UN-FRACTIONED HEPARIN AND LOW MOLECULAR WEIGHT HEPARIN IN PATIENTS WITH ACUTE CORONARY SYNDROME – A META ANALYSIS

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RA:Conducted the study and wrote the article. HK:Helped in review the article. AM:Re-arranged data and corrected article.HZ:Tables and figures. UA: Corrections and did the proof reading.

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ABSTRACT:

BACKGROUND: The choice of antiplatelet therapy and their efficacy and safety concerns are vital points to be discussed. The primary aim of this review was to evaluate the safety and efficacy of the low molecular weight heparin (LMWH) and un-fractionated heparin (UFH) in patients presenting with acute coronary syndrome (ACS) patients.

METHODS: This was a meta analysis / review where clinical trials were searched which compared the un-fractioned heparin and heparin with lower-molecular weight in patients with ACS using PubMed search. All trails of patients with ACS population that were treated with aspirin and fibrinolytic therapy were included whereas all trails which were randomized, comparative of low molecular weight heparin with UFH and who had piloted in ACS patients were also included.

RESULTS: A total of 9 trails were reviewed that constituted almost 48000 individuals. The number of individuals in STEM1 trails was almost 25000. Among the trails, 5 trials were open labeled and 4 trials were double blinded. In STEMI trails most of the patients were given fibrin-specific lytics. Other trails included patients with high risk features and almost 80% had raised cardiac biomarkers.

CONCLUSION: It is concluded from this review that the utmost suitable heparin type for ACS patients is Low molecular weight heparin (LMWH) that holds superior efficacy and lesser complications while comparing with the UFH.

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INTRODUCTION:

A well-established recommended guideline guided therapy is anti-coagulation therapy that is vital to the acute coronary syndromes (ACS) patient management. Conversely the ideal therapy mediator is nevertheless under debate.[1,2] Fewer of the trails, which were not held on large-scale based on the ST-segment elevation myocardial infarction (STEMI) and non-ST-elevation ACS (NSTEACS) patients exhibited improved efficacy with the administration low-molecular weight heparin (LMWH) in comparison to the un-fractionated heparin (UFH).[3-10] The choice of the anticoagulation therapy options and their efficacy and safety concerns are vital points to be discussed.[11-12] The primary aim of this review was to analyze or evaluate the safety and efficacy of the available anticoagulant therapies including LMWH or UFH in STEMI, NSTEMI with ACS patients.

MATERIAL AND METHODS:

This was a review / meta-analysis in which previous clinical trails were searched that compared the un-fractioned heparin and LMWH on patients with STEMI / NSTEMI in patients with ACS by using PubMed search. The analysis of trials was carried out over a period of six months. The analysis was conducted at Allama Iqbal Memorial Teaching Hospital, Sialkot. All trails of ACS patients which were randomized and compared the efficacy of LMWH with the UFH and who had piloted in STEMI, NSTEMI and ACS patients were included in this review. All the published articles were read carefully and compared. The clinical outcomes were evaluated after one month and these comprised of deaths, non-fatal MI and bleeding. If any of the individual suffered from two significant events, it was counted as only one outcome. This also compared the end-points in individual trails. Hospital ethical committee approval was taken.

STATISTICAL ANALYSIS:

The entire information from all the articles were noted and entered in MS Excel sheets that laterally transformed into SPSS version 21 and analyzed using appropriate statistics. The data was descriptively assessed through the descriptive statistics like the mean and standard deviation. All the qualitative variables were presented in the form of frequency distribution and as percentages. Any P value that is less than 0.05 was pondered statistically significant.

RESULTS:

In this study nine trails were included that constituted almost 48000 individuals. The number of individuals in STEMI trails was almost 25000. More over statistics on trails were given in table 1.

Table 1: Summary of the trails and their designs

	Trail	Population	n	Publishing year	Blinding	Outcome/ endpoints
1.	FAST-MI [17]	ACS	2854	2012	Double Blinded	30 days mortality and MI, FAST major bleeding at 30 days
2.	TRANSFER-AMI trial [19]	STEMI	946	2012	Double Blinded	30 days mortality and MI,TIMI major bleeding 30 days
3.	FINESSE trial [35]	STEMI	2452	2010	Double Blinded	30 days mortality and MI,; FAST major bleeding at 30 days
4.	SYNERGY [5]	NSTEMI	9975	2004	Open label	30 days mortality and MI,TIMI major bleeding in-hospital
5.	ASSENT 3 Plus [16]	STEMI	1635	2003	Open label	30 days mortality and MI in-hospital; major bleeding (requiring transfusion or intervention because of hemodynamic compromise or ICH) in-hospital
6.	Baird et al. [13]	STEMI	300	2002	Open label	90 days mortality and MI; major bleeding (clinically significant hemorrhage or ICH) on study drug
7.	ENTIRE-TIMI 23 [15]	STEMI	242	2002	Open label	30 days mortality and MI,TIMI major bleeding 30 days
8.	ACUTE II [18]	NSTEMI	525	2002	Double Blinded	30 days mortality and MI,TIMI major bleeding 30 days
9.	HART II [14]	STEMI	401	2001	Open label	30 days mortality and MI; TIMI major bleeding in-hospital

Among the trails five were open labeled and four were double blinded trials. In STEMI trails most of the patients were given fibrin-specific lytics. Other trails were containing patients with high risk features and almost 80% were having raised cardiac biomarkers. A detailed summary of the baseline features is shown in the table 2.

DISCUSSION:

A backbone of anti-thrombotic therapy at presentation of patients with ACS is heparin which may be LMWH or UFH. The effect of heparin can be monitored by activated clotting time.[20-23] It is observed that attaining the dependable anti coagulation levels is quite difficult because of its greater protein binding capacity, inactivation by platelet derived factors and heparin-induced nephropathy risks produced the UFH application limitations.[24-26] This analysis was conducted to determine the safety and efficacy of the LMWH and UFH among various clinical conditions and it was observed that LMWH had better clinical outcomes than UFH in these trials.

LMWH offers more constant and probable anticoagulation without the need for monitoring of activated clotting time.[24-26] Antithrombotic therapy acts by decreasing the risk of thrombotic occlusion of re-perfused infarct related arteries in STEMI

Table 2: The baseline features of ACS patients

	FINESSE		ACUTE II		SYNERGY		ASSENT-3		FAST-MI	
	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH	LMWH	UFH
Age	63	63	65	64	68	68	62	62	66	69
Female	677	701	108	69	1696	1684	194	184	590	310
Diabetes	385	393	75	45	1424	1502	115	128	424	231
ECG changes	1611	1626	NA	NA	3904	3941	818	821	970	551
Biomarker Positive	738	775	187	122	4198	4190	818	821	1932	922
Catheterization	794	840	187	126	4600	4588	13	19	NA	NA
PCI	243	271	89	66	2323	2364	394	422	NA	NA
CABG	118	137	49	40	899	899	27	36	NA	NA
Mortality	3.3	5.6	9.2	9.0	14.0	14.5	7.5	6.0	15.7	27.5
Major bleeding	2.6	4.4	0.3	1.0	9.1	7.6	4.0	2.8	1.7	3.5
Stroke	0.27	0.24	NA	NA	NA	NA	2.9	1.3	NA	NA
Re-MI	5.3	8.0	9.2	9.0	14.0	14.5	3.5	5.8	NA	NA

patients and thereby, reducing the risk of further formation of thrombus in NSTEACS by deterring thrombin generation and its activity. [27-29]

The appropriateness, safety and efficiency of the type of heparin for MI or ACS patients are not clear until now. We report in our findings that LMWH proved better as compared to UFH, hence preference should be given to the LMWH administration to attain complete perfusion. Similar findings were also reported by other studies.[30]

Our analysis revealed that the prevalence of optimal TIMI flow after myocardial infarction was different significantly among the LMWH and UFH receivers in terms of the administration route and clinical scenario (whichever ACS, non-STEMI or STEMI). Another finding of our study was that the enoxaparin also considerably lessened the occurrence of re-infarction. Earlier published literature had recommended the LMWH as more persuasive anticoagulant in relations to decreasing the re-infarction in comparison to UFH. The findings of our analysis has showed greater LMWH prophylactic effect while comparing with the UFH. It was also reported in other studies that the hemorrhage risk in high risk patients may also increase by increasing the LMWH efficiency for example the older patients with chronic renal impairment. Therefore, the LMWH dosage must be adjusted in high-risk population like patients with chronic kidney disease etc.[31-35]

But in our analysis or review of literature, it may be highlighted that hemorrhagic complications due to administration of LMWH as compared to UFH are not considerably high when administered according to the body weight of the patient. Similarly another published study by Puymirat et al. reported the reduced risk of bleeding and hemorrhagic complications of LMWH when administered according to body weight.[17]

CONCLUSIONS:

It may be concluded from this review that the utmost suitable heparin type for ACS patients is Low molecular weight heparin (LMWH) that holds superior efficacy and lesser complications as compared to UFH. However its dose needs to be adjusted according to body weight and haemorrhagic complications are mostly observed in high risk patients like elderly female and patients with chronic kidney disease.

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