Preoperative oral antibiotics and surgical-site infections in colon surgery (ORALEV): a multicentre, single-blind, pragmatic, randomised controlled trial

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Summary

Background Previous studies have found that mechanical bowel preparation with oral antibiotics can reduce the incidence of surgical-site infections, but no randomised controlled trial has assessed oral antibiotics alone without mechanical bowel preparation. The aim of this study was to determine whether prophylaxis with oral antibiotics the day before elective colon surgery affects the incidence of postoperative surgical-site infections.

Methods In this multicentre, pragmatic, randomised controlled trial (ORALEV), patients undergoing colon surgery were recruited from five major hospitals in Spain and 47 colorectal surgeons at these hospitals participated. 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 (1:1) using online randomisation tables 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. This study was registered with EudraCT, 2014-002345-21, and ClinicalTrials.gov, NCT02505581, and is closed to accrual.

Findings Between May 2, 2015, and April 15, 2017, we assessed 582 patients for eligibility, of whom 565 were eligible and randomly assigned to receive either no oral antibiotics (n=282) or oral antibiotics (n=282) before surgery. 13 participants in the control group and 16 in the experimental group were subsequently excluded; 269 participants in the control group and 267 in the experimental group received their assigned intervention. The incidence of surgical-site infections in the control group (30 [11%] of 269) was significantly higher than in the experimental group (13 [5%] of 267; χ^2 test p=0·013). Oral antibiotics were associated with a significant reduction in the risk of surgical-site infections compared with no oral antibiotics (odds ratio 0·41, 95% CI 0·20–0·80; p=0·008). More complications (including surgical-site infections) were observed in the control group than in the experimental group (76 [28%] *vs* 51 [19%]; p=0·017), although there was no difference in severity as assessed by Clavien-Dindo score. No differences were noted between groups in terms of local complications, surgical complications, or medical complications that were not related to septic complications.

Interpretation The administration of oral antibiotics as prophylaxis the day before colon surgery significantly reduces the incidence of surgical-site infections without mechanical bowel preparation and should be routinely adopted before elective colon surgery.

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Introduction

The optimal patient preparation for colorectal surgery has been a matter of debate for several decades, because it can determine the incidence of potentially devastating postoperative outcomes, such as anastomotic leakage or sepsis.[1] Surgical-site infections are serious postoperative complications that are a major source of morbidity and increased health-care costs.[2]

In an effort to lower the incidence of surgical-site infections, in the 1970s the use of mechanical bowel preparation and administration of oral non-absorbable antibiotics as prophylaxis became common practice before surgery.[1,3] In the past 40 years, many randomised controlled trials and cohort studies have tried to establish the relative benefits of mechanical bowel preparation and oral antibiotics with respect to complications after surgery such as infection, anastomotic leakage, and other morbidities.[4] These studies have consistently shown that mechanical bowel preparation has no benefit on the incidence of surgical-site infections or anastomotic leakage before elective colorectal surgery.[5–8] By contrast, many studies have suggested that oral antibiotics

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Research in context

Evidence before this study

We searched PubMed and Scopus, with no date restrictions on June 14, 2015, for publications in English and Spanish, using the terms "prophylaxis", "antibiotic", "colon surgery", and "surgical site infection". Several studies have suggested a possible role for preoperative oral antibiotics to reduce the risk of surgical-site infections after colorectal surgery. However, the available evidence is of low quality because most of the studies were retrospective and different treatment regimens were used. Definitive conclusions could not be drawn, due to the possible effects of additional factors on the incidence of surgical-site infections. Among these factors, mechanical bowel preparation is a relevant confounder if associated with oral antibiotics. Because no agreement exists about whether mechanical bowel preparation reduces the incidence of surgical-site infections after colon surgery, the ideal trial to address the effects of oral antibiotics on surgical-site infections should compare treatment with oral antibiotics versus no treatment with oral antibiotics, without mechanical bowel preparation; we identified no such trials.

Added value of this study

To our knowledge, this is the first pragmatic randomised controlled trial to assess the efficacy of oral antibiotics in reducing the incidence of surgical-site infections after colon surgery without mechanical bowel preparation. We found that use of oral antibiotics before colon surgery reduced the incidence of surgical-site infections, compared with no oral antibiotics, with no associated adverse events.

Implications of all the available evidence

In patients scheduled to undergo elective colon resection, preoperative oral antibiotics should be used to reduce the incidence of surgical-site infections.

substantially reduce the incidence of postoperative complications, including surgical-site infections.[9,10] A retrospective study of 40 446 patients showed that preoperative oral antibiotics in combination with mechanical bowel preparation significantly reduced surgical-site infections and complications after surgery (eg, anastomotic leaks, postoperative ileus, and major morbidity), and that when they were given alone they did not generate better results,[9] and an inclusive review of studies since 1980 reached the same conclusion.[10] A large comprehensive meta-analysis of the role of oral antibiotics in bowel preparation before colorectal surgery suggested that they are significantly beneficial in the prevention of postoperative complications, especially surgical-site infections, either alone or in combination with mechanical bowel preparation.[4] A second meta-analysis found that both randomised controlled trials and cohort studies showed lower incidences of surgical-site infections when patients were given oral antibiotics than when they were not.[11] If only considering cohort studies, the use of oral antibiotics was also associated with reduced incidences of organ-space surgical-site infections, anastomotic leakage, unplanned operations, hospital readmissions and stays, and mortality.[11] However, most of these reviews were based on studies that also used mechanical bowel preparation, and therefore often the value of oral antibiotics has been inferred from the combination of both procedures. Few studies have compared use of preoperative oral antibiotics directly with no preoperative treatment. Of these studies, a small retrospective cohort analysis[12] and a single-centre randomised controlled trial[13] found no benefits in administering oral antibiotics only. By contrast, two large retrospective cohort studies suggested that administration of preoperative oral antibiotics had strong effects in reducing the incidence of surgical-site infections.[7,14]

Despite the large number of studies, no universal consensus exists among practising colorectal surgeons on whether use of mechanical bowel preparation or oral antibiotics is beneficial or not. WHO guidelines suggest that mechanical bowel preparation should not be given in isolation, and recommend use of mechanical bowel preparation combined with oral antibiotics before elective colorectal surgery,[15] a position that is also shared by the American Society for Enhanced Recovery guidelines.[16] By contrast, the guidelines from the Enhanced Recovery After Surgery Society and the UK National Institute of Health and Care Excellence (NICE) suggest that mechanical bowel preparation should be not be used routinely.[17,18] NICE also recommends the use of preoperative oral antibiotic prophylaxis for gastrointestinal surgery.[18] However, an online survey of colorectal surgeons by the European Society of Coloproctology indicated that mechanical bowel preparation is still prescribed by 126 (30%) of 426 surgeons before colonic surgery and by 328 (77%) before rectal surgery in Europe, and that only 47 (11%) surgeons give preoperative oral antibiotics.[19] A subsequent survey, run in 2018 by the Association of Coloproctology of Great Britain and Ireland among its members, showed that prophylactic oral antibiotics were prescribed by 12–20% of surgeons (depending on the type of surgery: 12% in right colectomy, 18% in left sided resection without planned diverting stoma, and 20% in left sided resection with planned stoma).[20]

To date, no large, multicentre, randomised controlled trial has been done to assess the effectiveness of oral antibiotics alone versus no treatment before colon surgery. Here we assess the effect of oral antibiotic prophylaxis the day before surgery in patients undergoing colon surgery without mechanical bowel preparation compared with not receiving oral antibiotics, to determine if this treatment affects the incidence of surgical-site infections.

Methods

Study design and participants

In this multicentre, single-blind, pragmatic, randomised controlled trial, 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). 47 colorectal surgeons (including staff and surgeons in training mentored by staff surgeons) from these hospitals participated in the study. 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, and if they agreed to participate voluntarily in the study and signed an informed consent. Patients were excluded from the study if they had been given antibiotic treatment for any reason in the 2 weeks before surgery or had undergone mechanical bowel preparation the day before surgery. Those who had total or partial mesorectal excision; with a histological diagnosis of inflammatory bowel disease, active acute diverticulitis, ischaemic colitis, or infectious colitis; and those who had undergone palliative surgery due to advanced neoplastic disease were also excluded. Additional exclusion criteria were intra-abdominal sepsis before surgery, intraoperative faecal contamination (in which case an extended antibiotic treatment is indicated in the postoperative period), and antibiotic treatment for distant infections not directly related to surgery. Furthermore, patients were excluded if they did not comply with assigned prophylaxis regimen, or if they refused in writing to participate in the study.

All eligible patients provided written informed consent before undergoing study-related procedures. The study protocol was approved by the Ethics Commission of the Valle de Hebron University Hospital and done in accordance with the Declaration of Helsinki (World Medical Association, 2013).

Randomisation and masking

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. 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.

Procedures

The control group did not receive oral antibiotic prophylaxis the day before surgery. 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. Mechanical bowel preparation was not allowed in either group. Both groups received intravenous cefuroxime 1·5 g and metronidazole 1 g at the time of anaesthetic induction.

At baseline we collected the following data on all patients: body-mass index (BMI), American Society of Anaesthesiologists (ASA) score, and presence of diabetes, blood pressure, and comorbidities. We had no limitations on the surgical procedures allowed, all of which were recorded.

Outcomes

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.[21] The secondary endpoints were the incidence of adverse events directly related to prophylactic antibiotic treatment, the requirement for additional treatments in patients in both groups, total duration of stay in hospital in days, direct adverse reactions to the drug, occlusive problems, iatrogenic problems, impaired healing, bleeding problems, cardiac problems, nephrourinary complications, respiratory complications, vascular complications, gastrointestinal complications, neurological complications, local infections, and local complications. We categorised secondary endpoints that related to septic complications as key endpoints.

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. Postoperative outcomes were assessed according to two classifications: first, according to the general Clavien-Dindo classification of complications after surgery;[22] and second, according to postoperative treatment required (grades A–C, from lesser to greater severity) as suggested by Rahbari and colleagues[23] for anastomotic leakage after rectal cancer surgery. Grade A patients did not require postoperative invasive treatments (eg, antibiotics) and patients were clinically well; grade B patients required active treatment and interventional radiology; and grade C patients required emergency surgery (re-laparotomy) and presented with increased parameters of infection (leucocytosis, C-reactive protein). Data for adverse events were collected prospectively and classified according to frequency, severity, relation to treatment, and outcome.

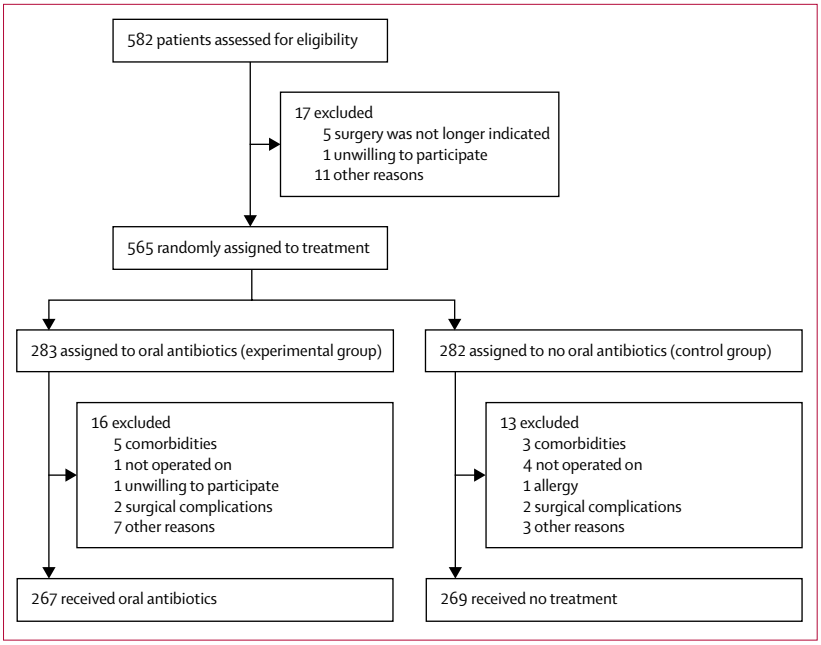

Figure: **Study profile**

	Experimental group (n=267)	Control group (n=269)
Age, years	70 (62–78)	71 (63–81)
Sex		
Male	142 (53%)	152 (57%)
Female	125 (47%)	117 (43%)
BMI	27·4 (24·9–30·5)	27·2 (25·0–30·5)
Site		
Vall d'Hebron University Hospital	144 (54%)	143 (53%)
Bellvitge University Hospital	43 (16%)	44 (16%)
Josep Trueta University Hospital	7 (3%)	7 (3%)
Lucus Augusti Hospital	40 (15%)	41 (15%)
Cruces University Hospital of Bilbao	33 (12%)	34 (13%)
ASA score		
I–II	145 (54%)	129 (48%)
III–IV	122 (46%)	140 (52%)
Comorbidities		
COPD	42 (16%)	48 (18%)
Cardiopathies	66 (25%)	65 (24%)
Chronic kidney disease	17 (6%)	17 (6%)
Surgical procedure		
Right hemicolectomy	137 (51%)	131 (49%)
Left hemicolectomy	121 (45%)	119 (44%)
Colectomy	7 (3%)	16 (6%)
Other	0	2 (1%)
Segment resection	2 (1%)	1 (<1%)
Surgery type		
Laparoscopy	206 (77%)	207 (77%)
Open	40 (15%)	37 (14%)
Conversion	20 (8%)	25 (9%)
Stoma*	9 (3%)	11 (4%)
Surgery time, min	186 (148–240)	185 (140–240)

Data are median (IQR) or n (%). The control group were not given oral antibiotics before surgery, and the experimental group were given oral antibiotics before surgery. ASA=American Society of Anesthesiologists. BMI=body-mass index. COPD=chronic obstructive pulmonary disease. *Given a stoma at the time of surgery.

Table 1: **Basic demographic and clinical data and surgical data of all patients who received their assigned treatment**

Statistical analysis

Assuming an incidence of surgical-site infections[3] of 17% with no prophylaxis with oral antibiotics and of 7·5% with prophylaxis with oral antibiotics (as estimated by pooling four studies on oral antibiotic prophylaxis in colorectal surgery[24–27]), a 5% patient loss, and a significance level of 95%, we calculated that 536 patients were required to achieve a power of 80%. The expected recruitment time for this number of patients was 18 months.

Data were collected prospectively by the investigators, and patients were followed up per protocol with individual case report forms converted manually to electronic case report forms; data were uploaded to an online database. We present quantitative data as mean (SD) or median (IQR). We present qualitative data as absolute numbers and proportions. We used an intention-to-treat approach for all analyses. We assessed differences between groups using parametric or non-parametric tests, as appropriate. We assessed the primary endpoint using the χ^2 test and calculated a confidence interval of differences. We used univariate logistic regression to calculate odds ratios (ORs) and 95% CIs. We calculated risk ratio (RR) and 95% CI for the primary endpoint. We used a mixed model to assess the effect of site and surgeon with a multivariate regression analysis to assess the effect of treatment adjusted for other variables (eg, age, sex, BMI, ASA score, comorbidities, surgical procedure, and surgical approach). We analysed secondary qualitative endpoints using the χ^2 test or Fisher's exact test. We analysed quantitative variables using Student's *t* test or the Mann–Whitney *U* test.

We did an interim analysis after approximately half of patients were allocated to each treatment group. In this analysis, if the superiority of the intervention had been significant at a level of $p<0·005575$, the study would have been terminated early.

We did all analyses using R (version 3.4.2), and a p value of less than 0·05 was considered significant.

The study is registered with EudraCT, number 2014-002345-21, and ClinicalTrials.gov, NCT02505581.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to

	All participants (n=536)	Experimental group (n=267)	Control group (n=269)	Treatment difference	p value
Primary endpoint					
Surgical-site infections	43 (8%)	13 (5%)	30 (11%)	–6·28 (–11·12 to – 1·61)	0·013
Key secondary endpoints					
Duration of stay in hospital, days	5 (4 to 8)	5 (4 to 7)	5 (4 to 9)	–1·68 (–4·32 to 0·96)	0·088
Time from surgery to infection detection, days (n=43)	6 (4 to 10)	9 (5 to 14)	5 (4 to 9)	5·99 (–0·63 to 12·60)	0·115
Type of surgical-site infection					
Superficial	16/43 (37%)	3/13 (23%)	13/30 (43%)	..	0·102
Deep	11/43 (26%)	2/13 (15%)	9/30 (30%)	..	..
Organ space	12/43 (28%)	5/13 (39%)	7/30 (23%)	..	..
No data	4/43 (9%)	3/13 (23%)	1/30 (3%)	..	..
Treatment of infection					
Only antibiotics	14/41 (34%)	3/12 (25%)	11/29 (38%)	..	0·629
Antibiotics and percutaneous drainage	12/41 (29%)	3/12 (25%)	9/29 (31%)	..	..
Antibiotics and re-operation	15/41 (37%)	6/12 (50%)	9/29 (31%)	..	..
All complications*	127 (24%)	51 (19%)	76 (28%)	–9·15 (–16·24 to 1·95)	0·017
Clavien-Dindo classification†					
I	12/127 (9%)	5 (10%)	7/76 (9%)	..	0·885
II	69/127 (54%)	26 (52%)	43 (55%)	..	..
IIIa	1/127 (1%)	0	1 (1%)	..	..
IIIb	10/127 (8%)	4 (8%)	6 (8%)	..	..
IVa	12/127 (9%)	5 (10%)	7 (9%)	..	..
IVb	1/127 (1%)	1 (2%)	0	..	..
V	3/127 (2%)	1 (2%)	2 (3%)	..	..
Complications*	117 (22%)	49 (18%)	68 (25%)	–6·93 (–13·35 to 0·08)	0·066
Grading according to postoperative treatment required‡					
Grade A	36 (7%)	18 (7%)	18 (7%)	–0·05 (–4·33 to 4·44)	>0·99
Grade B	69 (13%)	28 (11%)	41 (15%)	–4·75 (–10·47 to 0·95)	0·13
Grade C	49 (9%)	22 (8%)	27 (10%)	–1·80 (–6·79 to 3·17)	0·57

Data are n (%), n/N (%), median (IQR), or treatment difference with 95% CIs in parentheses. The control group were not given oral antibiotics before surgery, and the experimental group were given oral antibiotics before surgery. p values were calculated using the Mann–Whitney *U* test for quantitative data and the χ^2 test or Fisher's exact test for categorical data. *Not including surgical-site infection. †Including surgical-site infection. ‡Classification according to Rahbari and colleagues.[23]

Table 2: **Complications after surgery**

all the data in the study and had final responsibility for the decision to submit for publication.

Results

Between May 2, 2015, and April 15, 2017, 582 patients were assessed for eligibility and 565 were randomly assigned to receive either no treatment before surgery (n=282; control group) or oral antibiotics the day before colorectal surgery (n=283; experimental group). After exclusion of another 29 patients, 269 patients received no treatment and 267 received oral antibiotic prophylaxis the day before surgery (figure). The number of patients operated on by each surgeon are shown in the appendix (p 2). Our interim analysis, which took place after 138 patients had been allocated to the control group and 130 to the experimental group, found the intervention to not be superior (appendix pp 6–7), and so recruitment of participants continued per protocol. The trial was completed after reaching the planned sample size.

Baseline characteristics of the patients are shown in table 1. The median age of patients was 71 years (IQR 63–79), and 294 (55%) were male. Most patients underwent right hemicolectomies (268 [50%]) with laparoscopy (413 [77%]). Almost all patients assigned to the experimental group adhered to the treatment, with only one refusing to take the oral antibiotics before surgery.

More patients in the control group had surgical-site infections (30 [11%] of 269 patients) than did in the experimental group (13 [5%] 267; p=0·013; table 2). The OR of surgical-site infections in the experimental group versus the control group was 0·41 (95% CI 0·20–0·80; p=0·008). The RR of having a surgical-site infection after use of oral antibiotics versus no oral antibiotics was 0·44 (95% CI 0·23–0·83).

Overall, we observed more complications (including the surgical-site infections) in the control group than in the experimental group (p=0·017), but no differences were seen in the severity of these complications according

See Online for appendix

	All participants (n=536)	Experimental group (n=267)	Control group (n=269)	Treatment difference	p value
Local complications	36 (7%)	18 (7%)	18 (7%)	0·05 (–4·33 to 0·44)	1·00
Surgical wound	29 (5%)	15 (6%)	14 (5%)	0·41 (–3·58 to 4·44)	0·98
Haematoma	11/29 (38%)	7/15 (47%)	4/14 (29%)	..	..
Seroma	16/29 (55%)	7/15 (47%)	9/14 (64%)	..	..
Evisceration	2/29 (7%)	1/15 (7%)	1/14 (7%)	..	..
Stoma	7 (1%)	3 (1%)	4 (1%)	–0·36 (–2·75 to 1·95)	1·00
Prolapse	0	0	0	..	..
Necrosis	1/7 (14%)	0	1/4 (25%)	..	..
Invagination	0	0	0	..	..
Peristomal infection	0	0	0	..	..
Other	6/7 (86%)	3/3 (100%)	3/4 (75%)	..	..
Surgical complications	69 (13%)	28 (10%)	41 (15%)	–4·75 (–10·47 to 0·95)	0·13
Bleeding	14 (3%)	7 (3%)	7 (3%)	0·02 (–8·97 to 3·02)	1·00
Haemoperitoneum	1/14 (7%)	0	1/7 (14%)	..	..
Abdominal wall haematoma	2/14 (14%)	0	2/7 (29%)	..	..
Anastomotic bleeding	8/14 (57%)	5/7 (71%)	3/7 (43%)	..	..
Other	3/14 (21%)	2/7 (29%)	1/7 (14%)	..	..
Healing problems	19 (3%)	9 (3%)	10 (4%)	–0·35 (–3·73 to 3·02)	1·00
Suture dehiscence	12/19 (63%)	5/9 (56%)	7/10 (70%)	..	..
Urinary leak	0	0	0	..	..
Bowel anastomosis separation	0	0	0	..	..
Peritonitis	5/19 (26%)	2/9 (22%)	3/10 (30%)	..	..
Other	2/19 (11%)	2/9 (22%)	0	..	..
Obstruction and stenosis	39 (7%)	14 (5%)	25 (9%)	–4·05 (–8·62 to 0·40)	0·10
Small bowel obstruction	1/39 (3%)	1/14 (7%)	0	..	..
Anastomotic stricture	0	0	0	..	..
Extended duration of ileus (>5 days)	38/19 (97%)	13/14 (93%)	25/25 (100%)	..	..
Other	0	0	0	..	..
Medical complications	49 (9%)	22 (8%)	27 (10%)	–1·80 (–6·79 to 3·17)	0·57
Cardiac	9	4 (1%)	5 (2%)	–0·36 (–2·95 to 2·16)	1·00
Acute myocardial infarction	0	0	0	..	..
Congestive heart failure	3/9 (33%)	2/4 (50%)	1/5 (20%)	..	..
Angor	1/9 (11%)	0	1/5 (20%)	..	..
Atrial fibrillation	2/9 (22%)	1/4 (25%)	1/5 (20%)	..	..
Acute pulmonary oedema	1/9 (11%)	0	1/5 (20%)	..	..
Other	2/9 (22%)	1/4 (25%)	1/5 (20%)	..	..
Renal or urinary	20 (4%)	6 (2%)	14 (5%)	–2·96 (–6·51 to 0·53)	0·11
Acute urine retention	3/20 (15%)	0	3/14 (21%)	..	..
Acute kidney failure	5/20 (25%)	3/6 (50%)	2/14 (14%)	..	..
Cystitis	9/20 (45%)	2/6 (33%)	7/14 (50%)	..	..
Pyelonephritis	0	0	0	..	..
Other	3/20 (15%)	1/6 (17%)	2/14 (14%)	..	..
Neurological	5 (1%)	1 (<1%)	4 (1%)	–1·11 (–3·41 to 0·83)	0·37
Stroke	1 (20%)	0	1/4 (25%)	..	..
Disorientation	4 (80%)	1/1 (100%)	3/4 (75%)	..	..
Other	0	0	0	..	..
Digestive	5 (1%)	2 (1%)	3 (1%)	–0·37 (–2·55 to 1·71)	1·00
Liver failure	0	0	0	..	..
Upper gastrointestinal bleed	3/5 (60%)	1/2 (50%)	2/3 (67%)	..	..
Malnutrition	0	0	0	..	..
Other	2/5 (40%)	1/2 (50%)	1/3 (33%)	..	..

(Table 3 continues on next page)

	All participants (n=536)	Experimental group (n=267)	Control group (n=269)	Treatment difference	p value
(Continued from previous page)					
Respiratory	17 (3%)	7 (3%)	10 (4%)	−1·10 (−4·37 to 2·08)	0·63
Pneumonia	7/17 (41%)	2/7 (29%)	5/10 (50%)	..	..
Atelectasis	4/17 (23%)	3/7 (43%)	1/10 (10%)	..	..
Pulmonary thromboembolism	0	0	0	..	..
Acute respiratory distress syndrome	2/17 (12%)	0	2/10 (20%)	..	..
Other	4/17 (24%)	2/7 (29%)	2/10 (20%)	..	..
Vascular	6 (1%)	5 (2%)	1 (<1%)	1·50 (−0·51 to 3·96)	0·12
Deep vein thrombosis	1 (17%)	1/5 (20%)	0	..	..
Phlebitis (peripherical)	3 (50%)	3/5 (60%)	0	..	..
Thrombophlebitis (central)	2 (33%)	1/5 (20%)	1/1 (100%)	..	..
Other	0	0	0	..	..

Data are n, n (%), n/N (%), or treatment difference with 95% CIs in parentheses. The control group were not given oral antibiotics before surgery, and the experimental group were given oral antibiotics before surgery. The denominator for the proportion is the total group unless otherwise indicated.

***Table* 3: Additional secondary endpoints**

to the Clavien-Dindo classification (table 2). The number of superficial and deep infections was non-significantly lower in the experimental group than in the control group (table 2). We saw no differences between the control and experimental groups for the secondary outcomes not related to septic complications (additional secondary outcomes; table 3).

We also examined other variables using univariable logistic regression for their potential associations with surgical-site infections. Two significant predictors were type of surgery (open surgery *vs* laparoscopy OR 2·29, 95% CI 1·16–4·41; p=0·018) and the ASA grade of the patient (grade I–II *vs* grade III–IV 2·05, 1·08–4·05; p=0·028; appendix p 3).

At 1 month after surgery, four patients had died, two in each group (tumour progression, pneumonia, severe respiratory insufficiency, and septic shock). One patient who did not enter the study had an anaphylactic shock probably related to intravenous cefuroxime (severe, resolved (appendix p 9). No adverse events were assessed by the investigator to be due to oral antibiotics.

Discussion

In this randomised controlled trial, we investigated the effects of receiving prophylactic treatment with oral antibiotics, in the absence of mechanical bowel preparation, on the incidence of surgical-site infections in patients undergoing elective colorectal surgery. All patients were given prophylactic intravenous antibiotics during anaesthetic induction. Our results suggest that oral antibiotics reduce the incidence of surgical-site infections significantly compared with no intervention.

Clinical practice regarding preoperative interventions before elective colorectal surgery has been controversial. The described options of so-called bowel conditioning before colorectal surgery can be summarised as mechanical bowel preparation alone, mechanical bowel preparation plus oral antibiotics, oral antibiotics alone, and no preparation.[28] Many studies have shown that mechanical bowel preparation, despite having been the standard of care in elective colorectal surgery for many decades, does not seem to confer any advantage regarding the incidence of surgical-site infections, anastomotic leakage, or other potential complications after surgery.[5–7] However, combination therapy with oral antibiotics and mechanical bowel preparation seems to be beneficial for patients undergoing elective colorectal surgery according to many randomised controlled trials, large retrospective studies, and several meta-analyses.[4,10,11,28] Notably, in most of these meta-analyses, the comparison of oral antibiotic treatment alone versus other interventions was limited by the small number of trials considering this variable, and in most of these reports confusion and mixing of mechanical bowel preparation and oral antibiotics occurred, making interpretation of data regarding the benefit of each of the treatments (mechanical bowel preparation and oral antibiotics) extremely difficult with regards to the incidence of surgical-site infections. According to a 2018 network meta-analysis[28] on preoperative bowel conditioning, the association of mechanical bowel preparation and oral antibiotics should be the most effective strategy against surgical-site infections; however, no direct comparison was found between oral antibiotics and no conditioning in patients.

In our pragmatic randomised controlled trial, we found that the administration of oral antibiotics significantly reduced the likelihood of surgical-site infections, which is consistent with aggregated results from other studies. A meta-analysis showed that oral antibiotics with mechanical bowel preparation compared with mechanical bowel preparation alone was associated with a decreased incidence of surgical-site infections in randomised controlled trials and in cohort studies,[11] values that are similar to those in another meta-analysis including adults

undergoing elective colorectal surgery receiving oral antibiotics with or without mechanical bowel preparation.[4] The second meta-analysis also determined, on the basis of data from two cohort studies comprising 16 390 patients,[14,29] the RR of using oral antibiotics (in the absence of mechanical bowel preparation) versus no treatment was 0·56 (95% CI 0·38–0·83; p=0·004).[4] For comparison, we found an RR of 0·44 for this comparison in our study. When discussing mechanical bowel preparation, some associated factors should be considered, which justify why we decided not to include mechanical bowel preparation in our trial. For instance, no agreement exists between colorectal surgeons that mechanical bowel preparation reduces the likelihood of complications after colorectal surgery, with some evidence suggesting that in patients scheduled to receive colon surgery should not have mechanical bowel preparation because it could actually be a source of harms rather than benefits (eg, dehydration).[5] Mechanical bowel preparation is generally deemed beneficial in patients who are having rectal resections below the peritoneal verge. In our study, we excluded patients who were candidates for rectal surgery, making our study easier to be translated into clinical practice, because the majority of colorectal surgeons would omit mechanical bowel preparation in colonic surgery.[19] Finally, mechanical bowel preparation could have reduced adherence to the study and could have acted as a confounder during analysis.

The general requirements for the choice of an oral antibiotic for prophylaxis are that it must be active against aerobic and anaerobic bacteria present in faeces, and that its serum levels should be high at the time of surgery.[30] Previous studies have indicated that the combination of an aminoglycoside, such as kanamycin or neomycin with metronidazole, generates similar effects to reduce surgical-site infections.[11] However, no unequivocal evidence exists on which oral antibiotic regimen should be used before colorectal surgery. In our study we used a combined oral regimen of ciprofloxacin and metronidazole. This combination allowed us to cover infections caused by both aerobic and anaerobic bacteria. We chose ciprofloxacin because of its high bioavailability, favourable pharmacokinetics, and excellent tolerance.[31] Ciprofloxacin has good tissue diffusion at the time of surgery (elimination half-life of ciprofloxacin is 3–5 h), with up to 25% of the administered dose found in the faeces. Non-renal clearance of ciprofloxacin is mainly due to hepatic metabolism; hence, transluminal secretion across the intestinal mucosa and biliary excretion could also reduce the faecal bacterial load. Additionally, ciprofloxacin could prevent infections distant from the large bowel (eg, urinary). Metronidazole is well established as prophylaxis during colonic surgery since the 1980s.[32] We hypothesised that combining metronidazole and ciprofloxacin would have been the most beneficial combination when aiming to reduce surgical-site infections; additionally, both antibiotics are easy to deliver and readily available. Another aspect that needs to be discussed is the fact that fluoroquinolones like ciprofloxacin have been associated with the risk of developing antimicrobial resistance and with increased risk of *Clostridioides difficile* infection. However, none of the patients treated with oral antibiotics in our study developed any *C difficile* infection, suggesting that although extended duration or recurrent use of ciprofloxacin as an oral antibiotic could increase the faecal overgrowth of *C difficile*, its use in the context of 1-day preoperative prophylaxis is unlikely to result in such a situation.[33] A prudent option would be to avoid fluoroquinolones as oral antibiotics in patients with previous extended duration of exposure to such drugs or with previous history of *C difficile* infection.

The value of use of different regimens of oral antibiotics has not been established by prospective trials. Selective decontamination of the colon has been tried in some studies and this approach was assessed in a randomised controlled trial with 455 patients (SELECT trial), which was stopped after an interim analysis, but found a decrease in surgical-site infections in those with selective decontamination compared with the control group (24 [10·6%] of 227 *vs* five [2·2%] of 228).[34] Both patients who had and did not have mechanical bowel preparation were included in this study.[34]

We acknowledge that the strong effect of a short treatment based on a single day of oral antibiotics on incidence of surgical-site infections is somewhat surprising.[11] Some might think that antibiotics would have little influence without mechanical bowel preparation because of the faecal content present; however, little is known about the underlying changes in the gut and skin microbiota after antibiotic treatment, and possible severe disequilibria caused by systemic antibiotics and other perioperative interventions could lead to increased risk of some infections. For example, preoperative treatment with oral antibiotics has been found to strongly protect against the development of *Pseudomonas aeruginosa* surgical-site infections after elective colorectal surgery.[35] Although *P aeruginosa* does not normally have a key role in the intestinal microbiota, factors including systemic antimicrobial treatment and use of specific drugs (eg, analgesics) have been hypothesised to favour the disruption of the microbiota and the overgrowth of *P aeruginosa*, an effect that is countered by the action of oral antibiotics.[35] Characterisation of the changes in the intestinal microbiome that occur through the perioperative period, and which organisms need to be preserved or neutralised, should be the goal of future research.[36] This knowledge should lead to a more selective approach to the management and prevention of infectious complications from intestinal surgery.

Our study had several limitations. We did not use any placebo for the control group, which might be a source of bias. However, we decided not to use placebo for two

main reasons: first, because of the substantial increase in costs that would be incurred by the study, which would have jeopardised the possibility of its completion; and second, assessment was done by a masked collaborator, who was not working with the team, by means of objective and reproducible measures, and so a placebo would not be needed. Additionally, surgeons and patients were not masked to treatment group assignment because of logistical issues, which could be regarded as a source of bias. However, since the primary endpoint was an objectively assessed endpoint, the risk of misattribution of side-effects or benefits by participants was avoided. Furthermore, the nurses specialising in infections who were responsible for determining if a surgical-site infection had occurred were masked to the treatment. Moreover, confounders and imprecisions, which have recently been suggested to be more important than masking itself,[37] were carefully addressed in the present study.

Regarding indication for surgery, we included both neoplasia and diverticular disease, although few participants had benign disease. No patients with inflammatory bowel disease were included to reduce the possibility of bias due to concomitant medication in these patients.

To our knowledge, this is the first randomised controlled trial to directly investigate oral antibiotics versus no intervention before elective colonic surgery, in the absence of mechanical bowel preparation. The need for this type of approach had been suggested in many publications before. The strengths of our study are the large number of patients included and the multicentric nature of the study with over 40 surgeons involved.

In conclusion, our investigation of the benefits of administering oral antibiotics in the absence of mechanical bowel preparation shows that it is beneficial in reducing surgical-site infections. No adverse events associated with the oral antibiotics were recorded. Our study is consistent with many others that indicate the use of oral antibiotics in the context of mechanical bowel preparation. Together with previous evidence, our study suggests that surgeons should implement oral antibiotics when preparing patients for elective colon surgery. Further research should focus on a better understanding of microbiome dynamics and how they are used to determine the relative risk of surgical-site infections in each patient, and also the effect of mechanical bowel preparation or no mechanical bowel preparation in patients with oral antibiotics, which is the basis of our next study: ORALEV 2 (NCT04161599).

Contributors

EEB contributed to the study conception and design, data collection and interpretation, manuscript draft writing, and revision of the draft for important content. AS-P contributed to data collection and interpretation and manuscript draft writing. GP contributed to data interpretation and manuscript draft writing and revision following reviews. EK, DF, MM-L, OM-D, JMG-G, MS-O, and AC-C contributed to data collection and interpretation and revision of drafts for important content. SB contributed to study conception and design, data collection and interpretation, and revision of drafts for important content. All authors approved the final version of the manuscript.

Declaration of interests

We declare no competing interests.

Data sharing

Data were collected and registered on an online database. Data will not be made public, but de-identified data could be shared upon receipt of an adequately justified request to the corresponding author (EEB).

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