Preliminary Report

Effect of Un-Fractionated Heparin and Low Molecular Weight Heparin on Hospital Mortality in Patients with Non ST Elevation Acute Coronary Syndrome (ACS)

Kitiporn Angkasuwapala MD*, Kasem Ratanasumawong MD**,
Tachapong Ngarmukos MD***, Wirash Kehasukcharoen MD****,
Watana Boonsom MD*****, Siriporn Kamsa-ard MPH******

** Division of Cardiology, Department of Medicine, Rajavithi Hospital, Bangkok*
*** Division of cardiology, Department of Medicine, Police General Hospital, Bangkok*
**** Ramathibodi Hospital, Mahidol University, Bangkok*
***** Chest Disease Institute, Nonthaburi*
****** Department of Medicine, BMA Medical College and Vajira Hospital, Bangkok*
******* Faculty of Public Health, Khon Kaen University, Khon Kaen*

Background: *The Thai ACS registry is a multi-center, prospective registration that describes the epidemiology, management practices and in-hospital outcomes of patients with acute coronary syndromes.*
Objective: *Study the registry difference in hospital outcomes about cardiac death and length of stay between low molecular weight heparin (LMWH) and un-fractionated heparin (UFH).*
Material and Method: *This is an observational descriptive study. The authors collected data from the database of the Thai ACS registry.*
Results: *There were 233 of 3963 cases (5.9%) with cardiac death in the present study. Cardiac death in the non-ST elevated myocardial infraction (NSTEMI) group was larger than in the UA group (7.6% vs. 2.4%, p-value < 0.001). The heparin group had more cardiac death than the LMWH group (9.3% vs. 5.2%, p-value < 0.001). NSTEMI with heparin treatment had more cardiac deaths than LMWH treatment (11.8% vs. 6.8%, odd ratio 1.8). UA with heparin treatment had more cardiac deaths than LMWH treatment (4.0% vs. 2.0%, odd ratio 2.0). NSTEMI had a longer length of stay than UA (56.9% vs. 44.7%, p-value = 0.001). The heparin group had a longer stay than LMWH (58.8% vs. 51.7%, p-value < 0.001).*
Conclusion: *Low molecular weight heparin had benefit over un-fractionated heparin in reduction of hospital mortality and length of stay in both unstable angina and non-ST elevation myocardial infarction.*

Keywords: *NSTEMI, UA, LMWH,UFH, ACS, Myocardial infraction, Unstable angina, Low molecular weight heparin, Un-fractionated heparin, Heparin, Acute coronary syndromes, Non-ST elevation myocardial infraction*

J Med Assoc Thai 2007; 90 (Suppl 1): 109-14
Full text. e-Journal: *http://www.medassocthai.org/journal*

Acute coronary syndrome (ACS) is an important source of morbidity and mortality. The Thai ACS registry is established as a multi-center, prospective registry that describes the epidemiology, management practices and in-hospital outcomes of the patients with the whole spectrum of ACS in Thailand. Non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA) are some categories in these syndromes. Anticoagulant treatment is recommended in both groups. Low molecular weight heparin (LMWH) has advantages over un-fractionated heparin (UFH) in treatment and prevention of thrombotic disorders including ACS[1-5]. The present study observed different benefits between LMWH and UFH treatment in NSTEMI and UA.

Correspondence to : Angkasuwapala K, Division of Cardiology, Department of Medicine, Rajavithi Hospital, Bangkok 10400, Thailand. Phone: 089-695-9392, Fax: 0-2310-3088, E-mail: ped@post.com

Material and Method

Patients

The Thai ACS registry has recruited 17 centers from all the regions of Thailand, governmental and

private hospitals. The enrollment of the patients is consecutive, prospectively covering those who presented with chest pain or other symptoms that are suggestive of ACS for a period of less than 14 days, and have to have ST segment deviation or T wave changes. The registry classified the patients into three groups, ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA).

In the present study, the authors compared heparin and low molecular weight heparin (LMWH), the cases which received both treatments or no anticoagulant treatment were excluded.

Regimens

This is an observational descriptive study of cases enrolled in Thai ACS registry during August 2002 and October 2005. NSTEMI is determined by chest pain that is compatible with ACS and abnormal ST depression or T wave inversion with elevated biochemical markers of myocardial necrosis. If cardiac markers are normal, the patients are classified as UA. Treatment regimen depended on the physician of each center.

Outcomes

In the present study, the authors observed mortality as a primary end point and length of stay as a secondary end point.

Statistic analysis

The descriptive statistics (mean, median, range) were applied to describe patient characteristics and statistic analysis for primary end point is logistic regression. The death was defined as cardiac death. The length of stay was divided in to two groups by one-week period of hospitalization. The analysis was logistic regression and Chi square test and a p-value was set at less than 0.05.

Results

There were 9,373 patients with Acute coronary syndrome in the Thai ACS registry, 3548 cases were NSTEMI and 1989 cases were UA (Table 1, 2).

The characteristics of both groups are described in Table 3.

The patients in the NSTEMI group were slightly older than patients in the UA group. In NSTEMI, the patients had more severe presenting symptoms than in UA such as shock (129 vs. 12), post cardiac arrest (57 vs. 11) and dyspnea (1187 vs. 355). Diabetes was higher in NSTEMI but in hypertension UA was higher. Smoking and dyslipidemia were not significantly different (Table 4, 5).

The medication during hospitalization is shown in Table 4. There was no difference in both NSTEMI and UA in antiplatelet usage (ASA and ADP inhibitor) except glycoprotein IIb/IIIa inhibitor that was different (NSTEMI = 118 (4.5%) vs. UA = 45 (3.4%)). The usage of glycoprotein IIb/IIIa inhibitor was higher in NSTEMI because it was so expensive and only available in centers with a cardiac catheterization facility.

Beta-blocker and calcium-blocker usage were more in the UA group. Other medications were approximate in both groups.

Table 1. Number of cases received anticoagulants

	Heparin	LMWH	Both	Null	Total
NSTEMI	423	2,230	331	564	3,548
UA	199	1,111	128	551	1,989
Total	622	3,341	459	1,115	5,537

Table 2. Number of cases

	Heparin	LMWH	Total
NSTEMI	423	2,230	2,653
UA	199	1,111	1,310
Total	622	3,341	3,963

Table 3. Characteristics of patients with non-ST elevation myocardial infarction (NSTEMI) and unstable angina (UA)

Characteristics	NSTEMI (n = 2653)	UA (n = 1310)
Male (%)	1,452 (54.7)	679 (51.8)
Age, Mean $\pm$ SD	67.8$\pm$11.5	65.8$\pm$10.9
Age Median (min-max)	68.7 (26-104.8)	66.6 (33-102.2)
Refer	775 (30.4%)	922 (25.3%)
Angina	2,305 (86.9%)	1,269 (96.9%)
Shock	129 (4.9%)	12 (0.9%)
Post cardiac arrest	57 (2.2%)	11 (0.8%)
Dyspnea	1,187 (44.7%)	355 (27.1%)
Diabetes mellitus	1,330 (50.6%)	611 (46.9%)
Hypertension	1,892 (71.8%)	983 (75.3%)
Smoking	653 (25.1%)	307 (23.9%)
Dyslipidemia	1,909 (77%)	994 (79.4%)

The hospital outcomes and complications, the authors observed, were mortality, length of stay, heart failure, arrhythmia, cerebrovascular complications and bleeding. All of them were significantly higher in NSTEMI than that of the UA group ($p < 0.05$) (Table 6).

There was a difference between un-fractionated heparin and low molecular weight heparin in shock, post cardiac arrest, glycoprotein IIb/IIIa inhibitor usage and major bleeding that favored the LMWH group.

There were 233 of 3963 cases (5.9%) with cardiac death in the present study (Table 7). The number of cardiac deaths in the NSTEMI group was larger than the UA group (7.6% vs. 2.4%, p-value < 0.001). The UFH group had more cardiac deaths than the LMWH group (9.3% vs. 5.2%, p-value <0.001). In detail, NSTEMI cases which received UFH treatment had more cardiac deaths than LMWH treatment (11.8% vs. 6.8%). UA cases which received UFH treatment had more cardiac deaths than LMWH treatment (4.0% vs. 2.0%) (Table 8). The odds ratio of treatment between UFH and LMWH in each diagnosis was not statistically significant (p-value = 0.9). Regardless of diagnosis, the adjusted odd ratio of total treatment between heparin and LMWH has shown that UFH had more cardiac deaths 1.7 times than LMWH (p-value = 0.009, 95%CI 1.1-2.5).

The secondary outcome is length of stay (LOS). The authors divided the patients into 2 groups, more than 1 week (>1week) and not more than 1 week (≤ 1 week). NSTEMI had more cases with LOS > 1week than UA (56.9% vs. 44.7%, p-value = 0.001). UFH had more cases with LOS > 1 week than LMWH (58.8% vs. 51.7%, p-value < 0.001).

Table 4. Medication during hospitalization in NSTEMI and UA groups

Medication (%)	NSTEMI n = 2,653 (%)	UA n = 1,310 (%)
ASA	2,562 (96.6%)	1,263 (96.4%)
ADP inhibitor	1,561 (58.8%)	733 (56.0%)
ACEI	1,556 (58.7%)	781 (59.6%)
B-blocker	1,625 (61.3%)	946 (72.2%)
Nitrate	2,366 (89.2%)	1,243 (94.9%)
Glycoprotein IIb/IIIa inhibitor	118 (4.5%)	45 (3.4%)
LMWH	2,230 (84.1%)	1,111 (84.8%)
Angiotensin receptor blocker	240 (9.1%)	155 (11.8%)
Lipid lowering agent	105 (4.0%)	76 (5.8%)
Statin	2,211 (83.3%)	1,123 (85.7%)
Calcium blocker	646 (24.4%)	430 (32.8%)

Table 5. Hospital outcomes and complications of NSTEMI and UA

Characteristics	NSTEMI n = 2,653	UA n = 1,310
Mortality (%)	202 (7.6)	31 (2.4)
Length of stay, Mean ± SD	11.5 ± 11.9	9.0 ± 8.6
Heart failure (%)	1,494 (56.3)	394 (30.1)
Arrhythmia (%)	262 (9.9)	34 (2.6)
CVA (%)	48 (1.8)	9 (0.7)
Major bleeding (%)	136 (5.1)	26 (2.0)

Table 6. Characteristics of patients with LMWH and un-fractionated heparin treatment

Characteristics	LMWH (n = 3341) %	Heparin (n = 622) %
Male	51.3	54.2
Age		
<45	3.7	3.1
45-54	9.0	12.7
55-64	27.2	23.4
65-74	35.0	35.1
> 75	25.1	25.7
Refer	18.8	30.5
Angina	91.3	90.0
Shock	5.5	3.2
Post cardiac arrest	2.6	1.6
Dyspnea	40.7	38.6
Diabetes mellitus	49.2	49.4
Hypertension	73.6	72.8
Smoking	21.7	25.3
Dyslidemia	73.5	78.6
Medication		
ASA	94.9	96.8
ADP inhibitor	59.8	57.5
ACEI	53.7	60.0
B-blocker	65.3	64.8
Nitrate	88.8	91.5
Glycoprotein IIb/IIIa inhibitor	5.5	3.9
Angiotensin receptor blocker	9.2	10.1
Lipid lowering agent	4.2	4.6
Statin	80.1	84.9
Calcium blocker	27.8	27.0
Heart failure	51.8	46.9
Arrhythmia	8.5	7.3
CVA	1.5	1.4
Major bleeding	6.3	3.7

Table 7. Cardiac death outcome

Final diagnosis	Anticoagulant	Total (n)	Cardiac death (n)	Cardiac death (%)
NSTEMI	LMWH	2,230	152	6.8
	Heparin	423	50	11.8
UA	LMWH	1,111	23	2.0
	Heparin	199	8	4.0
Total	NSTEMI	2,653	202	7.6
Final diagnosis	UA	1,310	31	2.4
Total	LMWH	3,341	175	5.2
Anticoagulant	Heparin	622	58	9.3
Total		3,963	233	5.9

Table 8. Relation of cardiac death outcome with diagnosis and treatment

	Total n	Cardiac death n (%)	p-value
NSTEMI	2,653	202 (7.6)	<0.001
UA	1,310	31 (2.4)	
LMWH	3,341	175 (5.2)	<0.001
Heparin	622	58 (9.3)	

Discussion

The anticoagulant heparin was the recommended treatment of both NSTEMI and UA. LMWH had advantages over un-fractionated heparin (UFH) including a predictable pharmacokinetic profile, high bioavailability, long plasma half life and effective level of anticoagulant effect without laboratory monitoring[1]. Gurfinkel et al[2] demonstrated that LMWH was superior to UFH in the treatment patients with UA. FRAXIS[3] and FRIC[4] trial failed to demonstrate an advantage of LMWH over UFH. However, ESSENCE[5] and TIMI11B[6] trial confirmed the benefit of LMWH over UFH in the treatment of UA or NSTEMI. Now the authors can use LMWH as a treatment of UA and NSTEMI instead of UFH treatment.

The present study was the first multicenter report in Thailand about comparison in hospital outcomes of patients with NSTEMI or UA who were treated with LMWH or UFH. Unfortunately, the present report was an observational descriptive study but outcome results were similar to previous reports from others that were randomized trials[1-4].

First, the present report showed that NSTEMI had more severe symptoms than UA such as shock, post cardiac arrest and dyspnea because of more pathology. That means NSTEMI had poorer outcomes and complications such as mortality, heart failure, arrhythmia, CVA and length of stay than UA. With more aggressive treatment with anticoagulant and antiplatelet, NSTEMI had more bleeding complication and prolonged length of stay than the UA group.

Comparison between groups of treatment, LMWH had more shock, post cardiac arrest, heart failure and bleeding than heparin. The UFH group had slightly more smoking and dyslipidemia.

The NSTEMI group had more cardiac deaths than the UA group (7.6% vs. 2.4%, p-value < 0.001). NSTEMI is more severe pathology than UA, so cardiac death in this group was higher than UA. The UFH group had more cardiac deaths than LMWH group (9.3% vs. 5.2%, p-value < 0.001). Even in LMWH group had poor clinical symptoms and more complications as shown in Table 5, LMWH has shown a better outcome.

In the NSTEMI subgroup, the cases who received UFH had a higher cardiac death rate than LMWH. This result was seen in the UA subgroup also. The odds ratios in both NSTEMI and UA were no significantly different. The cardiac death outcome did not depend on diagnosis but depended on type of anticoagulant.

Cases with NSTEMI will prolong the length of stay because of severity. The authors found that NSTEMI had a longer stay than UA (56.9% vs. 44.7%, p-value = 0.001). In the treatment group, the authors found that UFH had a longer stay than LMWH (58.8% vs. 51.7%, p-value < 0.001). This may be from efficacy of LMWH over UFH but a randomized control trial needs to be conducted.

When the authors used UFH the level of PTT (partial thromboplastin time) was monitored and the level was fluctuated by several factors such as the patient's body weight, protein binding rate and level

of thrombinIII. The duration to check PTT was too long (every 6 hours), so the time to get effective level may alter. Therefore, this difficulty may alter the efficacy of the treatment. When the authors used LMWH, blood monitoring was not required and difficulty to adjust the anticoagulant level disappeared. This was an advantage of LMWH over UFH.

At the present time, physicians in many hospitals have switched treatment of UA and NSTEMI from UFH to LMWH because of the advantages in pharmacokinetics, need no blood monitoring, ease to use and some clinical benefit (reduce ischemic event and revascularization from ESSENCE[5]). Some patients have received UFH because of economic status, hospital policy and their physicians.

Limitation of the study

As mentioned above this report was an observational descriptive study so level of confidence was lower than a randomized control trial. However, the present report has shown the same result as a previous study with anticoagulant treatment in NSTEMI or UA. A randomized control trial should be conducted.

Conclusions

The recommended treatment of unstable angina and non ST elevated myocardial infarction is anticoagulant, UFH or LMWH was used. Some previous trials showed LMWH had benefit over UFH in reduction of recurrent ischemia and revascularization. The present report has shown that LMWH may have more benefit than UFH in reduction in hospital mortality and length of stay. However, the present study is an observational descriptive study, a good randomized control trial has a more confident result.

Contributors

The Thai Acute Coronary Syndrome Registry (TACSR) was supported by The Heart Association of Thailand under the Royal Patronage of H.M. the King, Thai Health Promotion Foundation, Clinical Research Collaboration Network (CRCN) and the Health Systems Research Institute (HSRI).

Acknowledgements

The authors wish to thank the patients and their relatives, to the personnel of the ICU and most of all, the research nurses who patiently and diligently assisted in all aspects of patient care and data collection and entry.

References

1. Magee KD, Sevcik W, Moher D, Rowe BH. Low molecular weight heparins versus unfractionated heparin for acute coronary syndromes. Cochrane Database Syst Rev 2003; 1: CD002132.
2. Gurfinkel EP, Manos EJ, Mejail RI, Cerda MA, Duronto EA, Garcia CN, et al. Low molecular weight heparin versus regular heparin or aspirin in the treatment of unstable angina and silent ischemia. J Am Coll Cardiol 1995; 26: 313-8.
3. Comparison of two treatment durations (6 days and 14 days) of a low molecular weight heparin with a 6-day treatment of unfractionated heparin in the initial management of unstable angina or non-Q wave myocardial infarction: FRAX.I.S. (FRAxiparine in Ischaemic Syndrome). Eur Heart J 1999; 20: 1553-62.
4. Klein W, Buchwald A, Hillis SE, Monrad S, Sanz G, Turpie AG, et al. Comparison of low-molecular-weight heparin with unfractionated heparin acutely and with placebo for 6 weeks in the management of unstable coronary artery disease. Fragmin in unstable coronary artery disease study (FRIC). Circulation 1997; 96: 61-8.
5. Cohen M, Demers C, Gurfinkel EP, Turpie AG, Fromell GJ, Goodman S, 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.
6. Antman EM, McCabe CH, Gurfinkel EP, Turpie AG, Bernink PJ, Salein D, 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: 1593-601.

ผลการรักษาในโรงพยาบาลผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดแบบ non-ST elevation และ unstable angina ด้วย low molecular weight heparin เทียบกับ un-fractionated heparin

กิติพร อังคะสุวพลา, เกษม รัตนสุมาวงศ์, ธัชพงศ์ งามอุโฆษ, วิรัตน์ เคหะสุขเจริญ, วัฒนา บุญสม, ศิริพร คำสะอาด

ภูมิหลัง: *ภาวะกล้ามเนื้อหัวใจขาดเลือดเฉียบพลัน (acute coronary syndromes) มีความรุนแรงถึงเสียชีวิต การรักษาภาวะนี้ขึ้นอยู่กับประเภทของภาวะกล้ามเนื้อหัวใจขาดเลือดเฉียบพลัน ในการศึกษานี้จุดประสงค์เพื่อเปรียบเทียบผลการรักษาขณะอยู่ในโรงพยาบาลของกลุ่มผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแบบ ST ไม่ยก และแบบเจ็บอกไม่คงที่ ด้วยการให้ยากันเลือดแข็ง 2 ชนิดคือ low molecular weight heparin และ un-fractionted heparin*

วัสดุและวิธีการ: *เป็นการศึกษาวิเคราะห์เชิงพรรณนา โดยเก็บรวบรวมข้อมูลจากการลงทะเบียนภาวะกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันใน 17 สถาบัน เปรียบเทียบอัตราการตายจากโรคหัวใจและระยะเวลาวันนอนในโรงพยาบาลของผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแบบ ST ไม่ยก และ แบบเจ็บอกไม่คงที่*

ผลการศึกษา: *ผู้ป่วยทั้งหมด 9,373 รายเป็นผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแบบ ST ไม่ยก 3,548 ราย เป็นผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแบบเจ็บอกไม่คงที่ 1,989 ราย ผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแบบ ST ไม่ยกได้รับ un-fractionted heparin 423 ราย, ได้ low molecular weight heparin 2,230 ราย, ผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแบบเจ็บอกไม่คงที่ได้รับ un-fractionted heparin 199 ราย, ได้ low molecular weight heparin 1,111 ราย ผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแบบ ST ไม่ยก มีอัตรา ตายสูงกว่าผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแบบเจ็บอกไม่คงที่ (7.6% vs. 2.4%, p-value < 0.001), ผู้ป่วยที่ได้รับ un-fractionted heparin มีอัตราตายสูงกว่าผู้ป่วยที่ได้รับ low molecular weight heparin (9.3% vs. 5.2%, p-value < 0.001), ผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแบบ ST ไม่ยกที่ได้รับ un-fractionted heparin มีอัตราตายสูงกว่าผู้ป่วยที่ได้รับ low molecular weight heparin (11.8% vs. 6.8%, odds ratio 1.8), ผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแบบเจ็บอกไม่คงที่ได้รับ unfractionted heparin มีอัตราตายสูงกว่าผู้ป่วยที่ได้รับ low molecular weight heparin (4.0% vs. 2.0%, odd ratio 2.0) ผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแบบ ST ไม่ยก มีระยะเวลาวันนอนในโรงพยาบาลนานกว่าผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแบบเจ็บอกไม่คงที่ (56.9% vs. 44.7%, p-value = 0.001), ผู้ป่วยที่ได้รับ un-fractionated heparin มีระยะเวลาวันนอนในโรงพยาบาลนานกว่า ผู้ป่วยที่ได้รับ low molecular weight heparin (58.8% vs. 51.7%, p-value < 0.001)*

สรุป: *Low molecular weight heparin ให้ผลการรักษาในแง่ลดอัตราตายในโรงพยาบาล และระยะเวลาวันนอนสั้นกว่า un-fractionated heparin ในกลุ่มผู้ป่วยกล้ามเนื้อหัวใจขาดเลือดเฉียบพลันแบบ ST ไม่ยกและแบบเจ็บอกไม่คงที่*