



## Clinical trial results:

## Spinal fentanyl or epidural analgesia in the early first phase of induced labor

### Summary

EudraCT number	2020-005506-26
Trial protocol	FI
Global end of trial date	18 May 2023

### Results information

Result version number	v1 (current)
This version publication date	13 September 2023
First version publication date	13 September 2023

### Trial information

#### Trial identification

Sponsor protocol code	Versio4
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#### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04645823
WHO universal trial number (UTN)	-

Notes:

### Sponsors

Sponsor organisation name	HUCH/Women's hospital
Sponsor organisation address	Haartmaninkatu 2, Helsinki, Finland, 00029
Public contact	department of Anaesthesia, HUCH/Women's hospital, 358 504271850, antti.vaananen@hus.fi
Scientific contact	department of Anaesthesia, HUCH/Women's hospital, 358 504271850, antti.vaananen@hus.fi

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	31 July 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	18 May 2023
Global end of trial reached?	Yes
Global end of trial date	18 May 2023
Was the trial ended prematurely?	No

Notes:

## General information about the trial

Main objective of the trial:

To compare analgesia achieved in 30 minutes by spinal fentanyl with analgesia by epidural lidocaine and fentanyl

Protection of trial subjects:

The participants (the parturients undergoing labor) were monitored by the study personnel and the midwives at the labor ward. The fetal wellbeing was monitored by continuous cardiotocography and the maternal neurological status and blood pressure was directly monitored by the care staff. The efficacy of analgesia (outcome of the trial) was monitored by the study personnel and the labor pain was treated as needed after the trial. The parturients' were checked for potential long term adverse effects after the delivery and lack of side effects was checked 30 days after the delivery from the patient files.

Background therapy:

Normal care for parturients undergoing induction of labor, including analgesics paracetamol per orally or intramuscular opioids (oxycodone) if needed.

Evidence for comparator:

The active comparator (intrathecal fentanyl) has been shown to be effective in alleviating labor pain and is routinely used for over 30 % of the parturients outside this study in our hospital district's hospitals (the treatment is used for approximately 4000 deliveries per year).

Actual start date of recruitment	01 February 2021
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Finland: 60
Worldwide total number of subjects	60
EEA total number of subjects	60

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)	60
From 65 to 84 years	0
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The parturients who were coming for the induction of labor were informed about the study in both oral and written form at the early phase of the induction. Those who agreed to participate were randomized to either group when they requested neuraxial analgesia for labor.

### Pre-assignment

Screening details:

The parturients were to have induced labor for their first attempted vaginal delivery. They were to have not contraindications for either intervention and they were to have BMI of 20-40 and a singleton pregnancy. The screening was done before the parturients had significant contraction pain.

### Period 1

Period 1 title	Onset of analgesia
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Assessor, Subject

Blinding implementation details:

The anesthesiologist who completed the analgesic intervention was not blinded. (S)he exited the labor suite after the analgesic intervention and the study investigator entered the room to monitor the parturient unaware of the intervention. The midwife and the parturient present in the room were not informed about the intervention given.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Epidural analgesia

Arm description:

A combination of lidocaine 80 mg and fentanyl citrate 100 micrograms given epidurally

Arm type	Experimental
Investigational medicinal product name	Lidocain Claris 10 mg/ml
Investigational medicinal product code	PR2
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Epidural use

Dosage and administration details:

8 millilitres of the 10 mg/ml solution is mixed with 2 ml of fentanyl citrate (PR3) and given epidurally

Investigational medicinal product name	Fentanyl hameln (50 microgram /ml)
Investigational medicinal product code	PR3
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Epidural use

Dosage and administration details:

2 ml of fentanyl citrate (PR3) is mixed with 8 ml of lidocain 10 mg/ml (PR2) and given epidurally

<b>Arm title</b>	Intrathecal fentanyl
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Arm description:

A dose of 20 micrograms of fentanyl citrate is given intrathecally in a total volume of 2 ml (dilution with sterile saline)

Arm type	Active comparator
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Investigational medicinal product name	Fentanyl hameln (50 microgram /ml)
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

0,4 ml (20 micrograms) is diluted with sterile saline to a volume of 2 ml and given intrathecally

Number of subjects in period 1	Epidural analgesia	Intrathecal fentanyl
Started	30	30
Completed	30	30

## Period 2

Period 2 title	duration of analgesia
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Carer, Assessor, Subject, Investigator

Blinding implementation details:

Neither the parturient, the midwife or the assessor in the labor room were aware of the intervention given to the parturient

## Arms

Are arms mutually exclusive?	Yes
Arm title	Epidural analgesia

Arm description:

A combination of lidocaine 80 mg and fentanyl citrate 100 micrograms given epidurally

Arm type	Experimental
Investigational medicinal product name	Lidocain Claris 10 mg/ml
Investigational medicinal product code	PR2
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Epidural use

Dosage and administration details:

8 millilitres of the 10 mg/ml solution is mixed with 2 ml of fentanyl citrate (PR3) and given epidurally

Investigational medicinal product name	Fentanyl hameln (50 microgram /ml)
Investigational medicinal product code	PR3
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Epidural use

Dosage and administration details:

2 ml of fentanyl citrate (PR3) is mixed with 8 ml of lidocain 10 mg/ml (PR2) and given epidurally

<b>Arm title</b>	Intrathecal fentanyl
Arm description: A dose of 20 micrograms of fentanyl citrate is given intrathecally in a total volume of 2 ml (dilution with sterile saline)	
Arm type	Active comparator
Investigational medicinal product name	Fentanyl hameln (50 microgram /ml)
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

0,4 ml (20 micrograms) is diluted with sterile saline to a volume of 2 ml and given intrathecally

<b>Number of subjects in period 2</b>	Epidural analgesia	Intrathecal fentanyl
Started	30	30
Completed	30	30

### Period 3

Period 3 title	Pre analgesia
Is this the baseline period?	Yes <sup>[1]</sup>
Allocation method	Not applicable
Blinding used	Not blinded

Blinding implementation details:

The allocation to either groups was done by opening a consecutively numbered sealed non-transparent envelope at the time of request for neuraxial analgesia. At baseline no allocation was made yet.

### Arms

Are arms mutually exclusive?	Yes
<b>Arm title</b>	Epidural analgesia

Arm description:

A combination of lidocaine 80 mg and fentanyl citrate 100 micrograms given epidurally

Arm type	Experimental
Investigational medicinal product name	Lidocain Claris 10 mg/ml
Investigational medicinal product code	PR2
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Epidural use

Dosage and administration details:

8 millilitres of the 10 mg/ml solution is mixed with 2 ml of fentanyl citrate (PR3) and given epidurally

Investigational medicinal product name	Fentanyl hameln (50 microgram /ml)
Investigational medicinal product code	PR3
Other name	

Pharmaceutical forms	Solution for injection
Routes of administration	Epidural use

Dosage and administration details:

2 ml of fentanyl citrate (PR3) is mixed with 8 ml of lidocain 10 mg/ml (PR2) and given epidurally

<b>Arm title</b>	Intrathecal fentanyl
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Arm description:

A dose of 20 micrograms of fentanyl citrate is given intrathecally in a total volume of 2 ml (dilution with sterile saline)

Arm type	Active comparator
Investigational medicinal product name	Fentanyl hameln (50 microgram /ml)
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intrathecal use

Dosage and administration details:

0,4 ml (20 micrograms) is diluted with sterile saline to a volume of 2 ml and given intrathecally

Notes:

[1] - Period 1 is not the baseline period. It is expected that period 1 will be the baseline period.

Justification: The "pre analgesia" - period (period 3) IS the baseline period.

<b>Number of subjects in period 3</b>	Epidural analgesia	Intrathecal fentanyl
Started	30	30
Completed	30	30

## Baseline characteristics

### Reporting groups

Reporting group title	Pre analgesia
Reporting group description:	
The parturients at the time of receiving their neuraxial analgesia	

Reporting group values	Pre analgesia	Total	
Number of subjects	60	60	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	60	60	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical			
Units: Subjects			
Female	60	60	
Male	0	0	
Pain VAS before intervention			
Maximum pain during contraction as measured by visual analog scale (VAS 0=no pain; 100=worst possible pain) before neuraxial analgesia measured on a 100 mm VAS line			
Units: millimetre(s)			
arithmetic mean	78		
standard deviation	± 13	-	

### Subject analysis sets

Subject analysis set title	Baseline
Subject analysis set type	Full analysis
Subject analysis set description:	
The baseline characteristics at the time of intervention	

Reporting group values	Baseline		
Number of subjects	60		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	60		
From 65-84 years	0		
85 years and over	0		
Gender categorical			
Units: Subjects			
Female	60		
Male	0		
Pain VAS before intervention			
Maximum pain during contraction as measured by visual analog scale (VAS 0=no pain; 100=worst possible pain) before neuraxial analgesia measured on a 100 mm VAS line			
Units: millimetre(s)			
arithmetic mean	78		
standard deviation	$\pm 13$		

## End points

### End points reporting groups

Reporting group title	Epidural analgesia
Reporting group description: A combination of lidocaine 80 mg and fentanyl citrate 100 micrograms given epidurally	
Reporting group title	Intrathecal fentanyl
Reporting group description: A dose of 20 micrograms of fentanyl citrate is given intrathecally in a total volume of 2 ml (dilution with sterile saline)	
Reporting group title	Epidural analgesia
Reporting group description: A combination of lidocaine 80 mg and fentanyl citrate 100 micrograms given epidurally	
Reporting group title	Intrathecal fentanyl
Reporting group description: A dose of 20 micrograms of fentanyl citrate is given intrathecally in a total volume of 2 ml (dilution with sterile saline)	
Reporting group title	Epidural analgesia
Reporting group description: A combination of lidocaine 80 mg and fentanyl citrate 100 micrograms given epidurally	
Reporting group title	Intrathecal fentanyl
Reporting group description: A dose of 20 micrograms of fentanyl citrate is given intrathecally in a total volume of 2 ml (dilution with sterile saline)	
Subject analysis set title	Baseline
Subject analysis set type	Full analysis
Subject analysis set description: The baseline characteristics at the time of intervention	

### Primary: Pain during contraction at 30 minutes

End point title	Pain during contraction at 30 minutes
End point description: The maximum pain during contraction at 30 minutes after the intervention	
End point type	Primary
End point timeframe: 30 minutes	

End point values	Epidural analgesia	Intrathecal fentanyl		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: millimetre(s)				
arithmetic mean (standard deviation)	17 ( $\pm$ 20)	18 ( $\pm$ 24)		

### Statistical analyses

<b>Statistical analysis title</b>	Pain during the contraction at 30 minutes
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Statistical analysis description:

Comparison between the treatment groups for maximum pain during contraction at 30 minutes after the analgesic intervention

Comparison groups	Epidural analgesia v Intrathecal fentanyl
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[1]</sup>
P-value	= 0.677
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - The study aimed for equal analgesia

## Secondary: Pain at 20 minutes

End point title	Pain at 20 minutes
End point description: pain at 20 minutes after the intervention	
End point type	Secondary
End point timeframe: 20 minutes	

End point values	Epidural analgesia	Intrathecal fentanyl		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: millimetre(s)				
arithmetic mean (standard deviation)	22 (± 23)	18 (± 23)		

## Statistical analyses

<b>Statistical analysis title</b>	PAin during contraction 20 minutes
Statistical analysis description: The maximum pain during contraction 20 minutes after the analgesic intervention	
Comparison groups	Epidural analgesia v Intrathecal fentanyl
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence <sup>[2]</sup>
P-value	= 0.661
Method	Wilcoxon (Mann-Whitney)

Notes:

[2] - The study aimed for equal analgesia

## Secondary: Duration of analgesia

End point title	Duration of analgesia
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End point description:

The time until the parturient receives the first epidural analgesia dose after the study analgesic intervention marking the duration of action of the studied intervention

End point type	Secondary
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End point timeframe:

0-180 minutes

End point values	Epidural analgesia	Intrathecal fentanyl		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: minute				
arithmetic mean (standard deviation)	91 (± 41)	82 (± 34)		

## Statistical analyses

Statistical analysis title	Duration of analgesia
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Statistical analysis description:

in minutes between the two treatment arms

Comparison groups	Epidural analgesia v Intrathecal fentanyl
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.36
Method	t-test, 2-sided

## Secondary: Maternal satisfaction with analgesia at 30 min

End point title	Maternal satisfaction with analgesia at 30 min
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End point description:

The parturients assessment of the satisfaction with the analgesia on a 100 mm visual analog scale (0=completely dissatisfied; 100= completely satisfied)

End point type	Secondary
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End point timeframe:

30 minutes

End point values	Epidural analgesia	Intrathecal fentanyl		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	30	30		
Units: millimetre(s)				
arithmetic mean (standard deviation)	88 (± 20)	88 (± 15)		

## Statistical analyses

<b>Statistical analysis title</b>	Maternal satisfaction
Statistical analysis description:	
Non parametric test for maternal satisfaction scores	
Comparison groups	Epidural analgesia v Intrathecal fentanyl
Number of subjects included in analysis	60
Analysis specification	Pre-specified
Analysis type	equivalence
P-value	= 0.486
Method	Wilcoxon (Mann-Whitney)

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

180 minutes

Adverse event reporting additional description:

The parturients were followed for the potential adverse events for upto 180 minutes

Assessment type	Systematic
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### Dictionary used

Dictionary name	SNOMED CT
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Dictionary version	1
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### Reporting groups

Reporting group title	Epidural analgesia
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Reporting group description:

The groups of parturients that received epidural analgesia (80 mg lidocaine 1 % and fentanyl citrate 100 micrograms)

Reporting group title	Intrathecal fentanyl
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Reporting group description:

The group of parturients that received intrathecal fentanyl (20 micrograms)

Serious adverse events	Epidural analgesia	Intrathecal fentanyl	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 30 (0.00%)	0 / 30 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 3 %

Non-serious adverse events	Epidural analgesia	Intrathecal fentanyl	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	7 / 30 (23.33%)	9 / 30 (30.00%)	
Pregnancy, puerperium and perinatal conditions			
Foetal heart rate abnormal	Additional description: The International Federation of Gynecology and Obstetrics -classification (2015) was used. Reversible pathological changes not indicative of acidemic were seen as non-serious AE, while irreversible requiring cesarean delivery were serious AE.		
alternative dictionary used: FIGO classification 2015			
subjects affected / exposed	3 / 30 (10.00%)	0 / 30 (0.00%)	
occurrences (all)	3	0	
Gastrointestinal disorders			

Nausea subjects affected / exposed occurrences (all)	Additional description: Nausea after epidural or intrathecal analgesia		
	4 / 30 (13.33%) 4	5 / 30 (16.67%) 5	
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	Additional description: Intrathecal or epidural opioid induced pruritus scored as severe or unbearable at least once during the observation period		
	0 / 30 (0.00%) 0	4 / 30 (13.33%) 4	

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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### Interruptions (globally)

Were there any global interruptions to the trial? No

### Limitations and caveats

None reported