



Clinical trial results:

The use of Low Molecular Weight Heparin during Hemodiafiltration, A Cross Over Randomised Trial

Summary

EudraCT number	2008-005224-91
Trial protocol	BE
Global end of trial date	15 May 2018

Results information

Result version number	v1 (current)
This version publication date	07 October 2020
First version publication date	07 October 2020

Trial information

Trial identification

Sponsor protocol code	AGO/2008/010
-----------------------	--------------

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT00756145
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Ghent University Hospital
Sponsor organisation address	C. Heymanslaan 10, Ghent, Belgium, 9000
Public contact	HIRUZ CTU, Ghent University Hospital, 32 93320500, HIRUZ.ctu@uzgent.be
Scientific contact	HIRUZ CTU, Ghent University Hospital, 32 93320500, HIRUZ.ctu@uzgent.be

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	02 February 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	15 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The aim of this study was to determine the optimal mode (place and time) of tinzaparin administration during postdilution hemodiafiltration.

Protection of trial subjects:

Ethics review and approval, informed consent, supportive care and routine monitoring.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	18 September 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Belgium: 14
Worldwide total number of subjects	14
EEA total number of subjects	14

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	3
From 65 to 84 years	10
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

22 patients were screened in the period from 18-Sep-2008 till 02-Mar-2010. 14 patients were included and randomized. 1 patient was excluded from the study due to infection. End of trial notification was dated 02-Mar-2010 (last patient last visit) and submitted to EC and CA 24-Jul-2018.

Pre-assignment

Screening details:

Inclusion criteria

- age > 18 years
- Chronic kidney disease (CKD) stadium 5 requiring chronic hemodiafiltration of hemodialysis
- haematocrit > 30%
- signed informed consent

Period 1

Period 1 title	overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	IN0-OUT0-IN5

Arm description:

Administration of tinzaparin in this arm

the first week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0),

the second week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

the third week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

Arm type	Experimental
Investigational medicinal product name	tinzaparin
Investigational medicinal product code	
Other name	Innohep, Leo Pharmaceutical Corp, Ballerup, Denmark
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Haemodialysis

Dosage and administration details:

Tinzaparin with median and interquartile range of 4500 (3500–4500) IU was routinely used. Before the study, tinzaparin was injected in the afferent blood line shortly after the start of the session. The doses had been defined prior to the start of the study, based on the presence or absence of visible clotting of membrane and circuit and/or prolonged bleeding after dialysis.

Arm title	IN0-IN5-OUT0
-----------	--------------

Arm description:

Administration of tinzaparin in this arm

the first week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0),

the second week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

the third week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

Arm type	Experimental
----------	--------------

Investigational medicinal product name	tinzaparin
Investigational medicinal product code	
Other name	Innohep, Leo Pharmaceutical Corp, Ballerup, Denmark
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Haemodialysis

Dosage and administration details:

Tinzaparin with median and interquartile range of 4500 (3500–4500) IU was routinely used. Before the study, tinzaparin was injected in the afferent blood line shortly after the start of the session. The doses had been defined prior to the start of the study, based on the presence or absence of visible clotting of membrane and circuit and/or prolonged bleeding after dialysis.

Arm title	OUT0-IN5-IN0
------------------	--------------

Arm description:

Administration of tinzaparin in this arm

the first week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

the second week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

the third week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0)

Arm type	Experimental
Investigational medicinal product name	tinzaparin
Investigational medicinal product code	
Other name	Innohep, Leo Pharmaceutical Corp, Ballerup, Denmark
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Haemodialysis

Dosage and administration details:

Tinzaparin with median and interquartile range of 4500 (3500–4500) IU was routinely used. Before the study, tinzaparin was injected in the afferent blood line shortly after the start of the session. The doses had been defined prior to the start of the study, based on the presence or absence of visible clotting of membrane and circuit and/or prolonged bleeding after dialysis.

Arm title	OUT0-IN0-IN5
------------------	--------------

Arm description:

Administration of tinzaparin in this arm

the first week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

the second week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0)

the third week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

Arm type	Experimental
Investigational medicinal product name	tinzaparin
Investigational medicinal product code	
Other name	Innohep, Leo Pharmaceutical Corp, Ballerup, Denmark
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Haemodialysis

Dosage and administration details:

Tinzaparin with median and interquartile range of 4500 (3500–4500) IU was routinely used. Before the study, tinzaparin was injected in the afferent blood line shortly after the start of the session. The doses had been defined prior to the start of the study, based on the presence or absence of visible clotting of membrane and circuit and/or prolonged bleeding after dialysis.

Arm title	IN5-IN0-OUT0
------------------	--------------

Arm description:

Administration of tinzaparin in this arm

the first week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

the second week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0)

the third week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

Arm type	Experimental
----------	--------------

Investigational medicinal product name	tinzaparin
Investigational medicinal product code	
Other name	Innohep, Leo Pharmaceutical Corp, Ballerup, Denmark
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Haemodialysis

Dosage and administration details:

Tinzaparin with median and interquartile range of 4500 (3500–4500) IU was routinely used. Before the study, tinzaparin was injected in the afferent blood line shortly after the start of the session. The doses had been defined prior to the start of the study, based on the presence or absence of visible clotting of membrane and circuit and/or prolonged bleeding after dialysis.

Arm title	IN5-OUT0-IN0
------------------	--------------

Arm description:

Administration of tinzaparin in this arm

the first week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

the second week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

the third week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0)

Arm type	Experimental
Investigational medicinal product name	tinzaparin
Investigational medicinal product code	
Other name	Innohep, Leo Pharmaceutical Corp, Ballerup, Denmark
Pharmaceutical forms	Solution for injection in pre-filled syringe
Routes of administration	Haemodialysis

Dosage and administration details:

Tinzaparin with median and interquartile range of 4500 (3500–4500) IU was routinely used. Before the study, tinzaparin was injected in the afferent blood line shortly after the start of the session. The doses had been defined prior to the start of the study, based on the presence or absence of visible clotting of membrane and circuit and/or prolonged bleeding after dialysis.

Number of subjects in period 1	IN0-OUT0-IN5	IN0-IN5-OUT0	OUT0-IN5-IN0
Started	2	3	1
Completed	2	3	0
Not completed	0	0	1
Adverse event, non-fatal	-	-	1

Number of subjects in period 1	OUT0-IN0-IN5	IN5-IN0-OUT0	IN5-OUT0-IN0
Started	3	3	2
Completed	3	3	2
Not completed	0	0	0
Adverse event, non-fatal	-	-	-

Baseline characteristics

Reporting groups

Reporting group title	overall trial
-----------------------	---------------

Reporting group description: -

Reporting group values	overall trial	Total	
Number of subjects	14	14	
Age categorical			
Units: Subjects			
Adults (18-64 years)	3	3	
From 65-84 years	9	9	
85 years and over	2	2	
Age continuous			
Units: years			
median	74		
inter-quartile range (Q1-Q3)	69 to 80	-	
Gender categorical			
Units: Subjects			
Female	5	5	
Male	9	9	
renal diagnosis			
Units: Subjects			
diabetic nephropathy	4	4	
vascular disease	3	3	
kidney disease	2	2	
other	5	5	
body weight			
Units: kg			
median	68		
inter-quartile range (Q1-Q3)	63 to 81.5	-	

End points

End points reporting groups

Reporting group title	IN0-OUT0-IN5
-----------------------	--------------

Reporting group description:

Administration of tinzaparin in this arm

the first week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0),

the second week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

the third week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

Reporting group title	IN0-IN5-OUT0
-----------------------	--------------

Reporting group description:

Administration of tinzaparin in this arm

the first week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0),

the second week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

the third week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

Reporting group title	OUT0-IN5-IN0
-----------------------	--------------

Reporting group description:

Administration of tinzaparin in this arm

the first week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

the second week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

the third week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0)

Reporting group title	OUT0-IN0-IN5
-----------------------	--------------

Reporting group description:

Administration of tinzaparin in this arm

the first week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

the second week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0)

the third week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

Reporting group title	IN5-IN0-OUT0
-----------------------	--------------

Reporting group description:

Administration of tinzaparin in this arm

the first week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

the second week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0)

the third week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

Reporting group title	IN5-OUT0-IN0
-----------------------	--------------

Reporting group description:

Administration of tinzaparin in this arm

the first week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

the second week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

the third week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0)

Subject analysis set title	IN0
----------------------------	-----

Subject analysis set type	Full analysis
---------------------------	---------------

Subject analysis set description:

analysis of the data of administration of tinzaparin at the inlet blood line just before the start of the blood pump

Subject analysis set title	IN5
----------------------------	-----

Subject analysis set type	Full analysis
---------------------------	---------------

Subject analysis set description:

analysis of the data of administration of tinzaparin at the inlet blood line 5 minutes after the detection of blood by the blood detector

Subject analysis set title	OUT0
Subject analysis set type	Full analysis

Subject analysis set description:

analysis of the data of administration of tinzaparin at the outlet blood line just prior the start of the blood pump

Primary: anti-Xa activity at the end of the session

End point title	anti-Xa activity at the end of the session
-----------------	--

End point description:

End point type	Primary
----------------	---------

End point timeframe:

anti-Xa activity at the end of the heamodiafiltration session

End point values	IN0	IN5	OUT0	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13	
Units: activity				
median (inter-quartile range (Q1-Q3))	0.14 (0.09 to 0.45)	0.24 (0.17 to 0.60)	0.25 (0.15 to 0.64)	

Statistical analyses

Statistical analysis title	chi square test
----------------------------	-----------------

Statistical analysis description:

continuous paired data were analyzed with repeated measures analysis of variance (Friedman) followed by Wilcoxon in case of significance. Chi square test was performed for categorical variables. Correlations were tested with Spearman correlation test.

Comparison groups	IN0 v IN5 v OUT0
Number of subjects included in analysis	39
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.05
Method	Chi-squared

Secondary: anti-Xa activity during the session

End point title	anti-Xa activity during the session
-----------------	-------------------------------------

End point description:

End point type	Secondary
----------------	-----------

End point timeframe:

Anti-Xa activity measured pre, 30min, 120min and 180min of the heamodiafiltration session

End point values	IN0	IN5	OUT0	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13	
Units: activity				
median (inter-quartile range (Q1-Q3))				
pre	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
30min	0.95 (0.88 to 1.27)	1.13 (1.06 to 1.33)	1.12 (0.89 to 1.37)	
120min	0.65 (0.46 to 0.97)	0.77 (0.56 to 0.97)	0.74 (0.57 to 1.07)	
180min	0.34 (0.25 to 0.75)	0.50 (0.34 to 0.78)	0.47 (0.29 to 0.85)	

Statistical analyses

Statistical analysis title	chi square test
Statistical analysis description:	
Continuous paired data were analyzed with repeated measures analysis of variance (Friedman) followed by Wilcoxon in case of significance. Chi square test was performed for categorical variables. Correlations were tested with Spearman correlation test.	
Comparison groups	IN5 v IN0 v OUT0
Number of subjects included in analysis	39
Analysis specification	Post-hoc
Analysis type	other
P-value	< 0.05
Method	Chi-squared

Secondary: Endogenous Thrombin Potential (ETP)

End point title	Endogenous Thrombin Potential (ETP)
End point description:	
End point type	Secondary
End point timeframe:	
ETP measured pre, 30min, 120min, 180min and 240 min of the heamodiafiltration session	

End point values	IN0	IN5	OUT0	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	13	13	13	
Units: ETP				
median (inter-quartile range (Q1-Q3))				

pre	0.96 (0.84 to 1.16)	0.97 (0.88 to 1.12)	0.97 (0.86 to 1.14)	
30min	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
120min	0 (0 to 0)	0 (0 to 0)	0 (0 to 0)	
180min	0 (0 to 0.07)	0 (0 to 0)	0 (0 to 0)	
240min	0.39 (0 to 0.60)	0.06 (0 to 0.17)	0.01 (0 to 0.09)	

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information^[1]

Timeframe for reporting adverse events:

overall trial

Assessment type	Non-systematic
-----------------	----------------

Dictionary used

Dictionary name	CTCAE
-----------------	-------

Dictionary version	5.0
--------------------	-----

Reporting groups

Reporting group title	IN0-OUT0-IN5
-----------------------	--------------

Reporting group description:

Administration of tinzaparin in this arm

the first week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0),

the second week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

the third week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

Reporting group title	IN0-IN5-OUT0
-----------------------	--------------

Reporting group description:

Administration of tinzaparin in this arm

the first week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0),

the second week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

the third week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

Reporting group title	OUT0-IN5-IN0
-----------------------	--------------

Reporting group description:

Administration of tinzaparin in this arm

the first week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

the second week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

the third week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0)

Reporting group title	OUT0-IN0-IN5
-----------------------	--------------

Reporting group description:

Administration of tinzaparin in this arm

the first week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

the second week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0)

the third week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

Reporting group title	IN5-IN0-OUT0
-----------------------	--------------

Reporting group description:

Administration of tinzaparin in this arm

the first week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

the second week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0)

the third week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

Reporting group title	IN5-OUT0-IN0
-----------------------	--------------

Reporting group description:

Administration of tinzaparin in this arm

the first week: administration at inlet blood line 5 minutes after the detection of blood by the blood detector (IN5)

the second week: administration at the outlet blood line just prior the start of the blood pump (OUT0)

the third week: administration of tinzaparin at the inlet blood line just before the start of the blood pump (IN0)

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.

Justification: No non-serious adverse events were found for these results

Serious adverse events	IN0-OUT0-IN5	IN0-IN5-OUT0	OUT0-IN5-IN0
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 1 (100.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	1 / 1 (100.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	OUT0-IN0-IN5	IN5-IN0-OUT0	IN5-OUT0-IN0
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	IN0-OUT0-IN5	IN0-IN5-OUT0	OUT0-IN5-IN0
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 2 (0.00%)	0 / 3 (0.00%)	0 / 1 (0.00%)

Non-serious adverse events	OUT0-IN0-IN5	IN5-IN0-OUT0	IN5-OUT0-IN0
Total subjects affected by non-serious adverse events			
subjects affected / exposed	0 / 3 (0.00%)	0 / 3 (0.00%)	0 / 2 (0.00%)

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

<http://www.ncbi.nlm.nih.gov/pubmed/26076014>