DANISH MEDICAL JOURNAL

Original Article

Dan Med J 2020;67(10):A04200286

Prevention of anastomotic leak following surgical treatment for rectal cancer

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Dan Med J 2020;67(10):A04200286

ABSTRACT

INTRODUCTION: Anastomotic leak (AL) is a major complication to surgical treatment of colorectal cancer affecting approximately 12% of patients. AL is associated with a 6-30% mortality. Finding methods that may reduce the incidence of AL is therefore important. In this study, we aimed to examine the effect of mechanical bowel preparation (MBP) and oral antibiotics on the rate of AL.

METHODS: This was a retrospective, single-centre analysis of patients undergoing surgical treatment for rectal cancer. We included 150 consecutive patients treated from July 2014 to October 2018. From June 2017 onwards, 50 patients comprised the study group (receiving MBP and oral antibiotics), while the preceding 100 patients served as a control group (receiving a rectal enema).

RESULTS: Two cases (4%) of AL were found in the study group and 20 cases (20%) in the control group ($p < 0.01$). Converting from laparoscopy to open surgery or having a World Health Organization performance score 2-3 were also associated with AL in univariate analysis.

CONCLUSION: Administrating MBP and oral antibiotics prior to surgery seems to reduce the incidence of AL following rectal cancer surgery.

FUNDING: none.
TRIAL REGISTRATION: not relevant.

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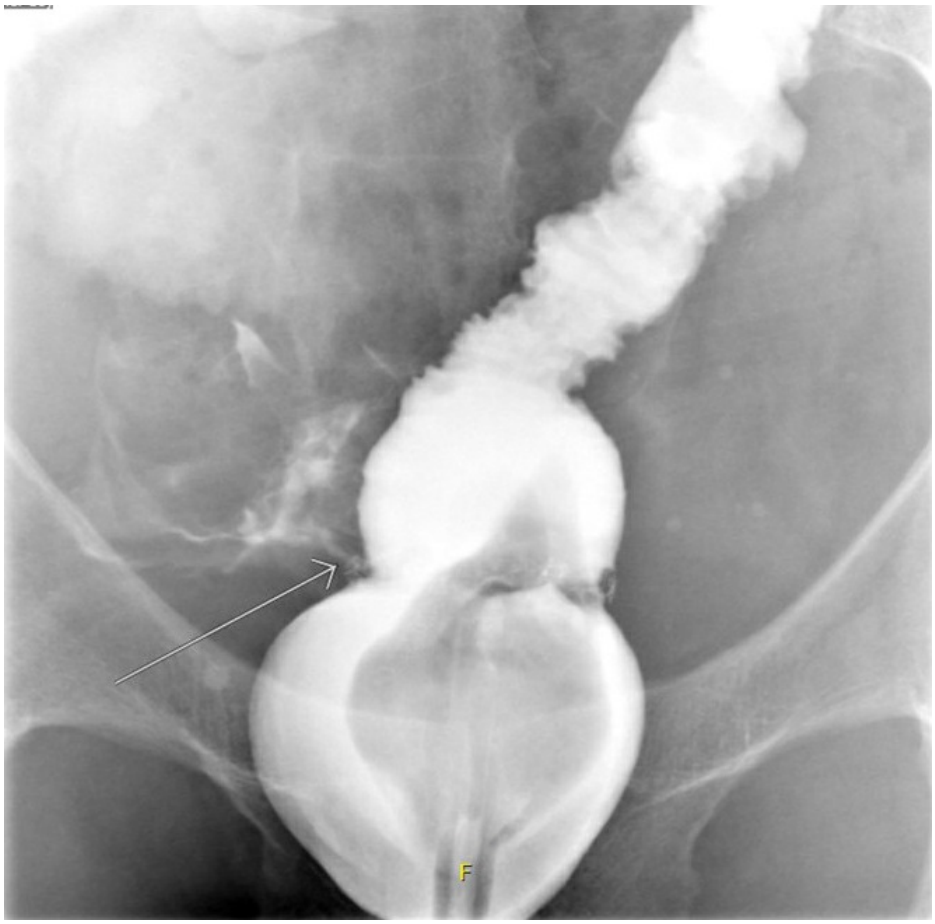
Colorectal cancer is a common disease worldwide, and the second most common cancer death in Western Europe [1]. Surgery is the foundation of curative treatment. However, some patients are affected by surgical-site infections (SSIs). The most serious SSI is anastomotic leak (AL) which affects approximately 12% of patients [2]. The occurrence of AL varies from 1-24% [3, 4], with increasing incidence for more distal colorectal and coloanal anastomoses [5, 6]. AL may have undesirable consequences such as unanticipated surgery, diverting stomas and severe sepsis with a reported mortality in the 6-30% range [5, 7].

A tension-free anastomosis with sufficient blood supply and a carefully executed apposition of the bowel wall, either via hand-sewn or stapled techniques, are widely accepted basic requirements to promote the healing of an anastomosis [8]. There is less consensus on the optimal preoperative bowel preparation. Bowel decontamination using mechanical bowel preparation (MBP) combined with oral antibiotics was adopted more than 60 years ago after Cohn & Rivers [9] found that local infusion of antibiotics prevented AL and reduced ischaemia in bowel anastomoses in dogs.



A small leak (arrow) from the colorectal anastomosis following low anterior resection.

As surgical techniques, anaesthesia and post-operative care improved, broad-spectrum intravenous antibiotics replaced oral antibiotics. The idea that the rate of AL was influenced by bowel content was discarded in favour of factors related to surgical technique and patient-related aspects, such as frailty. Meanwhile, the incidence rate of AL decreased more slowly than the general infection rate in the decades that passed. This prompted new research on MBP combined with oral antibiotics. Studies showed that this combination reduces SSIs, including AL [10, 11].

The typical oral antibiotic regimen in colorectal surgery uses non-absorbable antibiotics which work by reducing the impact of endogenous infections from gut microorganisms including gram-negative bacteria, *Staphylococcus aureus* and fungi [12, 13]. At our centre, we use erythromycin and gentamicin.

We investigated the effectiveness of preoperative MBP combined with oral antibiotics to prevent AL in patients undergoing surgical resection for rectal cancer.

METHODS

This is an observational before-and-after study conducted at the Department of Surgery, Bispebjerg Hospital, Copenhagen, Denmark. The study included 150 consecutive patients undergoing surgical treatment for rectal cancer from July 2014 to October 2018. From June 2017 onwards, 50 patients comprised the study group, while the preceding 100 patients served as a control group.

Patients eligible for inclusion were adults (aged ≥ 18 years) diagnosed with rectal cancer within 15 cm from the anal verge, treated with partial or total mesorectal resection with primary anastomosis, with or without a

diverting stoma. The criteria for exclusion were procedures intended to palliate, as well as emergency surgery.

The study group received oral antibiotics in addition to MBP the day before surgery. One 500 mg erythromycin tablet and one 80 mg gentamicin tablet were ingested at 12 p.m., 4 p.m., 8 p.m. and 12 a.m. The MBP (macrogol 3, 350 electrolyte) was mixed with 1 l of water and ingested at 2 p.m. and again at 10 p.m. The control group received a rectal enema (docusate sodium 240 mg and sorbitol 60 g) at 7 a.m. on the day of surgery. A perioperative single shot of intravenous antibiotics (1 g metronidazole and 1.5 g cefuroxime) was given to all patients, and was repeated after three hours in case of prolonged surgery. Both the study and the control group were treated in accordance with the principles of enhanced recovery after surgery [14].

The diagnosis of AL was based on clinical suspicion and confirmed using contrast-enhanced CT, endoscopic examination or during surgery. The extent of post-operative complications was characterised using the Clavien-Dindo classification system [15].

The primary endpoint of this study was to compare AL rates in the two groups. Secondary endpoints comprised other surgical complications including bowel obstruction and wound dehiscence, post-operative medical complications and 30- and 90-day mortality.

Approval to publish our data was obtained from the Danish Data Protection Agency (record number: 2020-522-0200).

The chi-squared test and univariate analysis were used for analytical statistics. The two-sided p-values were reported with the level of significance set as $p < 0.05$. A 95% confidence interval was used in all statistical analyses. Statistical analyses were performed.

Trial registration: not relevant.

RESULTS

Baseline characteristics

MBP in addition to oral antibiotics (study group) were administered to 50 consecutive cases and included 18 (36%) females and 32 (64%) males. The control group comprised the 100 preceding cases and included 46 (46%) females and 55 (55%) males.

Table 1 illustrates that the study group had a larger number of patients with high tumours; 31 (62%) versus 43 (43%) patients. The study group also had fewer patients with Union for International Cancer Control (UICC) stage IV; 3 (6%) versus 16 (16%) patients. However, no significant difference was found between the study group and the control group for any of the baseline characteristics.

TABLE 1 / Baseline characteristics of the study group (mechanical bowel preparation + oral antibiotics) and control group (rectal enema).

	Study group (N = 50)	Control group (N = 100)	p-value
Females, n (%)	18 (36)	46 (46)	0.24
Age, mean, yrs	64	62.6	0.46
ASA class, n (%)			
1	23 (46)	46 (46)	
2	24 (48)	49 (49)	
3	3 (6)	5 (5)	
WHO performance score, n (%)			0.12
0	47 (94)	81 (81)	
1	2 (4)	17 (17)	
2	1 (2)	1 (1)	
3	0	1 (1)	
Current smokers, n (%)	13 (26)	15 (15)	0.13
Alcohol consumption › national recommendations[a], n (%)	3 (6)	8 (8)	0.66
B MI, mean, kg/m^2	24.9	25.1	0.70
Diagnosed through screening programme[b], n (%)	13 (26)	27 (27)	0.90
UICC stage, n (%)			0.29
I	12 (24)	27 (27)	
II	18 (36)	28 (28)	
III	17 (34)	29 (29)	
IV	3 (6)	16 (16)	
Tumour distance from anal verge, n (%)			0.10
Low: ‹ 5 cm	0	1 (1)	
Middle: 5-10 cm	17 (34)	55 (55)	
High: › 10 cm	31 (62)	43 (43)	
pT, n (%)			0.53
1	6 (12)	17 (17)	
2	8 (16)	23 (23)	
3	32 (64)	52 (52)	
4	4 (8)	8 (8)	
pN, n (%)			0.29
0	30 (60)	62 (62)	
1	9 (18)	24 (24)	
2	11 (22)	12 (12)	
No preoperative oncological treatment, n (%)	49 (98)	93 (93)	0.33

ASA = The American Society of Anesthesiologists; pN = pathological node stage; pT = pathological tumour stage; UICC = Union for International Cancer Control; WHO = World Health Organization.
a) Females: › 14 U/wk; males: › 21 U/wk.
b) Danish Colorectal Cancer Screening Programme

Clinical findings and surgical approach

All operations were conducted by a team of two certified colorectal surgeons. During the study period, the number of colorectal surgeons was reduced from five to four. The anastomosis was stapled, end-to-end, in all but one case in the control group where it was hand sewn. The same stapler device was used throughout the study.

Left flexure mobilisation was significantly more common in the study group; 42 (84%) in the study group versus 51 (51%) in the control group ($p < 0.01$) (**Table 2**). This reveals a change of operative practice after MBP, and oral antibiotics were added to the preoperative regimen. Mobilisation of the left flexure was made mandatory during the study period as a means to reduce AL (reducing tension and increasing blood supply to the anastomotic site).

In this study, we were unable to demonstrate a significant reduction of AL by this effort alone (**Table 3**). Apart from mobilising the left flexure, no other changes were made regarding operative technique or the use of instruments.

TABLE 2 / Perioperative data comparing study group (mechanical bowel preparation + oral antibiotics) with control group (rectal enema).

	Study group (N = 50)	Control group (N = 100)	p-value
Surgical approach, n (%)			0.78
Laparoscopy	48 (96)	95 (95)	
Laparotomy	2 (4)	5 (5)	
Conversion	0	6 (6)	0.08
Mesorectal excision, n (%)			0.49
Partial	24 (48)	42 (42)	
Total	26 (52)	58 (58)	
Mobilising the left colic flexure, n (%)			< 0.01
No	8 (16)	49 (49)	
Yes	42 (84)	51 (51)	
Temporary colostomy, n (%)	20 (40)	44 (44)	0.64
Perioperative blood loss, mean, ml	108.5	140.6	0.51
Perioperative transfusion, n (%)	2 (4)	3 (3)	0.73

TABLE 3 / Univariate analysis of risk factors associated with anastomotic leak[a].

	AL (n = 22 (15%))	No AL (n = 128 (85%))	p-value
Age, mean, yrs	63.4	63.0	0.86
Sex, n (%)			0.27
Male	15 (68)	71 (55)	
Female	7 (32)	57 (44)	
ASA class 3-4, n (%)	3 (14)	5 (4)	0.06
WHO performance score 2-3, n (%)	2 (9)	1 (1)	0.01
Neoadjuvant therapy, n (%)	0	8 (6)	0.48
Laparoscopy converted to laparotomy, n (%)	3 (13)	3 (2)	0.01
Perioperative blood transfusion, n (%)	3 (14)	2 (2)	0.11
Diverting stoma, n (%)			0.52
No	14 (64)	72 (56)	
Yes	8 (36)	56 (44)	
Mobilising left flexure, n (%)			0.76
Yes	13 (59)	80 (62)	
No	9 (41)	48 (38)	
MBP + oral antibiotics, n (%)			< 0.01
Yes	2 (9)	48 (37)	
No, only rectal enema	20 (91)	80 (63)	

AL = anastomotic leak; ASA = The American Society of Anesthesiologists; MBP = mechanical bowel preparation; WHO = World Health Organization.
a) Only variables deemed clinically relevant were included.

Outcomes

Anastomotic leak

The rate of AL was significantly lower in the study group ($p < 0.01$) than in the control group. There were two cases (4%) of AL in the study group compared with 20 cases (20%) in the control group (**Table 4**). The two patients in the study group both had small leaks, verified by CT. Both had a diagnostic laparoscopy made where the anastomosis was found to be intact. One of these cases had some degree of peritonitis, and an abdominal drain was established. They both received anastomosis-saving treatment with a transverse colostomy. The colostomy was reversed after one and five months, respectively, following their index operation.

TABLE 4 / Outcomes in the study group (mechanical bowel preparation + oral antibiotics) compared with control group (rectal enema).

	Study group (N = 50)	Control group (N = 100)	p-value
Anastomotic leak, n (%)			< 0.01
Clavien-Dindo IIIa	0	7 (7)	
Clavien-Dindo IIIb	2 (4)	11 (11)	
Clavien-Dindo IVa	0	2 (2)	
Subtotal	2 (4)	20 (20)	
Time until anastomotic leak, days	3	7.8	0.31
Other surgical complications[a], n (%)			
Clavien-Dindo I-IIIa	8 (16)	6 (6)	0.03
Clavien-Dindo IIIb	7 (14)	3 (3)	0.03
Post-operative rectal bleeding	8 (16)	3 (3)	< 0.01
Bowel obstruction	3 (6)	0	0.03
Intra-abdominal abscess	1 (2)	1 (1)	0.29
Colostomy complications	0	1 (1)	0.48
Others	3 (6)	4 (4)	0.15
Subtotal	15 (30)	9 (9)	
Post-operative medical complications, n (%)			0.15
Pneumonia	0	1 (1)	0.48
Sepsis	1 (2)	3 (6)	0.74
Deep-vein thrombosis	0	1 (1)	0.48
Others	2 (4)	6 (6)	0.61
Subtotal	3 (6)	11 (11)	
Intensive care, n (%)	1 (2)	2 (2)	1.0
Length of stay, median, days (min./max.)	4 (1/39)	5 (2/56)	0.07
Mortality, n (%)			0.16
30 days	0	0	
90 days	1 (2)	0	

a) Each patient may have > 1 complication.

Among the 20 patients with AL in the control group, three had their anastomosis undone and underwent a sigmoid colostomy. One patient had his sigmoid colostomy reversed after almost nine months, whereas the other two did not due to their general condition.

Secondary outcomes

There was no difference between the two groups when comparing post-operative medical complications, intensive care, median days of admission and 30- and 90-day mortality. A single patient died in the study group three months after the initial operation for rectal cancer. The cause of death could not be established.

The study group had a higher incidence of post-operative bleeding from the anastomosis ($p < 0.001$) (Table 4). These cases were managed conservatively in five out of eight cases and through endoscopically applied haemoclips in the remaining three.

DISCUSSION

In two otherwise comparable groups, AL rates seem to be lowered by administering MBP combined with oral antibiotics prior to surgery for rectal cancer. Furthermore, AL seems to be more common in patients with a World Health Organization performance score of 2-3 or when conversion from laparoscopy to laparotomy is done. Though not significant, a difference in UICC stage and tumour level was recorded favouring the study group – possibly influencing the difference in AL rates between the two groups.

One limitation to this study is its retrospective design, which weakens the study conclusion due to the increased risk of confounders and bias. The relatively small size of the study group and the fact that it is a single-centre study are additional limitations. The relatively high rate of AL in the control group may explain some of the observed decrease in AL as a regression-to-the-mean phenomenon.

The use of prophylactic oral antibiotics and MBP is controversial. It disturbs the microbiome, the microbial ecosystem of the body, which under normal conditions provides resistance to pathogens through stimulation of systemic immunity. Maintaining the microbiome could therefore be a strategic approach to preventing infections [16]. Yet, prophylactic antibiotics have shown to be very successful when studied in an intensive care setting, with reduction of mortality rates and with low endemic levels of antibiotic resistance [17]. Whereas the microbiome works in our favour under normal conditions, major physiological insults provoke dramatic changes in the gut microbial density, function and spatial location. Injury to the intestine can result in the transformation of gut bacteria into a more virulent phenotype. Rodent models of AL after low colon resection and segmental de-vascularisation have shown that ischaemia was not the causative agent for AL which was rather due to the high collagenase activity expressed by *Enterococcus faecalis* strains colonizing the tissue [18].

The choice of oral antibiotics, gentamicin and erythromycin, was supported by the microbiologist advising our centre. That non-absorbable antibiotics significantly reduce the incidence of AL has been known since the 1970s [12]. The value of intravenous antibiotics in the immediate preoperative period is clearly established and intravenous antibiotics are currently used worldwide [10]. The effect of MBP alone has been debated, and some studies suggest that MBP might have no positive influence on SSIs [10, 13] and specifically on the risk of AL due to potentially unfavourable effects on post-operative complications such as a deranged fluid status [19]. However, MBP prior to colorectal resection may allow for a better perioperative bowel handling [20].

Lately, the use of oral antibiotics has been gaining ground. This is partly owed to Klinger et al who found that MBP combined with oral antibiotics prior to surgery results in significantly lower rates of SSIs compared with no preparation or oral antibiotics alone. Additionally, they found lower rates of SSIs when administering MBP combined with oral antibiotics compared with oral antibiotics alone [11]. Contradictory to Klinger's results are the findings of Abis et al [7], who conducted a randomised trial on 455 patients with colorectal cancer scheduled for elective surgery with primary anastomosis. The study group received oral antibiotics and MBP, and the control group received neither. Their data showed that MBP combined with oral antibiotics diminished the rate of SSIs, but not the rate of AL. Our study population differs from that of Abis by presenting purely rectal cancer cases. Another remarkable difference is the duration of the preoperative treatment. Whereas Abis administered MBP and oral antibiotics for three days prior to surgery and up to three days after surgery, our study group received MBP combined with oral antibiotics one day before surgery only.

Our results suggest that the rate of AL can be lowered by administering MBP combined with oral antibiotics the

day before surgery. We hope that these results may contribute to the discussion regarding the optimal preoperative bowel preparation in rectal restorative surgery.

CONCLUSIONS

Administering MBP combined with oral antibiotics prior to surgery seems to reduce the incidence of AL following rectal cancer surgery.

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Accepted: 13 August 2020

Conflicts of interest: none. Disclosure forms provided by the authors are available with the full text of this article at Ugeskriftet.dk/dmj

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