Enoxaparin versus Unfractionated Heparin in Elective Percutaneous Coronary Intervention; Efficacy and Safety Study

Haedar Nazar Kadim*, Hassan Farhan , Looiy Muhammad Alhallaq*****

ABSTRACT:

BACKGROUND:

Since long time, unfractionated heparin has been used as standard anticoagulant for percutaneous coronary intervention(PCI).however, recently several studies showed that intravenous enoxaparin safety and effectiveness is similar to that of unfractionated heparin.

OBJECTIVE :

To assess the safety and practicity of enoxaparin compared with un fractionated heparin in elective PCI using drug eluting stents (DES).

METHODS:

In this prospective, randomized trial, at the cardiac unit of Ashty hospital in Erbil city, from July 2014 to February 2016, we included 300 patients undergoing elective PCI. 150 patient received enoxaparin 0.6 mg per kilogram of body weight, the other 150 patient received unfractionated heparin 100 u per kilogram of body weight adjusted for activated clotting time.

The primary end point is the incidence of bleeding (minor or major). While the mortality and the incidence of acute coronary events within 24 hours after PCI was the secondary end point.

RESULTS:

There was reduction, however statistically insignificant (p value>0.05) in the rate of major and minor bleeding in Enoxaparin group in the first 24 hours as compared with unfractionated heparin (4 % vs. 5.25%; absolute difference –1.25).The acute coronary events and death rate was similar.

CONCLUSION:

In elective PCI using DES, a single intravenous bolus of Enoxaparin at a dose of 0.6 mg per kilogram was at least as safe as effective as unfractionated heparin with simpler use and faster indwelling sheath removal.

KEY WORDS: heparin, enoxaparin, pic.

INTRODUCTION:

Although, all the cardiac guidelines recommend the use of intravenous unfractionated heparin (UFH) during percutaneous coronary intervention (PCI) [1,2]. there are some restrictions of UFH, The use of unfractionated heparin during percutaneous coronary intervention is limited by its unpredictable effect, the need for close monitoring, and the uncertainty around optimal levels of activated clotting time. ([3,4]), In addition to the need for monitoring of coagulation, and risk of thrombocytopenia are indicative of the need for a better and safer anticoagulation regimens [5]. LMWH produces a more predictable and stable dose response comparing to UFH [6,7].

Enoxaparin is made from heparin.8 its a low molecular weight heparin family of medications,

It can be used in those with acute coronary syndrome (ACS) and heart attacks.[9]

Enoxaparin binds to and potentiates antithrombin (a circulating anticoagulant) to form a complex that irreversibly inactivates clotting factor Xa.10 "

Enoxaparin has predictable absorption, bioavailability (about 100%), and distribution therefore monitoring is not typically done.[11,12]

Also LMWH considered to have a longer half-life as well as a greater ratio of anti-factor Xa activity to anti-factor IIa activity, which reduces the generation and activation of thrombin [13,14]. Moreover, LMWH has less tendency to induce platelet activation, release of the von Willebrand factor, and inflammation [15,16]

*Ibn. Al-Nafees Cardiovascular Hospital.
**Baghdad Teaching Hospital. Medical City.
Iraqi Board for Medical Specializations
***Ibn. Al-Nafees Cardiovascular Hospital.

For long time the Society of Cardiac Angiography and Intervention and American Heart Association, as well as guidelines from the Task Force on Myocardial Revascularization of the European Society of Cardiology considered unfractionated heparin a class 1 recommendation for coronary intervention, despite the supporting evidence was limited (level of evidence C). [17] , without the need for monitoring, enoxaparin provides predictable anticoagulation, it is the leading low molecular weight heparin In the setting of percutaneous coronary intervention with the largest published information volume.[18] it can be administered as subcutaneous injection, as in the management of non-ST elevation acute coronary syndromes. Or ST elevation myocardial infarction treated with thrombolytic therapy.

In patients undergoing elective percutaneous coronary intervention or primary percutaneous coronary intervention, enoxaparin can be used as intravenous injections for immediate anticoagulation, as shown in several randomized studies. [19-21]

Although there is good evidence for the therapeutic benefits of LMWH over UFH in the medical management of patients with a high-risk ACS ([22-24]. data regarding the use of LMWH in patients undergoing PCI are restricted since most studies are uncontrolled or limited by sample size [25-30].

In the new era the use of (LMWH) is increasing in patients with ischemic heart disease (IHD) who undergo PCI [31-34]. In a meta-analysis of data from randomized studies comparing intravenous low-molecular-weight heparins and intravenous unfractionated heparin in patients undergoing PCI, there was no difference between groups in the occurrence of ischemic events and non significant reduction in major bleeding with low-molecular weight heparins [37]. In an additional analysis, a dose of less than 1 mg of enoxaparin per kilogram resulted in fewer ischemic and bleeding events than a dose of 1 mg per kilogram [35,36]

For all that we conducted a randomized, controlled trial to evaluate the efficacy and safety of intravenous enoxaparin versus UFH in patients with coronary artery disease who underwent PCI by drug eluting stent (DES).

MATERIALS AND METHODS:

In this prospective interventional study, patients with CAD referred for coronary angioplasty as a chronic stable angina were included if they were candidate for PCI as a result of anginal pain unresponsive or intolerant to anti anginal medications, ischemic heart failure or critical coronary stenosis involving a vessel supplying relatively large myocardial area ..

The exclusion criteria included patients with high risk of bleeding (aged 75 or older , serum creatinine≥2.5 mg/dl in male and ≥2.0 mg/dl in female , active peptic ulcer, abnormal bleeding time and abnormal INR, patients needed glycoprotein IIb/IIIa also have been excluded from the study because of increase bleeding rate.

Oral aspirin 300 mg/day and loading dose (600 mg) of clopidogrel given before the procedure for all patient. At time of the procedure, 150 patients were randomly assigned to receive an intravenous bolus of 8000-10000 IU unfractionated heparin to achieve a target activated clotting time of 300 to 350 seconds, other 150 patients received 0.6 mg/kg intravenous enoxaparin.

Using femoral sheath, PCI procedures were performed according to standard techniques.

Sheath removal is permitted when the activated clotting time between 150 and 180 seconds in the unfractionated heparin group (average of 3.5 h), and 1,5 h after the end of the PCI in the group given enoxaparin. No monitoring of anticoagulation was required before sheath removal in patients receiving enoxaparin.

Activated clotting time was measured with a standardized Hemochron device (ITC).

Patients were monitored for 24 hours after procedure for any bleeding, hematoma, abdominal pain, hypotension or any ischemic event including chest pain, dyspnea or any arrhythmia. Electrocardiograms (ECGs) were obtained routinely immediately after the procedure and at discharge for all patients.

Serum cardiac biomarkers including CK-MB and troponin I was used for any suspected ischemic event.

The primary end point of the trial was the occurrence of minor or major bleeding during the first 24 hours following the procedure, defined as hematoma at the femoral access site, uncontrolled bleeding from the sheath removal site, retroperitoneal hemorrhage documented by ultra sound, gastrointestinal hemorrhage, intracranial bleeding.

Major and minor bleeding was defined according to prespecified definitions (Table I).

Any coronary ischemic events or death were also reported.

Table I: Major and Minor Bleeding Definitions .

Major bleeding*
The Fatal bleeding
Intracranial, intraocular, retroperitoneal bleeding
Bleeding causing hemodynamic compromisation
Bleeding requiring decompression of a closed space or intervention to control or stop the event
Clinically overt bleeding, that requires transfusion of ≥1 unit of blood
Bleeding, that decrease hemoglobin ≥3 g/dl or hematocrit of ≥10%
Minor bleeding†
Non traumatic (e.g., from instrumentation) gross hematuria
Prolonged, repeated epistaxis, or requires plugging or intervention
Hemoptysis
Subconjunctival hemorrhage
Gastrointestinal hemorrhage
Clinically overt bleeding, that decrease hemoglobin of 2 to 3 g/dl
Hematoma >5 cm or needing new hospitalization
Uncontrolled bleeding requires administration of protamine sulfate

* Major bleeding was defined as bleeding that at least met one of the criteria listed.
† Minor bleeding was defined as bleeding that did not meet any of the criteria for major bleeding and that at least met one of minor bleeding criteria1.

Statistical analysis:
Statistical analyses were performed with EPI info. The variables were expressed as mean ± SD and data expressed as percentage. t-tests. Was used for the Comparisons of continuous variables between the two groups .with A p-value of <0.05 considered to indicate statistical significance.

RESULTS:

Characteristics of the patients and procedure.
A total of 300 patients were enrolled in a randomized interventional study, 150 were randomly assigned to receive unfractionated heparin intravenously. 150 patient to receive 0.6 mg of enoxaparin per kilo gram intravenously,

Baseline characteristics of both groups are presented in Table 1.
There were no significant differences in characteristics between patients receiving heparin or those receiving enoxaparin .
UFH group (12.4 %) received additional bolus after long procedure because they missed there target activated clotting time. No one of the enoxaparin group received an additional dose.
For the patient received UFH, the median activated clotting time at the start and end of PCI was 328±8 and 290±6 seconds, respectively.

Table 1: baseline characteristics of the patients .

Characteristics	Unfractioned Heparin (n=150)	LMWH (Enoxoparin) (n=150)	P Value
Age (year)	56.0±.8	58.0±.6	0.5
Male gender %	54	58.6	0.5
Hypertension %	61	64	0.1
Diabetes mellitus %	32	28.6	0.5
Hyperlipidemia %	43.2	48	0.4
Cigarette smoking %	30	27	0.6
Previous PCI %	10	13	0.5
Previous CABG %	3	2.6	0.7
Previous CVA %	1.3	0.00	0.1
LVEF<35%	14	11	0.5
Multivessel stenting %	16	20	0.4

Primary End Point

The percentage of minor bleeding during the first 24 hours were 4% in the enoxaparin group, major bleeding was zero .minor bleeding during the first 24 hours were 5.25% in in UFH group and the major bleeding was 0.33%.

Hemoglobin drop ≥ 3g/dl was reported in only one patients in the UFH group due to gastric hemorrhage and required blood transfusion gastroscopy and sclerotherapy While no one reported in enoxaparin group.

The primary end point relative reduction was 31% in the enoxaparin group compared with unfractionated heparin, that not meet the criteria for the superiority of enoxaparin over unfractionated heparin (P = 0.01), but it meets the prespecified criteria for non inferiority (95% CI, –4.0 to 0.0; excluding the non inferiority margin of 30% [absolute margin, +2.6%]).

Consistent results were found across all major subgroups with respect to the primary end point.

Table 2: Beeding and coronary events within 24 hour of PCI.

Criteria	Unfractioned Heparin no(%) (n=150)	LMWH (Enoxoparin) No(%) (n=150)	P Value
Incidence of major bleeding	0.0	0.0	Ns
Incidence of minor bleeding	14 (9.3)	11 (7.3)	0.5
Femoral sheath hematoma < 6 cm	8.0 (5.3)	7.0 (4.6)	
Femoral sheath hematoma > 6 cm	2 (1.3)	2 (1.3)	0.7
Uncontrolled sheath removal site bleeding	3.0 (2)	2.0 (1.3)	
Epistaxis that need plugging	0 (0.0)	0.0	0.6
Gasterointestinal bleeding	1 (0.6)	(0.0)	0.3
Gasterointestinal bleeding needed intervenntion	0.0	0.0	Ns
Retroperitoneal bleeding	0.0	0.0	Ns
Decrement of HB of more than 3 g/dl	1 (0.6)	0.0	0.3
Blood transfusion required	1 (0.6)	0.0	0.3
More than two pint blood transfusion required	0.0	0.0	Ns
Cerebro-vascular accident	0.0	0.0	Ns
Median time to sheath removal from end of PCI (in minute)	65	190	
Atypical chest pain	14 (9.3)	16 (10.6)	0.2
Anginal chest pain with ECG changes	4.0 (2.6)	5.0 (3.3)	0.7
Cardiac enzymes elevation	2 (1.3)	2 (1.3)	1
Emergent angiography	2 (1.3)	2 (1.3)	1
Repeated PCI	0 (0.0)	0 (0.0)	ND
Emergency CABG	0.0	0.0	ND
Mortality within 24h of PCI	0.0	0.0	ND

Secondary End Points

The incidence of documented coronary ischemia, myocardial infarction or urgent revascularization during the first 24h after the procedure were similar in both groups.

There was no death., there was no significant difference in end points variables in patients who received UFH or those with enoxaparin. Documented ischemic chest pain with ST-T ECG changes or raised cardiac enzymes within the first 24 hours of PCI were nine cases, 5 patients (3.3%) were in UFH and 4 patients (2.6%) in enoxaparin group. no one need urgent revascularization or urgent CABG in both groups. No one developed acute in-stent thrombosis.

Deaths did not reported in both groups within the 1st 24h of the procedure.

DISCUSSION:

In this study we compared the safety and practicability of enoxaparin versus conventional intravenous un fractioned heparin for elective PCI using drug-eluting stents .

The present studies shows evidence of non-inferiority of the new strategy of using Enoxaparin in PCI.

SYNERGY study demonstrated the safety of PCI performance in patients with acute coronary syndromes pretreated with enoxaparin, without increase rate of acute stent thrombosis, compared with patients who received UFH (1.3% vs. 1.7%, p=NS) 32. The result of meta-analysis of 8 randomized trials by De Luca et al. also demonstrated that LMWHs are associated with a significant decrease in re-infarction, trend in decrease death rate, however there was higher risk of major bleeding complications (36).

In the (ACTION) trial compared enoxaparin with heparin during elective PCI performed with ad-junctive small-molecule GP IIb/IIIa blockade 30. The study showed that 0.75 mg/kg of enoxaparin achieved therapeutic levels of anticoagulation during the procedure without an excess of bleeding or ischemic complications compared with heparin.

In (CRUISE) study using Integrilin and Single Bolus Enoxaparin randomized 261 patients undergoing PCI

to receive enoxaparin or heparin with concomitant double-bolus eptifibatide therapy28. This study revealed similar rates of bleeding complications, vascular access site complications, and ischemic events between the two groups.

However both The CRUISE and ACTION trials are limited by small sample size (28,30).

The recently completed The Safety and Efficacy of Enoxaparin in PCI Patients, an International Randomized Evaluation (STEEPLE) trial randomized 3528 patients who underwent elective PCI to receive enoxaparin (0.75 or 0.5 mg/kg intravenously) or heparin, thus permitting a definitive safety comparison of these 2 therapies (35). The slightly but not significantly higher death rate with low-dose enoxaparin remains unexplained and the trial was not large enough to provide a definitive comparison of efficacy in the prevention of ischemic events.

In our study however it lacked the statistical power to demonstrate significant differences in clinical end points between enoxaparin and heparin groups, enoxaparin found to be at least as safe as UFH regarding bleeding complications and PCI outcome. Larger sample size is required to better characterize the definitive efficacy and safety between enoxaparin and UFH during PCI.

The sheath removal time in the enoxaparin group was shorter, the treatment protocol was simpler, administered as a single intravenous dose of 0.6 mg per kilogram, without

Anticoagulation monitoring.

CONCLUSION:

The use of LMWH in elective PCI is more practical and is at least is as effective and safe as the UFH and it's more comfortable to the patient because of the shorter time of sheath removal and patient mobilization.

REFERENCES:

1. Smith SC Jr, Feldman TE, Hirshfeld JW Jr, et al. ACC/AHA/SCAI 20015 guideline update for percutaneous coronary intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/SCAI Writing Committee to
2. Update the 20011 Guidelines for Percutaneous Coronary Intervention). In:[http://www.cardiosource.com]. J Am Coll Cardiol 2001; 37: 1-121.
3. Silber S, Albertsson P, Aviles FF. Guidelines for percutaneous coronary interventions: the Task Force for Percutaneous Coronary Interventions of the European Society of Cardiology. Eur Heart J 2005; 26: 804-47.
4. Schulz S, Mehilli J, Neumann FJ, Schuster T, Massberg S, Valina C, et al. ISAR-REACT 3A: a study of reduced dose of unfractionated heparin in biomarker negative patients undergoing percutaneous coronary intervention. Eur Heart J2010;31:2482-91.
5. Steg PG, Jolly SS, Mehta SR, Afzal R, Xavier D, Rupprecht HJ, et al. Low-dose vs standard-dose unfractionated heparin for percutaneous coronary intervention in acute coronary syndromes treated with fondaparinux: the FUTURA/OASIS-8 randomized trial. JAMA2010;304:1339-49.
6. Cohen M. The role of low-molecular-weight heparin in the management of acute coronary syndromes. J Am Coll Cardiol 2003; 41 (Suppl 4): 55-61.
7. Drozd J, Opaliska E, Wójcik J, et al. The use of enoxaparin during percutaneous coronary angioplasty in patients with stable angina. Kardiol Pol 2001; 55: 520-24.
8. Collet JP, Montalescot G, Lison L, etal. Percutaneous coronary intervention after subcutaneous enoxaparin pretreatment in patients with unstable angina pectoris. Circulation 2001;103:658-63.
9. Network, Northern Neonatal (2008). Neonatal Formulary: Drug Use in Pregnancy and the First Year of Life. John Wiley & Sons. p. 96. ISBN 9780470750353. Archived from the original on 2016-12-20.
10. "Enoxaparin Sodium". The American Society of Health-System Pharmacists. Archived from the original on 21 December 2016. Retrieved 8 December 2016.
11. Alldredge, Brian; Corelli, Robin; Ernst, Michael; Guglielmo, B. Joseph; Jacobson, Pamela; Kradjan, Wayne; Williams, Bradley. Koda-Kimble and Young's Applied Therapeutics: The Clinical Use of Drugs (Tenth ed.). pp. 347–348. ISBN 1-60913-713-2.

12. "DailyMed - ENOXAPARIN SODIUM- enoxaparin sodium injection". dailymed.nlm.nih.gov. Archived from the original on 2015-10-19. Retrieved 2015-11-05.
13. "Lovenox® (enoxaparin sodium injection) for subcutaneous and intravenous use Prescribing Information". products.sanofi.us. Archived from the original on 2015-10-23. Retrieved 2015-11-03.
14. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease: Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. N Engl J Med 1997; 337: 447-52.
15. Samama MM, Gerotziafas GT. Comparative pharmacokinetics of LMWHs. Semin Thromb Hemost 2000;26:Suppl 1:31-8.
16. Montalescot G, Collet JP, Lison L, et al. Effects of various anticoagulant treatments on von Willebrand factor release in unstable angina. J Am Coll Cardiol 2000; 36:110-14.
17. Montalescot G, Bal-dit-Sollier C, Chibedi D, et al. Comparison of effects on markers of blood cell activation of enoxaparin, dalteparin, and unfractionated heparin in patients with unstable angina pectoris or non-ST-segment elevation acute myocardial infarction (the ARMADA study). Am J Cardiol 2003;91:925-30.
18. Wijns W, Kolh P, Danchin N, Di Mario C, Falk V, Folliguet T, et al. Guidelines on myocardial revascularization: The Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J2010;31:2501-55.
19. Silvain J, Beygui F, Ankri A, Bellemain-Appaix A, Pena A, Barthelemy O, et al. Enoxaparin anticoagulation monitoring in the catheterization laboratory using a new bedside test. J Am Coll Cardiol2010;55:617-25.
20. 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
21. coronary intervention patients, an international randomized evaluation) trial. JACC Cardiovasc Interv2009;2:1083-91.
22. Montalescot G, Ellis SG, de Belder MA, Janssens L, Katz O, Pluta W, et al. Enoxaparin in primary and facilitated percutaneous coronary intervention. A formal prospective nonrandomized substudy of the FINESSE trial (Facilitated INtervention with Enhanced Reperfusion Speed to Stop Events). JACC Cardiovasc Interv2010;3:203-12.
23. Montalescot G, Zeymer U, Silvain J, Boulanger B, Cohen M, Goldstein P, et al. Intravenous enoxaparin or unfractionated heparin in primary percutaneous coronary intervention for ST-elevation myocardial infarction: the international randomised open-label ATOLL trial. Lancet2011;378:693-703.
24. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B-ESSENCE meta-analysis. Circulation 1999; 100:1602-8.
25. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the thrombolysis in myocardial infarction (TIMI) 11B trial. Circulation 1999;100:1593-1601.
26. Cohen M, Antman EM, Gurfinkel E, et al. Impact of enoxaparin low molecular weight heparin in patients with a Q-wave myocardial infarction. Am J Cardiol 2000; 86:553-56.
27. Kereiakes DJ, Grines CL, Fry E, et al. Enoxaparin and abciximabadjunctive pharmacotherapy during percutaneous coronary intervention. J Invasive Cardiol 2001;13:272-78.
28. Chen WH, Lau CP, Lau YK, et al. Stable and optimal anticoagulation is achieved with a single dose of intravenous enoxaparin in patients undergoing percutaneous coronary intervention. J Invasive Cardiol 2002;14:439-42.

29. Dudek D, Dabrowski M, Ochala A, et al. Multicenter, prospective, double-blind randomized comparison of enoxaparin versus unfractionated heparin for percutaneous coronary interventions. Am J Cardiol 2000; 86 (Suppl 8A): 15.
30. Bhatt DL, Lee BI, Casterella PJ, et al. Safety of concomitant therapy with eptifibatide and enoxaparin in patients undergoing percutaneous coronary intervention: results of the Coronary Revascularization Using Integrilin and Single bolus Enoxaparin Study. J Am Coll Cardiol 2003;41:20-25.
31. Galeote G, Hussein M, Sobrino N. Combination abciximaband enoxaparin or unfractionated heparin during percutaneous coronary intervention: a randomised study. Eur Heart J 2001;22 (Suppl): 663-63.
32. Madan M, Radhakrishnan S, Reis M, et al. Comparison of enoxaparin versus heparin during elective percutaneous coronary intervention performed with either eptifibatide or tirofiban (the ACTION Trial). Am J Cardiol 2005;95:1295-301
33. Ferguson JJ, Antman EM, Bates ER, et al. Combining enoxaparin and glycoprotein IIb/IIIa antagonists for the treatment of acute coronary syndromes: final results of the National Investigators Collaborating on Enoxaparin-3 (NICE-3) study. Am Heart J 2003;146: 628-34.
34. Ferguson JJ, Califf RM, Antman EM, 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.
35. Choussat R, Montalescot G, Collet JP, et al. A unique, low dose of intravenous enoxaparin in elective percutaneous coronary intervention. J Am Coll Cardiol 2002;40:1943-50.
36. Borentain M, Montalescot G, Bouzamondo A, et al. Low-molecular-weight heparin vs. unfractionated heparin in percutaneous coronary intervention: a combined analysis. Catheter Cardiovasc Interv 2005; 65:212-21.
37. Montalescot G, White HD, Gallo G, et al. Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. N Engl J Med 2006;355:1006-17.
38. De Luca G, Marino P. Adjunctive benefits from low-molecular-weight heparins as compared to unfractionated heparin among patients with ST-segment elevation myocardial infarction treated with thrombolysis. A meta-analysis of the randomized trials. Am Heart J. 2007;154:1-6.