Nadroparin use in critically ill patients on the ICU ward: safe and steady form of coagulation?

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We want to investigate if in critically ill patients use of LMWH is associated with stable plasma levels of anti-Xa activity. Furthermore, we want to investigate if GFR and circulation influence anti-Xa activity and which complications can occur....

Ethical review	-
Status	Recruiting
Health condition type	Coagulopathies and bleeding diatheses (excl thrombocytopenic)
Study type	Observational invasive

Summary

ID

NL-OMON33800

Source
ToetsingOnline

Brief title
Nadroparin safe and steady form of anticoagulation?

Condition

- Coagulopathies and bleeding diatheses (excl thrombocytopenic)
- Nephropathies

Synonym
bleeding diathesis, hemostasis

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Centrum Alkmaar
Source(s) of monetary or material Support: Foreest Instituut Alkmaar

Intervention

Keyword: anti-Xa activity, clearence, intensive care unit, nadroparin

Outcome measures

Primary outcome

Anti-Xa activity

Secondary outcome

Bleeding diathesis

Thrombosis

Study description

Background summary

Critically ill patients on intensive care ward (ICU) have a higher chance to develop venous thromboembolism (VTE). Without prophylaxis the incidence of VTE varies between 22% and 80% in different patient categories. Use of low-molecular-weight heparin (LMWH) decreases risk to develop VTE with 50%. Advantage of LMHW is that it is easy to use. Studies in non critically ill patients have demonstrated a stable dose response curve. Therefore, daily monitoring of anti-Xa activity is not necessary. However, there are a few studies demonstrating a higher bleeding incidence in dialysis patients who were given LMHW. Reason for bleeding is a higher anti-Xa activity due to accumulation of LMHW in patients with renal insufficiency. Therefore, authors advise to be alert and even perhaps to monitor anti-Xa activity.
In intensive care patients regulations for prophylaxis of VTE are not totally clear. There is a necessity for VTE prophylaxis although the risk factors for bleeding are not concrete yet. Therefore, it is advised to choose prophylaxis individually for each patient taking safety and activity of prophylaxis into account. However, in ICU patients choice and dosage of drugs for VTE prophylaxis is difficult because of variable pharmacokinetics. Especially in the acute phase circulation is compromised and kidney function fluctuates every hour. For example, Dörffler-Melly et al have demonstrated that vasoactive drugs, which are used to optimise circulation, influence anti-Xa activity. At the same time critically ill patients have a significantly lower anti-Xa activity after one dose enoxaparin subcutaneously in comparison to non critically ill patients. It is not clear if a change in glomerular filtration rate (GFR) in critically ill patients affects the anti-Xa activity. However, it

is clear that intensive care patients have a higher risk of VTE and bleeding diathesis and accumulation of LMWH is not desirable.

Study objective

We want to investigate if in critically ill patients use of LMWH is associated with stable plasma levels of anti-Xa activity. Furthermore, we want to investigate if GFR and circulation influence anti-Xa activity and which complications can occur. Hopefully, at the end of the study we will be able to advise about the need to monitor anti-Xa activity in critically ill patients which use LMWH.

Study design

Study design: It is a prospective observational cohort study. All patients who are admitted to ICU and fulfil inclusion and exclusion criteria will be enrolled.
Patients stay enrolled in the study as long as they are on the ICU ward. Renal insufficiency will be defined as glomerular filtration rate of <= 30 mL/min.

Inclusion
criteria:

1. Patient with minimum age of 18 years and expected admission time on the ICU of minimum of 48 hours
2. Patient with prophylactic or therapeutic dosage of nadroparin daily

Exclusion
criteria:

1. thrombocytopenia (<
30)

2. heparin induced trombocytopenia and trombosis
(HITT)
3. bleeding diathesis in which the use of nadroparin is
contraindicated
4. use of unfractioned heparin exept during
dialysis
5. pregnancy

Data
collection:

Following data of patients will be noted on inclusion:
1. patient characteristics (age, gender, length,

weight)
2. medical
history

3. indication for
admittance

4. APACHE
score

5. medication use at
admittance

6. physical examination and vital parameters (hart frequency, blood pressure, temperature)

7. laboratory tests: Hb/Ht, T, APTT, PTT, fibrinogen, d-dimer, anti-Xa activity, creatinine, urea, GFR, bilirubin, albumin, IG#, Neut X, IPF, FEP/ZPP
Following data will be noted daily after inclusion:
1. medication use especially
inotropy

2. physical examination: delta weight, bleeding diathesis (nosebleed, blood loss from central lines, haematomas, haematuria, gastrointestinal (GI) bleeding, blood loss with tracheobronchial aspiration). Recurrence of VTE (deep vein thrombosis, lung embolism, clotted central
lines)
3. laboratory tests: Hb/Ht, T,
APTT, PTT, fibrinogen, d-dimer, anti-Xa activity, creatinine, urea, GFR, bilirubin, albumin, IG#, Neut X, IPF,
FEP/ZPP

4. amount of blood- and thrombocytic transfusions and
FFP*s
5. dialysis (CVVH, IHD and with or without use of fragmin or
heparin)
6. SOFA score

Medication:

Nadroparin is a low molecular heparin with a weak anti-IIa activity and a stronger anti-Xa activity. Indications for use are prophylactic to prevent VTE or therapeutic for lung embolism, rhythm disorders or angina pectoris.

Standard dosage of nadroparin:
1. Prophylactic: < 80 kg: 1 dd 2850 IE sc

>= 80 kg: 1 dd 3800 IE sc
2. Therapeutic: <= 50 kg: 2 dd 3800 IE sc
50-80 kg: 2 dd 5700 IE sc
>= 80 kg: 2 dd 7600 IE sc

Standard values of anti-Xa activity:
Peak anti-Xa activity on Cmax (Tmax = 4 uur) between 0.2 - 0.4 IU/ml is considered effective and safe. Therefore, definition of a stable form of anticoagulation is peak anti-Xa activity between 0,2 - 0.4 IU/ml.
Therapeutic use (2 times daily) Cmin (Tmin = 12 uur) of <= 0.1 IU/ml is considered non therapeutic and >= 0.4 IU/ml accumulation.
Area under the curve (AUC) is 4 - 6 IU/h/ml in prophylactic use and 7-9 IU/h/ml in therapeutic use.

Anti-Xa activity:
Anti-Xa activity will be assessed daily. In prophylactic use nadroparin will be given at 18.00. On day one and three 2,4,6,8,12,16,24 hours after the nadroparin dose anti-Xa activity will be measured and also just before the first nadroparin dose on day one. On all other days it will be measured 4,12,24 hours after dosing. In therapeutic use nadroparin will be given 2 times daily at 6.00 and 18.00 hours.On day one and day three 2,4,6,8,12,16,24 hours after the evening dose anti-Xa activity will be measured and just before the first dose. On the other days samples will be taken after 4,12,24 hours after the evening dose.

Method of
assessment:

Samples will be frozen and anti-Xa activity will be determined once a week.

Statistical
analysis:

It will be a prospective cohort study with 30 patients with a diminished GFR and 90 patients with normal GFR. On average there will be 5 blood samples taken per patient. After first 60 patients an interim analysis will be undertaken to search for statistical significance.

Further statistical analysis:
Nominal variables concerning subgroups will be analysed with Chi-square test. Ordinal variables concerning subgroups will be analysed with Mann-Whitney-test or Kruskall-Wallis-test. Interval/ ratio variables concerning subgroups will be analysed with T-test or ANOVA. Comparison of variables (depending on scale level) will be done with Chi-square test, paired T-test, Wilcoxon test, Friedman test and Pearson and Spearman correlation coefficient. Logistic and/ or linear regression will be used as multivariate technique to relate outcome variables and background variables. Nominal and ordinal variables will be

described with use of frequency tables, modus and median. Interval/ ratio variables will be described in terms of average, standard deviation and confidence intervals. If necessary Odd*s ratio and relative risk will be used.

Study burden and risks

Anti-Xa activity will be assessed daily. In prophylactic use nadroparin will be given at 18.00. On day one and three 2,4,6,8,12,16,24 hours after the nadroparin dose anti-Xa activity will be measured and also just before the first nadroparin dose on day one. On all other days it will be measured 4,12,24 hours after dosing. In therapeutic use nadroparin will be given 2 times daily at 6.00 and 18.00 hours. On day one and day three 2,4,6,8,12,16,24 hours after the evening dose anti-Xa activity will be measured and just before the first dose. On the other days samples will be taken after 4,12,24 hours after the evening dose. In total 67 ml of blood out of the arterial line will be drawn seperated over 24 times.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Patient with minimum age of 18 years and expected admission time on the ICU of minimum of 48 hours
2. Patient with prophylactic or therapeutic dosage of nadroparin daily

Exclusion criteria

1. thrombocytopenia (<30)
2. heparin induced trombocytopenia and trombosis HITT
3. bleeding diathesis in which the use of nadroparin is contraindicated
4. use of unfractioned heparin exept during dialysis
5. pregnancy

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-07-2009
Enrollment:	120
Type:	Actual

Ethics review

Not available

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL25308.094.08