Evaluation of Enoxaparin as Low Molecular Weight Heparin versus Standard Unfractionated Heparin in the Treatment of Acute Ischemic Stroke

Thesis

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by

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تقييم الاينوكسابارين كهيبارين ذو وزن جزيئي صغير بالمقارنة بالهيبارين الغير مجزأ في علاج جلطة المخ

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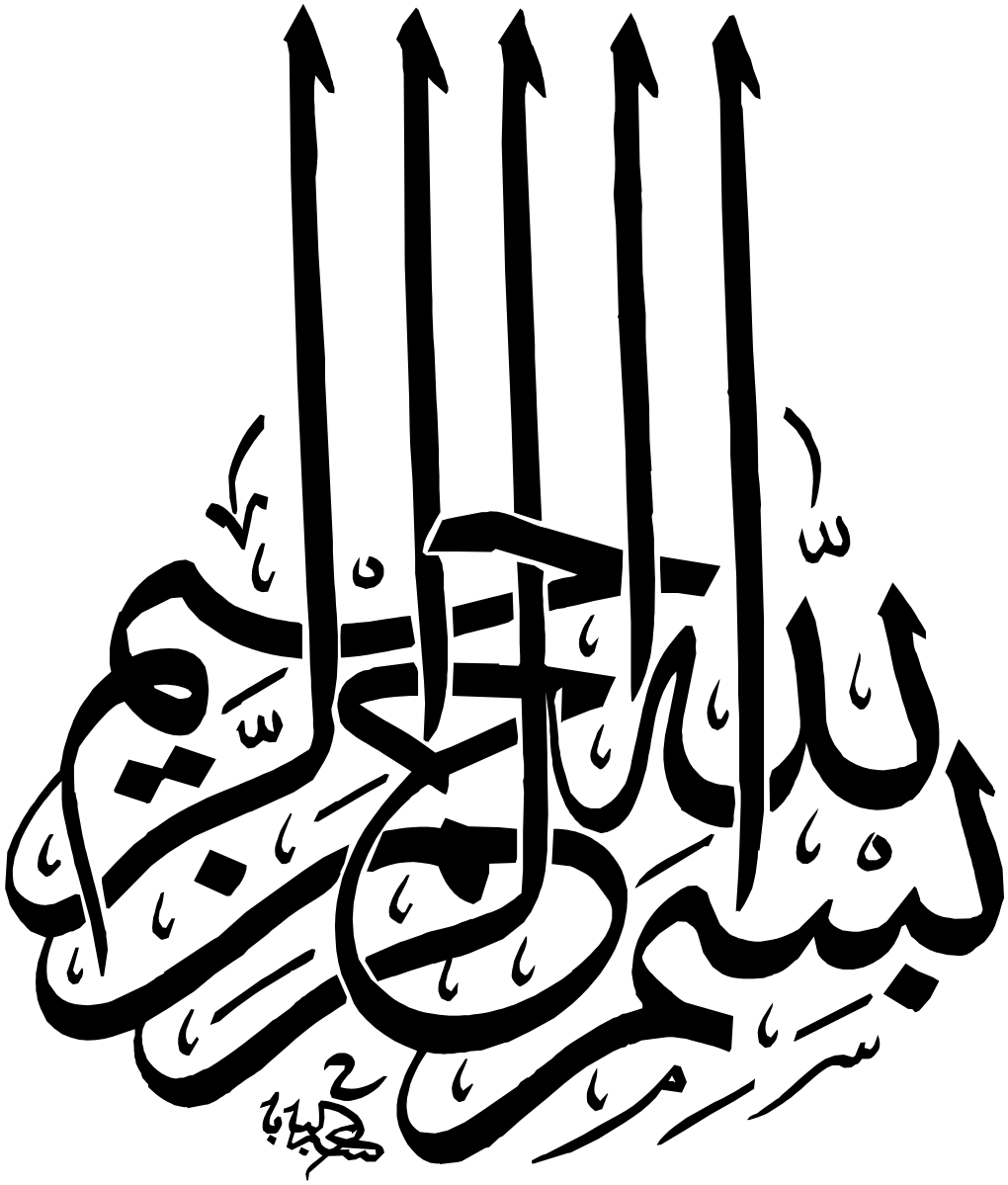
بسم الله الرحمن الرحيم

”قالوا سبحانك لا علم لنا
إلا ما علمتنا إنك أنت
العليم الحكيم“

سورة البقرة
الآية ٣٢

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LIST OF ABBREVIATIONS

ACCP	American College of Chest Physicians.
ACE	Angiotensin Converting Enzyme.
ADP	Adenosine Diphosphate.
AF	Atrial Fibrillation.
ALT	Alanine aminotransferase.
Anti-IIa	Anti-factor IIa.
Anti-Xa	Anti-factor Xa.
aPTT	Activated Partial Thromboplastin Time.
ARBs	Angiotensin II Receptor Blockers.
AST	Aspartate aminotransferase
AT	Antithrombin.
CAPRIE	Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events.
CAST	Chinese Acute Stroke Trial.
CHRISMA	Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance.
CT	Computed Tomography.
CVA	Cerebrovascular Accident.
Da	Dalton.
DVT	Deep Venous Thrombosis.
E	Electronic potential.
ECG	Electrocardiography.
EDTA	Ethylene Diamine Tetracetic Acid .
ELISA	Enzyme Linked Immuonosorbant Assay.
ESPS–٢	European Stroke Prevention Study–٢.
FISS	Fraxiparin International Stroke Study.
FRISC-II	Fragmin and Fast Revascularization During Instability in Coronary Artery Disease.
GHAT	The German Hip Arthroplasty Trial.
GP١b	Glycoprotein Ib.
H٢O٢	Hydrogen Peroxide.
HAEST	Heparin in Acute Embolic Stroke Trial..
HIT	Heparin-Induced Thrombocytopenia
HMG–CoA	Hydroxyl Methyl Glutaryl Co-enzyme A.

HRP	Horseradish-Peroxidase.
HTN	Hypertension.
INR	International Normalized Ratio.
ISE	Ion Selective Electrode.
IST	International Stroke Trial.
IV	Intravenous.
JNC٧	Joint National Committee ٧.
KCCT	Kaolin Cephalin Clotting Time.
LDL	Low Density Lipoprotein.
LIFE	Losartan Intervention for Endpoint Reduction in the Hypertension Study.
LMWHs	Low Molecular Weight Heparins.
MI	Myocardial Infarction.
MRI	Magnetic Resonance Imaging.
MW	Molecular Weight.
NIHSS	National Institutes of Health Stroke Scale.
NINDS	National Institute of Neurological Disorders and Stroke.
NSTEMI	Non-ST Elevation Myocardial Infarction.
O.D.	Optical Density.
PBS	Phosphate Buffered Saline.
PE	Pulmonary Embolism.
PF٤	Platelet Factor ٤.
RCTs	Randomized Controlled Trials.
rt–PA	Recombinant Tissue Plasminogen Activator.
S.E.M.	Standard Error of Mean.
SD	Standard Deviation.
STEMI	ST Elevation Myocardial Infarction.
SYNERGY	The Superior Yield of the New strategy of Enoxaparin, Revascularization and Glycoprotein IIb/IIIa inhibitors.
THRIFT	Thromboembolic Risk Factors.
TIAs	Transient Ischemic Attacks.
TMB	Tetramethylbenzidine.
TOAST	The trial of (ORG ١٠١٧٢) in Acute Stroke Treatment.
TOPAS	Therapy of Patients with Acute Stroke.
t–PA	Tissue Plasminogen Activator.
TRACE	Treatment with Anticoagulants in Cerebral Events.

TXA_2	Thromboxane A_2.
UFH	Unfractionated Heparin.
Vs	Versus.
VTE	Venous Thromboembolism.
vWF	von Willebrand Factor.
vWF: Antigen	von Willebrand Factor Antigen.
∆vWF	Change in von Willebrand Factor Level.

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Abstract

The significance of low-molecular-weight heparins (LMWHs) in the management of acute stroke remains controversial. Previous randomized controlled trials (RCTs) have demonstrated superiority of LMWHs over unfractionated heparin (UFH), in the setting of acute ischemic stroke, as to the likelihood of occurrence of deep vein thrombosis, but there are too few data to provide reliable information on their effects on other important outcomes, including death and intracranial hemorrhage. Previous randomized trials have enrolled patients within ١٤ days of the onset of an acute ischemic stroke. However, few if any data exist on the neurological outcomes in patients with stroke in evolution presenting within ٨ hours of symptom onset. The current study aims at assessing whether the early administration (in patients with stroke in evolution) of potentially more intensive antithrombotic therapy with Enoxaparin might reduce the risk of early recurrent ischemic strokes, death, and disability compared with UFH.

One hundred patients with acute ischemic stroke in evolution were enrolled (with symptoms of stroke within eight hours of randomization). Patients were randomized to receive UFH [٥٠٠٠ IU by IV bolus, followed by a continuous IV infusion] or Enoxaparin [٠,٥ mg per kilogram body weight subcutaneously every ١٢ hours]. All patients received ١٥٠ mg of oral aspirin daily. Therapy with UFH and Enoxaparin was continued for ١٠ days. The plasma concentrations of von Willebrand factor antigen were measured on admission and after ٤٨ hours. National Institutes of Health Stroke Scale (NIHSS) and Computed Tomography

(CT) imaging of the brain were performed in all patients at the time of admission and at regular intervals.

The mean baseline NIHSS was ٩,١٤ ± ٤,٤ among patients randomized to UFH, *vs.* ٩.٣٨ ± ٣,٨ among patients randomized to Enoxaparin (*p*> ٠,٠٥). At discharge, the mean NIHSS showed a statistically significant difference in favor of the Enoxaparin group (٧.٥± ٤,١ for the UFH arm *versus* ٤,٩٦ ± ٣,٨ for the Enoxaparin arm; *p*<٠,٠٥). The mean NIHSS after therapy in patients who demonstrated neurological improvement was ٥,٦ ± ٣,٢ in the UFH arm, as opposed to ٣,٦ ± ٢,٧ in the Enoxaparin arm (*p*<٠,٠١). A deterioration in the clinical neurological condition (progressive stroke symptoms) inspite of treatment with anticoagulant therapy was seen in ٢٠ % (n=١٠) of the patients in the UFH treatment arm and ٤٪ (n=٢) of the patients in the Enoxaparin treatment arm (*p*<٠,٠١). No statistically significant differences were observed for pulmonary embolism, deep venous thrombosis, recurrent strokes, or death. The mean baseline percentage value for von Willebrand factor antigen in the UFH group was ١١٩.١ ± ٣,٩, as opposed to ١٢٤.٤ ± ٣,٥٤ in the Enoxaparin group (*p*>٠.٠٥). The mean percentage value for von Willebrand factor antigen after ٤٨ hours of initiation of the study drug was ٢٧٢,٩ ± ٠,٩٩ in the UFH group, as opposed to ١٨٤.٨ ± ٠,٧ in the Enoxaparin group (*p*<٠,٠١).

Conclusion: Enoxaparin was superior to UFH in reducing adverse neurological outcome after acute ischemic stroke in evolution. This superiority was not associated with reductions in mortality, and could be explained by blunting of von Willebrand factor release by Enoxaparin.

Key words: Ischemic stroke, stroke in evolution, heparin, UFH, LMWHs, Enoxaparin, von Willebrand factor.