



Clinical trial results: Intraperitoneal administration of fosfomycin, metronidazole and molgramostim versus intravenous conventional antibiotics for perforated appendicitis – a pivotal quasi-randomized controlled trial Summary

EudraCT number	2017-004753-16
Trial protocol	DK
Global end of trial date	17 July 2018

Results information

Result version number	v1 (current)
This version publication date	27 November 2019
First version publication date	27 November 2019

Trial information

Trial identification

Sponsor protocol code	HEH-SF-02
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03435900
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Herlev Hospital
Sponsor organisation address	Herlev Ringvej 75, Herlev, Denmark, 2730
Public contact	CPO office, Department of Surgery, 0045 38683414, siv.fonnes@regionh.dk
Scientific contact	CPO office, Department of Surgery, 0045 38683414, siv.fonnes@regionh.dk

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	04 February 2019
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	17 July 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary outcome is the total length of hospital stay, defined as the number of hours in hospital after end of operation (not before operation) and until 30-day follow-up.

Protection of trial subjects:

The trial would be stopped if severe adverse effects or severe complications, which were not expected, arose from the trial treatment. This was to be decided by the sponsor. Assessment of harms: The participants were asked if they had experienced any changes both the first day after surgery and 10 days after the surgery in combination with an objective examination. This was documented in the CRF. Further, the patient was asked if they have experienced any adverse events defined as any unfavourable and unintended sign, symptom, or disease associated with the intraperitoneal treatment, whether or not related to that treatment. A follow-up was conducted 30 days after surgery. This was also be documented in the CRF.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 February 2018
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	Denmark: 13
Worldwide total number of subjects	13
EEA total number of subjects	13

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)	10

From 65 to 84 years	3
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The intervention group, who were planned for an acute surgery, and the control group, who had undergone laparoscopy appendectomy for perforated appendix, were approached by the trial personnel and informed about the trial.

Pre-assignment

Screening details:

A total of 82 patients were screened. 13 participants were quasi-randomised and 12 of these fulfilled the trial. The most common reasons for exclusion were a normal or non-perforated appendix found during surgery.

Period 1

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

Blinding implementation details:

Quasi-randomisation makes blinding impossible. However, allocation concealment would be impossible even in a proper randomized setting due to the intraperitoneal formulation in the intervention group.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intervention

Arm description:

A combination of fosfomycin, metronidazole and GM-CSF i.p. All drugs will be administered together intraperitoneally at the end of the surgery after the appendix has been removed. Postoperatively, the intervention group will receive orally administered antibiotics: 500 mg amoxicillin/125 mg clavulanic acid and 500 mg metronidazole administered three times daily for three days.

Arm type	Experimental
Investigational medicinal product name	Repomol
Investigational medicinal product code	PR1
Other name	molgramostim, rhGM-CSF
Pharmaceutical forms	Powder for suspension for injection
Routes of administration	Intraperitoneal use

Dosage and administration details:

A dose of 50 microgram Repomol (molgramostim/rhGM-CSF) in 0.2 ml of solution (water for injection) in combination with 4 g of fosfomycin and 1 g metronidazole, which were administered intraperitoneally and will remain as local installation. Postoperatively, orally administered antibiotic were given to the participants.

Investigational medicinal product name	Fosfomycin disodium salt
Investigational medicinal product code	PR2
Other name	fosfomycin
Pharmaceutical forms	Powder for injection
Routes of administration	Intraperitoneal use

Dosage and administration details:

A dose of 4 g of fosfomycin diluted in 300 ml of sterile water for injections in combination with 50 microgram Repomol (molgramostim/rhGM-CSF) and 1 g metronidazole, which were administered intraperitoneally and remained as local installation. Postoperatively, orally administered antibiotic were given to the participants.

Investigational medicinal product name	Metronidazole
Investigational medicinal product code	PR2
Other name	Metronidazole
Pharmaceutical forms	Infusion

Routes of administration	Intraperitoneal use
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Dosage and administration details:

A dose of 1 g metronidazole corresponding to 200 ml in combination with 50 microgram Repomol (molgramostim/rhGM-CSF) and 4 g of fosfomycin and 1 g metronidazole, which were administered intraperitoneally and remained as local installation. Postoperatively, orally administered antibiotic were given to the participants.

Arm title	Control
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Arm description:

Standard intravenous antibiotic agents during surgery (either 1.5 g cefuroxime or 4 g piperacillin/500 mg tazobactam and 1 g metronidazole). Furthermore, a minimum of 500 ml saline was used for irrigation of the abdominal cavity. Postoperatively, the control group received three days of intravenously administered antibiotic agents: 4 g piperacillin/500 mg tazobactam and 500 g metronidazole, three times daily for a minimum of three days.

Arm type	Active comparator
Investigational medicinal product name	Piperacillin/Tazobactam
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

During surgery, the control group received either 1.5 g cefuroxime or 4 g piperacillin/500 mg tazobactam and 1 g metronidazole intravenously. After surgery, the control group received an intravenous course of 4 g piperacillin/500 mg tazobactam and 500 g metronidazole for at least three days.

Investigational medicinal product name	Cefuroxime
Investigational medicinal product code	PR1
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

During surgery, the control group received either 1.5 g cefuroxime or 4 g piperacillin/500 mg tazobactam and 1 g metronidazole intravenously. After surgery, the control group received an intravenous course of 4 g piperacillin/500 mg tazobactam and 500 g metronidazole for at least three days.

Investigational medicinal product name	Metronidazole
Investigational medicinal product code	PR2
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

During surgery, the control group received either 1.5 g cefuroxime or 4 g piperacillin/500 mg tazobactam and 1 g metronidazole intravenously. After surgery, the control group received an intravenous course of 4 g piperacillin/500 mg tazobactam and 500 g metronidazole for at least three days.

Number of subjects in period 1	Intervention	Control
Started	7	6
Completed	6	6
Not completed	1	0
Consent withdrawn by subject	1	-

Baseline characteristics

Reporting groups

Reporting group title	Intervention
Reporting group description:	
A combination of fosfomycin, metronidazole and GM-CSF i.p. All drugs will be administered together intraperitoneally at the end of the surgery after the appendix has been removed. Postoperatively, the intervention group will receive orally administered antibiotics: 500 mg amoxicillin/125 mg clavulanic acid and 500 mg metronidazole administered three times daily for three days.	
Reporting group title	Control
Reporting group description:	
Standard intravenous antibiotic agents during surgery (either 1.5 g cefuroxime or 4 g piperacillin/500 mg tazobactam and 1 g metronidazole). Furthermore, a minimum of 500 ml saline was used for irrigation of the abdominal cavity. Postoperatively, the control group received three days of intravenously administered antibiotic agents: 4 g piperacillin/500 mg tazobactam and 500 g metronidazole, three times daily for a minimum of three days.	

Reporting group values	Intervention	Control	Total
Number of subjects	7	6	13
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	5	6	11
From 65-84 years	2	0	2
85 years and over	0	0	0
Gender categorical			
Units: Subjects			
Female	4	1	5
Male	3	5	8
ASA score			
Units: Subjects			
ASA I	4	6	10
ASA II	3	0	3
Preoperative antibiotics			
Units: Times administered			
median	2	2	
full range (min-max)	0 to 8	0 to 4	-
BMI			
Units: kilogram(s)/square meter			
median	29	28	
full range (min-max)	24 to 34	21 to 33	-
Height			
Units: meter			
median	1.73	1.85	

full range (min-max)	1.63 to 1.85	1.68 to 1.87	-
Weight			
Units: kilogram(s)			
median	82	92	
full range (min-max)	65 to 105	73 to 107	-

End points

End points reporting groups

Reporting group title	Intervention
Reporting group description: A combination of fosfomycin, metronidazole and GM-CSF i.p. All drugs will be administered together intraperitoneally at the end of the surgery after the appendix has been removed. Postoperatively, the intervention group will receive orally administered antibiotics: 500 mg amoxicillin/125 mg clavulanic acid and 500 mg metronidazole administered three times daily for three days.	
Reporting group title	Control
Reporting group description: Standard intravenous antibiotic agents during surgery (either 1.5 g cefuroxime or 4 g piperacillin/500 mg tazobactam and 1 g metronidazole). Furthermore, a minimum of 500 ml saline was used for irrigation of the abdominal cavity. Postoperatively, the control group received three days of intravenously administered antibiotic agents: 4 g piperacillin/500 mg tazobactam and 500 g metronidazole, three times daily for a minimum of three days.	

Primary: Primary, total length of stay within 30 days after surgery

End point title	Primary, total length of stay within 30 days after surgery
End point description: Total length of in hospital stay (measured in hours): defined as from end of the operation until discharge from the hospital plus length of stay during a possible readmission within 30 days from surgery.	
End point type	Primary
End point timeframe: Postoperatively (baseline) to 30 days postoperatively (+/-3 days)	

End point values	Intervention	Control		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6 ^[1]	6		
Units: hours				
median (full range (min-max))	13 (2 to 21)	84 (67 to 169)		

Notes:

[1] - 1 participant withdrew consent and data on the primary outcome could, therefore, not be collected.

Statistical analyses

Statistical analysis title	Primary analysis
Comparison groups	Intervention v Control
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.017
Method	Wilcoxon (Mann-Whitney)

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From the administration until 30 days postoperatively.

Adverse event reporting additional description:

Adverse events were collected through interview with participants the first postoperative day, at visit 10 days postoperatively and through medical records and contact with the participant by telephone until 30 days after surgery.

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	10.0
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Reporting groups

Reporting group title	Intervention group
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Reporting group description: -

Reporting group title	Control group
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Reporting group description: -

Serious adverse events	Intervention group	Control group	
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	3 / 6 (50.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Gastrointestinal disorders			
Abscess drainage			
subjects affected / exposed	0 / 7 (0.00%)	2 / 6 (33.33%)	
occurrences causally related to treatment / all	0 / 0	2 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	0 / 7 (0.00%)	1 / 6 (16.67%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Influenza			
subjects affected / exposed	1 / 7 (14.29%)	0 / 6 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0.05 %

Non-serious adverse events	Intervention group	Control group	
Total subjects affected by non-serious adverse events subjects affected / exposed	5 / 7 (71.43%)	5 / 6 (83.33%)	
Injury, poisoning and procedural complications			
Pain	Additional description: Pain in lower right quadrant		
subjects affected / exposed ^[1]	1 / 6 (16.67%)	0 / 6 (0.00%)	
occurrences (all)	1	0	
Haematoma			
subjects affected / exposed ^[2]	0 / 6 (0.00%)	1 / 6 (16.67%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed ^[3]	4 / 6 (66.67%)	3 / 6 (50.00%)	
occurrences (all)	4	3	
Nausea			
subjects affected / exposed ^[4]	1 / 6 (16.67%)	1 / 6 (16.67%)	
occurrences (all)	1	1	
Vomiting			
subjects affected / exposed ^[5]	0 / 6 (0.00%)	2 / 6 (33.33%)	
occurrences (all)	0	2	

Notes:

[1] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: As one participant withdrew consent, we cannot know if this adverse event arose in this participant.

[2] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: As one participant withdrew consent, we cannot know if this adverse event arose in this participant.

[3] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: As one participant withdrew consent, we cannot know if this adverse event arose in this participant.

[4] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: As one participant withdrew consent, we cannot know if this adverse event arose in this participant.

[5] - The number of subjects exposed to this adverse event is less than the total number of subjects exposed for the reporting group. These numbers are expected to be equal.

Justification: As one participant withdrew consent, we cannot know if this adverse event arose in this participant.

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Quasi-randomised design: no actual randomisation took place (risk of selection bias).

Notes: