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The effect of dalteparin versus unfractionated heparin on the levels of troponin I and creatine kinase isoenzyme MB in elective percutaneous coronary intervention: a multicenter study

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Background **The aim of this study was to investigate the safety and efficacy of dalteparin during an elective percutaneous coronary intervention (PCI) procedure in a large cohort.**

Materials and methods **In this prospective, randomized, open-label design study, 733 patients undergoing elective PCI were divided into an unfractionated heparin group (group 1, 323 patients) or a dalteparin group (group 2, 410 patients). Blood samples were collected before and 18–24 h after the PCI procedure to determine the serum levels of cardiac troponin I (cTnI) and creatine kinase isoenzyme MB. Major adverse cardiac events (MACEs) and bleeding events during hospitalization were also recorded. Patients with an increased level of serum cTnI before PCI were excluded from the study.**

Results **After PCI, the cTnI values were greater than three times the upper limit of normal in 43 cases (13.3%) in group 1 and 52 cases (12.7%) in group 2, without a statistically significant difference between the two groups ($P = 0.801$). An increased creatine kinase isoenzyme MB level of greater than two times the upper limit of normal was found in 10 cases (3.1%) in group 1 and 12 cases (2.9%) in group 2, without a statistically significant difference between the two groups ($P = 0.894$). Postoperative bleeding was observed in nine patients (2.8%) in group 1 and six patients (1.5%) in group 2. Postoperative MACEs were observed in two patients (0.6%) in group 1 and two patients (0.5%) in group 2. There were no significant differences between the two groups with respect to bleeding events or MACEs.**

Conclusion **Our study showed that dalteparin might be as effective and safe as unfractionated heparin for anticoagulation during elective PCI.** ***Coron Artery Dis*** **25:510–515 © 2014 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Plaque debris, which impacts blood flow to the capillaries, can result in microvascular mechanical obstruction, platelet activation, and the formation of microthrombi, leading to myocardial injury in patients undergoing a percutaneous coronary intervention (PCI) [1,2]. Anticoagulation with effective and safe measures is important during PCI. Currently, unfractionated heparin (UFH) is used widely as an anticoagulant during the PCI procedure. However, because of its undesirable defects in terms of structure and composition, UFH is associated with various problems, such as a short half-life, low bioavailability, nonspecific binding to proteins that leads to unpredictable anticoagulative reactions [3], intrinsic platelet activation, and aggregation [4,5]. The intravenous half-life of low-molecular-weight heparin (LMWH) is about 2 h, measured as anti-Xa activity, although somewhat shorter (about 80 min) when measured by anti-IIa assay. The half-life of UFH is dose dependent but, at usual intravenous doses, it is 45–60 min by both assay methods. Unlike subcutaneous UFH, which has a bioavailability of less than 50%, all LMWHs have a bioavailability after a subcutaneous injection of 90–100% [6]. Because of the unpredictability of heparin pharmacokinetics, activated clotting time monitoring is needed to adjust the dose of heparin during the PCI procedure. The use of LMWHs, especially enoxaparin, has gradually

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become more widespread and accepted by guidelines for anticoagulation during PCI, with advantages such as the more predictable anticoagulation and a lower incidence of heparin-induced thrombocytopenia. Our previous work and that of others have shown that elective PCI can be performed safely with dalteparin and other LMWHs instead of UFH [7–11]. However, there is a lack of sound evidence on the use of dalteparin as an anticoagulant during PCI. In addition, the changes in myocardial injury markers, such as cardiac troponin I (cTnI) and creatine kinase isoenzyme MB (CK-MB), after PCI have rarely been reported when using dalteparin as an anticoagulant during PCI.

Clinically, cTnI and CK-MB are commonly used sensitive and specific markers of myocardial injury. CK-MB, which has high specificity, has served as a classic indicator of myocardial injury in the diagnosis of myocardial injury [12] and also has a good long-term predictive value in patients undergoing PCI [13,14]. The sensitivity and specificity of cTnI as a myocardial injury marker are greater than those of CK-MB; in addition, cTnI has a longer diagnostic time window of up to 14 days [15,16].

Our preliminary data have confirmed the feasibility [17] and efficacy of dalteparin during PCI [18]. On the basis of these data, we designed this multicenter study to further compare the efficacy and safety of dalteparin as an anticoagulant during elective PCI.

Materials and methods

Patient selection

This study was a multicenter, randomized, controlled, and open-label design study. In total, 733 patients with coronary artery disease admitted to seven hospitals from February 2010 to April 2011 were enrolled in this study. All of the patients underwent elective PCI 3–5 days after admission. The 733 patients were randomized to the UFH group (group 1: $n = 323$; 232 men and 91 women; mean ± SD 59.0 ± 9.9 years) or the dalteparin group (group 2: $n = 410$; 325 men and 85 women; mean ± SD 58.1 ± 8.8 years). The exclusion criteria were as follows: increased serum level of cTnI before PCI; side-branch occlusion after PCI; allergy or intolerance to heparin, LMWH, aspirin, or clopidogrel (including heparin-induced thrombocytopenia); a past or present bleeding disorder including a history of bleeding (gastrointestinal bleeding, macroscopic hematuria, or a positive fecal occult blood test) within 3 months before enrollment; systolic blood pressure of at least 180 mmHg and/or diastolic blood pressure of at least 105 mmHg; a history of stroke, other intracranial lesions, or a transient ischemic attack within 1 year; a history of cardiopulmonary resuscitation within 2 weeks; serious body injury within the previous month; major surgery, including coronary artery bypass grafting (CABG), eye surgery, or biopsy within the previous month; a history of arteriovenous malformation, aneurysm, or aortic dissection; an active peptic ulcer within the last 3 months; acute pericarditis; significant retinopathy; platelet count less than 100×10^9/l; serum creatinine greater than 177 μmol/l; hemodialysis; and a lack of willingness to participate in the study.

All of the study protocols were approved by the Ethics Committee of the Second Hospital of Hebei Medical University and the six other participating hospitals. Informed consent was obtained from each patient before enrollment.

Methods

All of the patients were administered oral treatment with aspirin (75–150 mg, once daily, for ≥ 3 days), clopidogrel (75 mg, once daily, for ≥ 3 days), and subcutaneous LMWH (4000–6000 IU) at 12-h intervals for 3–5 consecutive days before the procedure.

The PCI procedures were performed through either the radial artery or the femoral artery approach, with discontinuation of subcutaneous LMWH 12 h before the procedure. After successful arterial canalization, the patients in group 1 were administered 3000–5000 IU (radial artery, 5000 IU; femoral artery, 3000 IU) UFH (Tianjin Biochemical Pharmaceutical Factory, Tianjin, China), supplemented to a total dose of 120 IU/kg immediately before PCI, with a maximum dose of 10 000 IU. The patients in group 2 were administered 3000–5000 IU anti-Xa (radial artery, 5000 IU; femoral artery, 3000 IU) and dalteparin (provided under the brand name of Fragmin by Pfizer Inc., New York, New York, USA), supplemented to a total dose of 120 IU/kg anti-Xa immediately before PCI, with a maximum dose of 10 000 IU anti-Xa. If the procedure continued for more than 2 h, 2000 IU of UFH or dalteparin was administered for each additional hour.

The sheath was removed immediately after PCI if the radial artery approach was adopted and it was removed after 2–4 h if the femoral artery approach was used. After PCI, the patients continued to take aspirin (100–300 mg, once daily), clopidogrel (75–150 mg, once daily), and subcutaneous LMWH (4000–6000 IU, twice daily) for 3–5 consecutive days.

Routine blood, urine, and stool tests; hepatic and renal function tests; prothrombin time; and ECG examinations were performed before the indexed procedure. The levels of cTnI and CK-MB were determined the day before and 18–24 h after the PCI procedure. The serum levels of cTnI and CK-MB were assessed using an ACCESS fully automated microparticle chemiluminescence immunoassay analyzer (Beckman Company, Pasadena, California, USA) and a myoglobin/CK-MB/troponin I triple kit (Beckman Company). Postprocedural myocardial infarction with CK-MB criteria was defined as more than two times the upper limit of normal (ULN). Postprocedural myocardial infarction with cTnI criteria was defined as more than three times the ULN.

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Table 1 Baseline characteristics of the patients

	Group 1 ($n=323$)	Group 2 ($n=410$)	*P*-values
Age (years)	59.0±9.9	58.1±8.9	0.17
Male	230 (71.2)	317 (77.3)	0.06
Hemoglobin (g/l)	130.1±11.2	135.3±12.6	0.16
BMI (kg/m^2)	25.3±3.59	25.7±3.10	0.08
Risk factors			
Hypertension	215 (66.7)	286 (69.8)	0.36
Hyperlipidemia	100 (30.1)	143 (34.9)	0.26
Diabetes mellitus	66 (20.5)	96 (23.4)	0.33
Smoking	176 (54.5)	224 (54.6)	0.97
Femoral artery approach (%)	24 (7.4)	18 (4.4)	0.08

Values are expressed as mean±SD or *n* (%).
P-values were derived from the independent-sample *t*-test for continuous variables or the χ^2-test for categorical variables.

The number of diseased vessels, lesion locations, number of implanted stents, total procedure time, maximum pressure of stent expansion, and other PCI parameters for each patient were recorded. Bleeding events and the incidence of major adverse cardiac events (MACEs) including death, complication of myocardial infarction, target lesion revascularization, and target vessel revascularization during hospitalization were also recorded. Death was defined as all-cause mortality during hospitalization. Complication of myocardial infarction was defined as resuscitated cardiac arrest, recurrent acute coronary syndrome, urgent revascularization, stroke, or peripheral or pulmonary embolism during hospitalization. Non-CABG major bleeding during hospital was defined according to the STEEPLE definition [19] as fatal bleeding, documented retroperitoneal, intracranial, or intraocular bleeding, bleeding resulting in hemodynamic compromise requiring specific treatment, bleeding requiring surgical intervention or decompression of a closed space to control the event, any transfusion, or a decrease in hemoglobin of 30 g/l or more.

Safety evaluation

Bleeding events were classified according to the Thrombin Inhibition in Myocardial Infarction bleeding criteria. Major bleeding was defined as a decrease in hemoglobin of greater than 50 g/l (known or unknown site of bleeding, not associated with CABG), intracranial hemorrhage, or cardiac tamponade. Minor bleeding was defined as a decrease in hemoglobin of greater than 30 g/l but 50 g/l or less (known bleeding site, not associated with CABG), spontaneous macroscopic hematuria, hematemesis, hemoptysis, or puncture-site hematoma.

Vascular complications at the access site were recorded as follows: size of the local hematoma (defined as a hematoma with a diameter >5 cm), pseudoaneurysm, and arteriovenous fistula.

Statistical methods

All of the statistical analyses were carried out using SPSS 16.0 software (SPSS Inc., Chicago, Illinois, USA). Continuous data were expressed as the mean±SD ($\bar{x}\pm$SD) and categorical data were expressed as a percentage (%). Measurements were compared between groups using the independent-sample *t*-test and categorical data were analyzed using the χ^2-test. A difference of *P*-value less than 0.05 was considered statistically significant.

Results

Baseline data

This study included 733 patients; almost all patients were deployed with drug-eluting stents and only two patients in group 1 and one patient in group 2 were implanted with bare metal stents. The drug-eluting stents were first-generation sirolimus drug-eluting stents, either Cypher or Chinese products (Partner, Lepu Medical, Beijing, China; and Excel, JWMS Medical, Weihai, China).

There were no significant differences between the two groups with respect to sex, age, hemoglobin, BMI, or other atherosclerotic risk factors (Table 1). In addition, there were no significant differences between the two groups in the number of diseased vessels, stent implant site, number of stents, balloon inflation pressure, expansion time, or size/length of stents (Table 2).

Changes in cardiac injury markers

Before the PCI procedure, the serum level of cTnI was within the normal upper limits (<1 μg/l) in both groups. At 18–24 h after PCI, the serum cTnI level increased significantly compared with the baseline values in both groups. The postoperative serum cTnI level was 1.88±4.14 μg/l in group 1 and 1.96±4.68 μg/l in group 2 ($t=0.47$, $P>0.05$). Serum cTnI values of greater than 1 μg/l, at least 3×ULN, and at least 5×ULN were found in 97 cases (30.0%), 43 cases (13.3%), and 23 cases (7.1%)

Table 2 Comparison of parameters of stent implantation between the groups

	Group 1 ($n=323$)	Group 2 ($n=410$)	*P*-values
Number of stents (*n*)	1.46±0.71	1.25±0.52	0.08
Balloon inflation pressure (atm)	13.13±3.27	12.86±2.12	0.63
Inflation time (s)	14.85±5.56	12.8±5.93	0.07
Size of stents (mm)	2.94±0.42	2.97±0.42	0.33
Length of stents (mm)	19.35±6.87	18.74±5.10	0.18
CRA			0.54
LAD	180 (55.7)	196 (47.8)	
LCX	74 (22.9)	88 (21.5)	
RCA	61 (18.9)	120 (29.3)	
LM	8 (2.5)	6 (1.5)	
Vascular lesion			0.09
Single-vessel disease	98 (30.3)	140 (34.2)	
Two-vessel disease	111 (34.4)	156 (38.0)	
Three-vessel disease	114 (35.3)	114 (27.8)	

Values are expressed as mean±SD or *n* (%).
CRA, criminal-related artery; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main coronary artery; RCA, right coronary artery.
P-values were derived from the independent-sample *t*-test for continuous variables or the χ^2-test for categorical variables.

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Table 3 Postoperative CK-MB and cTnI values in group 1 and group 2

	Group 1 ($n=323$)	Group 2 ($n=410$)	χ^2 values	*P*-values
cTnI				
> 1 μg/l	97 (30.0)	127 (31.0)	0.076	0.783
3 × ULN	43 (13.3)	52 (12.7)	0.064	0.801
5 × ULN	23 (7.1)	30 (7.3)	0.01	0.919
CK-MB				
> 25 μg/l	37 (11.5)	33 (8.1)	2.427	0.119
2 × ULN	10 (3.1)	12 (2.9)	0.018	0.894
5 × ULN	0 (0.0)	1 (0.2)	0.00	1.00

Values are expressed as *n* (%).
CK-MB, creatine kinase isoenzyme MB; cTnI, cardiac troponin I; ULN, upper limit of normal.
P-values were derived from the χ^2-test for categorical variables.

in group 1, whereas the corresponding values were 127 cases (31.0%), 52 cases (12.7%), and 30 cases (7.3%) in group 2, respectively. There were no significant differences between the two groups with respect to the above measurements (Table 3).

Preoperatively, the serum CK-MB levels were normal (< 25 μg/l) in both groups. Compared with those at baseline, after PCI, the serum CK-MB levels were significantly increased in both groups, with values of 15.67 ± 11.3 μg/l in group 1 and 12.85 ± 11.96 μg/l in group 2, respectively ($t = 2.00$, $P < 0.05$). Serum levels of CK-MB of greater than 25 μg/l, at least 2 × ULN, and at least 5 × ULN were found in 37 cases (11.5%), 10 cases (3.1%), and zero cases (0.0%) in group 1, whereas the corresponding values were 33 cases (8.1%), 12 cases (2.9%), and one case (0.2%) in group 2, respectively. There was no significant difference in the above measurements between the groups postoperatively (Table 3).

Bleeding events

One patient in group 1 developed major bleeding in the gastrointestinal tract. Seven hours after PCI, the patient presented with melena and a decrease in hemoglobin of 70 g/l, which suggested the presence of a stress ulcer. The patient's condition stabilized shortly after a blood transfusion. Two other patients in group 1 experienced minor bleeding presented as a large hematoma at the site of the femoral artery access. No major bleeding episodes occurred in group 2, whereas four patients developed minor bleeding manifested as a hematoma at the puncture site. The overall incidences of bleeding were 2.8% in group 1 and 1.5% in group 2, respectively ($P = 1.00$) (Table 4).

Thrombosis within the sheath

Thrombosis within the sheath did not occur in group 1, but was observed in one patient in group 2 (0 vs. 0.2%, $P > 0.05$).

Hospital follow-up

There were no postoperative deaths in either group. One patient presenting with gastrointestinal bleeding in group 1 developed a subacute stent thrombus 3 days after withdrawal of the antiplatelet agent and therefore underwent another PCI procedure. Myocardial infarction reoccurred in one patient in group 2 at 12 h after PCI and was subsequently confirmed to have acute stent thrombosis by coronary angiography. Accordingly, PCI was performed on this patient. The two patients were finally discharged uneventfully. The MACEs during hospitalization are presented in Table 5.

Table 4 Comparison of bleeding episodes between group 1 and group 2

	Group 1 ($n=323$)	Group 2 ($n=410$)	*P*-values
Major bleeding	1 (0.3)	0 (0)	1.00
Minor bleeding	2 (0.6)	4 (1.0)	0.60
Total number of bleeding events	9 (2.8)	6 (1.5)	0.21
Bleeding site			
Puncture-site hematoma (< 5 cm)	4 (1.2)	2 (0.5)	0.26
Puncture-site hematoma (>5 cm)	2 (0.6)	4 (1.0)	0.60
Gingival bleeding	2 (0.6)	0 (0)	1.00
Gastrointestinal bleeding	1 (0.3)	0 (0)	1.00
Hematuria	0 (0)	0 (0)	1.00
Thrombocytopenia	0 (0)	0 (0)	1.00
Cerebral bleeding	0 (0)	0 (0)	1.00

Values are expressed as *n* (%).
P-values were derived from the χ^2-test for categorical variables.

Table 5 Hospital follow-up of group 1 and group 2 after interventional therapy

	Group 1 ($n=323$)	Group 2 ($n=410$)	*P*-values
Death	0 (0)	0 (0)	1.00
Nonfatal myocardial infarction	0 (0)	1 (0.2)	1.00
TLR rate	1 (0.3)	1 (0.2)	0.87
TVR rate	1 (0.3)	1 (0.2)	0.87
MACE incidence	2 (0.6)	2 (0.5)	0.81
Incidence of stent thrombosis	1 (0.3)	1 (0.2)	0.87

Values are expressed as *n* (%).
MACE, major adverse cardiac event; TLR, target lesion revascularization; TVR, target vessel revascularization.
P-values were derived from the χ^2-test for categorical variables.

Discussion

This study shows that dalteparin as an anticoagulant during elective PCI might be as effective and safe as UFH. There was no significant difference between the two groups with respect to the mean serum levels and incidence of an increase in cTnI and CK-MB levels after PCI ($P = 0.80$ and 0.89). Moreover, the rates of bleeding and MACEs after PCI were also similar in both groups. These results suggest that dalteparin is a safe and effective anticoagulant for use in the context of elective PCI.

In recent years, researchers have confirmed the safety and effectiveness of using LMWH as an anticoagulant in PCI. Rabah *et al.* [20] first found that the use of

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enoxaparin as an anticoagulant during PCI was both safe and effective in patients vulnerable to bleeding episodes and vascular events compared with UFH. On monitoring the activated clotting time, these two drugs were found to be consistent in terms of the anti-Xa factor activity. After this work was published, more evidence accumulated on the use of LMWH as an adjunctive anticoagulant during PCI. The NICE 1 and NICE 4 studies showed that enoxaparin alone or combined with abciximab provides safe and effective anticoagulation during PCI as shown by a similar MACE rate within 30 days of indexed PCI as UFH [21]. The ATOLL study showed that even in the context of primary PCI, enoxaparin could reduce the rate of death, complications of myocardial infarction, and major bleeding compared with UFH in STEMI patients [22]. A meta-analysis found that the incidence of serious bleeding was significantly less in patients treated with LMWH compared with those treated with UFH (odds ratio, 0.57; 95% confidence interval, 0.40–0.82, $P = 0.002$), but showed no significant difference in terms of the incidence of other adverse events or anticoagulant effects [23].

In contrast to relatively sound evidence for using enoxaparin as an anticoagulant during PCI, there are only a few studies on dalteparin as an effective anticoagulant during PCI. Natarajan *et al.* [8] found that the anticoagulant effects of dalteparin and UFH are similar. In their patients, angiographic (success rates > 90% in both cases) and clinical events (death, myocardial infarction, and revascularization) were also similar in both groups. Li *et al.* [24] have reported that dalteparin alone or combined with tirofiban was effective and safe in primary PCI for patients with STEMI compared with UFH. In in-vitro studies, Raaz *et al.* [25] confirmed that the modulation of plasma coagulation with LMWH was critical to prevent catheter thrombus formation; thus, these authors favor dalteparin over enoxaparin in the setting of PCI. Our results in this current study further confirmed the conclusions from our preliminary study and the above-mentioned investigations [8,10,17,18,24].

Myocardial injury as measured by the serum cTnI or CK-MB level is not uncommon in patients after PCI, which may result from increased lesion complexity, occluded microcirculation by a thrombus or debris embolization, low perfusion pressure, vascular spasm, insufficient anticoagulation, or vessel dissection [26,27]. An increased serum level of cTnI or CK-MB after PCI usually predicts a worse short-term or long-term outcome [28,29]. Furthermore, the incidence of adverse cardiac events was positively related to increased levels of myocardial injury markers. Using an appropriate anticoagulant during PCI can reduce the postoperative levels of cTnI and CK-MB, resulting in a decreased rate of myocardial injury following the PCI procedure [1,30–32]. In this study, the promising results obtained with the use of dalteparin with a dosage of 120 IU anti-Xa during PCI provide some evidence of adjunctive anticoagulation in such a situation. Our results also further confirmed the feasibility of using dalteparin instead of UFH for anticoagulation during PCI.

Notwithstanding the weaker effect of LMWH against thrombosis induced by foreign objects compared with UFH [9,33], thrombosis within the sheath occurred in only one patient of the dalteparin group, which is not statistically different from that of the UFH group. Therefore, the choice of dalteparin does not mean that more thrombosis was induced by foreign objects.

Some studies indicate that LMWH can reduce the incidence of MACEs and stent thrombosis compared with UFH. Kim *et al.* [34] have suggested that tirofiban in combination with dalteparin in patients with acute coronary syndrome can significantly lower the incidence of MACEs compared with UFH plus tirofiban. In our study, no significant differences in the incidence of MACEs or stent thrombosis were found between the two groups ($P = 0.81$ and 0.87).

Limitations of the study

The present study had some limitations, including the selection of patients undergoing elective PCI and the limited number of patients treated with a platelet glycoprotein IIb/IIIa receptor antagonist in addition to the anticoagulant. In addition, coronary angiography was necessary to determine whether a patient should undergo PCI. The patients included in the study could therefore not be selected randomly. Furthermore, the dalteparin group enrolled more patients than the UFH group. Finally, considering the relatively small size of the study, the conclusion from this study should be confirmed in the future by a larger, double-blind, and randomized study.

Conclusion

Dalteparin is applicable for anticoagulation during elective PCI and is not inferior to UFH in terms of postoperative myocardial injury markers or bleeding complications. Thus, the use of dalteparin might be a feasible alternative to UFH in elective PCI. This study had a small sample size; therefore, the findings may be used to generate hypotheses rather than to provide definite conclusions.

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Conflicts of interest

There are no conflicts of interest.

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