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Nadroparine calcium or enoxaparine in acute coronary syndrome patients suffering renal insufficiency: The nadroparin versus enoxaparin (NaVe) study design

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Abstract

In the general population, mild renal impairment is associated with increases risk for coronary artery disease and stroke, suggesting that cardiovascular disease begins to develop early in the natural history of renal dysfunction. Patients with renal failure are known to be at increased risk of death following acute myocardial infarction or congestive heart failure.

In such sense, anticoagulation in addition to antiplatelet inhibitor drugs became the standard of care, particularly, among high risk unstable angina patients associated with a scarce side effects.

The Nadroparin calcium Versus Enoxaparin (NaVe) Study will evaluate in a head to head basis the anti Xa activity reached by nadroparine or enoxaparine, both low molecular weight heparins, in patients at high risk for ischemic episodes, and renal insufficiency to eventually be undergone to angiographic diagnosis studies, and in consequence proposing the best anticoagulant strategies for these patients before being invasively treated.

Patients will be randomly assigned to one of the two groups: Group 1: thirty patients will be given with subcutaneous enoxaparine injections into the abdominal wall in a dose of 0,85 mg/kg every 12 hours for a maximum of 48 hours. A saline infusion dose will be given in between. Total number of injections: 6. Group 2:Thirty patients will be receiving subcutaneous injections into the abdominal wall in a doses of 30% less in relationship with his / her body weight every 8 hours for a maximum of 48 hours.

In order to achieve the goal of the study, the antiXa activity will be measure using venous blood samples taken as follows: Group 1:*Within 3rd and 4 hour of the second doses of HBPM for enoxaparine.*Within 11 th and 12 th hour next to fourth doses of enoxaparine. Group 2: *Within 3rd and 4 th hour next to 3rd doses of HBPM for the nadroparine.*Within 7th and 8th hour next to 4th doses HBPM for the nadroparine.

The primary end point is to analyze during the in-hospital stay phase the stability of the anti Xa activity within the therapeutic ranges which will be estimated between 0.5 to 1.0 IU during the first 48 hours.

Background

In the general population, mild renal impairment is associated with increases risk for coronary artery disease and stroke, suggesting that cardiovascular disease begins to develop early in the natural history of renal dysfunction[1]. Patients with renal failure are known to be at increased risk of death following acute myocardial infarction or congestive heart failure[2].

Furthermore, their risk of Cardiovascular disease was higher if the serum creatinine concentration was > 1.5 mg/dl, a result which is supported by findings in a recent study[3].

The prevalence of mild renal dysfunction, defined as CC <60 ml/min, in heart failure trials was 25,9 % in SOLV Prevention Trial, 55.5% in Left Ventricular Systolic Dysfunction (SOLVD) treatment trial [4] and they found a parallel relation between total mortality, all cause death and arrhythmic death with renal dysfunction.

The benefits of administering low molecular weight heparins as a short-term treatment during the acute phases of coronary disease are widely acknowledged, worldwide accepted and embodied to most of protocols [5-7].

The low molecular weight heparins produce a more predictable anticoagulant response than unfractionated heparin, reflecting a better bioavailability, longer half-life, and dose independent clearance than the regular heparin.

The plasma half-life of low molecular weight heparins is two to four times as long as that of unfractionated heparin, ranging from two to four hours after intravenous injection and from three to six hours after subcutaneous injection the inhibitory activity of low molecular weight heparins against thrombin, reflecting the more rapid clearance of longer heparin chains, essentially among apparently healthy volunteers and patients without renal dysfunction.

In addition to this, the low molecular weight heparins (LMWH) reduced the combined incidence of myocardial infarction and death compared with another therapies such as unfractionated heparin associated with less sensitive administration, particularly enoxaparin [8].

In such sense, anticoagulation in addition to antiplatelet inhibitor drugs became the standard of care, particularly, among high risk unstable angina patients associated with a scarce side effects.

Both, fractionated and un fractionated heparins have a partial elimination through renal function. In the case of enoxaparine, the drug has shown a longer half-life in blood among patients with renal impairment than those treated with conventional heparin. According to this, Collet et al [9]have found, in a sole previous and prospective paper that a therapeutic range between 0.5 and 1 IU/ml of activated anti factor X a could be reached with a doses of 0.85 mg/kg in patients with renal insufficiency whose creatinine clearence is estimated between >30 and < 60 ml/min.

In such sense, a non enough body of evidences is supporting how to attempted to proceed with the treatment of these patients that daily are given complete anticoagulants having in consideration the renal function in order to avoid the accumulation of the doses with unpredictable hemorrhagic consequences.

Even more, various LMWHs were investigated and there were some inconsistencies of efficacy findings between those trials in which they were tested [10].

Methods/Design

Study objetive

The The Nadroparin calcium Versus Enoxaparin (NaVe) Study will evaluate in a head to head basis the anti Xa activity reached by nadroparine or enoxaparine, both low molecular weight heparins, in patients at high risk for ischemic episodes, and renal insufficiency to eventually be undergone to angiographic diagnosis studies, and in consequence proposing the best anticoagulant strategies for these patients before being invasively treated.

The hypothesis is to evaluate the use low reduced doses more frequently and / or the time interval between one intake, and the other giving place to an homogeneous movement of the anti-Xa activity within a therapeutic range.

Protocol

This study will be conducted following the Helsinki declaration the good clinical practices established by the International conference of harmonization, and any other national or international in force legislation. Patients must sign an Informed consent form. The Independent Ethic Committee of our Institute, approved the protocol.

This study is prospective, controlled, randomly assigned, in a double blind fashion (patient-hematologic team).

Patients suffering from an acute coronary syndrome as type IIIb of Braunwald's Classification will be eligible for the trial.

Inclusion criteria

1) unstable angina clase IIIb Braundwald's classification: chest pain that occurs in repose between 48 hours previously no lasting more than 20 minutes to admission plus new ST-T changes in at least two contiguous leads (ST elevation or depression ≥ 0.1 mV and/or T wave inversion).

2) Infarction without ST segment elevation.

3) Women's must be 6-month post menopause or tuba uterine ligature.

Exclusion

1) Patients with more than 100 kilograms.

2) Patients that had been treated with anticoagulants during the last 7 days prior to be admitted or currently under coagulation.

3) Women that could get pregnant, pregnant or nursing period because the side effects or these drugs are still unknown.

4) Patients with background of major haemorrhage, active bleeding within the last 2 weeks or wit blood discrasia.

5) patients with less than 75×10^3 platelets per mm3.

6) patients with thrombocytopenia induced by heparin.

7) Patients with active peptic ulcer.

8) Patients with neurological surgery or neurological impairment such as antecedents of intracraneal hemorrhage, subdural hematoma, epidural hematoma, any prior Stroke from any origin.

9) Patients with systolic hypertension at enrolment major of 180/100 MmHg.

10) Patients with renal insufficiency undergoing dialysis.

11) Patients minor than 21 years of age.

12) Those patients that do not want to sign the consent informed.

At admission, an electrocardiogram and blood sample will be obtained to measure platelet, creatinine, hemoglobin, enzymatic dosages, creatinine clearance.

From those, a total of 60 patients will be enrolled if renal function disorder is determined by creatinine clearance (no less than 30 ml/min determined by creatinine clearence (no minor than 30 ml/minutes or major than 60 ml minutes) using the Cockroft-Gault formula [11]

Once that informed consent was obtained, the anti thrombotic therapeutic is initiated.

All the patients will be randomly allocated to the following strategies: nadroparine or enoxaparine, plus anti ischemic medical therapy according with the international recommendations [12,13].

Patients will be randomly assigned to one of the two groups:

Group 1: thirty patients will be given with subcutaneous enoxaparine injections into the abdominal wall in a dose of 0,85 mg/kg every 12 hours for a maximum of 48 hours. A saline infusion dose will be given in between. Total number of injections: 6

Group 2:Thirty patients will be receiving subcutaneous injections into the abdominal wall in a doses of 30% less in relationship with his / her body weight every 8 hours for a maximum of 48 hours. Total number of injections: 6

Angiographic study: accomplished 48 hours of administration of low molecular weight heparins (routine therapeutic phase).

Those patients submitted to an angiographic study, will be previously treated with N acetylcistein as standard procedure in order to protect renal function before medium contrast side effects. Catheterizations with be performed 12 hours after the last doses of the LMWHs was given.

Since the range of antiXa will be measured within the research team the haematologist and biochemist will be not given the patient information in order to protect the double blind strategy. The team at the Coronary Care Unit (CCU) will remain unblended for the prescriptions of drugs. The haematological team will remain blinded for the prescription of the drugs at the CCU.

Data registration

Every patient will have complete personal records and individual registration form with all data both clinical and diagnostic needed in this study.

Laboratory

In order to achieve the goal of the study, the antiXa activity will be measure using venous blood samples taken as follows:

Table 1: Drug administration and sample collections.

	Group 1 Enoxaparin	Group 2 Nadroparine Calcium
Subcutaneous injection at:		
Day 1	Hour 8 – 16 – 20	Hour 8 – 16 – 20
Day 3	Hour 8 – 16 – 20	Hour 8 – 16 – 20
Blood samples taken at:		
Day 1	Hour 11 PM	Hour 11 PM
Day 3	Hour 6 AM	Hour 11 PM

Group 1

*Within 3rd and 4hour of the second doses of HBPM for enoxaparine.

*Within 11th and 12th hour next to fourth doses of enoxaparine. Table 1.

Group 2

*Within 3rd and 4th hour next to 3rd doses of HBPM for the nadroparine.

*Within 7th and 8th hour next to 4th doses HBPM for the nadroparine. Table 1.

Once the venous blood samples are obtained will be placed into tubes with sodium citrate using for its analysis a chromogenic essay.

To guarantee the double mind procedure the ampoule will be stored, provided and given by the coronary unit team in the character of no double blind team.

The lower level of sensing detection will be determinate.

Pharmacokinetics analysis in each patient will be obtained by individual characteristics taking into consideration that the maximum concentration should be detected near the second shot of heparin that verify the sample to be obtained within 3 to 4 hours after the shot.

Since all the samples will be obtained in the same period of time the inter individual variability will be equal to zero.

In addition, given that the traditional formula of the creatinine clearence could not correctly shows the glomerula filtration, in the final analyses will be included the age and the body mass.

Primary end point

The primary end point is to analyze during the in-hospital stay phase the stability of the anti Xa activity within the therapeutic ranges which will be estimated between 0.5 to 1.0 IU during the first 48 hours.

Secondary end points

Major bleeding complications

They are defined as: 1) intracraneal hemorrhage, with or without neurological secuelae. 2) The need of any transfusion due to the descending of hemoglobin more than > 3 mg.

Bleeding complications treatment

First, discontinuation of the low molecular weight heparin under study.

Secondly, protamine and hemoderivates will be indicated in the presence of descending hemoglobin, major bleeding and in cases of life threatening risk according with the international rules [12].

Study Termination

The study will terminated in those cases in which the patient wishes to withdraw the inform consent or in the case that the research team detects any bleeding complication that makes to presume an excess of the activity of anti-Xa over 1 IU/ml.

Discussion

Pharmacokinetic study is essential for dose recommendations but data in high-risk patients are often scant because of technical and ethical problems. The population approach provides the opportunity to deal with sparse data obtained in patients treated during usual care. In our study, we will include patients with renal failure as compared to major trials. In order to identify the pathophysiologic factors that cause changes in the dose-concentration relationship, non-restrictive inclusion criteria will be applied.

In patients treated with enoxaparin for unstable angina, a slightly higher plasma half-life about 5 hours was however is also found. A similar increase has been reported in patients with other extremes conditions (obese patients or

pre-dialyzed patients). The half-life increase is thus related to a reduction of the elimination rate (i.e., clearance) of enoxaparin. As enoxaparin shows a predominant renal elimination, this result could be linked to age-related decline in renal function. However, in the final model, age (but not creatinine clearance nor serum creatinine level) could be the only covariate related to low molecular weight heparin clearance. Due to the Cockroft and Gault mathematical formula for old patients and the inclusion of younger patients with renal failure, mean creatinine clearance could be lower in our study. Furthermore, it has been suggested by several previous studies that the Cockroft and Gault formula is not reliable for the correct assessment of the glomerular filtration rate, particularly in the elderly. Thus, the reduction of apparent clearance with age may be related to a reduction of renal filtration which is not accurately estimated by the surrogate marker creatinine clearance but only by the age of patients.

In prior studies, fixed (1 mg/kg twice a day) weight-adjusted dosing of enoxaparin is appropriate for most patients, our findings establish that a dosage reduction of 25% to 33% of the usual recommended dose would be needed in elderly patients and patients with renal failure in order to achieve the recommended therapeutic range of 0.5 to 1.0 IU/mL for anti-Xa activity. Even if the optimal level of anti-Xa neutralization has not been clearly stated, most trials have shown benefit of enoxaparin within this range and evidence suggests an increased risk of bleeding for maximal levels above 1 IU/ml[13].

In addition, clinical observations also suggest a need for dosage reduction in particular population. Collet et al 9 have thus found that the therapeutic range of 0, 5–1 IU/ml for anti-Xa activity will be reached with only 0, 64 mg/kg of enoxaparine in patients with severe renal failure (creatinine clearance < 30 ml/min) and 0, 85 mg/kg for those with a creatinine clearance between 30 and 60 ml/min.

Questions to be answered

Mildly elevated serum creatinine concentration has been proposed to be a marker of increased risk for mortality due to cardiovascular disease[14]. It has also been shown to be associated with the extent of coronary atherosclerosis independently of conventional risk factors; in this case, it is thought to indicate generalized vascular disease denoting early nephrovasculopathy in correlation with established atherosclerotic risk factors. In other studies, high serum creatinine concentration has been associated with increased mortality in hypertensive patients, elderly patients, and in those with myocardial infarction or stroke.

An increase on mayor bleeding was found as renal dysfunction worsened. Patients with renal impairment have decreased platelet function and elevated procoagulant activity, as reported by the National Kidney Foundation Task Force, but it is reasonable and strongly recommended to prescribe aspirin (75 to 325 mg/day) to reduce the risk for subsequent events in patients with coronary artery disease[15]. Studies are lacking regarding revascularization management in renal dysfunction patients, mainly because they have been excluded or were nor studied as a subgroup in the clinical trials. The criteria on which renal patients should undergo invasive diagnostic and therapeutics procedures have not been outlined yet. Paradoxically, overall utilization of antiplatelet agents like aspirin or clopidrogrel, beta blockers and statins were less frequently prescribed in renal disfunction patients, since it is well documented that the National Kidney Foundation Task Force strongly recommend them to disminish cardiovascular events at follow up[15].

Since the heparins are metabolized by the kidney, facing renal dysfunction these type of heparins could not be correctly eliminated inducing an inadequate accumulation of them in blood.

Unfortunately, the optimal dose in patients with renal dysfunction and acute coronary syndrome, has not yet been established.

Thus, we propose in the present study to test the hypothesis that a minimal useful dose may be achieved in the frame of renal dysfunction avoiding bleeding complications and or loosing efficacy in an acute coronary event.

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