


# Systemic versus Oral and Systemic Antibiotic Prophylaxis (SOAP) study in colorectal surgery: prospective randomized multicentre trial

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## Abstract

**Background:** There is no consensus regarding the role of mechanical bowel preparation (MBP) and oral antibiotic prophylaxis (OABP) in reducing postoperative complications in colorectal surgery. The aim of this study was to examine the effect of OABP given in addition to MBP in the setting of a prospective randomized trial.

**Methods:** Patients awaiting elective colorectal surgery in four Hungarian colorectal centres were included in this multicentre, prospective, randomized, assessor-blinded study. Patients were randomized to receive MBP with or without OABP (OABP+ and OABP– groups respectively). The primary endpoints were surgical-site infection (SSI) and postoperative ileus. Secondary endpoints were anastomotic leak, mortality, and hospital readmission within 30 days.

**Results:** Of 839 patients assessed for eligibility between November 2016 and June 2018, 600 were randomized and 529 were analysed. Trial participation was discontinued owing to adverse events in seven patients in the OABP+ group (2.3 per cent). SSI occurred in eight patients (3.2 per cent) in the OABP+ and 27 (9.8 per cent) in the OABP– group ( $P=0.001$ ). The incidence of postoperative ileus did not differ between groups. Anastomotic leakage occurred in four patients (1.6 per cent) in the OABP+ and 13 (4.7 per cent) in the OABP– ( $P=0.02$ ) group. There were no differences in hospital readmission (12 (4.7 per cent) versus 10 (3.6 per cent);  $P=0.25$ ) or mortality (3 (1.2 per cent) versus 4 (1.4 per cent);  $P=0.39$ ).

**Conclusion:** OABP given with MBP reduced the rate of SSI and AL after colorectal surgery with anastomosis, therefore routine use of OABP is recommended.

## Introduction

Although intravenous antibiotic prophylaxis is used routinely for colorectal surgery<sup>1</sup>, the role of preoperative oral antibiotic prophylaxis (OABP)<sup>2</sup> and mechanical bowel preparation (MBP)<sup>3</sup> is more controversial, despite a Cochrane review that supported the combined use of oral and intravenous antibiotics to reduce surgical-site infection (SSI)<sup>4</sup>.

The combination of OABP and MBP is used widely in North America, and several studies<sup>5–8</sup> have supported its use. Recent guidelines from the American Society of Colon and Rectal Surgeons<sup>9</sup> recommend the use of both MBP and OABP, a practice also endorsed by the American Society of Enhanced Recovery<sup>10</sup>. Data from several thousand patients in the American College of Surgeons' National Surgical Quality Improvement Program have shown that OABP given with MBP (and intravenous antibiotic prophylaxis) reduces SSI, anastomotic insufficiency, postoperative ileus, 30-day mortality, and 30-day readmission rates<sup>7,11–13</sup>. Several expert panels<sup>9,14</sup> and review studies<sup>15–19</sup> have addressed

the use of OABP, but relatively few prospective studies<sup>20–28</sup> have reported to date. The majority of meta-analyses concluded that OABP in combination with MBP reduces SSI after colorectal surgery<sup>16–19,22,29</sup>.

To date, European data have been conflicting. A non-randomized, multicentre audit<sup>30</sup> found significantly less anastomotic insufficiency after left-sided colorectal resection if the patients were given OABP in combination with MBP. However, a recent prospective, randomized trial<sup>31</sup> reported no benefit of OABP in combination with MBP compared with a no-preparation (NoPrep) policy. The results of some ongoing prospective trials are yet to be published<sup>32,33</sup>.

The aim of the SOAP (Systemic versus Oral and systemic Antibiotic Prophylaxis) trial was to examine the effects of OABP given in combination with MBP and intravenous antibiotic prophylaxis. The hypothesis was that patients who received MBP, intravenous antibiotic prophylaxis and OABP (OABP+ group) would have improved outcomes compared with those who received

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MBP and intravenous antibiotic prophylaxis only (OABP- group). The primary endpoints were rates of SSI and postoperative ileus, and secondary endpoints were anastomotic leak rate, mortality, and hospital readmission within 30 days.

## Methods

The SOAP study was non-commercial, multicentre, prospective, randomized, superiority, assessor-blinded study registered as EudraCT 2015-005614-30. Ethical approval was granted by both the Hungarian National Institute of Pharmacy and Nutrition and the Hungarian Medical Research Council.

All patients gave informed consent to participate in the study. All indications for colorectal anastomosis were considered eligible, including Hartmann's reversal, with the exception of loop colostomy closure. Patients were classified into left- and right-sided groups according to the site of resection and anastomosis. If both sides of the colon were removed (colectomy/double resection), the procedure was categorized as a left-sided resection. Anastomosis to the lower two-thirds of the rectum was considered a rectal anastomosis. Patients were excluded if they had received antibiotics within 2 weeks before randomization, were allergic to any of the drugs used, were aged less than 18 years, had abdominal sepsis within 6 months before randomization, were pregnant or breast feeding, were being treated with steroids or had any form of chronic immunosuppression, or had obstructive symptoms. Patients were excluded after randomization if they did not receive the study drugs according to the study protocol or if they did not have an anastomosis created during surgery for any reason.

All patients received bowel preparation comprising 40 ml castor oil with 20 ml paraffin on the day before surgery. An enema was given on the evening before surgery and again on the morning of surgery. All patients received intravenous 2 g ceftriaxone and 500 mg metronidazole within 60 min of the incision. This was repeated if operating time exceeded 4 h and/or blood loss exceeded 1500 ml. Patients in the investigation arm (OABP+) were given 500 mg metronidazole and 1000 mg neomycin sulphate orally at 13.00, 15.00, and 19.00 hours on the day before surgery.

Patients were followed until postoperative day 30, in accordance with recommendations from the Centers for Disease Control and Prevention<sup>34</sup>. Any wound discharge was considered to represent at least a superficial wound infection. If the deeper layers (fascia, musculature) were affected, it was classified as deep SSI. When infection manifested within the abdominal cavity (any fluid collection, abscess), it was regarded as an organ space (abdominal) SSI. Imaging was performed only when indicated clinically. Postoperative ileus was defined by the need for a nasogastric tube and/or the patient being nil by mouth on day 3 or more after operation. Any clinically or radiologically proven anastomotic suture dehiscence was counted as an anastomotic leak. If anastomotic leakage was proven, the patient was not included in the organ space SSI group for analysis. During surgery, the surgeon evaluated the success of MBP according to the Boston Bowel Preparation Scale (BBPS)<sup>35</sup>. MBP was considered successful if the BBPS score was at least 2. Four high-volume colorectal Hungarian centres participated in the study; the procedures were performed by 21 surgeons. All centres used the same colorectal care bundle and enhanced recovery after surgery (ERAS) protocol.

## Statistical analysis

The study power calculation was based on the international literature<sup>7,11,12</sup>, with an estimated 11 per cent incidence of SSI in the OABP- group and 5 per cent in the OABP+ group. Postoperative ileus was estimated to occur in 6 per cent of patients in the OABP- group and 3 per cent in the OABP+ group. Using  $\delta = 3$  and an adjusted study power of 80 per cent with a 95 per cent confidence interval, it was calculated that 282 patients were required for the SSI primary endpoint and 374 for the postoperative ileus endpoint. This was rounded up to 400 patients and, after adjusting for a possible 12.5 per cent loss, the final sample size was estimated to be 450 patients. Data were recorded in the Research Electronic Data Capture (REDCap) system, which was also used for randomization. Randomization was stratified by age. The assessors were blinded to the assigned intervention arm. R statistical software (R Foundation for Statistical Computing, Vienna, Austria) was used for data analysis. Variables were compared using the z test (with 1- or 2-sided confidence interval),  $\chi^2$  test, ANOVA or multivariable linear regression, as appropriate. A 5 per cent significance level was accepted.

## Results

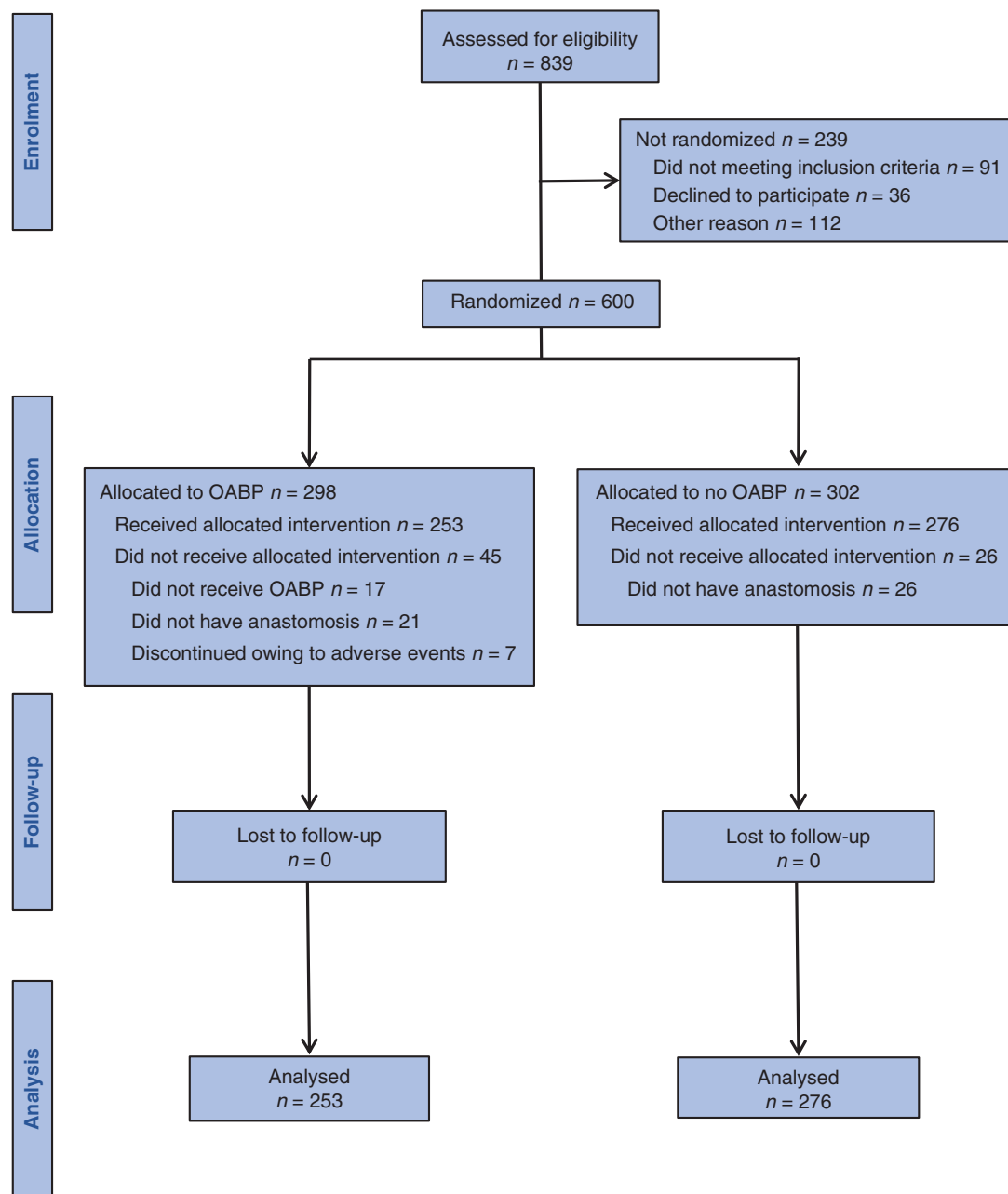
In the four participating centres, 839 patients undergoing elective colorectal surgery with a planned anastomosis were assessed for eligibility between November 2016 and June 2018, of whom 600 were randomized. Of these 600 patients, 71 patients were excluded either because of a protocol violation or because an anastomosis was not created, leaving 529 patients for analysis (Fig. 1). The breakdown of operations was 181 (34.2 per cent) involving the right colon, 167 (31.6 per cent) the left colon, and 181 (34.2 per cent) the rectum.

Indications for surgery were tumour (malignant or benign) in 461 patients (87.1 per cent), inflammatory bowel or diverticular disease in 33 (6.2 per cent), reversal of Hartmann's procedure in 30 (5.7 per cent), and other (angiodyplasia or functional bowel problems) in five patients (0.9 per cent). Patient characteristics of the study groups are summarized in Table 1.

Adverse events related to oral antibiotic use were reported by 32 patients: nausea or vomiting (29), abdominal cramps (2), dizziness (2), and numbness of fingers or toes (3); some patients experienced more than one adverse event. None required intervention. Seven of the 32 patients decided to withdraw from the study owing to side-effects.

The results for primary and secondary endpoints are shown in Table 2. There was an overall reduction in SSI in the OABP+ group ( $P = 0.001$ ), particularly in superficial SSIs ( $P = 0.01$ ). For organ space SSI, the difference approached significance ( $P = 0.06$ ) in favour of the OABP+ group. There was no difference in deep SSI between the study groups. The rate of postoperative ileus did not differ between groups. Regarding secondary endpoints, anastomotic leakage occurred less frequently in the OABP+ group, whereas there was no difference in 30-day mortality and readmission rates.

The results of multivariable linear regression analysis are shown in Table 3. The addition of OABP independently reduced rates of both SSI and anastomotic leak ( $P < 0.001$  and  $P = 0.048$  respectively). Laparoscopic surgical access also independently reduced SSI ( $P = 0.003$ ) and 30-day readmission ( $P = 0.03$ ) rates compared with open surgery. Rectal anastomosis was associated with a higher risk of anastomotic leak ( $P = 0.001$ ) and 30-day



**Fig. 1** CONSORT flow chart for SOAP study

OABP, oral antibiotic prophylaxis.

mortality ( $P=0.03$ ). Subgroup analyses of the impact of the success of MBP on SSI and anastomotic leak rates are provided in [Table 4](#).

## Discussion

In this study, OABP used with MBP reduced postoperative SSI after elective colorectal resection involving an anastomosis, regardless of the success of MBP. This effect was most marked for the rate of superficial SSI, but was also observed in deep and organ space SSI. It was also found that OABP used with MBP reduced the incidence of anastomotic leak. Subgroup analysis suggested that adequate MBP (BBPS score 2 or more) is important to reduce

anastomotic leakage and also the adequate MBP without OABP reduced SSI.

The two primary endpoints of this study were rates of SSI and postoperative ileus. Although SSI rates were reduced, no difference was seen in the incidence of postoperative ileus. This might be related to the lower than anticipated overall incidence of postoperative ileus in the study, which could be explained by the routine use of ERAS protocols in all four participating institutes.

The role of OABP before elective colorectal surgery is controversial; previous underpowered studies have demonstrated variable results. A single-centre study by Espin-Basany and colleagues<sup>23</sup> compared three groups: MBP and three doses of OABP, MBP and one dose of OABP, and no OABP. All patients received intravenous second-generation cephalosporin prophylaxis. It was

Table 1 Patient characteristics

	Oral antibiotic prophylaxis (n = 253)	No oral antibiotic prophylaxis (n = 276)
Age (years) <sup>*</sup>	66.1(12.1)	66.5(12.3)
BMI (kg/m <sup>2</sup> ) <sup>*</sup>	27.0(4.3)	27.3(4.5)
Sex ratio (F : M)	101 : 152	146 : 130
Cardiac disease	101 (39.9)	85 (30.8)
Diabetes mellitus	44 (17.4)	50 (18.1)
COPD	34 (13.4)	19 (6.9)
Anticoagulant therapy	44 (17.4)	37 (13.4)
Tumour category		
T1	18 (7.1)	13 (4.7)
T2	43 (17.0)	51 (18.5)
T3	98 (38.7)	114 (41.3)
T4	23 (9.0)	29 (10.5)
Not malignant or tumour unknown	71 (28.1)	69 (25.0)
BBPS score ≥ 2	159 (62.8)	169 (61.2)
Laparoscopic procedure	134 (53.0)	157 (56.9)
Rectal anastomosis	91 (36.0)	90 (32.6)
Neoadjuvant therapy for rectal cancer	36 of 67 (54)	42 of 81 (52)

Values in parentheses are percentages unless indicated otherwise; <sup>\*</sup> values are mean(s.d.). COPD, chronic obstructive pulmonary disease; BBPS, Boston Bowel Preparation Scale.

Table 2 Intraoperative and postoperative complications

	Oral antibiotic prophylaxis (n = 253)	No oral antibiotic prophylaxis (n = 276)	z	P <sup>*</sup>
Intraoperative anaesthetic complication	17 (6.7)	11 (4.0)	1.40	0.081
Complications by Clavien–Dindo grade				0.689 <sup>†</sup>
0	158 (62.5)	167 (60.5)		
I	41 (16.2)	42 (15.2)		
II	31 (12.3)	44 (15.9)		
IIIa	2 (0.8)	1 (0.4)		
IIIb	11 (4.3)	14 (5.1)		
IVa	6 (2.4)	4 (1.4)		
IVb	1 (0.4)	0 (0)		
V	3 (1.2)	4 (1.4)		
<i>Clostridium difficile</i> infection	4 (1.6)	2 (0.7)	0.92	0.176
Overall SSI	8 (3.2)	27 (9.8)	-3.06	0.001
Superficial SSI	6 (2.4)	18 (6.5)	-2.29	0.011
Deep SSI	1 (0.4)	4 (1.4)	-1.25	0.105
Organ space SSI	1 (0.4)	5 (1.8)	-1.53	0.061
Postoperative ileus	16 (6.3)	16 (5.8)	0.25	0.343
Anastomotic leak	4 (1.6)	13(4.7)	-2.03	0.020
Hospital readmission	12 (4.7)	10 (3.6)	0.64	0.251
Mortality	3 (1.2)	4 (1.4)	-0.26	0.397

Values in parentheses are percentages. SSI, surgical-site infection. <sup>\*</sup> z test, except <sup>†</sup>  $\chi^2$  test.

Table 3 P values from multivariable linear regression analysis of the effect of demographic and clinical variables on primary and secondary endpoints

	P				
	SSI	Postoperative ileus	Anastomotic leakage	Mortality	Hospital readmission
Age > mean (66.3 years)	0.437	0.464	0.127	0.170	0.287
BMI > mean (27.2 kg/m <sup>2</sup> )	0.391	0.391	0.174	0.307	0.421
Male sex	0.249	0.005	0.479	0.171	0.083
Cardiac disease	0.357	0.246	0.061	0.334	0.447
Diabetes mellitus	0.464	0.464	0.323	0.402	0.297
COPD	0.406	0.040	0.083	0.348	0.020
Anticoagulant therapy	0.083	0.153	0.347	0.446	0.161
Oral antibiotic prophylaxis	<0.001	0.332	0.048	0.392	0.256
BBPS score ≥ 2	0.052	0.190	0.481	0.106	0.242
Laparoscopic surgical access	0.003	0.121	0.337	0.252	0.031
Rectal anastomosis	0.118	0.207	0.001	0.031	0.232
Neoadjuvant therapy	0.461	0.216	0.208	0.133	0.116
Intraoperative surgical complication	0.164	0.336	0.404	0.024	0.581
Intraoperative anaesthetic complication	0.093	0.321	0.173	0.002	0.203

SSI, surgical-site infection; COPD, chronic obstructive pulmonary disease; BBPS, Boston Bowel Preparation Scale.

**Table 4** Subgroup analyses of impact of success of mechanical bowel preparation on surgical-site infection and anastomotic leak rates

	No. of patients	BBPS score $\geq 2$ (n = 328)	BBPS score $\leq 1$ (n = 129)	z	P*
<b>Surgical-site infection</b>					
Oral antibiotic prophylaxis	217	5 of 159 (3.1)	3 of 58 (5)	-0.70	0.242
No oral antibiotic prophylaxis	240	14 of 169 (8.3)	11 of 71 (15)	-1.67	0.047
z		-1.99	-1.87		
P*		0.023	0.031		
<b>Anastomotic leak</b>					
Oral antibiotic prophylaxis	217	1 of 159 (0.6)	2 of 58 (3)	-1.57	0.058
No oral antibiotic prophylaxis	240	10 of 169 (5.9)	3 of 71 (4)	0.53	0.298
z		-2.66	-0.23		
P*		0.004	0.409		

Values in parentheses are percentages. BBPS, Boston Bowel Preparation Scale. \*z test.

found that OABP did not influence SSI rates, but gastrointestinal side-effects were experienced by 40 per cent of patients who received OABP. In the present study, the side-effects of OABP were mild, and only 2.3 per cent of patients stopped the medication because of side-effects.

The recent MOBILE trial<sup>31</sup> compared patients who received MBP and OABP with those treated according to a NoPrep policy. Although there was a 50 per cent increase in complications in the NoPrep group (11 versus 7 per cent), the authors concluded that there was no significant difference between the two groups. This was most probably because the study was underpowered to detect a 4 per cent difference.

The present study has some weaknesses. It was not double-blinded; however, double-blinding might have hindered patient recruitment. Radiological screening for anastomotic leak was not undertaken routinely as this was not normal practice at any of the participating sites. The strength of the study is that it is a prospective, randomized, assessor-blinded study with wide inclusion criteria. Patients were not selected according to indications, procedure types or surgical approach (open/laparoscopic). Therefore, the study groups reflect current routine colorectal surgery performed in Hungary in both university and non-university hospitals, and in urban and rural centres.

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