Thrombolysis in myocardial infarction (TIMI) trial, phase I: A comparison between intravenous tissue plasminogen activator and intravenous streptokinase. Clinical findings through hospital discharge. Circulation 1987;76:142-54. doi: 10.1161/01.CIR.76.1.142.
11. Moussa ID, Klein LW, Shah B, Mehran R, Mack MJ, Brilakis ES, *et al.* Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: An expert consensus document from the society for cardiovascular angiography and interventions (SCAI). J Am Coll Cardiol 2013;62:1563-70. doi: 10.1016/j.jacc.2013.08.720.
12. Gong XH, Yu JM, Mao Y, Hu DY. Anticoagulant therapy for non-ST-segment elevation acute coronary syndrome in china: A multi-center observational study. J Transl Int Med 2016;4:25-8. doi: 10.1515/jtim-2016-0006.
13. He P, Liu Y, Wei X, Jiang L, Guo W, Guo Z, *et al.* Comparison of enoxaparin and unfractionated heparin in patients with non-ST-segment elevation acute coronary syndrome undergoing percutaneous coronary intervention: A systematic review and meta-analysis. J Thorac Dis 2018;10:3308-18. doi: 10.21037/jtd.2018.05.113.

14. Liu Z, Silvain J, Kerneis M, Barthélémy O, Payot L, Choussat R, *et al.* Intravenous enoxaparin versus unfractionated heparin in elderly patients undergoing primary percutaneous coronary intervention: An analysis of the randomized ATOLL trial. Angiology 2017;68:29-39. doi: 10.1177/0003319716629541.
15. Piccolo R, Galasso G, Capuano E, De Luca S, Esposito G, Trimarco B, *et al.* Transradial versus transfemoral approach in patients undergoing percutaneous coronary intervention for acute coronary syndrome. A meta-analysis and trial sequential analysis of randomized controlled trials. PLoS One 2014;9:e96127. doi: 10.1371/journal.pone.0096127.
16. Thomas O, Lybeck E, Strandberg K, Tynngård N, Schött U. Monitoring low molecular weight heparins at therapeutic levels: Dose-responses of, and correlations and differences between aPTT, anti-factor Xa and thrombin generation assays. PLoS One 2015;10:e0116835. doi: 10.1371/journal.pone.0116835.
17. Hamilton LA, Abbott GV, Cooper JB. High-risk non-ST elevation acute coronary syndrome outcomes in patients treated with unfractionated heparin monitored using anti-xa concentrations versus activated partial thromboplastin time. Hosp Pharm 2013;48:389-95. doi: 10.1310/hpj4805-389.
18. Montalescot G, Collet JP, Lison L, Choussat R, Ankri A, Vicaut E, *et al.* Effects of various anticoagulant treatments on von willebrand factor release in unstable angina. J Am Coll Cardiol 2000;36:110-4. doi: 10.1016/S0735-1097(00)00695-1.
19. Montoro-García S, Shantsila E, Lip GY. Potential value of targeting von willebrand factor in atherosclerotic cardiovascular disease. Expert Opin Ther Targets 2014;18:43-53. doi: 10.1517/14728222.2013.840585.
20. Franchi F, Rollini F, Angiolillo DJ. Antithrombotic therapy for patients with STEMI undergoing primary PCI. Nat Rev Cardiol 2017;14:361-79. doi: 10.1038/nrcardio.2017.18.
21. Ferguson JJ, Califf RM, Antman EM, Cohen M, Grines CL, Goodman S, *et al.* Enoxaparin vs. unfractionated heparin in high-risk patients with non-ST-segment elevation acute coronary syndromes managed with an intended early invasive strategy: Primary results of the SYNERGY randomized trial. JAMA 2004;292:45-54. doi: 10.1001/jama.292.1.45.
22. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators, Yusuf S, Mehta SR, Chrolavicius S, Afzal R, Pogue J, *et al.* Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med 2006;354:1464-76. doi: 10.1056/NEJMoa055443.

“普通肝素-依诺肝素”序贯抗凝在复杂冠脉的介入治疗中的应用

摘要

背景：尽管普通肝素有一些缺点，目前仍然作为介入手术过程中最主要的抗凝剂。研究发现依诺肝素（低分子肝素）也是一种安全而且有效的选择。依据国外指南（Class IIA），我们之前尝试在介入手术中单独应用低分子肝素，但是术中观察到导管内血栓的形成。鉴于此，我们推荐一种新的术中抗凝策略，即“普通肝素-依诺肝素”序贯抗凝。临床上，介入手术过程中使用低分子肝素会有稳定的抗凝时间，并不需要频繁的抗凝监测。我们这个回顾性研究的目的就是在复杂的冠脉介入手术中，对比普通肝素以及我们的方案的安全性和有效性。

方法：连续性收集来自2015年1月至2017年4月，600例行支架植入并接受我们方案（在3000U普通肝素的基础上按每公斤体重再给予0.75mg的低分子肝素导管内推注，观察组）的患者，以及另外600例接受普通肝素（按每公斤体重给予100U的普通肝素导管内推注，对照组）的患者。终点事件是术后48小时的TIMI出血、输血和30天以及1年的心脑血管事件的发生。

结果：除了观察组的每个病人的支架植入数量（2.13个）不同于对照组（2.25个，P=0.002），2组的其余基线临床资料基本相似。2组的TIMI出血并没有发现统计学差异(3.3% 对比 4.7%)。在30天的随访中，观察组中的心脑血管事件的发生率是0.9%，在对照组中是1.5%，同样也没有发现2组的差异性。在支架术后的30天以及1年的心脑血管事件的发生率、全因死亡、心梗、血运重建、脑卒中、心绞痛再发以及经股动脉的亚组分析中均没有发现2组之间有差异性。

结论：“普通肝素-依诺肝素”序贯抗凝在复杂冠脉手术中有着与普通肝素相似的抗凝效果以及安全性。