Low-Dose Unfractionated Heparin with Sequential Enoxaparin in Patients with Diabetes Mellitus and Complex Coronary Artery Disease during Elective Percutaneous Coronary Intervention

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Abstract

Background: Despite its limitations, unfractionated heparin (UFH) has been the standard anticoagulant used during percutaneous coronary intervention (PCI). This study compared the safety of low-dose UFH with sequential enoxaparin with that of UFH in patients with diabetes mellitus (DM) and complex coronary artery disease receiving elective PCI.

Methods: In this retrospective study, 514 consecutive patients with atherosclerotic cardiovascular diseases and type 2 DM were admitted to the hospital and received selective PCI, from January 2013 to December 2015. All patients with PCI received low-dose UFH with enoxaparin (intraductal 50 U/kg UFH and 0.75 mg/kg enoxaparin, $n = 254$; UFH-Enox group) or UFH only (intraductal 100 U/kg UFH, $n = 260$; UFH group). The study endpoints were major adverse cardiac events (MACEs), namely death, myocardial infarction (MI), stroke, target-vessel immediate revascularization (TVR), and thrombolysis in MI (TIMI) major bleeding, within 30 days and 1 year after PCI. Any catheter thrombosis during the procedure was recorded.

Results: Only one patient had an intraductal thrombus in the UFH group. At the 30-day follow-up, no MACE occurred in any group; seven and five cases of recurrent angina and/or rehospitalization were reported in the UFH-Enox and UFH groups, respectively; there was no significant difference between the two groups ($\chi^2 = 0.11$, $P = 0.77$). There was no TIMI major bleeding in the groups. With respect to the 1-year endpoint, two cases of recurrent MI and two of TVRs were reported in the UFH-Enox group, whereas in the UFH group, one case of recurrent MI and three of TVRs were reported; no significant difference existed between the two groups ($\chi^2 = 0$, $P = 0.99$). There were 30 and 25 recurrent angina and/or rehospitalizations in the UFH-Enox and UFH groups, respectively; there was no significant difference between the two groups ($\chi^2 = 0.37$, $P = 0.57$).

Conclusion: In elective PCI, low-dose UFH with sequential enoxaparin has similar effects and safety to the UFH-only method.

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

INTRODUCTION

The global prevalence of diabetes mellitus (DM) has continuously increased over the last decades.[1] DM is associated with cardiovascular morbidity and mortality. Patients with DM have a significantly higher mortality rate after presenting with an acute coronary syndrome (ACS). They also experience more frequent complications with procedures used during the management of ACS. Coronary revascularization to relieve angina is well established, and it has a positive outcome by reducing the rates of subsequent myocardial infarction (MI) and death.[2,3]

Anticoagulation during elective percutaneous coronary intervention (PCI) has traditionally been supported by unfractionated heparin (UFH) with the dose being adjusted for the activated clotting time. In recent years, the

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safety and efficacy of intravenous low-molecular-weight heparin anticoagulation in patients undergoing PCI has previously been demonstrated in a number of trials.[4-7] The American College of Cardiology (ACC), the American Heart Association (AHA), and the European Society of Cardiology recommend performing PCI with enoxaparin in patients who are either treated with "upstream" subcutaneous enoxaparin or who have not received prior antithrombin therapy and are receiving enoxaparin at the time of PCI. Although the guideline of the ACC/AHA in 2011 indicates that UFH should not be given to patients who were already receiving therapeutic subcutaneous enoxaparin, subcutaneous enoxaparin is the regular choice in ACS patients, and UFH is the option selected by most physicians in current real-world cases of PCI in China. The STACKENOX study demonstrated that the administration of stack-on UFH to individuals already recommended to receive enoxaparin may result in over-anticoagulation.[8] However, the dose and administration time were different from the current real-world practice. None of published studies has examined the long-term outcomes of PCI in patients receiving a new treatment option of intraductal low-dose UFH with sequential enoxaparin. The aim of this study is to compare the safety and efficacy in patients with DM receiving low-dose UFH with sequential enoxaparin or UFH-only treatment at our institution.

Methods

Ethical approval
The present study was conducted in accordance with the guiding principles for human experimentation summarized in the latest version of the *Declaration of Helsinki*. The study protocol was approved by the Institutional Review Board at Anzhen Hospital, and informed consent was obtained from all patients.

Study design
The primary database used in this study was our institutional PCI registry. The registry was developed in 2013 for the purpose of collecting information on all consecutive patients who had undergone PCI at our institution. The database contains information on demographics, comorbidities, biochemical indicators, left ventricular function, diseased vessels and vessels for which angioplasty was attempted, the type of anticoagulants, as well as their application, information on the types of device, including bare-metal stents and drug-eluting stents, and in-hospital adverse outcomes. The present study includes consecutive patients with DM who received elective PCI from January 1, 2013, to December 31, 2015. According to the different procedures, the patients were divided into two groups. One is UFH group, which received 50 U/kg UFH intraductally before the coronary angiography (CAG), and then 100 U/kg was added if it was decided that PCI was to be performed. The other is the low-dose UFH with sequential enoxaparin group (UFH-Enox), who received 50 U/kg UFH intraductally before CAG, and then received a dose of 0.75 mg/kg

enoxaparin intraductally if PCI was continued. Patients who had an acute MI within 24 h before revascularization were excluded.

The enrollment criteria to the study are described. In brief, patients with DM were eligible for the study if they were >30 years and <80 years of age, underwent elective PCI with a femoral or radial access, and CAG showed as complex coronary artery lesions, and they did not meet any of the exclusion criteria. The exclusion criteria included complications including infectious diseases and malignant tumors, pregnancy, serious renal dysfunction (glomerular filtration rate <60 ml·min^{-1}·1.73 m^{-2}), serious liver damage (alanine aminotransferase >4 times the upper limit than normal), and absences for the 12-month follow-up. All patients gave informed consent. The diagnosis of DM was based on the need for treatment with insulin or oral hypoglycemic drugs or a confirmed elevated blood glucose level. The diagnosis of coronary artery disease was documented on angiography (≥50% stenosis of a major epicardial coronary artery associated with a positive stress test or ≥70% stenosis of a major epicardial coronary artery and classic angina). Coronary angiograms were analyzed by two experienced chief physicians, and visual measurements were obtained. Complex coronary artery lesions were defined as follows: (1) a multivessel lesion was defined as at least two main branches (the left anterior descending branch, left circumflex branch, right coronary artery, and/or intermediate branch) with the extent of stenosis ≥50%; the lesions were ascribed to the branch to which they belonged, such as the diagonal branch or marginal branch. (2) A chronic total occlusion lesion was defined as a total occlusion lesion with no forward flow filling the distal artery (thrombolysis in MI [TIMI] flow grade: 0) and an occlusion time ≥3 months, as determined from the patient's medical history or prior CAG result. (3) An occlusion lesion was defined as a total occlusion lesion with no forward flow filling the distal artery (TIMI flow grade: 0) and an occlusion time <3 months. (4) A diffuse lesion was defined as a single-stenotic lesion that was ≥20 mm long. (5) A bifurcation lesion was defined as coronary artery stenosis occurring adjacent to and/or involving the origin of a significant side branch that has a great functional value that it cannot be lost during interventional treatment. (6) A severe tortuous lesion was defined as a lesion with severe tortuosity.

Anticoagulation procedures
All patients enrolled to the study received 50 U/kg of UFH before the CAG; the patients in the UFH-Enox group then received an intraductal bolus of 0.75 mg/kg enoxaparin without anticoagulation monitoring. This dose was shown to provide an immediate anti-Xa level >0.5 U/ml with an elimination half-life of approximately 3.4 h,[9] which is shorter than the half-life obtained with subcutaneous injections. When procedures were prolonged by more than 2 h or if the investigator needed stronger anticoagulation to manage per-procedural complications, an additionally intraductal

bolus of enoxaparin (nearly half the original dose, 0.3 mg/kg) was administered. All patients in the UFH group received 100 U/kg of UFH (including 50 U/kg of UFH administered before CAG) intraductally with anticoagulation monitoring to maintain an activated clotting time of 300–350 s. After the procedure, prolongation of anticoagulation was at the physician's discretion.

The operation accesses included radial and femoral access for which arterial closure devices may have been used.

Follow-up and endpoints

Clinical, procedural, and outcome data were followed and recorded by independent research personnel. Clinical follow-up after PCI was recommended at 1 month, 6 months, and 12 months, which was achieved by office visits or telephone contact. Angiographic follow-up for patients was recommended at 12 months after the procedure. Patients who were at high risk for procedural complications of angiography and had no symptoms or signs of ischemia did not undergo a follow-up angiography.

The primary endpoint of the study was the occurrence of major adverse cardiac events (MACEs) within 1 month. MACEs were defined as death, recurrent MI, and target-vessel immediate revascularization (TVR). Death was defined as death from any cause. Periprocedural MI was defined as the presence of a new significant Q wave in two contiguous leads or a total creatine kinase level or creatine kinase MB fraction that was ≥3 times more than the upper limit of the normal range during hospitalization for PCI. MI during follow-up was defined as either the documentation of a new abnormal Q wave after PCI or MIs at readmission (emergency admission with a principal diagnosis of MI). TVR was defined as the need for either surgical or percutaneous revascularization of the target (treated) vessel. All events were adjudicated by an independent clinical events committee whose members were unaware of the treatment difference. The secondary efficacy endpoints were catheter thrombosis during the procedure and the occurrence of MACE within 1 year.

Statistical analysis

The primary purpose of the study was to compare the differences in long-term outcomes between the two anticoagulation treatment methods during PCI procedures (low-dose UFH with sequential enoxaparin versus UFH-only), after considering the differences in procedural risk for patients with DM.

The continuous variables are presented as a mean ± standard deviation or median (25th–75th percentile). The categorical variables are described as proportions (percentages). Intergroup differences of continuous variables were analyzed by the independent-samples t-test. Categorical variables were compared with the Chi-square test. All data recordings and statistical analyses were performed using the SPSS 23.0 software (IBM Corp., Armonk, NY, USA). A value of $P <$ 0.05 was considered statistically significant.

Results

Patient characteristics

Between January 2013 and December 2015, 514 patients were included in the present study, and their mean age was 62.3 ± 8.1 years. The individuals were divided into two groups according to different anticoagulation methods used during PCI procedures: 254 patients received intraductal 50 U/kg of UFH with sequential 0.75 mg/kg of enoxaparin intraductally (UFH-Enox group) and 260 patients received 100 U/kg of UFH intraductally (UFH group). Baseline characteristics were similar between the two treatment groups [Table 1].

The procedural characteristics were similar between the two groups [Table 2]. Patients mainly underwent elective PCI with radial access (n = 454, 88.3%). More than half of the patients presented with multivessel lesions. Stent restenosis were discovered in 35 (6.8%) of 514 patients. Long diffuse lesion, bifurcation lesion, and chronic total occlusion were identified in 128 (24.9%), 23 (4.5%), and 97 (18.9%) of 514 patients, respectively. Only one patient had an intraductal thrombus in the UFH group.

Primary endpoint

At the 30-day follow-up, no MACE occurred in any of the groups, seven recurrent angina and/or rehospitalization were observed in the UFH-Enox group, and five in the UFH group. There was no TIMI major bleeding in the two groups. With respect to the 1-year MACE, one patient had recurrent MI, and two patients had TVR in the UFH-Enox group, while in the UFH group, one patient had recurrent MI, and three patients had TVR. There were 30 recurrent angina and/or rehospitalization in the UFH-Enox group and 25 in the UFH group. There were no differences in MACE in the groups of patients [Table 3].

Discussion

This study evaluated the efficacy and safety of receiving intraductal UFH with sequential enoxaparin versus UFH-only treatment in the interventional management of patients with DM. In this investigation, the data suggested similar primary endpoint events when comparing the strategy of intraductal UFH with sequential enoxaparin to the strategy of UFH only. The other endpoints including recurrent angina and/or rehospitalization and TIMI major bleeding had no significant difference between the two groups. The safety of the two medical plans was similar, and the overall clinical benefit was not significantly different.

We recruited a population that received selective PCI, without enrolling high-risk participants, including very elderly patients, patients with reduced renal function, and patients in shock or cardiac arrest. Consequently, the mortality and ischemic event rates were lower than those reported in recent randomized studies.[10-13] There was significant difference in the administered dosage of enoxaparin in our study compared to others. In our trial, patients received intraductal

Table 1: Baseline characteristics of two treatment groups

Characteristics	UFH-Enox group (n = 254)	UFH group (n = 260)	t/χ²	P
Male, n (%)	176 (68.8)	184 (70.3)	0.07	0.88
Age (years)	62.4 ± 8.2	61.7 ± 8.4	0.96*	0.45
BMI (kg/m²)	26.5 ± 3.2	26.4 ± 3.1	0.36*	0.23
Hypertension, n (%)	194 (76.4)	212 (81.5)	1.76	0.11
Hypercholesterolimia, n (%)	42 (16.5)	54 (20.8)	1.25	0.22
Oral hypoglycemic drugs, n (%)	215 (84.6)	232 (82.8)	1.99	0.42
Treatment with insulin, n (%)	46 (18.2)	52 (20.0)	0.19	0.52
Current smoking, n (%)	97 (37.9)	83 (31.9)	1.95	0.18
Prior infarction, n (%)	39 (15.2)	49 (18.8)	0.87	0.31
Prior CABG surgery, n (%)	6 (2.3)	11 (4.2)	0.88	0.32
Prior PCI, n (%)	46 (18.0)	54 (20.7)	0.42	0.44
Prior stroke, n (%)	32 (12.5)	45 (17.3)	1.88	0.17
LVEF (%)	62.2 ± 6.5	61.5 ± 6.3	1.24*	0.20
Fasting plasma glucose (mmol/L)	7.59 (4.98–9.26)	7.39 (4.58–8.86)	0.43*	0.66
TG (mmol/L)	1.55 (1.06, 2.25)	1.53 (1.10, 2.53)	0.22	0.35
HDL-C (mmol/L)	0.95 ± 0.32	0.92 ± 0.25	1.18*	0.22
LDL-C (mmol/L)	2.45 ± 0.79	2.55 ± 1.02	−1.24*	0.20
Coagulation indexes before PCI				
PT (s)	10.63 ± 0.66	10.71 ± 0.61	−1.43*	0.14
APTT (s)	25.92 ± 2.71	26.25 ± 3.42	−1.21*	0.21
ACT (s)	165.55 ± 53.10	159.72 ± 35.88	1.46*	0.13
Fibrinogen (g/L)	2.94 ± 0.82	3.03 ± 0.79	−1.27*	0.19

Data are presented as n (%) or mean ± standard deviation or median (25th–75th percentile).*t value. CABG: Coronary artery bypass graft; BMI: Body mass index; PCI: Percutaneous coronary intervention; LVEF: Left ventricular ejection fraction; TG: Triglycerides; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; PT: Prothrombin time; APTT: Activated partial thromboplastin time; ACT: Activated clotting time; UFH: Unfractionated heparin; UFH-Enox: UFH with enoxaparin.

Table 2: Procedure of two treatment groups

Items	UFH-Enox group (n = 254)	UFH group (n = 260)	t/χ²	P
Femoral access	36 (14.2)	27 (10.4)	1.38	0.20
Double-vessel lesion	96 (37.8)	93 (35.8)	0.15	0.73
Triple-vessel lesion	70 (27.6)	70 (26.9)	0	0.99
Long diffuse lesion	66 (26.0)	62 (23.8)	0.21	0.70
Chronic total occlusion	45 (17.7)	51 (19.6)	0.19	0.66
Stent restenosis	16 (6.3)	18 (6.9)	0.01	0.87
Bifurcation lesion	13 (5.1)	9 (3.5)	0.50	0.41
Severe calcified lesions	3 (1.2)	2 (0.8)	0	0.99
Coronary ostial lesions	23 (9.1)	29 (11.2)	0.41	0.58
Bridge vascular lesions	8 (3.1)	5 (1.9)	0.37	0.57
Mean stent numbers	2 (1–3)	2 (1–4)	1.27*	0.18
PCI failure	6 (2.4)	7 (2.7)	0	0.99
Only balloon dilation	3 (1.2)	2 (0.8)	0	0.99
Transfer to CABG	5 (2.0)	2 (0.8)	0.63	0.45
Intraductal thrombus	0	1 (0)	0	0.99

Data are presented as n (%) or mean ± standard deviation or median (25th–75th percentile).*t value. UFH: Unfractionated heparin; CABG: Coronary artery bypass graft; PCI: Percutaneous coronary intervention; UFH-Enox: UFH with enoxaparin.

50 U/kg UFH with sequential 0.75 mg/kg enoxaparin or intraductal 100 U/kg UFH. However, in almost all recent studies, patients received an intravenous bolus of 0.5 mg/kg enoxaparin. In our study, the administration and dosage was according to the Chinese population effect to low molecular heparin by Chen et al.[14] The effect on anticoagulation of a dosage of 0.75 mg/kg was better than that of 0.5 mg/kg, and clinical bleeding events were not significantly higher. The arterial sheaths could be removed immediately after the operation, the 0.75 mg/kg group had no thrombotic events, and the 0.5 mg/kg group had 6.5% of thrombotic events.

It is estimated that up to an additional 15% of patients presenting with ACS have previously undiagnosed DM.[15] DM is associated with a prothrombotic state marked by increased concentrations of fibrinogen, von Willebrand factor, plasminogen activator inhibitor-1, and decreased concentrations of antithrombin, as well as abnormalities in

Table 3: Endpoints of two treatment groups

Items	UFH-Enox group (*n* = 254)	UFH group (*n* = 260)	χ^2	*P*
Within 30 days				
MACE	0	0		
Recurrent angina and/or rehospitalization	7	5	0.11	0.77
TIMI major bleeding	0	0		
Within 1 year				
MACE	3	4	0	0.97
Recurrent angina and/or rehospitalization	30	25	0.44	0.51

MACE: Major adverse cardiac events; UFH: Unfractionated heparin; MI: Myocardial infarction; TIMI: Thrombolysis in MI; UFH-Enox: UFH with enoxaparin.

platelet function.[16] Coronary artery thrombosis accompanied by myocardial ischemia or MI can occur at any time in a coronary intervention procedure, during and after the operation, particularly in patients with DM. As such, there is a strong biologic plausibility for the potential of a particular benefit of a potent antithrombotic therapy in patients with DM. Furthermore, the damage to the coronary artery endothelium during the procedure results in the tissue factor being exposed to blood coagulation, inadequate balloon dilatation, and stent implantation; therefore, sufficient anticoagulant therapy should be incorporated in PCI.[17] Currently, the PCI guidelines recommend UFH as the first choice for anticoagulation in surgery (class I recommendation). However, better anticoagulation regimens are needed for PCI, considering the limitations of UFH, which include an unpredictable anticoagulation effect, the need for repeated monitoring of the coagulation, the narrow therapeutic window, the potential induction of platelet activation, and the risk of thrombocytopenia. Enoxaparin obtained IB and IIA/B recommendations by the 2015 AHA/Cardiovascular Angiography and Interventional Association and the European Society of Cardiology angina/non-ST elevation MI guide and the China percutaneous coronary interventional treatment guidelines (2016) recommended for anticoagulation during PCI.[18-20] Mortality rates were similar in enoxaparin and UFH treatment groups in the STEEPLE trial.[21] Our data are consistent with those reported in studies on patients with elective PCI. UFH and UFH with sequential enoxaparin are associated with similar efficacy.

In the OASIS-5 trial,[22] the use of standard UFH in place of fondaparinux at the time of PCI seems to prevent angiographic complications, including catheter thrombus, without compromising the benefits of upstream fondaparinux. Catheter thrombus was more common in patients receiving fondaparinux (0.9%) than enoxaparin alone (0.4%), but this was largely prevented by administrating UFH at the time of PCI, without an increase in bleeding. Although enoxaparin obtained recommendations by the American, European, and Chinese Association or Society of Cardiology in recent years, UFH is still a popular and classical strategy used during PCI, due to a great extent upon the risk of catheter thrombus. The OASIS-5 and OASIS-6 studies gave us inspiration, and that is how we came up with the anticoagulation strategy of UFH with sequential enoxaparin in PCI.[22]

Cross anticoagulation is not recommended during the perioperative period, due to the findings of the SYNERGY trial.[4] The trial indicated that the safety and efficacy of enoxaparin is not inferior to UFH during PCI, but the TIMI major bleeding rate was significantly higher than the UFH group. Further analysis showed that most of the patients who used cross anticoagulation in the trial were based on the clinician's provisional decision, rather than the pretrial design. Because of complications, the anticoagulant option of some patients had to be replaced. Therefore, the occurrence of bleeding events is not related to cross anticoagulation, which still needs to be confirmed by prospective trials. The aim of this study was to explore a sequential anticoagulation plan. Patients received an intraductal low dose of UFH before angiography with sequential 0.75 mg/kg enoxaparin during PCI, which is different from the SYNERGY trial. In conclusion, low-dose UFH with sequential enoxaparin has similar effects and safety to UFH in elective PCI; however, the sequential strategy did not need repeated monitoring and the sheathe could be removed immediately after operation.

This trial has numerous limitations. As data considered in this study were obtained from a single center, it cannot represent the actual situation of the whole population in China because of geographical and regional differences. The number of patients was not enough to provide adequate statistical power to detect meaningful differences. As an observational study, the major limitation is that the nonrandomized nature of the observational data limits any direct comparisons of the two strategies. Patients were subjected to a selection bias to decide whether to proceed with UFH-Enox or UFH only. The decision was at the discretion of the treating physicians on the basis of the patient's clinical findings. There are inherent limitations to use an observational method because of these unmeasured or undefined confounding factors; however, potentially important baseline factors are similarly presented in our study between the groups. Further studies are warranted to determine the relative long-term effects and safety of the two strategies.

Conflicts of interest

There are no conflicts of interest.

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小剂量普通肝素–依诺肝素序贯抗凝在糖尿病复杂冠脉病变患者择期冠脉介入术中的应用

摘要

背景：尽管具有一定的局限性，普通肝素目前仍是经皮冠脉介入术（percutaneous coronary intervention，PCI）中的标准抗凝方案。本研究的主要目的是评价与普通肝素比较择期PCI术中小剂量普通肝素-依诺肝素序贯抗凝方案的疗效和安全性。

方法：本回顾性研究纳入2013年1月至2015年12月期间于我科住院的接受择期PCI治疗的连续冠心病合并糖尿病患者514例。所有患者根据PCI术中接受抗凝方案的不同分为：小剂量普通肝素-依诺肝素组（UFH-Enox组，n=254例），方案为冠脉造影前导管内注射普通肝素50 U/kg，继之于PCI术前导管内注射依诺肝素0.75 mg/kg；普通肝素组（UFH组，n=260例），方案为造影前导管内注射普通肝素50 U/kg，继之于PCI术前补充UFH至总量（含造影时用量）100 U/Kg。研究终点观察PCI术后30天及1年时的死亡、心肌梗死、卒中、靶血管血运重建和心肌梗死溶栓治疗大出血等主要心血管事件的发生，并记录术中导管内血栓的发生。

结果：UFH组有1例患者发生导管内血栓。30天随访时，两组都无主要心血管事件发生，UFH-Enox组有7例发生再发心绞痛和/或再次住院，UFH组有5例。两组都没有心肌梗死溶栓治疗大出血的发生。1年随访时，UFH-Enox组有2例再发心肌梗死和2例靶血管重建，而UFH组则有1例再发心肌梗死和3例靶血管重建。UFH-Enox组有30例再发心绞痛和/或再次住院，UFH组则有25例。

结论：择期PCI术中小剂量普通肝素-依诺肝素序贯抗凝方案疗效和安全性与普通肝素相当。