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Original Research Article

Effects of early application of heparin on coronary blood flow during primary percutaneous coronary intervention

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Abstract

Purpose: *To investigate the efficacy and safety of unfractionated heparin (UFH) anticoagulant administered upstream in the ambulance or emergency room during primary percutaneous coronary intervention (pPCI) for patients with acute ST-segment elevation myocardial infarction (STEMI).*
Methods: *The study included STEMI patients who received either early UFH subcutaneously (SC) (n = 163) or intraoperative UFH (SC) during pPCI (n = 476) between January 2017 to August 2018. Baseline characteristics, infarct-related artery (IRA) status, and procedural characteristics were analyzed. The primary endpoint was thrombolysis in myocardial infarction (TIMI) flow grade 2 - 3 before intervention. The secondary endpoints were time from first medical contact to guidewire passage, postoperative TIMI 3 flow grade, acute stent thrombosis, and in-hospital bleeding events.*
Results: *Baseline characteristics were similar between the groups, with no significant difference in IRA location. Both groups underwent coronary angiography, with most patients receiving pPCI. The primary endpoint occurred in 18.1 % of patients in intraoperative UFH group and 27.6 % in the early UFH group, with a significant difference between the groups ($p < 0.05$). There was no significant difference in postoperative TIMI 3 flow grade or acute stent thrombosis, but bleeding events (BARC 2-5) were similar between groups (1.1 % in intraoperative group and 1.8 % in early UFH group, $p > 0.05$)*
Conclusion: *Early upstream administration of UFH anticoagulation in STEMI patients improves coronary artery potency before pPCI, and early use of fixed-dose UFH is safe and does not increase major bleeding complications.*

Keywords: *Acute ST-segment elevation myocardial infarction; Primary percutaneous coronary intervention; Heparin*

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INTRODUCTION

Early reperfusion therapy for ST-segment elevation myocardial infarction (STEMI) patients is the most effective way to reduce myocardial infarction size, protect cardiac function, and ultimately decrease mortality. Primary percutaneous coronary intervention (pPCI) is the preferred strategy for reperfusion therapy in STEMI patients [1]. Patients treated with pPCI have significantly better outcomes at discharge compared to those treated with thrombolytics or

those who do not receive reperfusion therapy, with lower rates of cardiac death [2].

The benefit of pPCI is mainly due to rapid reperfusion of the myocardium within the infarct-related artery (IRA). Current STEMI diagnostic and treatment guidelines emphasize the importance of early, rapid, and complete IRA opening as a key factor in improving patient outcomes [3]. Early and rapid IRA opening reduces myocardial infarction size by at least 30 %. The faster the IRA is opened, the higher the thrombolysis in myocardial infarction (TIMI) flow grade achieved, and the better the short- and long-term prognosis for patients [4,5].

The guidelines recommend the use of unfractionated heparin (UFH) as the preferred anticoagulant during pPCI, at 70 - 100 U/kg and a target-activated clotting time (ACT) of 250 - 300 sec. If platelet glycoprotein IIb-IIIa inhibitors (GPIs) are used in combination, intravenous UFH should be given at a dose of 50 - 70 U/kg and a target ACT of 200 - 250 s [6,7].

However, the timing of heparin anticoagulation during pPCI is currently unclear, and whether giving heparin upstream in the ambulance or emergency department is beneficial has not been studied systematically.

METHODS

Study population

A total of 825 patients were admitted to the emergency department of the Division of Cardiology, Beijing Anzhen Hospital, Capital Medical University, Beijing, from January 2017 to August 2018 with a diagnosis of STEMI. This study was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University, (approval no. 2018055X).

Inclusion criteria

Patients who underwent emergency coronary angiography and received anticoagulation therapy with heparin during the procedure were included in this study.

Exclusion criteria

Eleven patients who received intravenous thrombolytics, nine patients who had undergone coronary angiography at another hospital, eight patients who were taking oral anticoagulants, and seven patients who had received non-heparin anticoagulants prior to the procedure were excluded. In addition, 92 patients who had onset of symptoms for more than 12 hours and 59 patients with missing data were also excluded, resulting in a total of 639 patients included in this study, and complied with international guidelines for human studies.

Patient grouping

Patients were divided into two groups based on whether they received heparin subcutaneously (SC; 5000 IU) before or during the procedure, with 163 patients in the early heparin group and 476 patients in the intraoperative heparin group.

STEMI diagnosis was made according to the third edition of global unified definition of myocardial infarction. According to guidelines for percutaneous coronary intervention in China [7] all STEMI patients received oral loading antiplatelet therapy before primary percutaneous coronary intervention (pPCI), and specific pPCI procedure and intraoperative anticoagulation strategies were decided by the interventional cardiologist according to patient's individual condition.

The coronary angiography data were analyzed by two experienced physicians in Division of Cardiology, Beijing Anzhen Hospital, Capital Medical University. The determination of IRA was based on ST-segment elevation pattern in the patient's electrocardiogram, presence of segmental wall motion abnormalities on echocardiography, and analysis of coronary angiography results [6]. Forward blood flow of IRA was graded using TIMI flow grading system: grade 0: no forward flow of contrast medium in the occluded segment and distal to the occlusion; grade 1: contrast medium passed through the occlusion but did not fill the distal vessel; grade 2: contrast medium completely filled distal coronary artery, but rate of filling and clearance was slower than that in normal coronary arteries; grade 3: contrast medium completely and rapidly filled the distal vessel and cleared quickly [7].

Evaluation of parameters/indices

Baseline information of enrolled patients, including age, gender, body mass index (BMI), smoking history, history of hypertension, diabetes, hyperlipidemia, family history of coronary heart disease, history of coronary revascularization, estimated glomerular filtration rate (eGFR), systolic blood pressure, diastolic blood pressure, heart rate, Killip classification of heart function, ST-segment elevation in anterior leads, thrombolysis in myocardial infarction (TIMI) risk score, preoperative aspirin loading dose, clopidogrel or ticagrelor loading dose, and

proportion of preoperative intravenous use of GPI were recorded.

Basic information of infarct-related arteries such as characteristics of interventional procedures, primary endpoint (TIMI 2 - 3 blood flow before intervention), secondary endpoints (time from initial medical contact to wire passage), TIMI 3 blood flow after the operation, and acute intrastent thrombosis were also recorded.

Safety endpoint in patients was also assessed based on in-hospital bleeding grading. In-hospital bleeding is classified according to Bleeding Academic Research Consortium (BARC) criteria [8] as type 0 (no bleeding, or non-actionable bleeding that does not require medical attention or hospitalization, including bleeding caused by self-discontinuation of medication without consulting a doctor), type 2 (any bleeding that is not severe enough to meet the criteria for types 3 - 5, including bleeding that requires medical intervention, hospitalization, or escalation of care, or that requires rapid assessment. Type 2 (any overt bleeding that is not severe enough to meet the criteria for Types 3 - 5, but is severe enough to require medical intervention, hospitalization, or escalation of care, including the need for intravenous vasopressors).

Type 3a (overt bleeding with a decrease in hemoglobin level of 3 - 5 g/dL, requiring transfusion), Type 3b (overt bleeding with a decrease in hemoglobin level of ≥ 5 g/dL, cardiac tamponade, bleeding that requires surgical intervention or control (excluding dental, nasal, skin, and hemorrhoidal bleeding), or bleeding that requires intravenous anticoagulants. Type 3c (intracranial bleeding (excluding microbleeds or hemorrhagic conversion, including spinal cord bleeding) confirmed by autopsy, imaging, or lumbar puncture, or bleeding that impairs vision. Type 4 (bleeding related to coronary artery bypass grafting) type 5 (fatal bleeding).

Statistical analysis

SPSS 26.0 software (IBM, Armonk, NY, USA) was used for statistical analysis. All continuous variables are presented as mean ± standard deviation (SD) or median (first and third quartiles), and all categorical variables are presented as numbers (percentages). For continuous variables, Student's t-test and Mann-Whitney U test was used to assess comparisons between two groups. Chi-square test or Fisher's exact test was used to assess comparisons between categorical variables. *P > 0.05* was considered statistically significant.

RESULTS

Baseline characteristics

There were no significant differences between two groups of patients in terms of age, gender, BMI, smoking history, hypertension, diabetes, hyperlipidemia history, family history of coronary heart disease, or history of vascular reconstruction (Table 1). Comparison of renal function indicators between the two groups of patients showed that severe renal dysfunction with eGFR < 30 ml/min/1.73m^2 in the intraoperative heparin group was 2.1 %, and in the early heparin group was 2.5 %, with no significant difference between the two groups ($p > 0.05$). Analysis of cardiac function of two groups of patients showed that in the intraoperative heparin group, 223 cases were classified as Killip II-IV, accounting for 46.8 %, and in early heparin group, 79 cases were classified as Killip II-IV, accounting for 48.5 %, with no significant difference between the two groups (*p > 0.05)*. A comparison of TIMI risk scores between two groups of patients showed that there were 162 cases (34.0 %) in the intraoperative heparin group and 61 cases (37.4 %) in the early heparin group with TIMI risk scores ≥ 4 points, with no significant difference between the two groups (*p > 0.05*). The systolic blood pressure was significantly higher in intraoperative heparin (117.3 ± 19.4 mmHg) compared to early heparin group (113.7 ± 22.7 mmHg) ($p < 0.05$). Electrocardiogram results showed that there were 196 patients (41.2 %) in the intraoperative heparin group and 77 patients (47.2 %) in the early heparin group with ST segment elevation in the anterior leads. There was no significant difference in the range of ST segment elevation on the electrocardiogram between the two groups ($p > 0.05$) (Table 1).

Myocardial infarction-related arteries

There was no significant difference in cases of infarct-related artery (IRA) on left main coronary artery ($p = 0.659$), left anterior descending artery (LAD), ($p = 0.122$), left circumflex artery (LCX) ($p = 0.773$), right coronary artery ($p = 0.148$), and location of infarct-related arteries between the two groups (Table 2).

Characteristics of interventional treatment

All patients underwent coronary angiography. In the intraoperative heparin group, 96.8 % received radial artery access and 3.2 % received femoral artery access, while in the early heparin group, 95.1 % received radial artery access and 4.9 % received femoral artery access.

Table 1: Baseline characteristics of patients

Clinical feature	Intraoperative heparin group, n (%)	Early heparin group, n (%)	*P-value*
Age (years)	57.3 ± 11.4	58.2 ± 12.7	0.200
Male, n (%)	385 (80.9)	124 (76.1)	
Female, n (%)	91(19.1)	39(23.9)	0.188
BMI, kg/m^2	25.1±6.3	25.9±6.9	0.086
Smoking history, n (%)	161(33.8)	52(31.9)	0.653
Hypertension, n (%)	209(43.9)	78(47.9)	0.382
Diabetes, n (%)	114(23.9)	32(19.6)	0.257
History of hyperlipidemia, n (%)	235(49.4)	75(46.0)	0.459
Family history of coronary heart disease, n (%)	118(24.8)	42(25.8)	0.804
History of revascularization, n (%)	138(29.0)	37(22.7)	0.120
eGFR < 30 ml/min/1.73m^2, n (%)	10(2.1)	4(2.5)	0.790
Systolic Blood Pressure (mmHg)	117.3±19.4	113.7±22.7	0.025
Diastolic Blood Pressure (mmHg)	64.6±11.1	62.9±13.4	0.055
Heart rate (times/min)	71.5±23.3	68.2±30.6	0.076
Killip grading (II-IV), n (%)	223(46.8)	79(48.5)	0.721
Anterior wall lead ST-segment elevation, n (%)	196(41.2)	77(47.2)	0.177
TIMI score ≥ 4	162(34.0)	61(37.4)	0.433
Premedication			
Aspirin load (300 mg), n (%)	452(95.0)	158(96.9)	0.296
Bolivar or Ticagrelor load, n (%)	455(95.6)	156(95.7)	0.950
Preoperative venous GPI, n (%)	4(0.8)	2(1.2)	0.659

BMI: Body mass index; eGFR, estimated glomerular filtration rate; TIMI: thrombolytic therapy for myocardial infarction; GPI: Platelet glycoprotein IIbIIIa receptor antagonist. Intraoperative heparin group (n = 476), Early heparin group (n = 163)

Table 2: infarct-related arteries

Target Vessels for PCI	Intraoperative heparin group, n (%)	Early heparin group, n (%)	*P-value*
LM, n (%)	4(0.8)	2(1.2)	0.659
LAD, n (%)	212(44.5)	84(51.5)	0.122
LCX, n (%)	80(16.8)	29(17.8)	0.773
RCA, n (%)	188(39.5)	54(33.1)	0.148

LM: left main trunk; LAD: left anterior descending branch; LCX: left circumflex branch; RCA: Right coronary artery; PCI: percutaneous coronary intervention; Intraoperative heparin group (n = 476), Early heparin group (n = 163)

Table 3: Operation characteristics of interventional therapy

Characteristic	Intraoperative heparin group, n (%)	Early heparin group, n (%)	*P-value*
Coronary angiography, n (%)	476(100)	163(100)	NA
Radial approach, n (%)	461(96.8)	155(95.1)	0.299
Femoral artery approach, n (%)	15(3.2)	8(4.9)	0.299
pPCI, n (%)	457(96.0)	160(98.2)	0.194
Intraoperative or postoperative GPI, n (%)	91(19.1)	36(22.1)	0.412
Thrombus aspiration, n (%)	281(59.0)	84(51.1)	0.095

pPCI: direct percutaneous coronary intervention; GPI: Platelet glycoprotein IIbIIIa receptor antagonist; Intraoperative heparin group (n = 476), Early heparin group (n = 163)

There was no statistically significant difference in access routes (*p = 0.299*), direct percutaneous coronary intervention (pPCI) (*p = 0.194*), proportion of Platelet glycoprotein IIbIIIa (GPI) receptor antagonist used during and after the operation (*p = 0.412*), and proportion of thrombus aspiration between the two groups (*p = 0.095*) (Table 3).

Endpoint events

There was significant difference in PCI with preoperative TIMI 2-3 blood flow, between the two groups (*p < 0.05*). There was no significant difference in first medical contact-to-wire-crossing time (*p = 0.095*), proportion of postoperative TIMI 3 blood flow (*p = 0.131*), and incidence of acute intrastent thrombosis between the two groups (*p = 0.777*) (Table 4).

Table 4: Endpoint events

Endpoint events	Intraoperative heparin group, n (%)	Early heparin group, n (%)	*P*-value
Primary endpoint			
Preoperative TIMI level 2-3 blood flow, n (%)	86(18.1)	45(27.6)	0.009
Secondary endpoint			
Primary medical contact - wire passage time, min	112.5±101.4	124.4±94.9	0.095
Postoperative TIMI Grade 3 blood flow, n (%)	41(87.0）	149(91.4)	0.131
Acute stent thrombosis, n (%)	4(0.8)	1(0.6)	0.777

Table 5: Bleeding endpoint

BARC	Intraoperative heparin Group, n (%)	Early heparin Group, n (%)	*P-value*
Bleeding in hospital	5(1.1)	3(1.8)	0.434
BARC 2-5, n (%)			
BARC 2, n (%)	3(0.6)	2(1.2)	0.455
BARC 3a, n (%)	1(0.2)	0(0)	0.558
BARC 3b, n (%)	1(0.2)	1(0.6)	0.426
BARC 3c, n (%)	0	0	NA
BARC 4, n (%)	0	0	NA
BARC 5, n (%)	0	0	NA

Intraoperative heparin group (n = 476), Early heparin group (n = 163) BARC: Bleeding Academic Research Consortium

Bleeding events

Results of Bleeding Academic Research Consortium (BARC) revealed that there was no significant difference in total number of in-hospital bleeding events of BARC 2-5 ($p = 0.434$) among the two groups. However, there were 3 cases (0.6 %) of BARC 2 bleeding and 2 cases (1.2 %) in the intraoperative and early heparin group respectively ($p = 0.455$). There was no significant difference in incidence of BARC 3a ($p = 0.558$) and 3b ($p = 0.426$) bleeding event between the groups (Table 5).

DISCUSSION

ST-segment elevation myocardial infarction (STEMI) is a severe form of coronary artery disease caused by pathological factors such as rupture of coronary artery plaques and thrombotic occlusion. Any delay in diagnosis and timely treatment of STEMI patients increases the likelihood of serious complications, including heart failure, cardiogenic shock, life-threatening arrhythmias, and myocardial rupture [9]. Early opening of IRA reduces the size of myocardial infarction and improves short-term and long-term prognosis. The methods for opening IRA mainly include thrombolytic therapy and pPCI. Anticoagulation therapy with unfractionated heparin is recommended during both thrombolytic therapy and pPCI [7,10]. This study investigated whether early administration of unfractionated heparin before pPCI is beneficial for opening IRA. The results showed that early administration of unfractionated heparin improves coronary artery patency before pPCI, but has no significant effect on postoperative TIMI 3 blood flow rates in the coronary artery. Early use of fixed-dose (5000 IU) unfractionated heparin is safe and does not increase the risk of bleeding complications.

The risk factors and past medical history of coronary artery disease are helpful for the diagnosis of STEMI and have a certain influence on the treatment methods [11]. In this study, there were no significant differences in age, gender, BMI, smoking history, hypertension history, diabetes history, hyperlipidemia history, family history of coronary artery disease, blood supply reconstruction history, eGFR, diastolic blood pressure, heart rate, Killip classification of cardiac function, ST-segment elevation in anterior leads, TIMI risk score, and preoperative medication between two groups of patients. Systolic blood pressure in heparin group during the operation was slightly higher than that in early heparin group, and basic data of the two groups of patients were comparable. There was no significant difference in analysis of infarct-related arteries between the two groups of patients.

All patients in this study underwent coronary angiography, and majority of enrolled patients successfully received PCI treatment. The remaining patients either did not require intervention due to coronary spasm or TIMI 3 grade coronary blood flow with no significant

stenosis observed during angiography, or they were not eligible for intervention due to diffuse lesions. Routine thrombus aspiration is not recommended for STEMI patients undergoing pPCI, but thrombus aspiration may be considered in cases of high thrombus burden within the coronary artery. The proportion of patients receiving thrombus aspiration during the procedure was 59.0 % in heparin group and 51.1 % in early heparin group. Although the thrombus aspiration rate was slightly lower in the early heparin group, there was no statistically significant difference between the two groups [12,13]. Slow flow or no-reflow may occur during pPCI for STEMI, and the use of GPI during intracoronary injection has been shown to prevent or alleviate these conditions [6].

Early studies suggested that a high dose of unfractionated heparin (300 U/kg) was associated with higher rates of IRA patency before PCI, but this finding was not confirmed by larger-scale studies [14]. Results of this study indicated that giving a fixed dose of heparin (5,000 U) before pPCI and then supplementing with a dose of 100 U/kg based on body weight when treatment is needed, or supplementing with 70 U/kg of unfractionated heparin when used in combination with GPI, resulted in nearly 30 % of patients achieving TIMI blood flow grades of 2 - 3 before the procedure, which was significantly higher than proportion of patients who received heparin for the first time during the procedure. Previous studies of patients transferred from non-PCI centers to PCI centers have shown that administering unfractionated heparin before PCI significantly increases IRA patency before the procedure and improves clinical outcomes at 1 y after discharge, which is consistent with the results of this study [15]. The effect of UFH on TIMI 2 - 3 patency is time-dependent, with the greatest benefit obtained when UFH is administered within 120 mins of onset of symptoms. Early benefit of UFH diminishes gradually over time, reaching a minimum of 4 h after symptom onset. This indicated that STEMI patients who receive UFH at the first medical contact obtain the greatest benefit.

Management of STEMI patients should aim to maximize reperfusion efficiency from the initial medical contact, with efforts to minimize total time of myocardial ischemia, including patient delays, pre-hospital system delays, and in-hospital treatment delays [16]. This study indicated that there was no significant delay in time from initial medical contact to wire passage between early heparin group and intraoperative heparin group, and the use of heparin did not cause system delays. Previous studies have shown that compared to a TIMI flow grade of 0 - 1 during angiography, a TIMI flow grade of 2 - 3 in the vessel during angiography results in better clinical outcomes [17]. The TIMI 2 - 3 flow grade before pPCI is correlated with a higher rate of TIMI 3 flow after pPCI, and TIMI blood flow below 2 after pPCI is an independent predictor of death [18]. The results of this study indicated that there is no significant difference in the proportion of TIMI 3 flow after surgery between the two groups, which may be due to the fact that most of the cases in this study were not transfer cases but patients who directly visited the emergency department. Adequate anticoagulation during surgery is one of the essential measures to reduce acute thrombus formation within the stent after pPCI. Although there were differences in the timing of anticoagulation measures in the population included in this study, they were all administered before PCI treatment, so the incidence of acute thrombus within the stent was not significantly different [19].

Bleeding is an independent predictor of poor long-term prognosis, and radial artery access is associated with a lower incidence of bleeding and cardiac death [20]. Although current guidelines in China do not recommend pPCI access route for STEMI patients, with the development of technology, Chinese researchers have accumulated good experience in radial artery puncture, and most of them choose the radial artery route for elective or emergency PCI, which is consistent with the current European STEMI diagnosis and treatment guidelines [6]. In this study, 96.8 % in the perioperative heparin group and 95.1 % in the early heparin group were completed via radial artery access. The analysis of bleeding outcomes showed that early administration of UFH 5000 IU did not increase the incidence of complications at the puncture site or the incidence of major bleeding complications. In fact, a fixed dose makes the treatment plan easier and helps non-PCI centers, emergency medical services, and emergency department personnel remember and administer medication quickly while reducing dosage errors. Another issue in using UFH for pPCI before IRA patency in STEMI is the optimal timing of administration. From a pathophysiological point of view, anticoagulant therapy administered earlier is more effective in treating thrombotic lesions.

Limitations of this study

The subjects in this study were all patients admitted to the hospital at a specific period, and the number is relatively small; hence the results may not apply to other settings.

CONCLUSION

Early upstream administration of UFH in STEMI patients improves coronary artery patency before pPCI, and early use of a fixed dose (5000 IU) of UFH is safe and does not increase the incidence of bleeding complications.

DECLARATIONS

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Ethical approval

This study was approved by the Ethics Committee of Beijing Anzhen Hospital, Capital Medical University, China (approval no. 2018055X).

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflict of Interest

No conflict of interest associated with this work.

Contribution of Authors

The authors declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by them.

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