Clinical trial results:
Antibiotic prophylaxis oral vs parenteral + parenteral in colonic surgery: a prospective, randomized, multicenter clinical trial.

Summary

EudraCT number	2014-002345-21
Trial protocol	ES
Global end of trial date	28 April 2017

Results information

Result version number	v1 (current)
This version publication date	30 September 2021
First version publication date	30 September 2021

Trial information

Trial identification

Sponsor protocol code	2011/001/PROF-ATB

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	VHIR
Sponsor organisation address	Passeig Vall dHebron 119-129, Barcelona, Spain, 08035
Public contact	VHIR/Technical Secretariat, Joaquin Lopez-Soriano, 34 934893807, joaquin.lopez.soriano@vhir.org
Scientific contact	Colorectal Surgery Unit, Dr Eloy Espin, 934893807 9342720006587, eespinbasany@gmail.com

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	28 April 2017
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	28 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Patients undergoing colon surgery were recruited from five major hospitals in Spain. Patients were eligible for inclusion if they were diagnosed with neoplasia or diverticular disease and if a partial colon resection or total colectomy was indicated. Participants were randomly assigned to either administration of oral antibiotics the day before surgery (experimental group) or no administration of oral antibiotics before surgery (control group). For the experimental group, ciprofloxacin 750 mg was given every 12 h (two doses at 1200 h and 0000 h) and metronidazole 250 mg every 8 h (three doses at 1200 h, 1800 h, and 0000 h) the day before surgery. All patients were given intravenous cefuroxime 1·5 g and metronidazole 1 g at the time of anaesthetic induction. The primary outcome was incidence of surgical-site infections. Patients were followed up for 1 month after surgery and all postsurgical complications were registered.

Protection of trial subjects:

The detection and evaluation of surgical-site infections and complications after surgery followed current clinical practice guidelines, consisting of daily physical examination of the patient in the immediate period after surgery and outpatient visits at the study centre in the first, second, and fourth weeks after surgery. All examinations for surgical-site infections were done by a nurse specialising in infections. Complementary tests for the screening of infections after surgery were blood tests, cultures of wound exudates of intra-abdominal abscesses, abdomen–pelvic CT, and surgical exploration.

Background therapy:

Mechanical bowel preparation is a relevant confounder if associated with oral antibiotics.

Evidence for comparator: -

Actual start date of recruitment	04 August 2014
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	Spain: 536
Worldwide total number of subjects	536
EEA total number of subjects	536

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)	501
From 65 to 84 years	35
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited from five hospitals in Spain: the Vall d'Hebron University Hospital (Barcelona), Bellvitge University Hospital (Barcelona), the Josep Trueta University Hospital (Girona), Lucus Augusti Hospital (Lugo), and the Cruces University Hospital (Bilbao).

Pre-assignment

Screening details:

Patients were eligible if they were diagnosed with neoplasia or diverticular disease and if a partial colon resection or total colectomy was indicated. Patients were excluded if they had been given antibiotic treatment in the 2 weeks before surgery or had undergone mechanical bowel preparation the day before surgery.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Monitor[1]

Blinding implementation details:

Patients were randomly assigned (1:1), using online randomisation software, stratified by study site, to two parallel groups, the control group (no oral antibiotics) or the experimental group (oral antibiotics). Randomisation was done by an external statistician.

Arms

Are arms mutually exclusive?	Yes
Arm title	Control

Arm description:

No oral antibiotics

Arm type	Active comparator
Investigational medicinal product name	Cefuroxime
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1500 mg at the time of anaesthetic induction.

Investigational medicinal product name	Metronidazole
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for infusion
Routes of administration	Intravenous use

Dosage and administration details:

1 g at the time of anaesthetic induction.

Arm title	Oral antibiotic

Arm description:

The experimental group was treated with a regimen of ciprofloxacin 750 mg every 12 h (two doses at 1200 h and 0000 h) and metronidazole 250 mg every 8 h (three doses at 1200 h, 1800 h, and 0000 h) orally the day before the scheduled surgery.

Arm type	Experimental

Investigational medicinal product name	Ciprofloxacin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Ciprofloxacin 750 mg every 12 h (two doses at 1200 h and 0000 h) orally

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: The investigators, surgeons, patients, and statistician were unmasked to the group the patient was randomly assigned to, but the nurse who assessed the presence or absence of a surgical-site infection was masked to treatment assignment.

Number of subjects in period 1	Control	Oral antibiotic
Started	269	267
Completed	269	267

Baseline characteristics

Reporting groups	
Reporting group title	Control
Reporting group description:	
No oral antibiotics	
Reporting group title	Oral antibiotic
Reporting group description:	
The experimental group was treated with a regimen of ciprofloxacin 750 mg every 12 h (two doses at 1200 h and 0000 h) and metronidazole 250 mg every 8 h (three doses at 1200 h, 1800 h, and 0000 h) orally the day before the scheduled surgery.	

Reporting group values	Control	Oral antibiotic	Total
Number of subjects	269	267	536
Age categorical Units: Subjects			
Adults (18-64 years)	74	82	156
From 65-84 years	195	185	380
Gender categorical Units: Subjects			
Female	117	125	242
Male	152	142	294

End points

End points reporting groups

Reporting group title	Control
Reporting group description:	
No oral antibiotics	
Reporting group title	Oral antibiotic
Reporting group description:	
The experimental group was treated with a regimen of ciprofloxacin 750 mg every 12 h (two doses at 1200 h and 0000 h) and metronidazole 250 mg every 8 h (three doses at 1200 h, 1800 h, and 0000 h) orally the day before the scheduled surgery.	
Subject analysis set title	Full study
Subject analysis set type	Full analysis
Subject analysis set description:	
All patients	

Primary: Surgical-site infections

End point title	Surgical-site infections
End point description:	
The primary endpoint was the incidence of surgical-site infections, defined as the sum of skin superficial, deep incisional, and organ-space infections, according to the criteria of the US Centers for Disease Control and Prevention	
End point type	Primary
End point timeframe:	
End of study	

End point values	Control	Oral antibiotic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	267		
Units: Number				
number (not applicable)	30	13		

Statistical analyses

Statistical analysis title	Site infections
Comparison groups	Control v Oral antibiotic
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.013
Method	Chi-squared

Secondary: Duration of stay in hospital

End point title	Duration of stay in hospital

End point description:

End point type	Secondary

End point timeframe:

End of study

End point values	Control	Oral antibiotic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	267		
Units: day				
arithmetic mean (full range (min-max))	5 (4 to 9)	5 (4 to 7)		

Statistical analyses

Statistical analysis title	Stay in hospital
Comparison groups	Control v Oral antibiotic
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.088
Method	Chi-squared

Secondary: Time from surgery to infection detection

End point title	Time from surgery to infection detection

End point description:

End point type	Secondary

End point timeframe:

All the study

End point values	Control	Oral antibiotic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	267		
Units: day				
arithmetic mean (full range (min-max))	5 (4 to 9)	9 (5 to 14)		

Statistical analyses

Statistical analysis title	Time to infection
Comparison groups	Control v Oral antibiotic
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.115
Method	Chi-squared

Secondary: Complication	
End point title	Complication
End point description: Not including surgical-site infection	
End point type	Secondary
End point timeframe: All the study	

End point values	Control	Oral antibiotic		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	269	267		
Units: Number				
number (not applicable)	76	51		

Statistical analyses

Statistical analysis title	Complications
Comparison groups	Control v Oral antibiotic
Number of subjects included in analysis	536
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.017
Method	Chi-squared

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: All the study	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	14.1

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

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 adverse events associated with the oral antibiotics were recorded. A full list of local, surgical, and medical complications is given in the publication, recorded as secondary end points.

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.

Placebo was not used for the control group, which might be a source of bias. Additionally, surgeons and patients were not masked to treatment group assignment because of logistical issues, which could be regarded as a source of bias.

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/32325012