The State of Mechanical Bowel Preparation in Colorectal Surgery

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Colofon

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The State of Mechanical Bowel Preparation in Colorectal Surgery

Huidige inzichten in de toepassing van mechanische darmvoorbereiding
bij colorectale chirurgie

Proefschrift

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Contents

Chapter 1

Introduction and outline of this thesis

Introduction

*Dogma: a point of view or tenet put forth as authoritative without adequate grounds.

Anastomotic leakage

Surgical resection is the cornerstone of treatment for patients with colorectal cancer and has an important role in patients with inflammatory bowel disease or other benign bowel conditions requiring surgical treatment. Generally, restoration of bowel continuity with a primary anastomosis is pursued in uncomplicated colorectal resections. The most serious complication of colorectal surgery with restoration of bowel continuity is anastomotic leakage. When the abdominal cavity is exposed to faeces due to anastomotic leakage it causes peritonitis with possible sepsis, need for reintervention and increased morbidity and mortality. The incidence of anastomotic leakage after colon surgery varies in literature between 3 and 6.4%. [1] There is a particularly high incidence following low colorectal and coloanal anastomosis accompanied by high morbidity and mortality rates ranging from 6 to 22%. [2-7]

Several other risk factors such as male sex, higher American Society of Anesthesiologists (ASA), intraoperative bloodloss, type of anastomosis (side-to-end vs. end-to-end) are associated with significantly higher anastomotic leakage rates in multivariate analysis. However the cause of anastomotic leakage is probably often multifactorial and many more risk factors have been identified such as obesity, diabetes, corticosteroids, preoperative pelvic irradiation, surgical experience, malnutrition, operative time etc. [1] [3] [6] [8]

The application of a defunctioning ileostoma decreases the rate of symptomatic anastomotic leakage and is recommended after low anterior resection in literature. By diverting the faecal stream and keeping the anastomosis free and clean of faecal contamination, anastomotic leakage rate is reduced and in case of anastomotic leakage may cause less or milder septic complications. [9-11]

Why mechanical bowel preparation

Traditionally mechanical bowel preparation (MBP) is used to clean the bowel lumen of faeces preoperatively. The aim of cleansing the bowel using MBP is to reduce the faecal mass and bacterial load inside the bowel lumen. [12] In theory the effects of MBP are two-fold: this procedure would decrease the risk of faecal spillage peroperatively and limit contamination of the peritoneal cavity and infection of the abdominal wound and/or possibly limit mechanical disruption of the anastomosis due to passage of solid faecal material and therefore prevent against anastomotic leakage. Also MBP would reduce the amount of fecal matter contaminating the peritoneal cavity once leakage has occurred. [12-17]

As mentioned above a defunctioning stoma protects against symptomatic anastomotic leakage by keeping the anastomosis clear of faeces. However, the use of a diverting ileostomy in an unprepared colon is controversial in the eyes of many colorectal surgeons for the remaining faeces, distally to the ileostomy, may still jeopardize the anastomosis and increase the risk of leakage and septic complications. Therefore many surgeons prefer a cleansed bowel in combination with a defunctioning ileostomy. [18] However, the rational for MBP was no more than a theory, a belief and a tradition amongst colorectal surgeons rather than evidence based medicine. This dogma*, although over time and at present still widely practiced, has been regularly questioned in the past few decades.

Why no mechanical bowel preparation

Besides these proposed beneficial effects of MBP, some negative effects of MBP have been reported. Due to the osmolitic effect of MBP, causing diarrhea, valuable electrolytes are lost, fluid shifts may occur and one may be presented with a dehydrated patient with an imbalance in electrolytes prior to surgery. Especially the elderly, cardiac patients or renal patients would be susceptive to these side-effects of MBP, potentially putting them at risk for complications during and after surgery [19-20]

MBP has also been associated with morphologic alterations and inflammatory changes in the large bowel wall. Polyethylene glycol has been shown to cause microscopic damage in the different layers of the gastrointestinal wall in rats. One previous study also shows polyethylene glycol given before colonoscopy to cause eosinophilic cell infiltration and increased oedema of the lamina propria.[21-23] It is, however, unclear if these changes have a direct relation to the possible deleterious effects of MBP in terms of abdominal morbidity. [24] MBP also causes an imbalance in the bowel microflora as reported by Watanebe et al. They found no difference in the total colonic bacterial count in patients treated with and without MBP. Moreover they found significantly lower levels of beneficial contents of the gut such as probiotic bacteria and short-chain fatty acids playing a key role in colonic health. They suggest this imbalance in bowel microflora may lead to bacterial translocation. [25]

Another concern is that inadequate MBP may lead to liquid bowel contents in contrast to solid stool when not treated with MBP. Excessive intraoperative spillage of liquid bowel contents due to inadequate MBP has been reported, possibly causing more postoperative infectious complications. [26]

MBP is also generally described as unpleasant and distressing by patients. It does not rarely cause abdominal pain, bloating, nausea and other abdominal discomforts. In addition many patients need assistance requiring hospital admission the day before surgery. It is also associated with prolonged time to first bowel emptying, again adding on days in hospital. This increases the workload on hospital staff and the cost to society. [27]

A chronologic review of the literature

Sir William Halsted first proposed the use of some form of MBP in 1887 with the aims of decreasing surgical site infections and anastomotic dehiscence in colorectal surgery. [28] Since then many surgeons dogmatically adapted the application of MBP and considered it general practice. Until around 1970 the evidence for MBP is scarce.

The 1971 landmark article from Nichols and Condon really set the stage for the ensuing debate on whether or not MBP should be applied. [13] Anecdotal evidence from their clinical experience demonstrated improved morbidity and mortality with mechanical removal of gross faeces. The only controversy in their eyes was whether or not to add antibiotics. Hewitt et al. state in the Lancet in 1973: "Published reports on this subject are confusing but it is generally agreed that thorough cleansing of the bowel is beneficial", showing the disposition for MBP. [15] Surgeons of that time not so much questioned whether MBP was mandatory but more so focused on which regimen was superior for cleansing and decontaminating the bowel prior to colorectal surgery. In 1971 Rosenberg et al. randomized 150 patients between MBP alone, MBP plus one kind of antibiotic and MBP plus two kinds of antibiotics. Their findings suggested that in the prevention of postoperative infection at least three precautions are desirable: the correction of gross faecal loading before the operation, the use of preoperative intestinal antiseptics, and the avoidance of peritoneal contamination during surgery. [14] Barker et al. endorsed this theory that same year finding more wound infections in patients with gross loading of faeces after radical surgery for ulcerative colitis and Crohn's disease of the large bowel despite two different antibiotic regimens.[16] A retrospective study by Irving et al. noted that the incidence of dehiscence was significantly increased in cases where faecal loading of the bowel was present. [17]

An extensive review was published by Keighley et al. in 1983 who strongly advocated MBP and depicted the different methods of bowel preparation and added an addendum: "formulation and preparation of the authors' recommended bowel preparation". [12]

Again the main query had become which antibiotics should be added to the bowel preparation and trials were not so much focused on MBP or not but more on the different kinds of MBP in combination with or without oral antibiotics. [29-31]

Although quality randomized controlled trials were scarce and methodology and comparisons were diverse and far between MBP had by now become common practice for many surgeons. The first contradictive studies on MBP appeared and were not inferior compared to the literature supporting MBP. Hughes published one of the first clinical randomized trials already in 1972 stating: "This study has shown that vigorous mechanical preparation is not necessary. It is surprising how empty the bowel can be without any preparation at all and how loaded a prepared bowel can remain" and "omission of enemas and bowel washes from the preoperative procedures will be welcomed by both patients and nursing staff". [32] However his conclusions concerning MBP were highly disregarded. Thereafter Irving et al.

(1987) studied a consecutive series of 72 elective and emergency colectomies without any mechanical bowel preparation and only preoperative systemic antibiotics. Their conclusion was that MBP or oral antibiotics were unnecessary provided appropriate intravenously antibiotics were administered. [33] Also this study was highly criticized. In addition to Irving et al. Brownson et al. (1992) randomized 179 patients between MBP and no MBP and found a significantly higher rate of abdominal sepsis and anastomotic leakage in the MBP+ group. They were one of the first showing the possible detrimental effects of MBP in a randomized trial. [34] Several randomized trials followed and were incorporated in a meta-analysis by Slim et al. in 2004.[35] They found significantly more anastomotic leakage after MBP (5,6% versus 3,2%, P=0,032), confirming the earlier discovered possible detrimental effects of MBP. A Cochrane Database Review in that same period by Guenega et al. (2005) support this finding. [36]

Only in 2007 two of the largest clinical randomized trials were published with adequate power analysis. Jung et al. evaluated 1343 patients, 686 randomized to MBP and 657 to no MBP. [37] There were no significant differences in overall complications between the two groups. Mid/low rectal resections were excluded from the study which led to the clear conclusion that MBP could be omitted before colonic resection. Contant et al. randomized 1354 patients between MBP and no MBP. [8] Again they found no differences in anastomotic leakage rates between groups. Patients with anastomoses performed below the peritoneal verge were included in this study. Not long after Slim et al updated their meta-analysis consisting of 14 randomized trials and providing the best available evidence on the role of MBP in colorectal surgery in 2009. [38] In addition, Guenaga et al. (2009) updated the Cochrane Database Systemic Review incorporating 13 randomized clinical trials with 4777 participants. [39]

Both studies stated there is now no statistical evidence that patients benefit from MBP. Also results of detrimental effects of MBP were not reproduced in these updates. One might find it strange, that the conclusion changes over time in two main meta-analyses and two Cochrane Database reviews, but this reflects the performance and inclusion of larger, and better trials during the last update period.

Methods of mechanical bowel preparation.

Several methods of MBP were used. There was the traditional preparation which was a time consuming procedure usually consisting of a period of starvation for five days before surgery. The patient was encouraged to drink only a liquid diet followed by purgation with magnesium sulphate, magnesium citrate or sennasides, followed by an enema and rectal washout. The second method introduced by Hewitt et al. was whole bowel irrigation with an electrolyte solution through a nasogastric tube. [15] The technique was subsequently modified for use as bowel preparation. The procedure involved administration of an 10-12 liter electrolyte solution originally with normal saline. At last oral bowel preparation was introduced with

hypertonic solutions consisting of 4 liters of polyethylene glycol (PEG) or mannitol. Patients were able to drink this the day before surgery and acceptability improved as flavoring was added. It soon become clear that polyethylene glycol-electrolyte had several advantages over the other cleansing regimens. The traditional mechanical bowel preparation was tedious, time-consuming for medical staff, added to the period of hospitalization and required a starvation period possibly causing changes in serum electrolytes. Whole gut irrigation with isotonic normal saline and hypertonic mannitol solutions required a nasogastric tube and not seldom resulted in significant sodium and water retention and was therefore contraindicated in elderly patients and patients with cardiopulmonary and renal disease. In addition there was the explosive risk of mannitol in combination with diathermia. In 1985 Fleites et al. published a randomized trial advocating the use of oral polyethylene glycol-electrolyte lavage solutions. [40] They concluded that in addition to being a quicker and safer preparation compared to other preparations it was better tolerated and resulted in a cleaner colon containing fewer aerobic and anaerobic bacteria. More important infection rates were similar. In 1990 two surveys were conducted to document the current methods of MBP among 260 members of The American Society of Colon and Rectal Surgeons. Fifty-one percent used cathartics and enemas, 43% used polyethylene glycol and 4% used mannitol. [41] Among 352 colon and rectal surgeons in the United States and Canada 58% used polyethylene glycol, 36% used enemas and cathartics in combination with dietary restrictions and mannitol was used in 5%. [42] In both surveys whole gut irrigation was performed in less than 1% of patients. In 1997 around 800 North American, colorectal surgeons were surveyed for their current bowel preparation practices before elective procedures. All used some form of mechanical preparation: oral polyethylene glycol solution in 70.9%, oral sodium phosphate solution with or without bisacodyl in 28.4% showing a growing preference for oral polyethylene glycol. [43] Although PEG-based solutions are safe and effective, it requires the intake of large volumes of fluid compared to sodium phosphate with similar cleansing effects. [44] However, sodium phosphate has been associated with serious side effects such as calcium deposition in the kidneys (i.e. nephrocalcinosis) causing possible acute kidney injury. [45]

In literature there is a lot of controversy on the use of sodium phosphate with studies showing increased risk of acute kidney injury and no increased risks compared to PEG, not even in high-risk clinical subgroups. [45-46]

Large randomized trials on this side effect have not been performed up to now. Until then PEG is the preferred MBP for most clinicians. In the large multicentre randomized trial by Contant et al. discussed in Chapter 2, two out of 13 participating hospitals used sodium phosphate instead of PEG (12% versus 88% respectively). [8] The meta-analysis by Slim et al. (2009) demonstrated no difference between PEG and sodium phosphate regarding anastomotic leakage rate and other septic complications.[38] In addition in the randomized trial by Jung et al PEG was used in 47,2% and sodium phosphate in 48,5 % of patients. No effect

on incidence of infectious or surgical-site complications , including anastomotic leakage was found comparing both forms of MBP.[37]

The problem

Despite the conclusion drawn by the most recent meta-analysis by Slim et al and the most recent Cochrane Systematic Database Review (2011) that stated there is no statistical evidence that patients benefit from MBP, they included randomized clinical trials with great heterogeneity and the majority consists of small sample size. [38,47] Only two randomized trials included performed sufficient power analysis and meet up to a sufficient sample size. One of these trials was performed by Contant et al. and is described in Chapter 2.[8] The other trial was performed by Jung et al. in 2007. [37]

Slim et al performed a sensitivity analysis between small and large trials finding significant differences in several outcomes showing the importance of large trials and potential bias of underpowered small trials. [38] However, in order to achieve large numbers of patients and sufficient sample size, heterogeneity regarding level of anastomosis, diagnosis (cancer, inflammatory bowel disease, diverticulitis) or application of a loop ileostomy is inevitable, all potentially influencing the outcome of the trials. Therefore analysis of the influence of MBP in more specific and detailed subgroups such as low anterior or rectal surgery, surgery for inflammatory bowel disease or diverticulitis and patients with or without a deviating ileostomy are warranted and expressed in this thesis.

References

1. IS Bakker, I Grossmann, D Henneman, et al. Risk factors for anastomotic leakage and leak-related mortality after colonic cancer surgery in a nationwide audit. BJS 2014; 101: 424-432.
2. E Rullier, C Laurent, JL Garrelon, P Michel, J Saric, M Parneix. Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg 1998;85:355-8.
3. WM Chambers WM, NJMcC Mortensen. Postoperative leakage and abscess formation after colorectal surgery. Best practice and research clinical gastroenterology. 2004;18:865-880.
4. WL Law, KW Chu. Anterior resection for rectal cancer with mesorectal excision. A prospective evaluation of 622 patients. Ann Surg 2004;240:260-268.
5. WO Karanji, AP Corder, P Bearn, RJ Heald. Leakage from stapled low anastomosis after total mesorectal excision for carcinoma of rectum. Br J Surg 1994;81:1224-6.
6. PB Soeters, JP de Zoete, CH Dejong, NS Williams, CG Baeten. Colorectal Surgery and Anastomotic Leakage. Dig Surg 2002;19:150-155.
7. A Alves, Y Panis, P Mathieu, G Mantion, F Kwiatkowski, K Slim, et al. Postoperative Mortality and Morbidity in French Patients Undergoing Colorectal Surgery. Arch Surg 2005;140:278-283.
8. CME Contant, WCJ Hop, HP van't Sant et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomized trial. Lancet 2007;370:2112-17.
9. N. Hüser, CW Michalski, M Erkan et al. Systematic review and meta-analysis of the role of defunctioning stoma in low rectal cancer surgery. Ann Surg 2008;248:52-60.
10. WS Tan, CL Tang, L Shi et al. Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer. Br J Surg 2009;96:462-472.
11. P Matthiessen, O Hallböök, J Rutegard et al. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer. Ann Surg 2007;246:207-214.
12. Keighley MR, Lee JR, and Ambrose NS. Indications and techniques for bowel preparation in colorectal cancer. International Advances in Surgical Oncology 1983;6:257-270.
13. Nichols RL, Condon RE. Preoperative preparation of the colon. Surg Gynecol Obstet 1971; 132: 323-37.
14. Rosenberg IL, Graham NG, Dombal FT, and Goligher JC. Preparation of the intestine in patients undergoing major large-bowel surgery, mainly for neoplasm of the colon and rectum. Br J Surg 1971;58(4):266-269.
15. Hewitt J, Reeve J, Rigby J, Cox AG. Whole-gut irrigation in preparation for large-bowel surgery. Lancet. 1973 Aug 18;2(7825):337-40.
16. Barker K, Graham NG, Mason MC, et al. The relative significance of preoperative oral antibiotics, mechanical bowel preparation, and preoperative peritoneal contamination in the avoidance of sepsis after radical surgery for ulcerative colitis and Crohn's disease of the large bowel. Br J Surg. 1971;58(4):270-3.
17. TT Irving, JC Goligher. Aetiology of disruption of intestinal anastomoses. Br J Surg 1973; 60(6)461–464.
18. RJ Drummond, RM McKenna and DM Wright. Current practice in bowel preparation for colorectal surgery: a survey of the members of the Association of Coloproctology of GB & Ireland. Colorectal Disease 2011;13:708-710.
19. O Zmora, AJ Pikarsky, SD Wexner. Bowel preparation for colorectal surgery. Dis Colon Rectum 2001;44:1537-1549
20. CE Pineda, AA Shelton, T Hernandez-Boussard et al. Mechanical bowel preparation in intestinal surgery : a meta-analysis and review of the literature. J Gastrointest Surg 2008;12:2037-2044.

21. Bingol-Kologlu M, Emin Senocak M. A comparative histopathologic evaluation of the effects of three different solutions used for whole bowel irrigation: an experimental study. J Ped Surg 2000;35:564-68.
22. Coskun A, Uzunkoy A, Duzgun SA et al. Experimental sodium phosphate and polyethylene glycol induce colonic tissue damage and oxidative stress. Br J Surg 2001;88:85-89.
23. Pockros PJ, Foroozan P. Golytely. Lavage versus a standard colonoscopy; preparation effect on normal colonic mucosal histology. Gastroenterology 1986;81:652-55).
24. Bucher P, Gervaz P, Egger JF, Soravia C, Morel P. Morphologic alterations associated with mechanical bowel preparation before elective colorectal surgery: a randomized trial. Dis Colon Rectum. 2006 Jan;49(1):109-12.
25. M Watanabe, M Murakami, K Nakao et al. Randomized clinical trial of the influence of mechanical bowel preparation on faecal microflora in patients undergoing colonic cancer resection. Br J Surg 2010 ;97 :1791-1797.
26. Mahajna A, Krausz M, Rosin D et al. Bowel preparation is associated with spillage of bowel contents in colorectal surgery. Dis Colon Rectum. 2005 Aug;48(8):1626-31.
27. B Jung, O Lannerstad, L Pahlman et al. Preoperative mechanical preparation of the colon: the patient's experience. BMC Surgery 2007;7:5.
28. Halsted WS. Circular suture of the intestine: an experimental study. Am J Med Sci. 1887;94:436-461.
29. Wolff BG, Beart RW, Dozois RR, et al. A new bowel preparation for elective colon and rectal surgery. 1988;123:895-900.
30. Bartlett JG, Condon RE, Gorbach SL, et al. Veterans administration cooperative study on bowel preparation for elective colorectal operations: impact of oral antibiotic regimen on colonic flora, wound irrigation cultures and bacteriology of septic complications. Ann Surg 1978;188:249-254.
31. Gottrup F, Diederich P, Sørensen K, et al. Prophylaxis with whole gut irrigation and antimicrobials in colorectal surgery. Am J Surg 1985;149:317-322.
32. Hughes ES. Asepsis in large-bowel surgery. Ann. Roy. Coll. Surg. Engl. 1972;51:347-356.
33. Irving AD, Scrimgeour D. Mechanical bowel preparation for colonic resection and anastomosis. Br J Surg 1987;74:580-581.
34. Brownson P, Jenkins SA, Nott D, et al. Mechanical bowel preparation before colorectal surgery: results of a prospective, randomized trial. Br J Surg 1992;79:461-2 (SRS Abstracts).
35. Slim K, Vicaut E, Panis Y, et al. Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation. Br J Surg 2004; 91: 1125–30.
36. Guenaga KK, Matos D, Castro AA, et al. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev 2005;25:CD001544.
37. Jung B, Påhlman L, Nystrom PO, et al. Mechanical bowel preparation study group. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. Br J Surg 2007;94:689-695.
38. Slim K, Vicaut E, Launay-Savary MV, et al. Updated systemic review and meta-analysis of randomized clinical trials on the role of mechanical bowel preparation before colorectal surgery. Ann Surg 2009;249:203-209
39. Guenaga KK, Matos D, Wille-Jørgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev 2009;1:CD001544.
40. Fleites RA, Marshall JB, Eckhauser ML, et al. The efficacy of polyethylene glycol-electrolyte lavage solution versus traditional mechanical bowel preparation for elective colonic surgery: a randomized, prospective, blinded clinical trial. Surgery 1985;4:708-717.
41. Beck DE, Fazio VW. Current preoperative bowel cleansing methods. Results of a survey. Dis Colon Rectum 1990;33:12-15.

42. Solla JA, Rothenberger DA. Preoperative bowel preparation. A survey of colon and rectal surgeons. Dis Colon Rectum 1990;33:154-159.

43. Nichols RL, Smith JW, Garcia RY, Waterman RS, Holmes JW. Current practices of preoperative bowel preparation among North American colorectal surgeons. Clin Infect Dis. 1997;24(4):609-19.

44. Bae SE, Kim KJ, Eum JBA et al. Comparison of 2 L of Polyethylene Glycol and 45 mL of Sodium Phosphate versus 4 L of Polyethylene Glycol for Bowel Cleansing: A Prospective Randomized Trial. Gut Liver. 2013 Jul;7(4):423-9.

45. Bradley Layton J, Klemmer PJ, Christiansen CF et al. Sodium Phosphate Does Not Increase Risk For Acute Kidney Injury After Routine Colonoscopy, Compared With Polyethylene Glycol. Clin Gastroenterol Hepatol. 2014 Jan 28.[Epub ahead of print]

46. Russmann S, Lamerato L, Motsko SP et al. Risk of further decline in renal function after the use of oral sodium phosphate or polyethylene glycol in patients with a preexisting glomerular filtration rate below 60 ml/min. Am J Gastroenterol. 2008 Nov;103(11):2707-16.

47. Guenaga KK, Matos D, Wille-Jørgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev 2011;9:CD001544.

Outline of this thesis

This thesis describes the influence and effects of mechanical bowel preparation (MBP) on colorectal surgery in general and on underexposed and distinguished features of MBP within colorectal surgery.

In **chapter 1** a general introduction is presented with a chronologic overview of literature, fundamentals of MBP and current matters of debate.
Chapter 2 presents one of two largest randomized trials to date comparing rate of anastomotic leakage after elective overall colorectal surgery between patients who were and were not treated with MBP. **Chapter 3** addresses the influence of MBP on anastomotic leakage rate in patients with anastomosis below the peritoneal verge after elective lower colorectal surgery. In addition all patients with a diverting ileostomy in this subgroup were evaluated.
In **chapter 4** we compared short-term outcome of patients confronted with anastomotic leakage treated with and without MBP prior to surgery.
Chapter 5 displays the current opinion of colorectal surgeons in the Netherlands on the role of MBP in laparoscopic colorectal surgery.
In **chapter 6** patients electively operated for Hinchey I/II diverticulitis were evaluated and compared with regard to being pretreated with MBP or not. **Chapter 7** discusses the influence of MBP on long-term survival in patients operated for colorectal cancer.
In **chapter 8** a general discussion is provided including recommendations for future research.

Chapter 2

Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial

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Abstract

Background Mechanical bowel preparation is a common practice before elective colorectal surgery. We aimed to compare the rate of anastomotic leakage after elective colorectal resections and primary anastomoses between patients who did or did not have mechanical bowel preparation.

Methods We did a multicentre randomised non-inferiority study at 13 hospitals. We randomly assigned 1431 patients who were going to have elective colorectal surgery to either receive mechanical bowel preparation or not. Patients who did not have mechanical bowel preparation had a normal meal on the day before the operation. Those who did were given a fluid diet, and mechanical bowel preparation with either polyethylene glycol or sodium phosphate. The primary endpoint was anastomotic leakage, and the study was designed to test the hypothesis that patients who are given mechanical bowel preparation before colorectal surgery do not have a lower risk of anastomotic leakage than those who are not. The median follow-up was 24 days (IQR 17–34). We analysed patients who were treated as per protocol. This study is registered with ClinicalTrials.gov, number NCT00288496.

Findings 77 patients were excluded: 46 who did not have a bowel resection; 21 because of missing outcome data; and 10 who withdrew, cancelled, or were excluded for other reasons. The rate of anastomotic leakage did not differ between both groups: 32/670 (4·8%) patients who had mechanical bowel preparation and 37/684 (5·4%) in those who did not (difference 0·6%, 95% CI −1·7% to 2·9%, p=0·69). Patients who had mechanical bowel preparation had fewer abscesses after anastomotic leakage than those who did not (2/670 [0·3%] *vs* 17/684 [2·5%], p=0·001). Other septic complications, fascia dehiscence, and mortality did not differ between groups.

Interpretation We advise that mechanical bowel preparation before elective colorectal surgery can safely be abandoned.

Introduction

Symptomatic anastomotic leakage is the most important surgical complication after colorectal surgery and can cause morbidity and mortality. Mechanical bowel preparation has been regarded as an e client strategy to prevent anastomotic leakage and septic complications. Observational data and expert opinions[1–4] have traditionally held that mechanical bowel preparation before colorectal surgery reduces faecal mass and bacterial count in the lumen. However, in the past few decades, the practice has been questioned.[5–10] In two studies, anastomotic leakage was more likely to occur in patients who had received mechanical bowel preparation before surgery.[7,8] However, these trials were underpowered, because of insufficient participants. We aimed to compare the outcome of elective colorectal resections with and without mechanical bowel preparation in terms of anastomotic leakage and other complications.

Methods

Study participants

Between April, 1998, and February, 2004, we enrolled patients at 13 participating hospitals (including nine teaching hospitals) in the Netherlands. The main criterion for inclusion was an indication for elective colorectal surgery with primary anastomosis. Patients were excluded if they had an acute laparotomy; had laparoscopic colorectal surgery; had a contraindication for the use of mechanical bowel preparation; had an a priori deviating ileal stoma; or were aged younger than 18 years. Surgeons in the participating hospitals enrolled patients in the study at the last visit before they were scheduled to have elective colorectal surgery. We obtained written informed consent from all patients.

Procedures

Enrolled patients were randomly assigned to either receive mechanical bowel preparation or not. A computer-generated randomisation list, stratified by centre, was prepared by the trial statistician (WCJH) at a central coordination centre. At the hospital where the trial was coordinated, patients were allocated to each intervention by means of numbered sealed envelopes that corresponded to the randomisation list; other centres were advised by telephone of the intervention allocated to each patient. The study was reviewed and approved by the ethics committees at participating hospitals.

Mechanical bowel preparation consisted of 2–4 L of polyethylene glycol bowel lavage solution in combination with bisacodyl (at 11 hospitals) or sodium phosphate solution (at two hospitals). Patients who had mechanical bowel preparation had a fluid diet (of beverages,

yoghurt, and soup) on the day before their operations. Patients who did not were allowed to have normal meals.

Before their operations, all patients were given intravenous antibiotic prophylaxis according to the guideline for prevention of surgical-site infection issued by the infectious diseases department of each hospital. All procedures were done by open laparotomy. Anastomoses were done according to the judgement of the surgeon.

The primary endpoint of the study was anastomotic leakage. Clinical suspicion based on persistent fever, abdominal pain, local or generalised peritonitis, or leucocytosis was followed by contrast radiography, CT scan, or laparotomy to substantiate the diagnosis. No effort was made to screen for asymptomatic leakage. Secondary endpoints were septic complications (wound infection, urinary infection, pneumonia, and intra-abdominal abscesses); fascia dehiscence; and death. Wound infection was regarded as mild if it manifested only with erythema or discharge of seroma, and severe if it was characterised by discharge of pus, wound necrosis, or wound dehiscence. We suspected urinary tract infections on the basis of clinical signs such as painful micturition, frequent micturition or urge, lower abdominal pain, or fever. The diagnosis of urinary infection was made for a urinary sample with a bacterial density of more than 10^2 per mL of urine for patients with symptoms and without a catheter, and of more than 10^5 per mL of urine for patients with a catheter. Clinical suspicion of pneumonia was based on cough, saliva, dyspnoea, or fever. We diagnosed pneumonia if radiography of the thorax showed infiltrative signs, and a saliva swab was positive for bacteria. The suspicion of an intra-abdominal abscess was based on clinical symptoms such as intermittent rise in temperature, persistent ileus, or abdominal pain. If an intra-abdominal abscess was suspected, we used CT or ultrasonography to investigate. This diagnosis could be also supported by perioperative findings. Fascia dehiscence was defined as receding of the abdominal fascia at the site or next to the fascia suture. The follow-up period was defined as the time from the operation until first outpatient visit, which usually took place 2 weeks after discharge from the hospital.

Statistical analysis

The study was designed to test the hypothesis that patients given no mechanical bowel preparation before colorectal surgery do not have a higher risk of anastomotic leakage than those given mechanical bowel preparation. We specified that for non-inferiority to apply, the upper limit of the two-sided 95% CI for the difference in anastomotic leakage rates (no mechanical bowel preparation group minus bowel preparation group) had to be less than 3%. We calculated that we would need a sample of 1400 patients to show with 80% probability that the upper limit of the 95% CI did not exceed the margin of 3%, assuming that the rate of anastomotic leakage in both groups was 5%.

We used the χ^2 test or Fisher's exact test to compare complication rates between groups, and the Mann-Whitney test to compare continuous or graded outcomes. The same tests were used in a univariate exploratory analysis to assess the risk of anastomotic leakage associated with: age, presence of hypertension, American Society of Anesthesiologists (ASA) classification, concurrent use of corticosteroids, preoperative radiation therapy, diabetes, coronary or peripheral ischaemic disease, smoking, body-mass index, indication for operation, type of anastomosis, technique of anastomosis (stapled versus handsewn), type of surgeon (length of training), and perioperative blood loss. We used multiple logistic regression to test risk factors simultaneously for any association with anastomotic failure. We regarded p=0·05 as the limit of significance in all analyses. This study is registered with ClinicalTrials.gov, number NCT00288496.

Results

The figure shows the trial profile. Between April, 1998, and February, 2004, we enrolled 1431 patients. 77 patients were excluded from analysis of the primary end-point: 46 (3·2%) because they did not have a bowel re-section; 21 (1·5%) because we did not have outcome data; and 10 (0·7%) because they either withdrew consent, died, had an acute laparotomy, underwent surgery elsewhere, or cancelled their operation. Baseline characteristics are shown in table 1. By chance, more patients who smoked and had inflammatory bowel disease were assigned to have mechanical bowel preparation. Table 2 sets out postoperative complications, and shows that the rate of anastomotic leakage was about 5%, whether patients had mechanical bowel preparation or not (difference 0·6%, 95% CI −1·7% to 2·9%, p=0·69). The treatment effect did not differ between the 13 participating centres (OR homogeneity, p=0·67). 30 of the 69 cases of anastomotic leakage were verified by radiographic examination. 57 of the 69 patients had major anastomotic leakages that needed relaparotomy. The rate was about 4% in each group, whether patients had mechanical bowel preparation or not (difference 0·6%, 95% CI −1·6% to 2·8%, p=0·64). 6 patients in each group had minor anastomotic leakages that were treated conservatively. The median follow-up time for the 1354 patients who had bowel resection was 24 days (IQR 17–34).

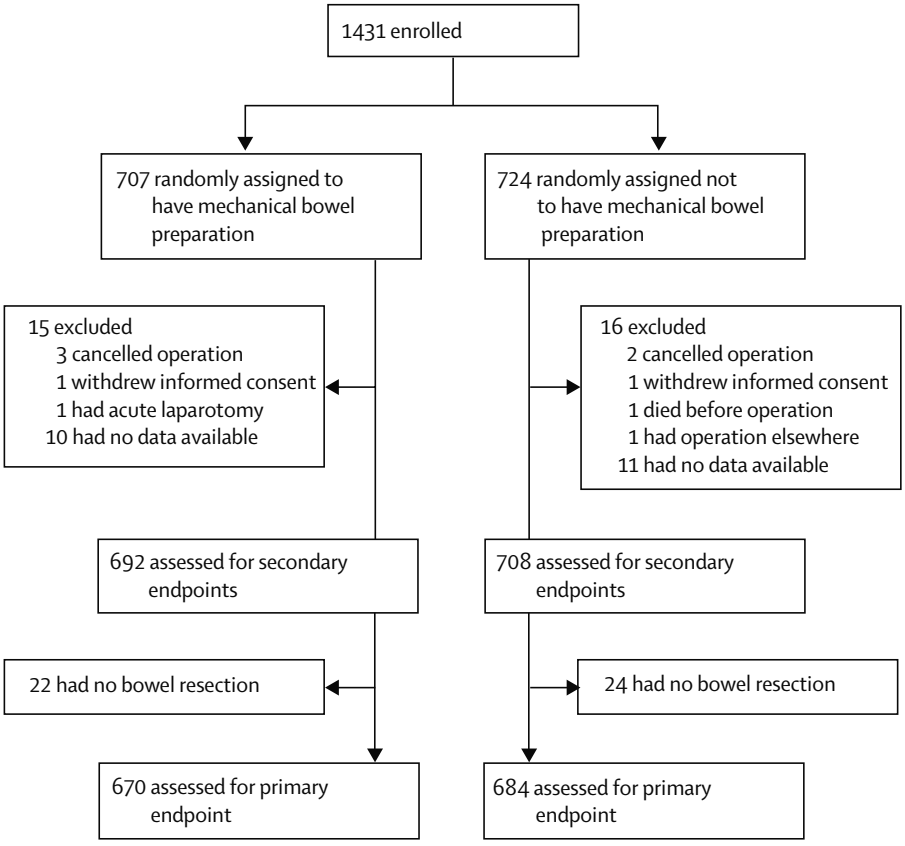

Figure. Trial profile

	Mechanical bowel preparation (n=670)	No mechanical bowel preparation (n=684)
Mechanical bowel preparation solution		
Polyethylene glycol	588 (88%)	602 (88%)
Sodium phosphate	82 (12%)	82 (12%)
Sex		
Female	333 (50%)	339 (50%)
Male	337 (50%)	345 (50%)
Mean age (years)	67 (13)	67(12)
ASA classification		
I	207 (31%)	212 (31%)
II	384 (57%)	386 (56%)
III	77 (12%)	83 (12%)
IV	2 (0·3%)	3 (0·4%)
Diabetes	66 (10%)	76 (11%)
Radiation	32 (5%)	22 (3%)
Corticosteroids	32 (5%)	27 (4%)
Coronary ischaemic disease	98 (15%)	109(16%)
Peripheral ischaemic disease	38 (6%)	36 (5%)
Smoking	165 (25%)	118 (17%)
Body-mass index		
≤25 kg/m²	329 (50%)	346 (52%)
>25 kg/m²	328 (50%)	319 (48%)
Indication for operation		
Colorectal cancer	487 (73%)	538 (79%)
Inflammatory bowel disease	122 (18%)	105 (15%)
Other*	61 (9%)	41 (6%)
Antibiotic prophylaxis		
Cefuroxim+metronidazole	320 (48%)	329 (48%)
Cefazolin+metronidazole	83 (12%)	80 (12%)
Cefamandole+metronidazole	70 (10%)	80 (12%)
Gentamycine+metronidazole	51 (8%)	56 (8%)
Amoxicillin-clavulanate	128 (19%)	130 (19%)
Others	19 (3%)	9 (1%)
Type of anastomosis		
Ileocolic	190 (28%)	209 (31%)
Colocolic	217 (31%)	237 (35%)
Colorectal	236 (34%)	213 (31%)
Other†	27 (4%)	25 (4%)
Technique of anastom osis I		
Stapled	207 (30%)	208 (30%)
Handsewn	444 (66%)	462 (68%)
Technique of anastomosis II		
End-to-end	291 (43%)	304 (46%)
Side-to-end	238 (37%)	239 (34%)
Side-to-side	93 (15%)	109 (17%)
End-to-side	19 (3%)	14 (2%)
Pouch	9 (1%)	5 (1%)

The number of patients for whom data were missing was less than 1% for all variables except body-mass index (n=34), technique of anastomosis I (n=75), and technique of anastomosis II (n=73). ASA=American Society of Anaesthesiologists. Data are number (%) or mean (SD).*Other reasons were radiation induced stenosis, endometriosis, and correction of Hartmann's procedure. †Coloanal anastomosis or ileorectal anastomosis.

Table 1: **Baseline characteristics of patients who had bowel resection**

Table 2 shows that fewer intra-abdominal abscesses occured after anastomotic leakage in those who had mechanical bowel preparation than in those who did not (p=0·001, 95% CI 0·9–3·4% for the difference). Of the 17 patients who did not have mechanical bowel preparation, and who developed intra-abdominal abscesses after anastomotic leakage, only three needed a relaparotomy for drainage of the abscess.

Rates of other septic complications, fascia dehiscence, and mortality did not differ between the two groups (table 2). Faecal contamination, number of days until resumption of a normal diet, and duration of hospital stay were similar in both groups (table 2). Results were similar when we analysed the 1400 patients for whom we had some outcome data, except that the rate of intra-abdominal abscesses did not differ between the groups (data not shown).

	With mechanical bowel preparation† n=670	Without mechanical bowel preparation† n=684	Difference (95% CI)	p value
No postoperative complication	462 (69·0%)	452 (66·1%)	−2·9 (−7·9 to 2·1)	0·28
Anastomotic leakage	32 (4·8%)	37 (5·4%)	0·6 (−1·7 to 2·9)	0·69
Minor anastomotic leakage	6 (0·9%)	6 (0·9%)	0·0 (−1·0 to 1·0)	1·0
Major anastomotic leakage	26 (3·9%)	31 (4·5%)	0·6 (−1·6 to 2·8)	0·64
Wound infection	90 (13·4%)	96 (14·0%)	0·6 (−3·2 to 4·4)	0·82
Mild wound infection	49 (7·3%)	51 (7·4%)	0·1 (−2·7 to 2·9)	1·0
Severe wound infection	41 (6·1%)	45 (6·6%)	0·4 (−2·2 to 3·0)	0·83
Fascia dehiscence	19 (2·8%)	16 (2·3%)	−0·5 (−2·2 to 1·2)	0·69
Urinary tract infection	71 (10·6%)	70 (10·2%)	−0·4 (−3·6 to 2·9)	0·90
Pneumonia	39 (5·8%)	51 (7·5%)	1·6 (−1·0 to 4·3)	0·27
Intra-abdominal abscess	15 (2·2%)	32 (4·7%)	2·4 (0·5 to 4·4)	0·02
Abscess without anastomotic leakage	13 (1·9%)	15 (2·2%)	0·3 (−1·3 to 1·8)	0·85
Abscess with anastomotic leakage	2 (0·3%)	17 (2·5%)	2·2 (0·9 to 3·4)	0·001
Secondary intervention	58 (8·7%)	58 (8·5%)	−0·2 (−3·2 to 2·7)	0·99
Deaths	20 (3·0%)	26 (3·8%)	0·8 (−1·1 to 2·7)	0·50
Faecal contamination*	..	..	..	0·42
Clean contaminated	389 (58·1%)	380 (55·8%)	−2·3 (−7·6 to 2·9)	0·41
Contaminated	250 (37·4%)	276 (40·5%)	3·2 (−2·0 to 8·4)	0·26
Dirty	30 (4·5%)	25 (3·7%)	−0·8 (−2·9 to 1·3)	0·54
Operation time (min)	120 (90–150)	120 (90–144)	0·0 (−5·0 to 5·0)	0·48
Resumption of normal diet (days)	6 (4–8)	6 (4–8)	0·0 (−0·4 to 0·4)	0·91
Hospital stay (days)†	10 (8–14)	10 (8–13)	0·0 (−1·0 to 1·0)	0·40

Data are number (%) or median (IQR) unless otherwise specified. The number of patients for whom data were missing was less than 1% for all variables except for days until resumption of a normal diet (n=31) and hospital stay (n=29). *Clean contaminated=colon resection with minimal spill; contaminated=colon resection with severe spill of bowel contents, no pus; and dirty=intraperitoneal pus or bowel perforation. †Excluding postoperative deaths.

Table 2: **Postoperative complications, surgery data, and hospital stay for the 1354 patients who had bowel resections**

Exploratory univariate analysis of putative risk factors for anastomotic leakage showed that type of anastomosis (ie, ileocolic, colocolic, and colorectal anastomosis); ASA classification; and blood-loss during operation were associated with anastomotic leakage. These three associations remained significant in multivariate analysis (table 3). The two factors that were not well balanced between study groups (smoking and indication for operation), were not related to the primary outcome. Furthermore, the requirement for a stoma during the operation did not affect the leakage rate (table 3).

	Leakage rate	Odds ratio (OR)	95% CI	Multivariate analysis p values	Univariate analysis p values
Mechanical bowel preparation					
No	37/684 (5·4%)	1·0*	..	..	..
Yes	32/670 (4·8%)	0·81	0·48–1·34	0·42	0·69
ASA classification					
I	15/419 (3·6%)	1·0*	..	..	..
II	35/770 (4·5%)	1·33	0·71–2·47	0·37	..
III/IV	19/165 (11·5%)	3·83	1·87–7·84	0·0002	0·001‡
Type of anastomosis					
Ileocolic	12/399 (3·0%)	1·0*	..	..	..
Colocolic	23/454 (5·1%)	1·56	0·74–3·29	0·24	0·007§
Colorectal	32/449 (7·1%)	2·14	1·05–4·35	0·04	..
Other	2/52 (3·8%)	0·93	0·18–4·91	0·93	..
Operation indication					
Carcinoma	48/1025 (4·7%)	1·0*	..	..	..
Inflammatory bowel disease	14/227 (6·2%)	1·22	0·64–2·34	0·55	0·46¶
Other	7/102 (6·9%)	1·60	0·66–3·86	0·30	..
Smoking					
No	51/1066 (4·8%)	1·0*	..	..	..
Yes	18/283 (6·4%)	1·32	0·73–2·36	0·36	0·36
Blood loss					
<median†	22/664 (3·3%)	1·0*	..	..	..
≥median†	47/677 (6·9%)	1·93	1·12–3·32	0·02	0·004
Diverting stoma peroperatively					
No	63/1257 (5·0%)	1·0*	..	..	..
Yes	6/97 (6·2%)	0·99	0·38–2·59	0·99	0·79

Data are number (%), unless otherwise specified. ASA=American Society of Anaesthesiologists. *Reference category. †Median blood loss was 400 mL. ‡p value for trend. §p value for trend, excluding "other" types of anastomosis. ¶Overall p value.

***Table* 3: Anastomotic leakage rates, according to various factors and results of multivariate analysis for the 1354 patients who had bowel resection**

Discussion

Our study did not show any differences in anastomotic leakage between patients who were given preoperative mechanical bowel preparation before elective colorectal surgery and those who we not. Mortality and length of hospital stay were also similar in the two groups.

However, patients who did not have mechanical bowel preparation had a slightly higher rate of intra-abdominal abscesses after anastomotic leakage. We did not regard the very low rate of abscesses to be of major clinical importance; abscesses did not influence the number of reinterventions, length of hospital stay, or mortality.

Efficient mechanical bowel preparation is generally supposed to help to prevent infectious complications after colorectal surgery. Theoretically, this procedure diminishes faecal load in the bowel and prevents disruption of the anastomosis by reduction of faecal impaction at the site of the anastomosis. Therefore, the risks of faecal contamination or infection of the peritoneal cavity and the abdominal wound are thought to be decreased. However, mechanical bowel preparation liquefies solid faeces, which could increase the risk of intraoperative spillage of contaminant.[5,11] Although some investigators believe that mechanical bowel preparation can reduce the bacterial load in the bowel, the large number of microorganisms in the digestive tract makes this almost impossible.[7,12] Mechanical bowel preparation has been shown to have potentially negative side-effects in terms of bacterial translocation,[13,14] electrolyte disturbance,[15–18] and discomfort to patients.[15,19–21] Despite these drawbacks, mechanical bowel preparation is still commonly practised in colorectal surgery, without evidence from randomised trials that it decreases complication rates in patients.[6–9,22]

Of the three published meta-analyses, the first showed that in three trials, with 497 patients, those who had mechanical bowel preparation had a significantly greater rate of wound infection than those who did not.[23] The second meta-analysis showed that in nine trials, with 1592 patients, mechanical bowel preparation was associated with a higher rate of anastomotic leakage, although wound infection and other complications did not differ between groups.[24] The third meta-analysis showed that in seven trials, with 1454 patients, those who had mechanical bowel preparation were significantly more likely to have anastomotic leakage.[25] Only one recent study has reported an increased risk of anastomotic leakage in patients who had colorectal resections after mechanical bowel preparation with a single phosphate enema compared with oral polyethylene glycol.[21] Mortality was higher in the oral polyethylene glycol group, but neither septic complications nor length of hospital stay differed between groups. After submission, we learned of another randomised trial of mechanical bowel preparation for elective colonic resection, in which the results paralleled ours.[26]

Multivariate analysis showed that ASA classification, type of anastomosis, and blood loss during operation were independent risk factors for anastomotic leakage. A possible explanation for risk associated with loss of blood is that decreased oxygen delivery at the anastomotic site due to anaemia might compromise anastomotic healing and therefore cause anastomotic leakage. Golub and colleagues[27] reported that a perioperative transfusion of more than two units of blood was independently associated with leakage, and suggested that the immunosuppressive effect of blood transfusions might have a role.

Our trial had several limitations. First, observers were not blinded to whether a patient had mechanical bowel preparation or not. However, since the number of surgical interventions for severe leakages did not differ between groups, the lack of double blinding probably did not cause bias. Second, we did not register all eligible patients who could potentially have been enrolled. However, because the characteristics of the patients in our study (table 1) corresponded closely to those of patients in the three published meta-analyses, we do not think that the external validity of our study was compromised by this omission.

Third, we used two different oral regimes for mechanical bowel preparation, since two hospitals had switched from use of polyethylene glycol to sodium phosphate for mechanical bowel preparation, on the basis of a report that these substances were equally effective and safe.[19] Our analysis showed that neither the difference in the rate of anastomotic leakage nor the difference in overall complication rate varied according to which type of mechanical bowel preparation was used.

Fourth, we did not record the exact height of anastomosis below the pelvic verge. Anastomotic leakage has been studied in relation to patient characteristics (such as malnutrition, body-mass index, cardiovascular disease, steroid use, smoking, alcohol abuse, and preoperative pelvic irradiation) and to surgery (level of anastomosis, operating time, perioperative blood transfusion, ASA classification, and intraoperative contamination of the operative field). The factor most consistently shown to predict leakage is a low rectal anastomosis.[27] Two recent randomised studies advised that patients undergoing elective anterior resections that were low or very low, should have mechanical bowel preparation because of a high risk of anastomotic leakage in extraperitoneal anastomosis.[28,29] However this advice was not based on solid evidence, since one study excluded extraperitoneal anastomosis[28] and the other only included 79 patients with a (low) anterior resection.[29] Platell and colleagues[21] studied 294 patients, 60% of whom had a low anterior resection. All anastomoses under the pelvic verge were radiologically assessed for leakage, whereas intra-abdominal anastomoses were only assessed if clinically indicated.[21] Although radiological assessment of anastomotic leakage did not differ between patients who did and did not have mechanical bowel preparation, both clinically relevant anastomotic leakage and severe anastomotic leaks were more common in the enema group.[21] In our study, 449 patients underwent a colorectal anastomosis below the level of the peritoneal verge. In this subgroup, we noted no differences with regard to anastomotic leakage or septic complications, whether patients had mechanical bowel preparation or not (data not shown).

Last, although we only analysed 1354 patients, statistical power was not greatly reduced because the resulting confidence interval for the primary endpoint was sufficiently narrow to exclude a relevant difference. Therefore, the conclusion that elective colorectal surgery can be safely done without mechanical bowel preparation is justified. In view of possible disadvantages of this practice, patient discomfort, and the absence of clinical value, we advise that mechanical bowel preparation before elective colorectal surgery should be abandoned.

References

1. Nichols RL, Condon RE. Preoperative preparation of the colon. *Surg Gynecol Obstet* 1971; 132: 323–37.
2. Chung RS, Gurll NJ, Berglund EM. A controlled clinical trial of whole gut lavage as a method of bowel preparation for colonic operations. *Am J Surg* 1979; 137: 75–81.
3. Barker K, Graham NG, Mason MC, De Dombal FT, Goligher JC. The relative significance of preoperative oral antibiotics, mechanical bowel preparation, and peroperative peritoneal contamination in avoidance of sepsis after radical surgery for ulcerative colitis and Crohn's disease of the large bowel. *Br J Surg* 1971; 58: 270–73.
4. Dunphy JE. Preoperative preparation of the colon and other factors affecting anastomotic healing. *Cancer* 1971; 28: 181–82.
5. Irving AD, Scrimgeour D. Mechanical bowel preparation for colonic resection and anastomosis. *Br J Surg* 1987; 74: 580–81.
6. Burke P, Mealy K, Gillen P, Joyce W, Traynor O, Hyland J. Requirement for bowel preparation in colorectal surgery. *Br J Surg* 1994; 81: 907–10.
7. Santos JC, Batista J, Sirimarco MT, Guimaraes AS, Levy CE. Prospective randomized trial of mechanical bowel preparation in patients undergoing elective colorectal surgery. *Br J Surg* 1994; 81: 1673–76.
8. Brownson P, Jenkins SA, Nott D, Ellenbogen S. Mechanical bowel preparation before colorectal surgery: results of a prospective randomized trial. *Br J Surg* 1992; 79: 461–62.
9. Miettinen RP, Laitinen ST, Makela JT, Paakkonen ME. Bowel preparation with oral polyethylene glycol electrolyte solution versus no preparation in elective open colorectal surgery: prospective, randomized study. *Dis Colon Rectum* 2000; 43: 669–75.
10. Zmora O, Mahajna A, Bar-Zakai B, et al. Colon and rectal surgery without mechanical bowel preparation: a randomized prospective trial. *Ann Surg* 2003; 237: 363–67.
11. Mahajna A, Krausz M, Rosin D, et al. Bowel preparation is associated with spillage of bowel contents in colorectal surgery. *Dis Colon Rectum* 2005; 48: 1626–31.
12. Fa-Si-Oen PR, Verwaest C, Buitenweg J, et al. Effect of mechanical bowel preparation with polyethyleneglycol on bacterial contamination and wound infection in patients undergoing elective open colon surgery. *Clin Microbiol Infect* 2005; 11: 158–60.
13. Poole GV. Spontaneous bacterial peritonitis during bowel preparation: an example of clinical translocation. *South Med J* 1991; 1412–13.
14. Kale TI, Kuzu MA, Tekeli A, Tanik A, Aksoy M, Cete M. Aggressive bowel preparation does not enhance bacterial translocation, provided the mucosal barrier is not disrupted: a prospective, randomized study. *Dis Colon Rectum* 1998; 41: 636–41.
15. Hamilton D, Mulcahy D, Walsh D, Farrelly C, Tormey WP, Watson G. Sodium picosulphate compared with polyethylene glycol solution for large bowel lavage: a prospective randomised trial. *Br J Clin Pract* 1996; 50: 73–75.
16. Frizelle FA, Colls BM. Hyponatremia and seizures after bowel preparation: report of three cases. *Dis Colon Rectum* 2005;
17. Hookey LC, Depew WT, Vanner SJ. A prospective randomized trial comparing low-dose oral sodium phosphate plus stimulant laxatives with large volume polyethylene glycol solution for colon cleansing. *Am J Gastroenterol* 2004; 99: 2217–22.
18. Beloosesky Y, Grinblat J, Weiss A, Grosman B, Grafter U, Chagnac A. Electrolyte disorders following oral sodium phosphate administration for bowel cleansing in elderly patients. *Arch Intern Med* 2003; 163: 803–08.

19. Oliveira L, Wexner SD, Daniel N, et al. Mechanical bowel preparation for elective colorectal surgery. A prospective, randomized, surgeon-blinded trial comparing sodium phosphate and polyethylene glycol-based oral lavage solutions. *Dis Colon Rectum* 1997; 40: 585–91.
20. Ell C, Fischbach W, Keller R, et al; Hintertux Study Group. A randomized, blinded, prospective trial to compare the safety and efficacy of three bowel-cleansing solutions for colonoscopy (HSG-01*). *Endoscopy* 2003; 35: 300–04.
21. Platell C, Barwood N, Makim G. Randomized clinical trial of bowel preparation with a single phosphate enema or polyethylene glycol before elective colorectal surgery. *Br J Surg* 2006; 93: 427–33.
22. Bucher P, Gervaz P, Soravia C, Mermillod B, Erne M, Morel P. Randomized clinical trial of mechanical bowel preparation versus no preparation before left-sided colorectal surgery. *Br J Surg* 2005; 92: 409–14.
23. Platell C, Hall J. What is the role of mechanical bowel preparation in patients undergoing colorectal surgery? *Dis Colon Rectum* 1998; 41: 875–82.
24. Guenaga KF, Matos D, Castro AA, Atallah AN, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. *Cochrane Database Syst Rev* 2005; 1: CD001544.
25. Slim K, Vicaut E, Panis Y, Chipponi J. Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation. *Br J Surg* 2004; 91: 1125–30.
26. Jung B, Pahlman L, Nystrom PO, Nilsson E. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. *Br J Surg* 2007; 94: 689–95.
27. Golub R, Golub RW, Cantu R, Stein HD. A multivariate analysis of factors contributing to leakage of intestinal anastomoses. *J Am Coll Surg* 1997; 184: 364–72.
28. Fa-Si-Oen PR, Roumen RM, Buitenweg J, et al. Mechanical Bowel Preparation or not? Outcome of a multicenter, randomized trial in elective open colon surgery. *Dis Colon Rectum* 2005; 48: 1509–16.
29. Ram E, Sherman Y, Weil R, Vishne T, Kravarusic D, Dreznik Z. Is mechanical bowel preparation mandatory for elective colon surgery? A prospective randomized study. *Arch Surg* 2005; 140: 28

Chapter 3

The Influence of Mechanical Bowel Preparation in Elective Lower Colorectal Surgery

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Abstract

Objective This study evaluates the effects of mechanical bowel preparation (MBP) on anastomosis below the peritoneal verge and questions the influence of MBP on anastomotic leakage in combination with a diverting ileostomy in lower colorectal surgery.

Summary Background Data In a previous large multicentre randomized controlled trial MBP has shown to have no influence on the incidence of anastomotic leakage in overall colorectal surgery. The role of MBP in lower colorectal surgery with or without a diverting ileostomy remains unclear.

Methods This study is a subgroup analysis of a prior multicentre (13 hospitals) randomised trial comparing clinical outcome of MBP versus no MBP. Primary endpoint was the occurrence of anastomotic leakage and secondary endpoints were septic complications and mortality.

Results 449 Patients underwent a low anterior resection with a primary anastomosis below the peritoneal verge. The incidence of anastomotic leakage was 7.6% for patients who received MBP and 6.6% for patients who did not. Significant risk factors for anastomotic leakage were ASA-classification (p=0.005) and male gender (p=0.007). 48 Patients received a diverting ileostomy during initial surgery. 27 Patients received MBP and 21 patients did not. There were no significant differences regarding septic complications and mortality between both groups.

Conclusion MBP has no influence on the incidence of anastomotic leakage in low colorectal surgery. Furthermore, omitting MBP in combination with a diverting ileostomy has no influence on the incidence of anastomotic leakage, septic complications, and mortality rate.

Introduction

Symptomatic anastomotic leakage is a severe complication of any intestinal anastomosis. There is a particularly high incidence following low colorectal and coloanal anastomosis accompanied by high morbidity and mortality rates ranging from 6 to 22% [1-6]. Traditionally mechanical bowel preparation is believed to clean the colon or rectum from faecal contents and bacterial load to reduce the incidence of postoperative anastomotic and infectious complications[7]. However, an increasing number of studies have shown the use of mechanical bowel preparation to be controversial in colorectal surgery and even show negative effects of MBP concerning anastomotic dehiscence and septic complications[8-10]. Although increasing evidence is appearing in favour of abandoning MBP in elective colorectal surgery many surgeons are still hesitant in omitting mechanical bowel preparation especially in patients undergoing low or very low anterior resections. Some studies recommend MBP only in patients undergoing low or very low anterior resection as anastomotic leakage mainly occurs in this group of patients[11,12]. However, no studies are available in which mechanical bowel preparation is significantly proven beneficial in patients undergoing a low or very low anterior resection and even more little is known about the effects of MBP on septic complications at this level of anastomosis.

Another measure believed to reduce and prevent anastomotic leakage and septic complications in anastomoses performed below the level of the peritoneal verge is the use of a temporary diverting ileostomy. By diverting the faecal stream and keeping the anastomosis free and clean of faecal contamination, anastomotic leakage is presumed to cause less or milder septic complications. However, the role of a protective ileostomy in preventing anastomotic leakage is discussed repeatedly and prospective randomised studies are rare and results contradictory[13-17].

Despite the fact a diverting ileostomy and mechanical bowel preparation are still debatable there have been no studies questioning the use and influence of mechanical bowel preparation in combination with a diverting ileostomy. The use of a diverting ileostomy in an unprepared colon seams controversial for the remaining faeces, distal from the ileostomy, could still jeopardize the low anastomosis and increase the risk of leakage and septic complications. The aim of this study is to investigate the influence of mechanical bowel preparation on anastomotic leakage and septic complications in especially lower colorectal surgery and in addition with or without a temporary diverting ileostomy.

Methods

This study is a subgroup analysis of a prior large multicentre, randomised clinical trial performed by Contant et al. to compare elective colorectal resections and primary anatomises with and without the use of mechanical bowel preparation[18]. In this trial 1354 patients were randomised before elective colorectal surgery to receive mechanical bowel preparation: 2-4 litres of polyethylene glycol bowel lavage solution (Klean Prep) in combination with bisacodyl (11 hospitals) or sodium phosphate solution (2 hospitals). Endpoints were anastomotic leakage and other septic complications. Exclusion criteria were an acute laparotomy, laparoscopic colorectal surgery, contraindications for the use of mechanical bowel preparation, an a priori diverting ileostomy, and age less than 18 years old.

In the present subgroup analysis, 449 from 1354 patients were selected by the criterion of having undergone an elective low anterior resection with primary anastomosis (fig.1). Low anterior resections were defined as anastomosis performed below the level of the peritoneal verge. The peritoneal verge divides the intraperitoneal colon and cranial part of the rectum from the extraperitoneal part of the rectum. The peritoneal verge may also be called peritoneal reflection, pelvic diaphragm or visceral pelvic fascia.

The diagnosis of anastomotic leakage was based on clinical suspicion (prolonged fever, abdominal pain, local or generalised peritonitis, leucocytosis) resulting in contrast radiography (X-ray or CT-scan) or laparotomy to confirm the diagnosis. No effort was made to screen for asymptomatic leakage. Wound infection was defined as mild in case of erythema or discharge of seroma and as severe in case of discharge of pus, wound necrosis, or wound dehiscence. The follow-up period was defined as the time from operation until first outpatient visit after discharge from the hospital, which usually occurred after 2 weeks.

Surgical technique

Antibiotic prophylaxis was given intravenously to all patients according to the guideline for prevention of surgical site infection issued by the department of infectious diseases of each hospital. All low anterior resections were performed by open laparotomy for colonic malignancy, diverticular disease or benign lesion or stricture. Anastomoses were performed according to the preference of the surgeon. No exact criteria for the appliance of a diverting ileostoma were stated and a diverting ileostomy was applied when assumed necessary by the surgeon. Common reasons for applying a diverting ileostomy were difficult operation, faecal contamination, tension on the anastomosis, very low anastomosis, high comorbidity and incomplete donuts when a circular stapler was used.

Statistical analysis

Groups were compared with respect to complication rates by the Chi-square test or Fisher's exact test. The same test was used to compare risk groups for anastomotic dehiscence. Comparison of continuous or graded outcomes was determined by the Mann-Whitney test. Multiple logistic regression was used to evaluate various risk factors simultaneously regarding anastomotic related failure rates. P=0.05 (two-sided) was considered the limit of statistical significance.

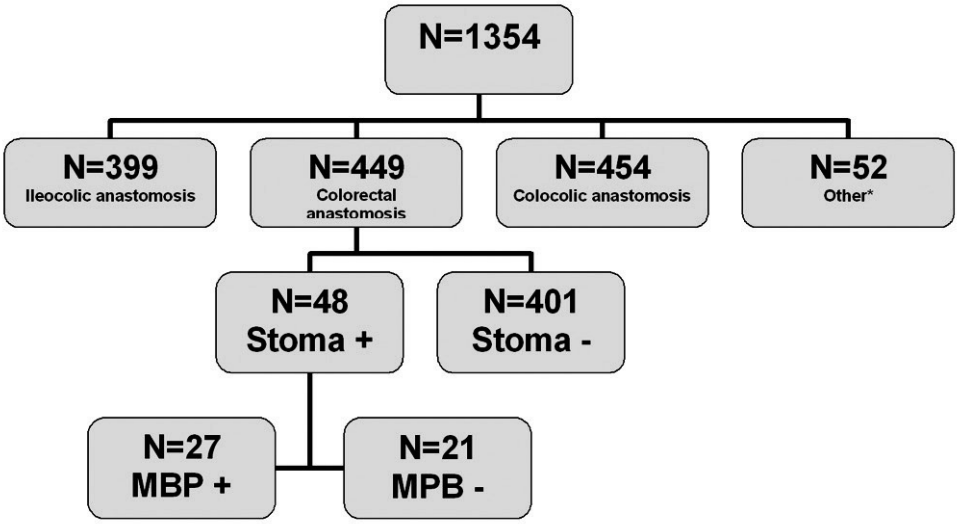

Fig. 1 Organisation chart for the subgroup patient selection.
* Inoperable, Kraske, abdominal perineal resection, ileal pouch-anal anastomosis.

Results

Between April 1998 and February 2004, 449 (33%) of 1354 patients underwent a low anterior resection. 236 patients received mechanical bowel preparation (MBP+) and 213 patients did not receive mechanical bowel preparation (MBP-). Anastomotic leakage occurred in 32 (7%) of the 449 patients. Mechanical bowel preparation had no significant influence on anastomotic leakage rate regarding lower colorectal anastomosis**:** 7.6% in MBP+ versus 6.6% in MBP- (difference 1.0%, 95% CI:- 3.7% to 5.7%; P=0.803). Table I shows the evaluated risk factors for anastomotic leakage. Sex (p=0.007) and ASA (p=0.005) showed to be significant risk factors for anastomotic leakage in both uni- and multivariate analysis.

Table I. Risk factors for anastomotic leakage in 449 patients with elective lower colorectal surgery. Due to occasional missing data numbers do not always add up to 449.

Risk factor for leakage	n/n (%)	P (univariate)
MBP		0.803
+	18/236 (7.6)	
-	14/213 (6.6)	
Gender		0.007
female	7/209 (3.3)	
male	25/240 (10.4)	
Age		0.583
<60 years	7/124 (5.6)	
≥60 years	25/325 (7.7)	
ASA		0.005
I	5/133 (3.8)	
II	18/264 (6.8)	
III/IV	9/52 (17.3)	
Diabetes		1.00
+	3/45 (6.7)	
-	29/404 (7.2)	
Radiation therapy		1.00
+	2/32 (6.3)	
-	30/417 (7.2)	
Corticosteroids		1.00
+	1/14 (7.1)	
-	31/435 (7.1)	
Coronary ischemic disease		0.119
+	9/77 (11.7)	
-	22/370 (5.9)	
Peripheral ischemic disease		1.00
+	2/28 (7.1)	
-	29/419 (6.9)	
Smoking		0.805
+	8/97 (8.2)	
-	24/350 (6.9)	
BMI (kg/m^2)		0.405
≤ 25	17/203 (8.4)	
> 25	14/238 (5.9)	
Diverting ileostomy		1.00
+	3/48 (6.3)	
-	29/401 (7.2)	
Operation indication		0.528
Colorectal cancer	24/342 (7.0)	
Inflammatory Bowel Disease	8/94 (8.5)	
Other	0/13 (0)	

Surgeon		0.841
Resident	11/160 (6.9)	
Surgeon < 10 years	7/113 (6.2)	
Surgeon ≥ 10 years	14/176 (8.0)	
Suture of anastomosis		0.940
Stapled	19/274 (6.9)	
handsewn	13/171 (7.6)	
Type of anastomosis		0.062
End-to-end	17/165 (10.3)	
Side-to-end	12/241 (5.0)	
Other	1/38 (2.6)	
Peri-operative PC		0.110
≤ 2	26/400 (6.5)	
> 2	6/43 (14.0)	
Operating time (min.)		0.763
≤ 130	18/233 (7.7)	
> 130	14/214 (6.5)	
Blood loss (cc)		0.442
≤400	9/159 (5.7)	
>400	23/283 (8.1)	

Table II displays the multivariate analysis results of the major risk factors for anastomotic leakage. Adjusted for gender and ASA there was still no significant difference regarding anastomotic leakage between MBP+ and MBP- (p=0.714)

Table II. Multivariate analysis (logistic regression) of risk factors for anastomotic leakage.

	Odds ratio (95% CI)	**p-value**
MBP (+ vs. -)	1.16 (0.53-2.52)	0.714
Gender (F vs. M)	0.22 (0.08-0.56)	0.002
ASA		0.006#
ASA II vs. I	1.74 (0.62-4.93)	0.294
ASA III/IV vs. I	6.44 (1.90-21.83)	0.003
Type of anastomosis		0.012#
Side-to-end vs. end-to-end	0.31 (0.14-0.71)	0.005
Other vs. end-to-end	0.20 (0.02-1.61)	0.130

Overall p-value

An overview of septic complications in patients with lower colorectal surgery is shown in table III. In total 48 of 449 patients received a diverting ileostomy during surgery. There was no significant difference in anastomotic leakage rate in patients with and without a diverting ileostomy (uni- and multivariate analysis). Faecal contamination (p=0.004), blood loss (p<0.001), operating time (p<0.001) and gender (p=0.001) were significant parameters associated with the incidence of a diverting ileostomy (table IV).

Table III. Morbidity and mortality rate after colorectal resection with and without preoperative MBP.

Complication	MBP+ (n=236)	MBP- (n=213)	P-value
Overall complications*	92 (39%)	83 (39%)	1.0
Anastomotic dehiscence	18	14	0.95
- minor	4 (2%)	3 (1%)	
- major	14 (6%)	11 (5%)	
Wound infection			0.43
- Mild	18 (8%)	22 (10%)	
- Severe	21 (9%)	14 (7%)	
Urinary tract infection	34 (14%)	26 (12%)	0.58
Pneumonia	16 (7%)	20 (9%)	0.39
Intraabdominal abscess	6 (3%)	9 (4%)	0.43
Fascia dehiscence	7 (3%)	2 (1%)	0.18
Mortality	7 (3%)	9 (4%)	0.61

* Patients can have more than one complication at a time.

Table IV. Patient characteristics and parameters associated with a diverting ileostomy in 48 patients.

	n/n(%)	p (univariate)
MBP		0.698
+	27/236 (11.4)	
-	21/213 (9.9)	
Age		0.443
<60 years	16/124 (12.9)	
≥60 years	32/325 (9.8)	
Gender		0.001
female	11/209 (5.3)	
male	37/240 (15.4)	
ASA-classification		0.690
I	16/133 (12.0)	
II	28/264 (10.6)	
III/IV	4/52 (7.7)	
BMI		0.509
<25 kg/m^2	19/203 (9.4)	
>25 kg/m^2	28/238 (11.8)	
Corticosteroids		0.380
+	0/14	
-	48/435 (11.0)	
Radiation		0.765
+	4/32 (12.5)	
-	44/417 (10.6)	
Faecal contamination:		0.004
- mild	24/244 (9.8)	
- moderate	19/192 (9.9)	
- severe	5/13 (38.5)	
Blood loss		P<0.001
≤400	1/159 (0.6)	
>400	46/283 (16.3)	
Operating time		P<0.001
≤ 130	7/233 (3.0)	
> 130	41/214 (19.2)	

Septic complications in patients who received a diverting ileostomy with or without mechanical bowel preparation are presented in table V. There were no significant differences in anastomotic leakage rate or intra abdominal abscesses in patients with a diverting ileostomy with or without prior mechanical bowel preparation. Besides urinary tract infections there were no other significant difference in extra-peritoneal septic complications between both groups (Table V).

Table V. Morbidity and mortality rate after colorectal resection for all patients with a diverting ileostomy with or without MBP.

Complication	MBP+ (n=27)	MBP- (n=21)	P-value
Overall complications*	14	10	NS
Anastomotic dehiscence	1	2	NS
- major	0	1	
- minor	1	1	
Wound infection	5	5	NS
- Mild	2	2	
- Severe	3	3	
Urinary tract infection	6	0	0.029
Pneumonia	4	5	NS
Intraabdominal abscess	1	1	NS
Fascia dehiscence	2	0	NS
Mortality	1	2	NS

* Patients can have more than one complication at a time.

Discussion

Anastomotic leakage is one of the most severe complications after low anterior resection with high morbidity and mortality rates. Especially anastomoses below the peritoneal verge and in combination with total mesorectal excision (TME) are associated with high anastomotic leakage rates[3-5].

Faecal contamination of the anastomosis is still believed to be a major contributing factor in septic complications and anastomotic dehiscence. Some even state MBP in combination with anti- and synbiotics can reduce bacterial bowel translocation although no differences in clinical effects where noticed[19]. For this reason the anastomosis and the peritoneal cavity is routinely protected against faeces by either preparing the bowel by the means of mechanical bowel preparation or diverting the faecal stream in the form of an ileostomy or colostomy in many surgical units.

Multiple studies and meta-analysis have researched the effect of mechanical bowel preparation concerning elective open colon surgery. Two recent large multicentre

randomised trials state that MBP can be safely omitted and induces no lower complication rates in elective colorectal surgery whereas smaller randomized and prospective studies are controversial in this matter[12,18,20-22.] Most meta-analysis conclude there is little difference in anastomotic leakage and complication rate between MBP+ and MBP-[8,23,24]. Many factors have been studied in relation to anastomotic leakage, both patient and surgery related (i.e. malnutrition, BMI, cardiovascular disease, steroid use, smoking, alcohol abuse and preoperative pelvic irradiation, level of anastomosis, operating time, perioperative blood transfusion, ASA classification, intraoperative contamination of the operative field). However, the single factor consistently shown to predict leakage is an anastomosis below the level of the peritoneal verge[2,5,6].

Few studies have dedicated their research primarily to the anastomosis below the peritoneal verge, which are especially prone to leakage and septic complications. Ram et al. conducted a randomised prospective study for MBP in general elective colon surgery that consisted of 329 patients of whom 29 underwent a low anterior resection. They found no significant difference in overall anastomotic leakage but expressed their concern for the need of MBP in patients with a low anterior resection as all leakages (n=3) occurred in this group[11]. Another randomised study performed by Miettinen et al. consisting of 267 patients of whom only 23 patients underwent a low anterior resection and 14 patients an ileal pouch-anal anastomosis showed no significant difference in leakage and septic complications but did not differentiate between the level of anastomosis[25]. Fa-Si-Oen et al. excluded low anterior resections from their randomised multicentre study to avoid a selection bias as the anastomotic leakage rate is higher in this subgroup[26]. Bretegnal et al. focussed their study on patients with rectal cancer and evaluated the effects of MBP on 52 patients deprived of MBP undergoing lower colorectal surgery matched with a group of 61 patients with MBP. Although anastomotic leakage rate was similar in both groups they found a positive trend concerning intra-peritoneal complications, significantly more extra-peritoneal complications and a longer hospital stay in patients who received MBP prior to surgery[10]. Although these studies do not show any significant side-effects when omitting MBP regardless of the level of anastomosis in elective colorectal surgery, they all advise or emphasize the possible need for MBP in elective lower colorectal surgery.

Although our study is underpowered and a subgroup analysis, it has the highest number of patients concerning elective surgery below the peritoneal verge compared to other studies. ASA classification and male gender were the single significant independent risk factors for anastomotic leakage confirmed by previous studies[2-5]. We found no differences in anastomotic leakage or septic complications between patients who received MBP and who did not for low colorectal surgery.

Another measure believed to reduce and/or prevent anastomotic leakage and septic complications is the use of a temporary diverting ileostomy. It's appliance and benefit

regarding colorectal surgery has been widely investigated and results are controversial regarding the incidence of anastomotic leakage and septic complications[13-17,27-29]. Four studies showed that an ileostomy significantly reduces the risk of clinical anastomotic leakage[13-15,27,28]. The Dutch Colorectal Cancer Group observed a significant correlation between the absence of a diverting ileostomy and anastomotic failure rate[28]. Gastinger et al. showed no significant difference regarding anastomotic leakage in patients with and without a diverting ileostomy but observed a reduction in anastomotic leakage rates requiring surgical re-intervention in patients with a protective stoma, mitigating the sequelae of such leakage[14]. Wong et al. found no significant difference in postoperative anastomotic leakage rate and recommends no routine appliance of a diverting ileostomy in patients undergoing a low or ultra low anterior resection. However, they do emphasize among other things, that the bowel segment distal to the stoma should be cleared of any remaining faeces before fashioning the anastomosis[17]. It is believed that by diverting the faecal stream and keeping the anastomosis free from faecal contamination the risks of anastomotic leakage and septic complications are reduced. Keeping this in mind, however, it seems controversial to apply a diverting ileostomy in patients without MPB, for the remaining faeces in the short bowel still has to pass the anastomosis. However, the effect of remaining faeces on the anastomosis in an unprepared colon with a diverting ileostomy remains unclear and no studies have been performed regarding this query. Although enough evidence has arisen to abandon MBP in elective colorectal surgery in general, no clear statement can be made regarding the importance of MBP in combination with a diverting ileostomy in lower colorectal surgery. In the present study, although numbers are small, we found no difference in rate of anastomotic leakage, pelvic abcesses when looking at intraperitoneal complications between both groups. Besides urinary tract infections which occurred significantly more in the MBP group there were no other septic complications in patients with a diverting ileostomy with or without MBP. We interpreted this difference in urinary tract infections as clinically insignificant.

Our results suggest that the remaining faeces distant from an ileostomy in an unprepared colon does not influence the risk of anastomotic leakage and septic complications. Therefore, even in case of a low anterior resection, MPB could be omitted safely even in combination with a diverting ileostomy. This is supported by the fact that we found no overall higher risk of anastomotic leakage and septic complications in patients who underwent low colorectal surgery with or without MBP.

References

1. E Rullier, C Laurent, JL Garrelon, P Michel, J Saric, M Parneix. Risk factors for anastomotic leakage after resection of rectal cancer. *Br J Surg* 1998;85:355-8.
2. WM Chambers WM, NJMcC Mortensen. Postoperative leakage and abscess formation after colorectal surgery. *Best practice and research clinical gastroenterology.* 2004;18:865-880.
3. WL Law, KW Chu. Anterior resection for rectal cancer with mesorectal excision. A prospective evaluation of 622 patients. *Ann Surg* 2004;240:260-268.
4. WO Karanji, AP Corder, P Bearn, RJ Heald. Leakage from stapled low anastomosis after total mesorectal excision for carcinoma of rectum. *Br J Surg* 1994;81:1224-6.
5. PB Soeters, JP de Zoete, CH Dejong, NS Williams, CG Baeten. Colorectal Surgery and Anastomotic Leakage. *Dig Surg* 2002;19:150-155
6. A Alves, Y Panis, P Mathieu, G Mantion, F Kwiatkowski, K Slim, et al. Postoperative Mortality and Morbidity in French Patients Undergoing Colorectal Surgery. *Arch Surg* 2005;140:278-283.
7. PR Fa-Si-Oen, C Verwaest, J Buitenweg, H Putter, JW de Waard, CJ van de Velde, et al. Effect of mechanical bowel preparation with polyethyleneglycol on bacterial contamination and wound infection in patients undergoing elective open colon surgery. *Clin Microbiol Infect* 2005;11:158-60.
8. K Slim, E Vicaut, Y Panis, J Chipponi. Meta-analysis of randomised clinical trials of colorectal surgery with or without mechanical bowel preparation. *Br J Surg* 2004;91:1125-1130.
9. JCM Santos, J Batista, MT Sirimarco, AS Guimaraes, CE Levy. Prospective randomized trial of mechanical bowel preparation in patients undergoing elective colorectal surgery. *Br J Surg* 1994;81:1673-1676.
10. F Bretagnol, A Alves, A Ricci, P Valleur, Y Panis. Rectal cancer surgery without mechanical bowel preparation. *Br J Surg* 2007;94:1266-1271.
11. E Ram, Y Sherman, R Weil, V Tali, D Kravarusic, Z Dreznik . Is mechanical bowel preparation mandatory for elective colon surgery? *Arch Surg* 2005;140:285-288.
12. AAFA Veenhof, C Sietses, GF Giannakopoulos, DL van der Peet, MA Cuesta. Preoperative Polyethylene Glycol versus a Single Enema in Elective Bowel Surgery. *Dig Surg* 2007;24:54-58.
13. F Marusch, A Koch, U Schmidt, S Geibetaler, H Dralle, HD Saeger, et al. Value of a protective stoma in low anterior resections for rectal cancer. *Dis Colon Rectum* 2002;45:1164-1171.
14. I Gastinger, F Marusch, R Steinert, S Wolff, F Koeckerling, H Lippert. Protective defunctioning stoma in low anterior resection for rectal carcinoma. *Br J Surg* 2005;92:1137-1142.
15. RT Poon, KW Chu, JW Ho, CW Chan, WL Law, J Wong. Prospective evaluation of selective defunctioning stoma for low anterior resection with total mesorectal excision. *World J Surg* 1999;23:463-467.
16. FH Remzi, VW Fazio, E Gorgun, SO Boon, J Hammel, M Preen, et al. The outcome after restorative proctocolectomy with or without defunctioning ileostomy. *Dis Colon Rectum* 2006;49:470-477.
17. NY Wong, KW Eu. A defunctioning ileostomy does not prevent clinical anastomotic leak after a low anterior resection: a prospective, comparative study. *Dis Colon Rectum* 2005;48:2076-2079.
18. CME Contant, WCJ Hop, HP van't Sant, HJM Oostvogel, HJ Smeets, LPS Stassen, et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. *Lancet* 2007;370:2112-17.
19. BS Reddy, J MacFie, M Gatt, CN Larsen, SS Jensen, TD Leser. Randomised clinical trial of effect of synbiotics, neomycin and mechanical bowel preparation on intestinal barrier function in patients undergoing colectomy. *Br J Surg* 2007;94:546-554.

20. O Zmora, A Mahajna, B Bar-Zakai, D Rosin, D Hershko, M Shabtai. Colon and rectal surgery without mechanical bowel preparation: a randomised prospective trial. *Ann Surg* 2003;237:363-367.
21. B Jung, L Pahlman, P-O Nystrom, E Nilsson. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. *Br J Surg* 2007;94:689-695.
22. D van Geldere, P Fa-Si-Oen, LA Noach, PJGM Rietra, JL Peterse, RPA Boom. Complications after colorectal surgery without mechanical bowel preparation. *J Am Coll Surg* 2002;194:40-47.
23. P Bucher, B Mermillod, P Gervaz, P Morel. Mechanical Bowel Preparation for Elective Colorectal Surgery. *Arch Surg* 2004;139:1359-1364.
24. O Zmora, AJ Pikarsky, SD Wexner. Bowel Preparation for Colorectal Surgery. *Dis Colon Rectum* 2001;44:1537-1549.
25. RP Miettinen, ST Laitinen, JT Makela, ME Paakkonen. Bowel preparation with oral polyethylene glycol electrolyte solution versus no preparation in elective open colorectal surgery; prospective randomised study. *Dis Colon Rectum* 2000;43:669-675.
26. PR Fa-Si-Oen, R Roumen, J Buitenweg, CJ van de Velde, D van Geldere, H Puter,et al. Mechanical bowel preparation or not? Outcome of a multicentre, randomised trial in elective open colon surgery. *Dis Colon Rectum* 2005;48:1509-16
27. N Dehni, RD Schlegel, C Cunningham, M Guiget, E Tiret, R Parc. Influence of a defunctioning stoma on leakage rates after low colorectal anastomosis and colonic J pouch-anal anastomosis. *Br J Surg* 1998;85:1114-1117.
28. KCMJ Peeters, RAEM Tollenaar, CAM Marijnen, E Klein Kranenbarg, WH Steup, T Wiggers, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. *Br J Surg* 2005;92:211-216.
29. EA Vlot, CJ Zeebregts, JGM Gerritsen, HJ Mulder, WJB Mastboom, JM Klaase. Anterior Resection of Rectal Cancer Without Bowel Preparation and Diverting Stoma. *Surg Today* 2005;35:629-633.

Letters to the Editor

The Influence of Mechanical Bowel Preparation in Elective Lower Colorectal Surgery

Annals of Surgery 2010:252(3):574-575

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To the Editor:

We read with interest the randomized trial by van't Sant et al.1 This is an excellent article with the aim of investigating the influence of mechanical bowel preparation (MBP) on anastomotic leakage and septic complications in lower colorectal surgery with or without a temporary diverting ileostomy. Although the study is underpowered and is a subgroup analysis, it presents the highest number of anastomoses performed below the level of the peritoneal verge compared with other studies. According to the authors, we believe that symptomatic anastomotic leakage is a severe complication of any intestinal anastomosis. During the past 2 decades, remarkable progress has been made in the treatment of rectal cancer. The main goal of rectal surgery for malignancy is oncologic radicality in an effort to achieve the preservation of sphincters and sexual-urinary function. Sphincter-saving procedures associated with partial or total mesorectal excision (TME) for the treatment of mid and distal rectal cancer have become increasingly prevalent, as their safety and efficacy have been proved. The introduction of circular stapling devices is largely responsible for their increasing popularity and utilization. Furthermore, neoadjuvant radiochemotherapy has become an integral part of the multidisciplinary approach to rectal cancer to reduce the risk of local recurrences.

The meticulous dissection, however, is not without consequence.2 The most important surgical complication following rectal resection with anastomosis is symptomatic anastomotic leakage.3,4 The incidence of anastomotic leak varies widely depending on the anastomosis type and the distance from the anal verge. The introduction of the circular stapler reduced technical difficulties and leakage risk. Stapled techniques for colorectal and coloanal anastomosis in anterior resection have gained widespread acceptance over hand-sewn anastomosis. Different randomized studies comparing stapled and hand-sewn anastomosis confirmed the validity of the stapler associated with reduction of sphincter injury, operative time, and risk of abdominal contamination.

For more than a century surgeons believed dogmatically that efficient MBP is an important factor in preventing infectious complications and anastomotic dehiscence after colorectal surgery. Clinical experiences and observational studies have shown that mechanical removal of gross faeces from the colon has been associated with decreased morbidity and mortality in patients undergoing operations of the colon.5 Authors were categorical that the most important factor to affect the outcome of a colonic operation, which is within the control of a surgeon, is the degree of bowel emptiness.6,7 Several clinical trials questioned this dogma and concluded that vigorous MBP was not necessary. The authors of one meta-analysis concurred with this point of view,8,9 whereas in another trial,10 the authors argued that preoperative MBP is time-consuming and expensive, unpleasant to the patients, and completely unnecessary.11

Different MBP methods have been tested and approved. The potential danger of having faeces in contact with a newly performed anastomosis has led to the construction of a defunctioning stoma when the colon is not prepared. Experimental studies 12,13 and clinical trials in emergency surgery 14,15 have been published to support this theory. In a review of literature in 1998,16 it was concluded that there was limited evidence in the literature to support the use of MBP in patients undergoing colorectal surgery. Several studies evaluating a consecutive series of patients who underwent resection and primary anastomosis concluded that MBP is not essential for safe colorectal surgery.17,18

The authors of a trial that analyzed the bowel contents suggested that participants receiving MBP had a tendency toward a higher incidence of bowel contents spillage compared with participants who did not receive it, but without statistical significance. Spillage of bowel contents into the peritoneal cavity may increase the rate of postoperative complications.19 A recent case-controlled study that analyzed patients with rectal cancer who submitted to elective resection with mesorectal excision concluded that “elective rectal surgery for cancer without MBP may be associated with reduced postoperative morbidity.”20

We have noted that incomplete or poor bowel preparation, need for blood transfusions, and location of anastomosis were statistically related to the development of the anastomotic leakage. In a recent study, early and late postoperative complications in 77 T1-T2 rectal cancer patients who underwent rectal resection with stapled end-to-end anastomosis or end-to-side anastomosis were evaluated. Postoperative outcomes of the 2 procedures, clinicopathologic features between patients with and without anastomotic leakage have been compared. The overall incidence of anastomotic leakage was 16.8% (13/77 patients). Anastomotic leakage after end-to-end anastomosis was 29.2%, whereas after end-to-side anastomosis leakage was 5% (P = 0.005). In the end-to-end group, 11 patients had anastomotic leaks: 9

patients needed a reintervention with colostomy creation; 2 patients were treated with local washouts and intravenous antibiotics. Two patients of the end-to-side group experienced anastomotic leakage and were successfully treated with local washouts and antibiotics for 6 weeks. In this prospective study, outcome was compared between end-to-end and end-to-side anastomosis in anterior resection with mesorectal excision for T1-T2 rectal cancer. The patients studied presently were those with a potentially resectable tumor without signs of spread and in whom restorative surgery deemed possible to perform. Patients were randomized at a late stage of surgery. Thus, after a TME had been performed, and whether there were no macroscopical signs of local residual disease, both methods had to be deemed possible to perform before randomization took place. Today, the need for MBP continues to be debated. Moreover, we have noted that poor bowel preparation is related to a high leak rate ($P = 0.01$).

The technique used to design a colorectal anastomosis is largely based on surgeon preference. Numerous clinical studies reported a significantly higher leak rate (8.1%) in patients who underwent TME than those who underwent partial mesorectal excision (1.3%); additionally, a higher anastomotic leakage rate was associated with male gender, absence of stoma, and increased blood loss. Many advantages of performing a temporary stoma have been reported. It should be noted that the creation of a proximally diverting stoma to protect a low pelvic or technically inadequate anastomosis does not alter the risk for dehiscence, but does ameliorate the septic effects of the leak. Recently, emphasis on the quality of surgical care offered has increased tremendously. There is an increasing awareness of the outcomes of surgical care as a marker of quality. Lower mortality rates have been reported in patients undergoing surgery for colorectal cancer, when these procedures were performed in high-volume centers. Thus, hospital volume can also have an impact on colostomy rates, postoperative mortality, and overall survival.

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References

1. Van't Sant HP, Weidema WF, Hop WC, et al. The influence of mechanical bowel preparation in elective lower colorectal surgery. Ann Surg. 2010;251:59-63.
2. Rullier E, Laurent C, Bretagnol F, et al. Sphincter-saving resection for all rectal carcinomas: the end of the 2-cm distal rule. Ann Surg. 2005;241:465-469.
3. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. Ann Surg. 2004;240:260-268.
4. Brisinda G, Vanella S, Cadeddu F, et al. End-to-end versus end-to-side stapled anastomoses after anterior resection for rectal cancer. J Surg Oncol. 2009;99:75-79.
5. Nichols RL, Gorbach SL, Condon RE. Alteration of intestinal microflora following preoperative mechanical preparation of the colon. Dis Colon Rectum. 1971;14:123-127.
6. Clarke JS, Condon RE, Bartlett JG, et al. Preoperative oral antibiotics reduce septic complications of colon operations: results of prospective, randomized, double-blind clinical study. Ann Surg. 1977;186:251-259.
7. Chung RS, Gurll NJ, Berglund EM. A controlled clinical trial of whole gut lavage as a method of bowel preparation for colonic operations. Am J Surg. 1979;137:75-81.
8. Slim K, Vicaut E, Launay-Savary MV, et al. Updated systematic review and meta-analysis of randomized clinical trials on the role of mechanical bowel preparation before colorectal surgery. Ann Surg. 2009;249:203-209.
9. Slim K, Vicaut E, Panis Y, et al. Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation. Br J Surg. 2004;91:1125-1130.
10. Irving AD, Scrimgeour D. Mechanical bowel preparation for colonic resection and anastomosis. Br J Surg. 1987;74:580-581.
11. Bucher P, Gervaz P, Soravia C, et al. Randomized clinical trial of mechanical bowel preparation versus no preparation before elective left-sided colorectal surgery. Br J Surg. 2005;92:409-414.
12. O'Dwyer PJ, Conway W, McDermott EW, et al. Effect of mechanical bowel preparation on anastomotic integrity following low anterior resection in dogs. Br J Surg. 1989;76:756-758.
13. Schein M, Assalia A, Eldar S, et al. Is mechanical bowel preparation necessary before primary colonic anastomosis? An experimental study. Dis Colon Rectum. 1995;38:749-752; discussion 752-754.
14. Dorudi S, Wilson NM, Heddle RM. Primary restorative colectomy in malignant left-sided large bowel obstruction. Ann R Coll Surg Engl. 1990;72:393-395.
15. Duthie GS, Foster ME, Price-Thomas JM, et al. Bowel preparation or not for elective colorectal surgery. J R Coll Surg Edinb. 1990;35:169-171.
16. Platell C, Hall J. What is the role of mechanical bowel preparation in patients undergoing colorectal surgery? Dis Colon Rectum. 1998;41:875-882; discussion 882-883.
17. Fa-Si-Oen PR, Penninckx F. The effect of mechanical bowel preparation on human colonic tissue in elective open colon surgery. Dis Colon Rectum. 2004;47:948-949.
18. van Geldere D, Fa-Si-Oen P, Noach LA, et al. Complications after colorectal surgery without mechanical bowel preparation. J Am Coll Surg. 2002;194:40-47.
19. Mahajna A, Krausz M, Rosin D, et al. Bowel preparation is associated with spillage of bowel contents in colorectal surgery. Dis Colon Rectum. 2005;48:1626-1631.
20. Bretagnol F, Alves A, Ricci A, et al. Rectal cancer surgery without mechanical bowel preparation. Br J Surg. 2007;94:1266-1271.

Reply:

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We thank Dr. Brisinda and colleagues for their interest in our article and their comments.[1] They gave an excellent overview of the recent opinions on mechanical bowel preparation (MBP) and elective colorectal surgery. They also rightly state that the debate on MBP in elective colorectal surgery is not yet over. Many factors influence the incidence of anastomotic leakage, which makes it challenging to reveal which patients undergoing colorectal surgery may benefit from MBP, if any, and which patients are treated without reason.

At present, there is convincing evidence with adequate patient numbers and power that MBP can be safely omitted in overall colorectal surgery.[2-4] However, there is still hesitance among many colorectal surgeons to omit MBP in lower colorectal surgery. Brisinda et al rightly mentioned that the introduction of total mesorectal excision and low or very low anterior resections with anastomosis close to the anal verge is associated with a greater risk of anastomotic leakage compared with anastomosis more proximally in the colon.[5,6] In our study, we aimed to shed light on the influence of MBP on lower colorectal surgery, thus with greater risk of anastomotic leakage. We found that omitting MBP was not a significant risk factor for anastomotic leakage in contrast to male gender and the American Society of Anesthesiologists-classification. However, our study is a subgroup analysis and is underpowered. Brisinda et al noted that in their study, comparing the outcome of end-to-end versus end-to-side stapled anastomosis that incomplete bowel preparation and need for blood transfusions were statistically related to the development of anastomotic leakage. However, numbers were small (35 vs. 29) and no multivariate analysis was performed.[7] They do conclude that end-to-side anastomosis is significantly superior to end-to-end anastomosis in preventing leakage, which is a great contribution in this field of surgery. Presently, there is no adequate powered randomized controlled trial proving that MBP can be omitted safely in lower colorectal surgery, and until then the debate concerning MBP in the subgroup of lower colorectal surgery remains open.

Another matter commented on by Brisinda et al is the role of a temporary stoma in colorectal surgery. They state that a temporary stoma does not alter the risk of anastomotic dehiscence, but does ameliorate the septic effects. In our opinion, a temporary stoma does decrease the risk of anastomotic leakage as shown by Matthiessen et al.[8] They randomized 234 patients to a defunctioning loop stoma or no stoma. Patients randomized to a defunctioning stoma (n = 116) had leakage in 10.3% (12 of 116) and those without stoma (n = 118) in 28.0% (33 of 118), P< 0.001. They therefore recommend a defunctioning loop stoma in low anterior resection for cancer. Furthermore, there are 2 other meta-analysis suggesting that a defunctioning loop stoma reduces the rate of clinically relevant anastomotic leakage.[9,10] As mentioned in our study, it seems irrational to apply a defunctioning ileostoma when the bowel is not cleansed, as the remaining feces in the rest of the colon can still jeopardize the anastomosis. In our opinion, however a preoperative not cleansed bowel should not withhold any surgeon from applying a defunctioning ileostoma, taking into account the results by Matthiessen et al. We concur with Brisinda et al on the fact that a defunctioning loop stoma at least mitigates the consequences of leakage which leaves us with the interesting query whether MBP may also mitigate the consequences of leakage.

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References

1. Van't Sant HP, Weidema WF, Hop WC, et al. The influence of mechanical bowel preparation in elective lower colorectal surgery. Ann Surg. 2010;241:59-63.
2. Slim K, Vicaut E, Launay-Savary MV, et al. Updated systematic review and meta-analysis of randomized clinical trials on he role of mechanical bowel preparation before colorectal surgery. Ann Surg. 2009;249:203-209.
3. Contant CME, Hop WCJ, van't Sant HP, et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomized trial. Lancet. 2007;370:2112- 2117.
4. Jung B, Pahlman L, Nystrom PO, et al. Multicentre randomized trial of mechanical bowel preparation in elective colonic resection. Br J Surg. 2007;94:689-695.
5. Rullier E, Laurent C, Garrelon JL, et al. Risk factors anastomotic leakage after resection of recta cancer. Br J Surg. 1998;85:355-358.
6. Matthiessen P, Hallbook O, Andersson M, et al. Risk factors for anastomotic leakage after anterior resection of the rectum. Colorectal Dis. 2004;6:462-469.
7. Brisinda G, Vanella S, Cadeddu F, et al. End-to-end versus end-to-side stapled anastomosis after anterior resection in cancer. J Surg Oncol. 2009;99:75-79.
8. Matthiessen P, Hallbook O, Rutegard J, et al. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer. Ann Surg. 2007;246:207-214.
9. Huser N, Michalski CW, Erkan M, et al. Systemic review and met-analysis of the role of defunctioning stoma in low rectal cancer surgery. Ann Surg. 2008;248:52-60.
10. Tan WS, Tang CL, Shi L, et al. Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer. Br J Surg. 2009;96:462-472.

Chapter 4

Evaluation of morbidity and mortality after anastomotic leakage following elective colorectal surgery in patients treated with or without mechanical bowel preparation

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Abstract

Background A previous multi-centre randomized trial demonstrated that mechanical bowel preparation (MBP) does not guard against anastomotic leakage in elective colorectal surgery. This aim of this complementary study was to evaluate the effects of MBP on morbidity and mortality after anastomotic leakage in elective colorectal surgery.

Methods A subgroup analysis was performed of a randomized trial comparing the incidence of anastomotic leakage and septic complications with and without MBP in patients undergoing elective colorectal surgery.

Results Elective colorectal surgery was performed in 1433 patients with primary anastomosis, of whom 63 patients developed anastomotic leakage. Twenty-eight patients received MBP and 35 patients did not (44% vs. 56%). Mortality rate, initial need for surgical re-intervention and extent of bowel contamination did not differ between groups (29% vs.40% P=0.497, P=0.667 and P=0.998, respectively).

Conclusion No benefit of MBP was found regarding morbidity and mortality after anastomotic leakage in elective colorectal surgery.

Introduction

Symptomatic anastomotic leakage is one of the most severe complications after colorectal surgery and causes substantial morbidity and mortality. Rates of anastomotic leakage vary in literature ranging from 6 to 22%[1-5]. Traditionally, many clinics practicing colorectal surgery have relied on mechanical bowel preparation (MBP) as one of the prerequisites for safe colorectal resection and anastomosis. At present, however, there is sufficient evidence to omit MBP in elective colorectal surgery. Two large multicenter randomized trials and a recent large meta-analysis showed no benefit from MBP regarding leakage rate and septic complications [6-8]. Some studies even observed potentially hazardous effects from MBP in elective colorectal surgery[9-11]. Although MBP does not affect the primary leakage rate, it may affect the severity of an anastomotic leakage in case such an event does occur. Some reports state that by diminishing the fecal load at the site of the anastomosis, the clinical sequelae of an anastomotic leakage may be reduced[12-16]. However, this has been investigated mainly in relation to a diverting ileostomy, and evidence that MBP has beneficial effects concerning the severity of an anastomotic leakage has not been put forth. In this study we aimed to evaluate the effect of MBP on the severity and consequences of anastomotic leakage in elective colorectal surgery.

Methods

This study was a subgroup analysis of a prior large multicentre, randomized trial performed by Contant et al.[6] comparing elective colorectal resection and primary anastomosis with or without the use of MBP. In this study, 1433 patients were randomized before elective colorectal surgery to receive MBP: 2 to 4 L of polyethylene glycol bowel lavage solution (Klean-Prep; Helix BioPharma Corporation, Aurora, Canada) in combination with bisacodyl (11 hospitals) or sodium phosphate solution (2 hospitals). Exclusion criteria were an acute laparotomy, laparoscopic colorectal surgery, contraindications for the use of MBP, an a priori diverting ileostomy, and age <18 years. Informed consent was obtained from all patients who participated and approval was obtained from a designated review board of the institution involved[6].

In the present subgroup analysis, 69 (4.8%) of 1433 patients had anastomotic leakage. The data of 63 patients were available for re-evaluation with regard to the consequences of anastomotic leakage. Additional data of 6 patients could retrospectively not be obtained because of absent or incomplete documentation. Of these 6 patients, 4 had been previously randomized for MBP and 2 had been randomized for no MBP. Diagnosis of anastomotic

leakage was based on clinical suspicion (prolonged fever, abdominal pain, local or generalised peritonitis, leucocytosis) and confirmed after either contrast radiography (X-ray or computer tomography scan) or laparotomy. No effort was made to screen for asymptomatic leakage. Endpoints of this study were mortality rate, extent of bowel contamination, need for surgical re-intervention, number of surgical re-interventions, intra-abdominal abscess formation, days of admission to the intensive care unit (ICU), days of mechanical ventilation, and the implementation of inotropic agents. Extent of bowel contamination was based on the Hinchey classification normally applied in cases of diverticular disease and diverticulitis.

Surgical technique

Antibiotic prophylaxis was given intravenously to all patients according to the guidelines for prevention of surgical site infection issued by the department of infectious diseases of each participating hospital. All surgical procedures were elective procedures performed by open laparotomy for either colonic malignancies, or benign lesions such as diverticular disease or strictures. Anastomoses were performed depending on the preference of the surgical team. Criteria for the application of a diverting ileostomy were not stated in advance; a diverting ileostomy was performed when deemed necessary. All secondary surgery stated in this study occurred in acute situations after an elective primary procedure.

Statistical analysis

Groups were compared with respect to complication rates using the Chi-square test or Fisher's exact tests. Comparison of continuous or graded outcomes was performed using Mann-Whitney *U* tests. The Mantel-Haenszel test and the stratified Mann-Whitney *U* test were used, allowing for an imbalance in American Society of Anaesthesiologists (ASA) classification in the comparison of MBP-positive and MBP-negative patient groups. Two-sided *P*-values <,05 were considered statistically significant.

Results

Sixty-three patients with an anastomotic leakage were available for re-evaluation after elective colorectal surgery. Twenty-eight patients had received preoperative MBP and 35 patients had not. Study group characteristics are shown in Table I. No significant differences were found in either gender, age, number of diverting ileostomies, ASA-classification, diagnosis or level of anastomosis between patients who had received MBP and patients who had not received MBP before colorectal surgery. Mortality rates were not significantly different between the patient groups (Table II). The necessity for initial surgical re-intervention and the number of subsequent procedures did not differ between the patient groups (Table II). There was some

imbalance in ASA classification between the patient groups (Table I). Reanalysis of all data with adjustment for ASA classification resulted in the same findings (data not shown).

Table I. Group characteristics for patients with anastomotic leakage with and without mechanical bowel preparation (MBP).

	MBP+ (n=28)	MBP- (n=35)	p-value
Gender			1.000
Male	20	25	
Female	8	10	
Age in years (mean)	67 (40-87)	69 (38-86)	0.658
Diverting ileostomy	1	4	0.371
ASA-classification‡			0.148
I	6	6	
II	11	22	
III	11	7	
Diagnosis			0.405
Colorectal cancer	9	14	
IBD#	4	8	
Other¥	15	13	
Type of anastomosis			0.444
Ileocolic	5	7	
Colocolic	9	10	
Colorectal	14	15	
Other*	0	3	

‡American Society of Anesthesiologists
#Irritable bowel disease
¥Benign disease or stenosis, diverticulitis, reversal of Hartmann's procedure or volvolus
*Reversal of Hartmann's procedure or ileorectal anastomosis.

The frequency of surgical re-interventions in both study groups is stratified in Table III. Types of secondary surgical procedures included double-loop ileostomy, end ileostomy, Hartmann's procedure, double-loop colostomy, abdominal lavage, additional anastomotic suture, additional surgery due to fascia dehiscence, and new anastomosis.

Table II. Parameters associated with the extent of illness and indicating the severity of anastomotic leakage in elective colorectal surgery with and without mechanical bowel preparation (MBP).

	MBP+(n=28)	MBP-(n=35)	p-value
Mortality	8(29%)	14(40%)	0.497
Inotropic agents	10(36%)	15(43%)	0.751
ICU[#] admission	20(71%)	24(69%)	1.000
Mechanical ventilation	14(50%)	16(46%)	0.933
Days of ICU admission (mean)*	6.2/1.0 (0-55)	8.9/1.0 (0-59)	0.867
Days of mechanical ventilation (mean)*	3.6/.0 (0-41)	5.6/.0 (0-59)	0.440
C**ontamination grade**[†]			0.998
I	6(21%)	4(11%)	
II	3(11%)	9(26%)	
III	4(14%)	7(20%)	
IV	9(32%)	10(29%)	
Surgical re-intervention[¥]			0.667
- Alive with surgical re-intervention	16(54%)	17(49%)	
- Alive without surgical re-intervention	4(18%)	4(11%)	
- Deceased with surgical re-intervention	7(25%)	13(37%)	
- Deceased without surgical re-intervention	1(4%)	1(3%)	
Number of surgical re-interventions (mean)[¥]	1.3/1.0 (0-6)	1.6/1.0 (0-5)	0.106
Hospital stay in days (mean)*	34.6/22.5 (15-86)	51.6/41.0 (9-156)	0.061
Time of anastomotic leakage in days (mean)	8.6/6.5 (3-33)	8.2/7.0 (2-26)	0.729

*Deceased patients were not included in these calculations (N=22)
[†]Hinchey classification.
[#]Intensive Care Unit.
[¥]Deceased patients without secondary surgical intervention were not included in these calculations (N=2).

Table III. Numbers of surgical re-interventions specified.

Number of surgical re- interventions	MBP+ (n=27)	MBP- (n=34)
0	5	4
1	18	15
2	2	8
3	0	5
4	1	1
5	0	1
6	1	0
total	27	34

Deceased patients without secondary surgical intervention were not included in this table (n=2, one in each group).

Discussion

In this subgroup analysis of a large randomized trial , previously demonstrating that MBP can safely be abandoned regarding leakage and complication rate, we aimed to evaluate the clinical significance and severity of anastomotic leakage in patients confronted with this complication after elective colorectal surgery[6]. Many studies have investigated the effects of MBP, diverting ileostomies, and pelvic drains on the rate of anastomotic leakage in elective colorectal surgery, but few studies have focused on the clinical sequelae and consequences of these events. Most studies investigating the clinical consequences of anastomotic leakage concentrate on the role of a diverting ileostomy. By diverting the faecal stream, and thereby protecting the anastomosis from faeces, one might rationally expect a decrease in leakage rate. However, the results on this matter reported in literature are nonuniform, and prospective, randomized trials are few and far between[12-19]. Although MBP does not divert the faecal stream, it is thought to reduce the faecal load at the site of the anastomosis through cleansing of the bowel before surgery. However the effects of MBP are only temporary compared with a diverting ileostomy. Studies investigating the effects of MBP on the clinical significance and consequences of an anastomotic leakage in colorectal surgery have not been reported.

There is no accepted method of stratifying the severity of anastomotic leaks. One may subdivide anastomotic leakages in clinically significant leakages and clinically insignificant leakages. Clinically significant leakages require secondary surgical intervention and clinically insignificant leakages may be treated expectantly. Most studies use a combination of clinical and radiologic features to define an anastomotic leak. A major leak may be described as one of major clinical consequences, including peritonitis and sepsis, often requiring secondary surgery. Minor leaks may be described as leaks of no clinical significance, confirmed by radiologic studies but needing no surgical intervention[2]. All leaks in the present subgroup analysis were either confirmed by laparotomy or by radiologic studies, and both major as well as minor leakages have been included. Sepsis, as a common result of anastomotic leakage, may be stratified according to several scores such as the APACHE-score. However, our data in this regard was not sufficient for analysing such specific parameters as an accurate score of sepsis. Instead, we chose other more accessible parameters associated with the sequelae of leakage and the extent of sepsis.

In this study, the necessity for initial surgical reintervention and the number of subsequent proecedures did not differ between the patient groups, and the number of patients treated conservatively varied little between the groups. However, a diverting ileostomy or colostomy might influence the number of subsequent surgical reintervetions. Twenty-four patients (69%) in the MBP-negative group and 23 patients (82%) in the MBP positive group received diversion during the surgical reintervention (P=0,348). This difference can be partially

explained because 1 patient in the MBP-positive group versus 4 patients in the MBP-negative group had diverting ileostomies at primery surgery. Patients with diversion at primary surgery were less likely to receive a diversion at secondary surgery.

Evidence concerning the effect of MBP on the clinical sequelae of anastomotic dehiscence is scarce with most studies focusing on diverting ileostomies and pelvic drains. This study demonstrates no clinical differences regarding mortality rate or other septic related complications after anastomotic leakage in patients treated with or without MBP after elective colorectal surgery. We therefore propose that MBP has no clinical benefit in patients confronted with anastomotic leakage after elective colorectal surgery. However, as mentioned before the data used in this study derived from an earlier multicentre randomized trial designed for a different purpose. Therefore more ad hoc and prospective designed studies are needed.

References

1. Rullier E, Laurent C, Garrelon JL, Michel P, Saric J, Parneix M. Risk factors for anastomotic leakage after resection of rectal cancer. Br J Surg 1998;85:355-8.
2. Chambers WM, Mortensen NJMcC. Postoperative leakage and abscess formation after colorectal surgery. Best practice and research clinical gastroenterology. 2004;18:865-880.
3. Soeters PB, De Zoete JP, Dejong CH, Williams NS, Baeten CG. Colorectal Surgery and Anastomotic Leakage. Dig Surg 2002;19:150-155
4. Geldere van D, Fa-Si-Oen P, Noach LA, Rietra PJGM, Peterse JL, RPA Boom. Complications after colorectal surgery without mechanical bowel preparation. J Am Coll Surg 2002;194:40-47.
5. Alves A, Panis Y, Mathieu P, Mantion G, Kwiatkowski F, Slim K et al. Postoperative Mortality and Morbidity in French Patients Undergoing Colorectal Surgery. Arch Surg. 2005;140:278-283.
6. Contant CME, Hop WCJ, van't Sant HP, Oostvogel HJM, Smeets HJ, Stassen LPS et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomized trial. Lancet 2007;370:2112-17.
7. Jung B, Pahlman L, Nystrom P-O, Nilsson E. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. Br J Surg. 2007;94:689-695.
8. Slim K, Vicaut E, Launay-Savary M, Contant C, Chipponi J. Updated systemic review and meta-analysis of randomized clinical trials on the role of mechanical bowel preparation before colorectal surgery. Ann Surg 2009;249:203-209.
9. Slim K, Vicaut E, Panis Y, Chipponi J. Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation. Br J Surg 2004;91:1125-1130.
10. Santos JCM, Batista J, Sirimarco MT, Guimaraes AS, Levy CE. Prospective randomized trial of mechanical bowel preparation in patients undergoing elective colorectal surgery. Br J Surg 1994;81:1673-1676.
11. Bretagnol F, Alves A, Ricci A, Valleur P, Panis Y. Rectal cancer surgery without mechanical bowel preparation. Br J Surg 2007;94:1266-1271.
12. Dehni N, Schlegel RD, Cunningham C, Guiget M, Tiret E, Parc R. Influence of a defunctioning stoma on leakage rates after low colorectal anastomosis and colonic J pouch-anal anastomosis. Br J Surg 1998;85:1114-1117.
13. Marusch F, Koch A, Schmidt U, Geibetaler S, Dralle H, Saeger HD et al. Value of a protective stoma in low anterior resections for rectal cancer. Dis Colon Rectum 2002;45:1164-1171.
14. Gastinger I, Marusch F, Steinert R, Wolff S, Koeckerling F, Lippert H. Protectice defunctioning stoma in low anterior resection for rectal carcinoma. Br J Surg 2005;92:1137-1142.
15. Peeters KCMJ, Tollenaar RAEM, Marijnen CAM, Klein Kranenbarg E, Steup WH, Wiggers T, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 2005;92:211-216.
16. Poon RT, Chu KW, Ho JW, Chan CW, Law WL, Wong J. Prospective evaluation of selective defunctioning stoma for low anterior resection with total mesorectal excision. World J Surg 1999;23:463-467.
17. Remzi FH, Fazio VW, Gorgun E, Boon SO, Hammel J, Preen M et al. The outcome after restorative proctocolectomy with or without defunctioning ileostomy. Dis Colon Rectum 2006;49:470-477.
18. Wong NY, Eu KW. A defunctioning ileostomy does not prevent clinical anastomotic leak after a low anterior resection: a prospective, comparative study. Dis Colon Rectum 2005;48:2076-2079.
19. Mathiessen P, Hallbook O, Rutegard J, Simert G, Sjodahl R. Defunctioning Stoma Reduces Symptomatic Anastomotic Leakage After Low Anterior Resection of the Rectum for Cancer. Ann Surg 2007;246:207-214.

Chapter 5

Bowel preparation prior to laparoscopic colorectal resection: what is the current practice?

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Abstract

Background Much has been published on the role of mechanical bowel preparation (MBP) in open colorectal resection; however current literature shows little evidence on the use of MBP prior to laparoscopic colorectal resections. In contrast to open procedures, MBP could influence the diameter of the bowel and thus the exposure of the surgical field in laparoscopy. This study aimed to assess the current practice of Dutch laparoscopic surgeons regarding MBP prior to colorectal resections.

Methods In January 2010 members of the Dutch Association for Endoscopic Surgery (NVEC) were invited to fill out an online questionnaire investigating whether MBP is prescribed prior to laparoscopic colorectal surgery, and which considerations are taken into account when choosing or omitting MBP.

Results The 82 (49%) returned questionnaires showed that 20% of respondents prescribe MBP prior to colonic resections, while 63% prescribe MBP prior to rectal resections. The most common reasons for giving MBP were the construction of a protective ileostoma (22%), improvement of the surgical field exposure (16%), and 'other reasons' specified by free text (21%). The three most common reasons for conversion were inadequate surgical field exposure (88%), locally advanced tumour (68%), and adhesions (29%). Concerning the question which stages of the operation are influenced by MBP 29% of respondents believed the diameter of the small bowel was influenced by MBP, 29% indicated that the exposure of the surgical field was influenced by MBP, and 52% did not believe that any of the stages of the operation were influenced by MBP.

Conclusion The results of this questionnaire indicate that the implementation of MBP in laparoscopic colorectal surgery is based on individual preferences in the Netherlands. This emphasizes the need of new studies investigating the role of MBP on surgical field exposure in colorectal laparoscopic surgery.

Introduction

The introduction of laparoscopic procedures has led to an important progress in colorectal surgery. Not only does this technique achieve similar long-term results as the conventional open procedure, short-term results have been shown to be superior(1-4). These include less postoperative pain, earlier recovery of bowel function, less blood loss, and shorter hospital stay. In case of colorectal cancer, which is the third most common cancer in the developed world, colorectal resection is the only curative treatment and short-term advantages obtained by laparoscopy represent an important difference for the operated patient. Long-term results, defined as disease-free survival, do not differ between patients operated through laparotomy or laparoscopy(2, 3).

Thorough mechanical cleansing of the bowel has long been considered essential prior to colorectal operations(5-7). It was believed an empty bowel would diminish the risk of anastomotic leakage and septic complications. However, during the last decade several studies have been conducted investigating the use of mechanical bowel preparation (MBP). Most recent randomized controlled trials and meta-analyses uniformly conclude that there is no advantage of MBP prior to colorectal resections, finding equal or lower rates of anastomotic leakage and septic complications in patients without MBP compared to patients with pre-operative MBP(8-17). However, these studies have not included patients operated by means of minimally invasive techniques, and therefore this conclusion cannot be extrapolated to laparoscopic surgery. Logically, one does not expect the effect of MBP on anastomotic leakage and other septic complications to be different between patients with a laparoscopic or open approach. However, the effect of bowel preparation on the volume of the bowel, and thus on exposure, could play an important role in the course of the laparoscopic intervention itself. Contradictory opinions are found in literature concerning this subject(12, 16, 18), and very few studies have investigated the role of MBP prior to laparoscopic interventions(19, 20). To evaluate the current practice among Dutch laparoscopic gastrointestinal surgeons we performed a questionnaire survey. The aim of this questionnaire was to investigate whether MBP is prescribed prior to laparoscopic colorectal surgery, and which considerations are taken into account when choosing or omitting MBP.

Materials and methods

The Dutch Society for Endoscopic Surgery (NVEC, Nederlandse Vereniging Endoscopische Chirurgie) was contacted and asked to participate in the study by sharing their members' contact information. In January 2010 members of the NVEC were invited by e-mail to fill out an online questionnaire on MBP prior to laparoscopic procedures. The target group

of this study comprised surgeons performing laparoscopic colorectal surgery. The answers were automatically submitted online at the end of the questionnaire. After two weeks the questionnaire was again sent to the members who had not yet responded.
The questionnaire consisted of 10 questions; 4 open and 6 multiple-choice questions. Of these 6 multiple-choice questions 4 could be answered with ''other'' and specified with free text. Answers specified by free text were reviewed for validity (i.e. not just one letter or incoherent text).
Surgeons were asked whether they use MBP for laparoscopic procedures, what type of MBP they use, for what reason they use it, and what aspects of the procedure could be influenced by MBP. Because of the interest of this study in surgical field exposure, major reasons for conversion were asked, as well as the degree of Trendelenburg-positioning of the patient.

Table 1 shows a summarized version of the questionnaire. Results are presented as percentages or medians with inter-quartile ranges.

Table 1. Summarized version of the questionnaire.

- What is your surgical field of interest?
- How many laparoscopic colonic- or rectal resections do you perform per month?
- Do you subscribe MBP to your patient prior to laparoscopic colonic resections?
- If yes: What MBP do you subscribe?
- Do you subscribe MBP to your patient prior to laparoscopic rectal resections?
- If yes: What MBP do you subscribe?
- Why do you use MBP? (more than one answer possible)
  - this is according to the guideline of the department
  - to improve exposure of the surgical field
  - to diminish postoperative septic complications
  - I do not use MBP
  - other:
- How many degrees Trendelenburg do you position your patient?
- What are your three major reasons for conversion?
  - adhesions
  - locally advanced tumour
  - inadequate surgical field exposure
  - difficult localization of the tumour
  - intra-abdominal haemorrhage or injury to organs
  - technical difficulties
  - patient obesity
  - other:
- Do you feel MBP can influence: (more than one answer possible)
  - the diameter of the small bowel
  - the ease of mobilizing the small bowel
  - operation time
  - exposure of the surgical field
  - risk of conversion
  - none of mentioned above
  - other:

Results

The NVEC has 247 members. Fifty-three surgeons not performing general surgery or gastro-intestinal surgery were not contacted (mostly gynaecologists, urologists, and thoracic surgeons). The online survey was sent to the remaining 194 members. Thirty-five members did not receive it due to incorrect e-mail addresses (defined as emails that could not be delivered due to errors in the address or non-existing addresses), or responded that they did not perform gastro-intestinal surgery. Of the 169 laparoscopic surgeons that received the online survey, 82 responded (49%). In 84.1% of respondents lower gastro-intestinal surgery was included in their field of interest, while 15.9% indicated that their field of interest was upper gastro-intestinal surgery. The median quantity of colorectal resections performed per month was 5 (3-7).

Twenty percent of respondents declared to give MBP prior to laparoscopic colorectal resections, while 63% of respondents declared to give MBP prior to laparoscopic rectal resections. The distribution of the different types of MBP can be found in figures 1 and 2. The median percentage Trendelenburg positioning of the patient was 30 degrees (26.5- 42.5 degrees).

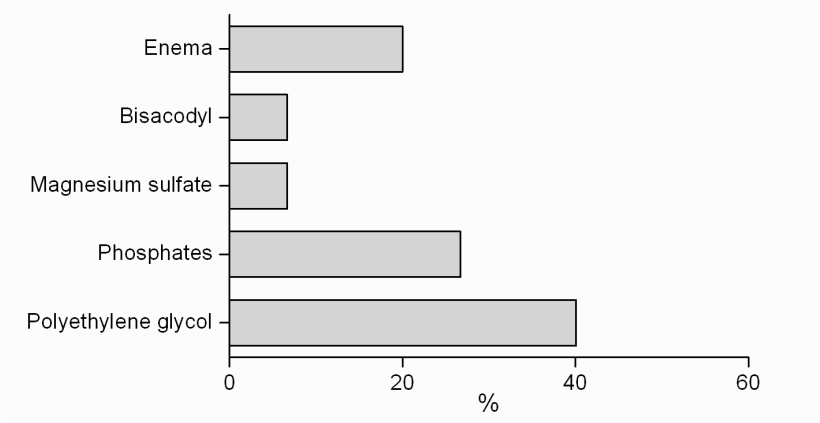

Figure 1. MBP used prior to colonic resection

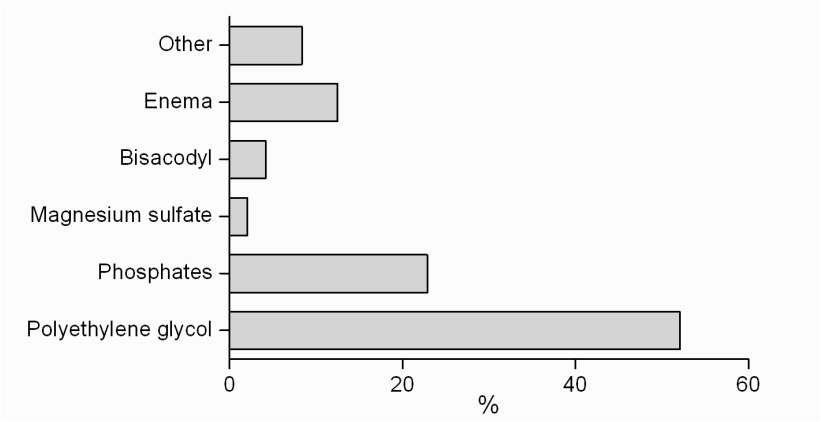

Figure 2. MBP used prior to rectal resection

Of the 63% of respondents giving MBP, the most common reasons for giving MBP are shown in figure 3. The construction of a protective ileostoma, not intending to leave a 'filled' colon, was the most frequent answer (22%), followed by 'other reasons' and free text (21%), and improvement of the surgical field exposure (16%). The two most frequent text when choosing 'other reasons' was (1) better handling of the bowel when it is empty and (2) easier introduction of the stapler. The three most common reasons for conversion were inadequate surgical field exposure (88%), locally advanced tumour (68%), and adhesions (29%) (figure 4). Concerning the question which stages of the operation are influenced by MBP, 52% of respondents believed that MBP does not influence any stage of the operation. Twenty-nine per cent of respondents thought that the diameter of the small bowel was influenced by MBP, and 29% indicated that the exposure of the surgical field was influenced by MBP (figure 5).

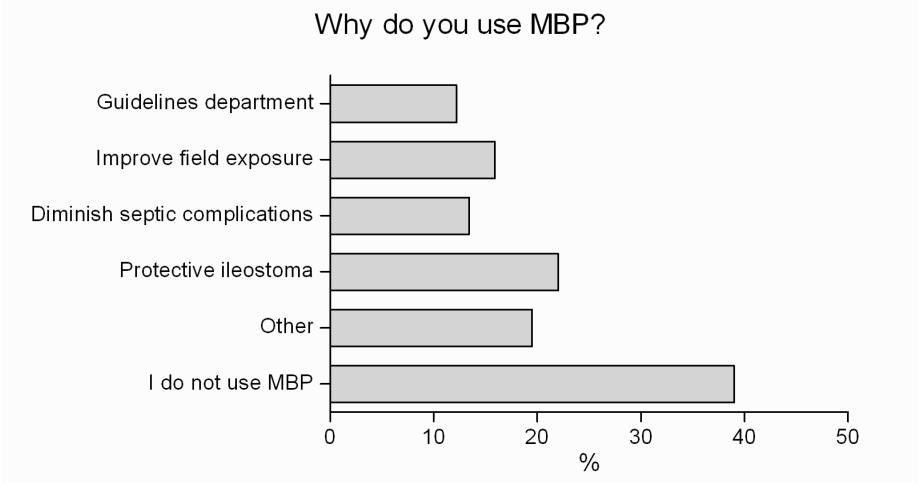

Figure 3. Reasons for giving MBP

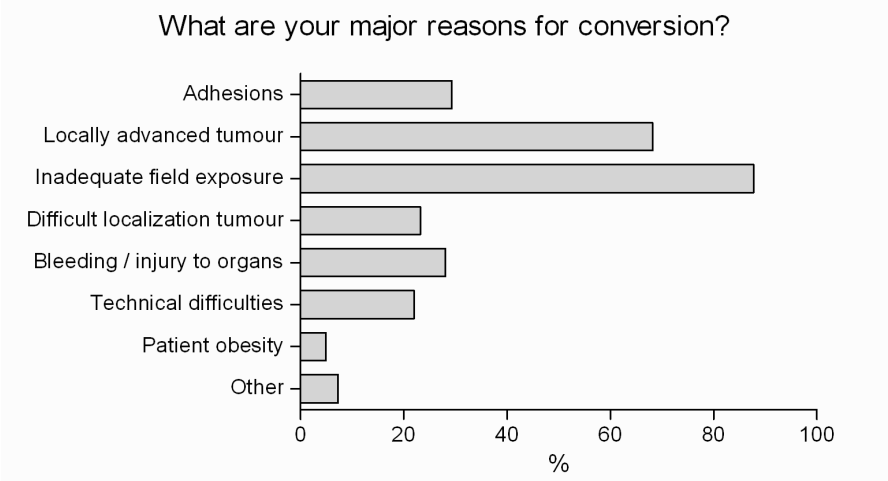

Figure 4. Reasons for conversion from laparoscopic to open approach

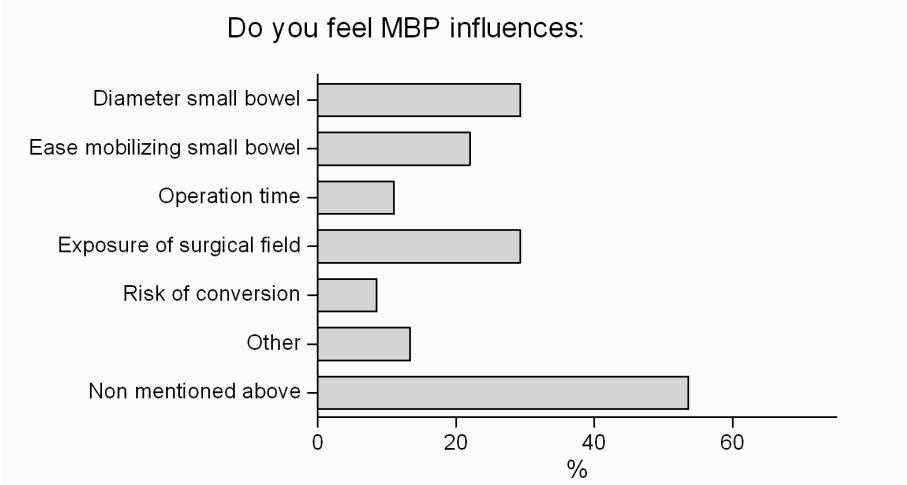

Figure 5. Influence of MBP on different stages of the operation

Discussion

Due to strong evidence that MBP does not lower the risk of anastomotic leakage and other septic complications in elective colorectal surgery(8-17), its standardized use has been abandoned in many centres. However, no studies regarding MBP have yet been conducted focusing on patients operated by means of minimally invasive techniques. In the Netherlands, nowadays, a significant part of colorectal resections are performed through laparoscopy, and

the improved short-term results (less postoperative pain, earlier recovery of bowel function, less blood loss, and shorter hospital stay) and similar disease-free survival rates have resulted in the important increase of laparoscopic procedures(1-4).

In our opinion the results of studies on MBP and infectious complications can also be applied to laparoscopic surgery; however the effect of MBP on the volume of the bowel and its competition with the insufflated CO^2 influencing exposure could play an important role in the course of the laparoscopic intervention itself. Evidence-based guidelines concerning this issue are lacking, and contradictory opinions are found in literature concerning this subject. Guenaga et al.(12) mention in their Cochrane review that it has been argued that it is easier to perform laparoscopic surgery if the bowel contains solid matter in order to use gravity to obtain better overview. Slim et al.(16) state in a meta-analysis that MBP usually results in dilated bowel which could hamper laparoscopic vision and make mobilization of the intestines more difficult. Cheung et al.(18) have described their results of a questionnaire on the technique of laparoscopic total mesorectal excision. They find that most surgeons apply MBP routinely for different reasons, and that reduction of intestinal volume to facilitate laparoscopic exposure appears to be a specific incentive.

Two studies in literature evaluated the effect of MBP on exposure in gynaecologic laparoscopy. In the first study, performed by Muzii et al.(19), patients were randomized between pre-operative MBP (90ml sodium phosphate) and no MBP; the endpoint was the appropriateness of the surgical field as judged by the surgeon on a scale going from poor to excellent in five steps. No advantage of MBP on the evaluation of the surgical field could be demonstrated. Another randomized trial, performed by Yang et al.(21), divided patients into two groups. The first group received MBP through oral sodium phosphate solution; the second group received only a sodium phosphate enema. Assessment of the quality of the surgical field and bowel characteristics was performed using a surgeon questionnaire with Likert and visual analog scales. No significant differences were observed between the 2 groups in evaluation of the surgical field, bowel handling, degree of bowel preparation, or surgical difficulty(21).

The results of this questionnaire show that bowel preparation is still frequently used in laparoscopic colorectal procedures in the Netherlands, mostly in rectal resection. Sixteen per cent of respondents prescribe MBP prior to surgery in order to improve surgical field exposure; on the other hand inadequate surgical field exposure was by far the most common reason for conversion (88%). Almost a third of the respondents felt MBP might influence the diameter of the small bowel and the exposure; this can be placed in either a positive or a negative perspective since some feel MBP results in an emptied bowel and some in a bowel filled with liquid or gas bowel contents(22).

The most important limitation of this questionnaire is the response rate of 49%. A low response rate to questionnaires is a well-known problem, and to make the chances of response as high as possible we sent an online questionnaire by email, made it as short as possible (10

questions), and with automatic sending of the results at the end of the questionnaire. Another limitation is the fact that ideally all Dutch surgeons performing laparoscopic gastro-intestinal procedures should have been contacted, however from a practical point of view that was not feasible. We have chosen to send this questionnaire through the Dutch Association of Endoscopic Surgery since that provided us with an email-list of Dutch surgeons with particular interest for laparoscopic surgery.

A different questionnaire was performed by Wells et al.(23), amongst 110 members of the Society of Gynecologic Oncologists of Canada to assess the practice pattern and beliefs on MBP. The results show that half of the respondents routinely use MBP for gynaecologic oncologic surgery (laparotomy and laparoscopy). The most common reasons for using MBP were to decrease the risk of anastomotic leak and improve visualization.

To present, no evidence exists on the role of MBP on the diameter of the bowel and exposure in colorectal laparoscopy. To achieve optimal exposure in laparoscopic colorectal surgery, the small bowel has to be mobilized cranially. Several aspects can influence the ease of mobilizing the small bowel: the degree of muscle relaxation and Trendelenburg-position, the thickness of the omentum and mesocolon of the small bowel (related to body mass index), and the diameter of the small bowel. The first aspect is in the hands of both surgeon and anaesthetist; the second aspect is patient-dependent and cannot be influenced. Concerning the diameter and contents of the small bowel and the ease in which it can be mobilized only little is known. Whether a completely emptied bowel is preferable over normal stool contents in order to use gravity remains an unanswered question until now. Furthermore, it is questionable whether MBP can achieve a complete emptied bowel at all, or whether it will result in a more voluminous small bowel due to inadequate bowel cleansing and liquid or gas bowel contents(22). The latter could also be influenced by the type of MBP being administrated and patient compliance.

The scarce quantity of studies regarding the subject of MBP in laparoscopy indicates the following: (1) Questionnaires regarding MBP indicate a number of laparoscopic surgeons use MBP with the aim to improve surgical field exposure (Wells et al.23). (2) Randomized studies on MBP in gynecologic laparoscopy seem to conclude that there is no amelioration of surgical field exposure with MBP. The difficulty in these studies is the outcome measure, which is the evaluation of the surgical field using a surgeon questionnaire(19, 21).

In conclusion, the results of this questionnaire show that the indication of MBP in laparoscopic colorectal surgery is undefined in the Netherlands. A review of literature shows that the influence of MBP on diameter of the bowel and thus laparoscopic vision is not clear. Studies investigating the role of MBP on intestinal volume and surgical field exposure in colorectal laparoscopic surgery are necessary.

References

1. Breukink S, Pierie J, Wiggers T. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev. 2006(4):CD005200.
2. Clinical Outcomes of Surgical Therapy Study G. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med. 2004 May 13;350(20):2050-9.
3. Reza MM, Blasco JA, Andradas E, Cantero R, Mayol J. Systematic review of laparoscopic versus open surgery for colorectal cancer. Br J Surg. 2006 Aug;93(8):921-8.
4. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol. 2005 Jul;6(7):477-84.
5. Chung RS, Gurll NJ, Berglund EM. A controlled clinical trial of whole gut lavage as a method of bowel preparation for colonic operations. Am J Surg. 1979 Jan;137(1):75-81.
6. Dunphy JE. Preoperative preparation of the colon and other factors affecting anastomotic healing. Cancer. 1971 Jul;28(1):181-2.
7. Nichols RL, Condon RE. Preoperative preparation of the colon. Surg Gynecol Obstet. 1971 Feb;132(2):323-37.
8. Bretagnol F, Alves A, Ricci A, Valleur P, Panis Y. Rectal cancer surgery without mechanical bowel preparation. Br J Surg. 2007 Oct;94(10):1266-71.
9. Bucher P, Gervaz P, Soravia C, Mermillod B, Erne M, Morel P. Randomized clinical trial of mechanical bowel preparation versus no preparation before elective left-sided colorectal surgery. Br J Surg. 2005 Apr;92(4):409-14.
10. Contant CM, Hop WC, van't Sant HP, Oostvogel HJ, Smeets HJ, Stassen LP, et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. Lancet. 2007 Dec 22;370(9605):2112-7.
11. Fa-Si-Oen P, Roumen R, Buitenweg J, van de Velde C, van Geldere D, Putter H, et al. Mechanical bowel preparation or not? Outcome of a multicenter, randomized trial in elective open colon surgery. Dis Colon Rectum. 2005 Aug;48(8):1509-16.
12. Guenaga KK, Matos D, Wille-Jorgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev. 2009(1):CD001544.
13. Jung B, Pahlman L, Nystrom PO, Nilsson E, Mechanical Bowel Preparation Study G. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. Br J Surg. 2007 Jun;94(6):689-95.
14. Pena-Soria MJ, Mayol JM, Anula R, Arbeo-Escolar A, Fernandez-Represa JA. Single-blinded randomized trial of mechanical bowel preparation for colon surgery with primary intraperitoneal anastomosis. J Gastrointest Surg. [Randomized Controlled Trial]. 2008 Dec;12(12):2103-8; discussion 8-9.
15. Ram E, Sherman Y, Weil R, Vishne T, Kravarusic D, Dreznik Z. Is mechanical bowel preparation mandatory for elective colon surgery? A prospective randomized study. Arch Surg. [Clinical Randomized Controlled Trial]. 2005 Mar;140(3):285-8.
16. Slim K, Vicaut E, Panis Y, Chipponi J. Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation. Br J Surg. 2004 Sep;91(9):1125-30.
17. Zmora O, Mahajna A, Bar-Zakai B, Hershko D, Shabtai M, Krausz MM, et al. Is mechanical bowel preparation mandatory for left-sided colonic anastomosis? Results of a prospective randomized trial. Tech Coloproctol. 2006 Jul;10(2):131-5.
18. Cheung YM, Lange MM, Buunen M, Lange JF. Current technique of laparoscopic total mesorectal excision (TME): an international questionnaire among 368 surgeons. Surg Endosc. 2009 Jun 24.

19. Muzii L, Angioli R, Zullo MA, Calcagno M, Panici PB. Bowel preparation for gynecological surgery. Crit Rev Oncol Hematol. 2003 Dec;48(3):311-5.
20. Zmora O, Lebedyev A, Hoffman A, Khaikin M, Munz Y, Shabtai M, et al. Laparoscopic colectomy without mechanical bowel preparation. Int J Colorectal Dis. 2006 Oct;21(7):683-7.
21. Yang LC, Arden D, Lee TT, Mansuria SM, Broach AN, D'Ambrosio L, et al. Mechanical bowel preparation for gynecologic laparoscopy: a prospective randomized trial of oral sodium phosphate solution vs single sodium phosphate enema. J Minim Invasive Gynecol. 2011 Mar-Apr;18(2):149-56.
22. Mahajna A, Krausz M, Rosin D, Shabtai M, Hershko D, Ayalon A, et al. Bowel preparation is associated with spillage of bowel contents in colorectal surgery. Dis Colon Rectum. 2005 Aug;48(8):1626-31.
23. Wells T, Plante M, McAlpine JN. Preoperative Bowel Preparation in Gynecologic Oncology: A Review of Practice Patterns and an Impetus to Change. Int J Gynecol Cancer. 2011 Jun 22.

Chapter 6

The Influence of Mechanical Bowel Preparation in Elective Colorectal Surgery for Diverticulitis

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Abstract

Background Mechanical bowel preparation (MBP) has been shown to have no influence on the incidence of anastomotic leakage in overall colorectal surgery. The role of MBP in elective surgery in combination with an inflammatory component such as diverticulitis is yet unclear. This study evaluates the effects of MBP on anastomotic leakage and other septic complications in 190 patients who underwent elective surgery for colonic diverticulitis.

Methods A subgroup analysis was performed of a prior multicentre (13 hospitals) randomized trial comparing clinical outcome of MBP versus no MBP in elective colorectal surgery. Primary endpoint was the occurrence of anastomotic leakage in patients operated on for diverticulitis, secondary endpoints were septic complications and mortality.

Results Out of a total of 1354 patients 190 underwent elective colorectal surgery (resection with primary anastomosis) for (recurrent or stenotic) diverticulitis. One hundred and three patients underwent MBP prior to surgery and 87 did not. Anastomotic leakage occurred in 7.8% of patients treated with MBP and in 5.7% of patients not treated with MBP (p=0.79). There were no significant differences between the groups in septic complications and mortality.

Conclusion Mechanical bowel preparation has no influence on the incidence of anastomotic leakage, or other septic complications, and may be safely omitted in case of elective colorectal surgery for diverticulitis.

Introduction

In the last decade evidence challenging the general use of mechanical bowel preparation (MBP) prior to elective colorectal surgery has been reported in the literature. A recent meta-analysis of 14 randomized clinical trials suggests MPB can be safely omitted prior to elective colorectal surgery [1]. However most of these randomized trials include data covering different types of colorectal surgery (right-sided colectomies, left-sided colectomies and low-anterior resections) and distinction between elective surgery for cancer and inflammatory bowel disease is lacking.

To date, four trials focus on rectal surgery and low anastomosis including two subgroup analyses [2, 3], one case-control study [4] and one randomized trial [5]. Results of these studies showed no difference in anastomotic leakage rates in patients treated with or without MBP. Only the French Research Group of Rectal Cancer Surgery (GRECCAR) demonstrated that rectal cancer surgery without MBP is associated with a higher surgical site infection rate although anastomotic leakage rates were not higher [5]. In contrast Bucher et al. showed that elective left-sided colorectal surgery was safe without MBP [6]. Besides, patients who did not undergo MBP prior to surgery had a lower postoperative morbidity rate.

Due to controversy between studies concerning the use of MBP mentioned above with heterogeneous indications, surgeons still hesitate to omit MBP in some specific cases of colorectal surgery. This is also the case for patients with recurrent diverticulitis. To date there is no published data regarding MBP and elective colorectal surgery with an inflammatory component such as diverticulitis.

The prevalence of diverticulosis is estimated at 50-70% in individuals older than 80 years of age. Diverticulosis is most notable in the left-sided colon with up to 99% involvement of the sigmoid [7]. Diverticulitis is the most common complication of diverticulosis and affects 15-20% of patients [8]. The benefit of elective surgery for the prevention of recurrent or complicated episodes of diverticulitis is still a matter of debate [9]. The supposed benefit of preventive resection must be weighed against the possible complications related to surgery, such as anastomotic leakage. Elective surgery for diverticular disease is associated with major complications such as anastomotic leakage in 5-10% of patients and even with mortality (0-1%) [10]. However, in patients presenting with persistent complaints and prolonged abdominal tenderness due to diverticulitis affecting their quality of life, an elective resection may be legitimate. Due to the fact that anastomotic leakage occurs more frequently in left-sided resections (most common site for diverticulitis), and because of the presence of an inflammtory component patients surgically treated for diverticulitis may be prone to anastomotic leakage and other septic complications. Therefore, most colorectal surgeons consider a no MBP regimen in elective surgery for diverticulitis an additive risk factor for postoperative morbidity. In this study we performed an explorative subgroup analysis of

data from a prospective randomized trial to assess the influence of MBP on anastomotic leakage rates and other septic complications in patients who underwent surgical treatment of diverticulitis.

Materials and methods

This study is a subgroup analysis of a prior large multicentre, randomized clinical trial performed by Contant et al. to compare elective colorectal resections and primary anastomosis with and without the use of MBP [10]. In the trial 1354 patients were randomized to receive mechanical bowel preparation: 2-4 liters of polyethylene glycol bowel lavage solution (Klean Prep) in combination with bisacodyl (11 hospitals) or sodium phosphate solution (2 hospitals) prior to elective colorectal surgery. Endpoints were anastomotic leakage and other septic complications. Exclusion criteria were an acute laparotomy, laparoscopic colorectal surgery, contraindications for the use of mechanical bowel preparation, an a priori diverting ileostomy, and age less than 18 years old. In the present subgroup analysis, 190 (14%) out of the 1354 patients, treated in the period from April 1998 to February 2004, were selected for the present study because they had undergone an elective left-sided colon and/or sigmoid resection with primary anastomosis for diverticulitis.
The diagnosis of anastomotic leakage was based on clinical suspicion (prolonged fever, abdominal pain, local or generalized peritonitis, leucocytosis) and confirmed during contrast radiography (X-ray or computed tomography (CT)-scan) or laparotomy. No effort was made to screen for asymptomatic leakage. A distinction was made between major and minor anastomotic leakage, in which major anastomotic leakage required surgical reintervention, whereas minor anastomotic leakages could be treated conservatively or by radiologic intervention. Wound infection was defined as mild in case of erythema or discharge of seroma and as severe in case of discharge of pus, wound necrosis, or wound dehiscence. The follow-up period was defined as the time from the operation until the first outpatient visit after discharge from the hospital, which usually occurred after 2 weeks.

Surgical technique

Antibiotic prophylaxis was given intravenously to all patients according to the guidelines for prevention of surgical site infection issued by the department of infectious diseases of each hospital. All resections for diverticular disease were performed by open laparotomy. Anastomoses were fashioned according surgeon preference. No exact criteria for the creation of a diverting ileostomy were established and a diverting ileostomy was applied when deemed necessary by the surgeon. Common reasons for applying a diverting ileostomy were difficult operation, faecal contamination, tension on the anastomosis, very low anastomosis,

high number of comorbidities, severe inflammation and incomplete donuts when a circular stapler was used.

Statistical analysis

Groups were compared with respect to complication rates using the chi-square test or Fisher's exact test. The same test was used to compare risk groups for anastomotic dehiscence. Comparison of continuous or graded outcomes was determined by the Mann-Whitney test. Multiple regression analysis was performed to evaluate various risk factors simultaneously regarding anastomosis- related failure rates. A p-value ≤ 0.05 (two-sided) was considered statistically significant.

Results

One hundred and three patients received MBP (MBP+) and 87 patients did not (MBP-). A diverting ileostomy was fashioned in 5 MBP+ patients (4.9%) and in 9 (10.3%) MBP- patients. Reasons for ileostomy creation were: doubt about the integrity of the donuts after stapled anastomosis (n=3), a technically difficult operation (n=5), fecal spillage (n=2), and standard procedure of the surgeon on call (n=4). None of the MBP+ patients received a diverting ileostomy because of inadequate bowel preparation. Nevertheless, there was a trend for MBP- patients to receive a diverting ileostomy more frequently (p=0.08, table 1).

Anastomotic leakage occurred in 13 (7%) of the 190 patients. Mechanical bowel preparation was not significantly related to anastomotic leakage**:** 7.8% in MBP+ versus 5.7% in MBP- (difference 2.1%, 95% CI:- 3.7% to 5.7%). Baseline characteristics of patients operated on for diverticulitis are shown in table 1. More patients of the MBP+ group were smokers, but were generally operated on by the more experienced surgeons. The other parameters compared did not differ significantly between the groups.

Table I. Baseline characteristics of patients operated for diverticulitis n (%)

	MBP+ (n=103)	MBP- (n=87)
Gender		
female	55 (53%)	49 (56%)
male	48 (47%)	38 (44%)
Age		
<60 years	46 (45%)	39 (45%)
≥60 years	57 (55%)	48 (55%)
ASA		
I	40 (39%)	32 (37%)
II	55 (53%)	47 (54%)
III/IV	8 (8%)	8 (9%)
Diabetes		
+	9 (9%)	3 (3%)
-	94 (91%)	84 (97%)
Corticosteroids		
+	3 (3%)	4 (5%)
-	100 (97%)	83 (95%)
Coronary ischemic disease		
+	15 (15%)	7 (8%)
-	88 (85%)	80 (92%)
Peripheral ischemic disease		
+	6 (6%)	4 (5%)
-	97 (94%)	83 (95%)
Smoking		
+	45 (44%)	25 (29%)
-	58 (56%)	62 (71%)
BMI (kg/m²)		
≤ 25	42 (41%)	40 (46%)
> 25	61 (59%)	47 (54%)
Diverting ileostomy		
+	5 (5%)	9 (10%)
-	98 (95%)	78 (90%)
Surgeon		
Resident	48 (47%)	34 (39%)
Surgeon < 10 years	29 (28%)	19 (22%)
Surgeon ≥ 10 years	25 (25%)	34 (39%)
Suture of anastomosis		
Stapled	30 (29%)	31 (36%)
hand sewn	72 (71%)	54 (64%)
Type of anastomosis		
End-to-end	67 (66%)	57 (67%)
Side-to-end	26 (26%)	24 (28%)
Other	8 (8%)	4 (5%)
Level of anastomosis		
Colocolic	54 (53%)	45(52%)
Colorectal	48 (47%)	41 (48%)
Peri-operative PC		
≤ 2	95 (92%)	85 (98%)
> 2	7 (8%)	2 (2%)

Operating time (min.)		
< 120	44 (43%)	41 (47%)
≥ 120	59 (57%)	46 (53%)
Blood loss (cc)		
≤350	57 (56%)	43 (50%)
>350	45 (44%)	44 (50%)
Contamination		
Minor	51 (49%)	52 (60%)
Moderate	45 (44%)	29 (33%)
Severe	7 (7%)	6 (7%)

MBP mechanical bowel preparation, *ASA* American Society of Anaesthesiologists, *BMI* body mass index, *DM* diabetes mellitus, *PC* packed cells

Table 2 displays the results of univariate analysis of the major risk factors for anastomotic leakage. There was no difference in the listed risk factors for occurrence of anastomotic leakage between MBP+ and MBP- patients. The same results were obtained when multivariate analysis was performed (table 3). Septic complications are listed in table 4. There was no significant difference in septic complication rates or mortality rates between MBP+ and MBP- patients

Table II. Risk factors for anastomotic leakage in 190 patients with elective surgery for diverticulitis.

Risk factor for leakage	n/n (%)	P (univariate)
MBP		0.79
+	8/95 (7.8%)	
-	5/82 (5.7%)	
Gender	5/99 (4.8%)	0.35
female	8/78 (9.3%)	
male		
Age		0.45
<60 years	4/81 (4.7%)	
≥60 years	9/96 (8.6%)	
ASA		0.41
I	3/69 (4.2%)	
II	8/94 (7.8%)	
III/IV	2/14 (12.5%)	
Diabetes		0.58
+	1/11 (8.3%)	
-	12/166 (6.7%)	
Corticosteroids		0.40
+	1/6 (14.3%)	
-	12/171 (6.6%)	
Coronary ischemic disease		0.65
+	2/20 (9.1%)	
-	11/157 (6.5%)	
Peripheral ischemic disease		1.0
+	0/10	
-	13/167 (7.2%)	
Smoking		0.14
+	2/68 (2.9%)	
-	11/109 (9.2%)	
BMI (kg/m²)		0.72
≤ 25	5/77 (6.1%)	
> 25	8/100 (7.4%)	
Diverting ileostomy		1.0
+	1/13 (7.1%)	
-	12/164 (6.8%)	
Surgeon		0.64
Resident	4/78 (4.9%)	
Surgeon < 10 years	4/44 (8.3%)	
Surgeon ≥ 10 years	5/54 (8.5%)	
Suture of anastomosis		0.23
Stapled	2/59 (3.3%)	
hand sewn	11/115 (8.7%)	
Type of anastomosis		0.74
End-to-end	9/115 (7.3%)	
Side-to-end	4/46 (8.0%)	
Other	0/12	
Level of anastomosis		0.44
Colocolic	5/94 (5.1%)	
Colorectal	8/81 (9.0%)	

Peri-operative PC	11/169 (6.1%)	0.12
≤ 2	2/7 (22.2%)	
> 2		
Operating time (min.)	4/81 (4.7%)	0.45
< 120	9/96 (8.6%	
≥ 120		
Blood loss (cc)		0.72
≤350	8/92 (8.0%)	
>350	5/84 (5.6%)	
Contamination		0.49
Minor	5/98 (4.9%)	
Moderate	7/67 (9.5%)	
Severe	1/12 (7.7%)	

Due to occasional missing data numbers do not always add up to 190.
MBP mechanical bowel preparation, *ASA* American Society of Anaesthesiologists, *BMI* body mass index, *DM* diabetes mellitus, *PC* packed cells

Table III. Multivariate analysis of the listed covariates for their influence on the occurrence of anastomotic leakage.

Covariate	*p* value
MBP	0,40
Age	0,68
ASA	0,29
BMI	0,58
Stapled anastomosis	0,59
DM	0,69
Smoking	0,14

MBP mechanical bowel preparation, *ASA* American Society of Anaesthesiologists, *BMI* body mass index, *DM* diabetes mellitus

Table IV. Morbidity and mortality rate after elective surgery for diverticulitis with and without preoperative MBP.

Complication	MBP+ (n=103)	MBP- (n=87)	P-value
Nr of patients with complications*	37/66 (35.9%)	26/61 (29.9%)	0.38
Anastomotic leakage			
- minor	2/101 (1.9%)	1/86 (1.1%)	1.0
- major	6/97 (5.8%)	4/83 (4.6%)	0.76
Wound infection			0.26
- Mild	6/87 (5.8%)	5/82 (5.7%)	
- Severe	6/87 (5.8%)	1/86 (1.1%)	
Urinarytract infection	12/91 (11.7%)	7/80 (8.0%)	0.41
Pneumonia	9/94 (8.7%)	8/79 (9.2%)	0.91
Intraabdominal abscess	1/102 (1.0%)	4/83 (4.6%)	0.18
Fascia dehiscence	5/98 (4.9%)	1/86 (1.1%)	0.22
Mortality	2/101 (1.9%)	2/85 (2.3%)	1.00

* Patients can have more than one complication at a time.
MBP mechanical bowel preparation

Discussion

In this study we aimed to assess the value of preoperative MBP in patients undergoing elective colorectal surgery for diverticulitis (Hinchey I/II). Although our study is a subgroup analysis it is, to the best of our knowledge, the first study in literature to focus on the value of MBP before elective colorectal surgery for diverticulitis. We found that elective colorectal surgery without MBP was not significantly associated with a higher anastomotic leakage rate (7.8% vs. 5.7, p=0.79) or other septic complications (35.9% vs. 29.9%, p=0.38). The present study did show a trend toward a higher incidence of intra-abdominal abscesses in the MBP-group, corresponding to the results in the primary multicentre randomized trial from which this subgroup was derived by Contant et al [11]. However this difference did not become statistically significant (1.0% vs. 4.6%, p=0.18).

The prevalence of diverticulosis in Western countries is high and increases with age. A study by Mendeloff et al. reports that one-third of the general population of the United States had developed diverticulosis by the age of 45 years and two-thirds by the age of 80 [12]. Although most patients will remain asymptomatic, 10% to 20% will develop symptoms or complications [13]. Traditionally, patients were advised to undergo resection of the affected colon segment after two episodes of diverticulitis due to a supposed higher risk of complications (fistula, abscess formation, perforation) and even mortality in case of recurrence [14, 15]. At present the indication and timing for elective surgery for diverticulitis is a matter of debate as elective colon resection is not risk-free. Eglinton et al. and Janes et al. challenge the dogma of surgery after two attacks of diverticulitis and support a more conservative approach. They weigh the morbidity and mortality associated with subsequent episodes of diverticulitis in patients treated conservatively against the morbidity and mortality associated with elective resection. They conclude that elective resection performed after two attacks of diverticulitis to prevent recurrence or the development of complications, should not be routine management [12, 16].

Resection with primary anastomosis in patients with diverticular disease is associated with higher rates of morbidity and mortality compared to elective colorectal resection for colon cancer [17]. This is why many colorectal surgeons are reluctant to omit MBP prior to elective surgery for diverticular disease.

In theory MBP is believed to clean the colon and rectum of remaining feces in order to reduce the bacterial load and protect the patient against postoperative anastomotic and infectious complications [18]. This may well be true for patients undergoing left-sided colectomies when an infectious component such as diverticulitis is involved. However, the effect of MBP prior to surgery for diverticulitis in lowering morbidity and mortality rates has not been thoroughly investigated. Two studies investigated risk factors for anastomotic leakage in sigmoid colectomy for diverticulitis. Lehmann et al. note that stapled anastomosis were

associated with lower leak rate than hand sewn anastomosis and Levack et al. found that anastomotic leakage occurred less frequently after laparoscopic surgery compared to open surgery for diverticulitis [19, 20]. Neither studies mention the use of MBP. Two other studies investigated primary resection and anastomosis with intraoperative colonic lavage compared to Hartmann's procedure for complicated diverticulitis with peritonitis. The authors are in favor of primary resection and anastomosis with intraoperative colonic lavage aimed at reducing anastomotic complications [21, 22]. None of the studies mentioned consider whether MBP or colonic lavage should be applied in elective colorectal surgery for Hinchey stage I or II diverticulitis. The present study only included patients with Hinchey stage I and II diverticular disease. Mechanical bowel preparation was not related to the occurrence of anastomotic leakage, other septic complications, or mortality.

The present study has some limitations. As mentioned before, this is a subgroup analysis and the data used was derived from an earlier multicentre randomized trial designed for a different purpose [11]. About half of the patients underwent sigmoid resection with colo-colonic anastomosis, whereas generally recommended surgical treatment in cases of diverticulitis involves resection with a distal margin at the upper rectum. The risk of recurrent diverticulitis might be lower when resection extends to the proximal rectum [23], and this seems to be correlated with a lower risk of anastomotic leakage. The existing literature about this issue is rather limited and not uniform.

In addition, no distinction was made between Hinchey stage I and II diverticular disease. Data such as type and duration of complaints, number of episodes of diverticulitis and prior antibiotic treatment (besides antibiotic prophylaxis), which may be related to the outcome of surgery, was not collected. A recent meta-analysis has shown a significant decrease in wound infection complications after surgery in patients receiving oral antibiotics with MBP compared with intravenous antibiotic prophylaxis [24]. In this study the patients received routine intravenous antibiotic prophylaxis. The risk of anastomotic leakage in patients receiving intravenous antibiotics alone was not increased [24], but recently a prospective randomized trial has started to investigate this issue further.

Conclusions

Mechanical bowel preparation before elective colorectal surgery for diverticulitis, Hinchey stage I and II, is not related to the occurrence of anastomotic leakage and other septic complications. It therefore appears that MBP could safely be omitted for patients scheduled to undergo elective resectional surgery. However, this statement is based on a subgroup analysis of an earlier multicentre randomized trial designed for a different purpose. Therefore more prospective randomized designed studies are warranted.

References

1. Slim K, Vicaut E, Launay-Savary MV, et al. Updated systemic review and meta-analysis of randomized clinical trials on the role of mechanical bowel preparation before colorectal surgery. *Ann Surg* 2009;249:203-209.
2. Guenaga KK, Matos D, Wille-Jørgensen P. Mechanical bowel preparation for elective colorectal surgery. *Cochrane Database Syst Rev* 2009;1;(1):CD001544.
3. Van't Sant HP, Weidema WF, Hop WC, et al. The influence of mechanical bowel preparation in elective lower colorectal surgery. *Ann Surg* 2010;251:59-63.
4. Bretagnol F, Alves A, Ricci A, et al. Rectal cancer surgery without mechanical bowel preparation. *Br J Surg* 2007;94:1266-1271.
5. Bretagnol F, Panis Y, Rullier E, et al. Rectal cancer surgery with or without bowel preparation. The French Greccar III multicenter single-blinded randomized trial. *Ann Surg* 2010;252:863-868.
6. Bucher P, Gervaz P, Soravia C, et al. Randomized clinical trial of mechanical bowel preparation versus no preparation before elective left-sided colorectal surgery. *Brit J Surg* 2005;92:409-414.
7. Loffeld RJ, van der Putten AB. Newly developing diverticular disease of the colon in patients undergoing repeated endoscopic evaluation. *J Clin Gastroenterol* 2002;35:205-6.
8. Sjozda MM, Cuesta MA, Mulder CM, et al. Management of diverticulitis. *Aliment Pharmacol Ther* 2007;26:67-76.
9. Vermeulen J, Lange JF. Surgical treatment of perforated diverticulitis. Past, present and future. *World J Surg 2010;34:587-93.*
10. Klarenbeek BR, Veenhof AA, Bergamaschi R, et al. Laparoscopic sigmoid resection for diverticulitis decreases major morbidity rates: a randomized control trial: short-term results of the Sigma Trial. *Ann Surg* 2009;249:218-24.
11. CME Contant, WCJ Hop, HP van't Sant, HJM Oostvogel, HJ Smeets, LPS Stassen, et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. *Lancet* 2007;370:2112-17.
12. Eglinton T, Nguyen T, Raniga S, et al. Patterns of recurrence in patients with acute diverticulitis. *Br J Surg* 2010;97:952-957.
13. Larson DM, Masters SS, Spiro HM, et al. Medical and surgical therapy in diverticular disease: a comparative study. *Gastroenterology* 1976;71:734-7.
14. Rafferty J, Shellito P, Hyman NH, et al. Standards committee of American society of colon and rectal surgeons. Practice parameters for sigmoid diverticulitis. *Dis Colon Rectum* 2006;49:939-44.
15. Stollman NH, Raskin JB. Diagnosis and management of diverticular disease of the colon in adults. Ad Hoc Practice Parameters Committee of the American College of Gastroenterology. *Am J Gastroenterol* 1999;94:3110-12.
16. Janes S, Meagher A, Frizelle FA. Elective surgery after acute diverticulitis. *Br J Surg* 2005;92:133-142.
17. Bokey EL, Chapius PH, Pheils MT. Elective resection for diverticular disease and carcinoma. Comparison of postoperative morbidity and mortality. *Dis Colon Rectum* 1981;24:181-182.
18. Fa-Si-Oen PR, Verwaest C, Buitenweg J, et al. Effect of mechanical bowel preparation with polyethyleneglycol on bacterial contamination and wound infection in patients undergoing elective open colon surgery. *Clin Microbiol Infect* 2005;11:158-160.
19. Lehmann RK, Brounts LR, Johnson EK, et al. Does sacrifice of the inferior mesenteric arterie or superior rectal artery affect anastomotic leak following sigmoidectomy for diverticulitis? A retrospective review. *Am J Surg* 2011;201:623-627.

20. Levack M, Berger D, Sylla P, et al. Laparoscopy decreases anastomotic leak rate in sigmoid colectomy for diverticulitis. *Arch Surg* 2011;146(2):207-210.
21. Biondo S, Perea MT, Ragué JM, et al. one-stage procedure in non-elective surgery for diverticular disease complications. *Colorectal Dis* 2001;3(1):42-5.
22. Regenet N, Pessaux P, Hennekinne S, et al. Primary anastomosis after intraoperative colonic lavage vs. Hartmann's procedure in generalized peritonitis complicating diverticular disease of the colon. *Int J Colorectal Dis* 2003;18(6):503-7
23. Thaler K, Baig MK, Bertho M et al (2003) Determinants of recurrence after simoid resection for uncomplicated diverticulitis. Dis Colon Rectum 46:385-388
24. Bellows CF, Mills KT, Kelly TN, Gagliardi G (2011) Combination of oral non-absorbable and intravenous antibiotics versus intravenous antibiotics alone in the prevention of surgical site infection after colorectal surgery: a meta-analysis of randomized controlled trials. Tech Coloproctol 15:385-395

Chapter 7

The influence of mechanical bowel preparation on long-term survival in patients surgically treated for colorectal cancer

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Abstract

Objective The objective of this study was to compare long-term survival in patients who did or did not receive mechanical bowel preparation (MBP) prior to colorectal surgery for cancer.

Summary Background Data Previous meta-analyses have demonstrated that MBP has no evident benefit for patients surgically treated for colorectal cancer. However, the influence of MBP on long-term outcomes and survival in patients with colorectal cancer is yet unclear.

Methods This study evaluated long-term outcomes of patients surgically treated for colorectal cancer of two main participating hospitals in a prior multicenter (13 hospitals) randomized trial comparing clinical outcome of MBP versus no MBP prior to elective colorectal surgery. Primary endpoint was disease related mortality and secondary endpoint was all-cause mortality.

Results A total of 382 patients underwent potentially curative surgery for colorectal cancer. 177 (46%) Patients were treated with MBP prior to surgery and 205 (54%) were not. Median follow-up was 7.6 (mean 6.6, range 0.01-12.73) years. There was no significant difference in both overall mortality and cancer-related mortality in patients treated with MBP and without MBP (p=0.36 and p=0.76, respectively).
Cancer specific survival at 5- and 10 years in the MBP+ arm was 67% (+/- 4% se) and 59% (+/- 4%), respectively. In the MBP- arm these figures were 68% (+/- 3%) and 60% (+/- 4%), respectively. Multivariate analysis, taking account of age, gender, Dukes' stage and American Society of Anaesthesiologists-classification also showed that MBP had no significant effect on all-cause and cancer related mortality.

Conclusion Our results indicate that withholding MBP is not harmful regarding long term survival in patients surgically treated for colorectal cancer.

Introduction

Traditionally mechanical bowel preparation (MBP) was believed to clean the colon and rectum from residual faecal contents and lower the bacterial load in order to prevent anastomotic failure and reduce postoperative infectious complications[1]. To date, however, there is significant evidence that questions the beneficial effects of MBP. Recent systematic reviews and meta-analyses of randomized controlled trials have shown no evidence that MBP is associated with reduced rates of anastomotic leakage or septic complications after elective colorectal surgery[2-4]. Most studies only evaluated the effects of MBP on short-term outcomes and studies on the effects on long term outcomes are scarce especially cancer related. At present there is strong evidence that postoperative complications influence the long-term outcome and survival in patients with colorectal cancer. Patients confronted with anastomotic leakage have poorer long-term cancer specific survival rates[5-7].In this study we tested the hypothesis that MBP has no positive influence on cancer specific long-term survival (>6 years) after colorectal cancer surgery as MBP is not associated with reduced anastomotic leakage rates in literature.

Methods

This study is a subgroup analysis of a prior large multicenter randomized clinical trial published by Contant et al[8]. They enrolled 1354 patients from 1998 to 2004 and randomized between MBP and no MBP prior to elective colorectal surgery and compared the incidence of anastomotic leakage and septic complications. Patients randomized for MBP received 2-4 litres of polyethylene glycol bowel lavage solution (Klean Prep®) in combination with bisacodyl (11 hospitals) or sodium phosphate solution (2 hospitals). Exclusion criteria were an acute laparotomy, laparoscopic colorectal surgery, contraindications for the use of MBP, an a priori diverting ileostomy, and age less than 18 years old.

In the present subgroup analysis 382 patients of two main participating hospitals in the previously mentioned randomized trial were selected by the criteria of having undergone potentially curative elective colorectal surgery for cancer (Fig 1).

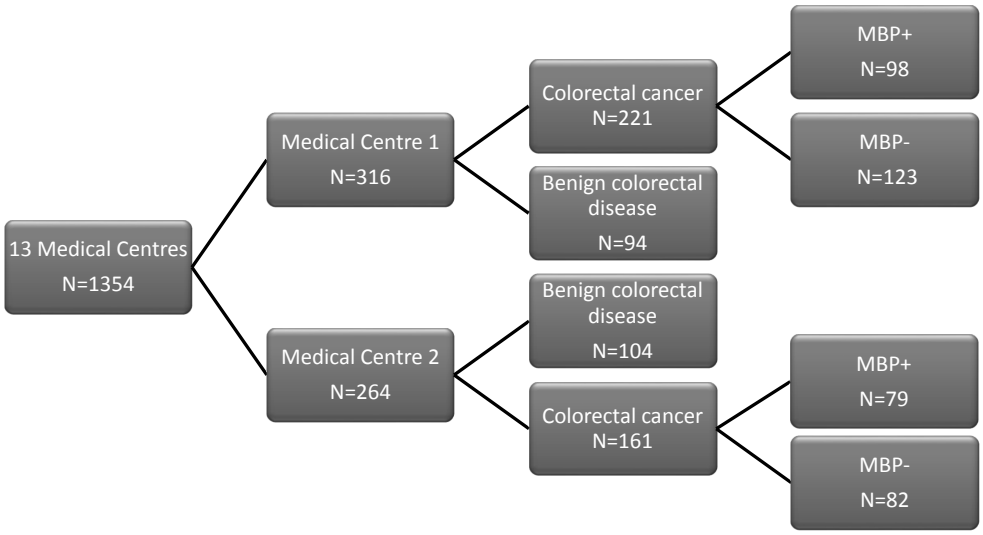

Fig.1 Organization chart for patient selection[9].

Clinical data was obtained through the previous study by Contant et al. with permission and linked to death records to create a novel data set[8]. Death records up to 31 December 2010 were obtained. The diagnosis of colorectal cancer was confirmed by pathology reports. Dukes' stage was determined through pathology reports, radiology reports and clinical audit records. Our primary endpoint was cancer related mortality and secondary endpoint was all-cause mortality

Statistical analysis

Kaplan Meier curves for overall and colon cancer specific survival and logrank tests were used to compare the MBP arms. In the calculation of cancer specific survival, the survivals of patients who had died due to other causes were considered censored survival times. As the large majority of deaths were due to cancer and there were only a few patients who had died from an unknown cause, the latter patients were considered to have died from cancer. Cox-regression analysis was used to assess the independent effect of various putative prognostic factors (age, gender, Dukes' stage and ASA classification) besides MBP. Analysis was by intention-to-treat. Two-sided $P<0.05$ was considered statistically significant.

Results

Data was collected from 382 patients retrospectively. Patient selection is shown in figure 1. 177 (46%) Patients were treated with MBP prior to surgery and 205 (54%) were not. Baseline characteristics of patients are shown in table 1 and were well balanced between treatment groups.

Table 1. Baseline characteristics of 382 patients undergoing elective surgical treatment for colorectal cancer.

	MBP – (n=205)	**MBP + (n=177)**
Gender		
Male	98 (48%)	91 (51%)
Female	107 (52%)	86 (49%)
Age		
≤60	50 (24%)	42 (24%)
61-70	70 (34%)	56 (32%)
>70	85 (42%)	79 (44%)
Dukes' stage		
A	34 (16%)	35 (20%)
B	98 (48%)	77 (43%)
C	55 (27%)	51 (29%)
D	18 (9%)	14 (8%)
ASA-classification		
I	57 (28%)	39 (22%)
II	113 (55%)	116 (66%)
III/IV	35 (17%)	22 (12%)

Overall median follow-up was 7.6 (mean 6.6, range 0.01-12.73) years. Median follow-up for MBP + was 7.8 (mean6.8, range 0.01-12.6) and for MBP- 7.4 (mean 6.4, range 0.01-12.7). 193 Patients deceased during follow-up. Cancer related deaths occurred in 128 patients. Non-cancer related deaths occurred in 48 patients. In 17 patients the cause of death could not be discovered. There was no significant difference in both overall mortality and cancer-related mortality in patients treated with MBP and without MBP prior to elective colorectal surgery for cancer (logrank test p=0.36 and p=0.76, respectively (figure 2).

Cancer specific survival at 5- and 10 years in the MBP+ arm was 67% (+/- 4% standard error) and 59% (+/- 4%), respectively. In the MBP- arm these figures were 68% (+/- 3%) and 60% (+/- 4%), respectively (figure 2).

Overall survival at 5- and 10 years in the MBP+ arm was 64% (+/- 4%) and 54% (+/- 4%), respectively. In the MBP- arm these figures were 62% (+/- 3%) and 47% (+/- 4%), respectively (figure 2).

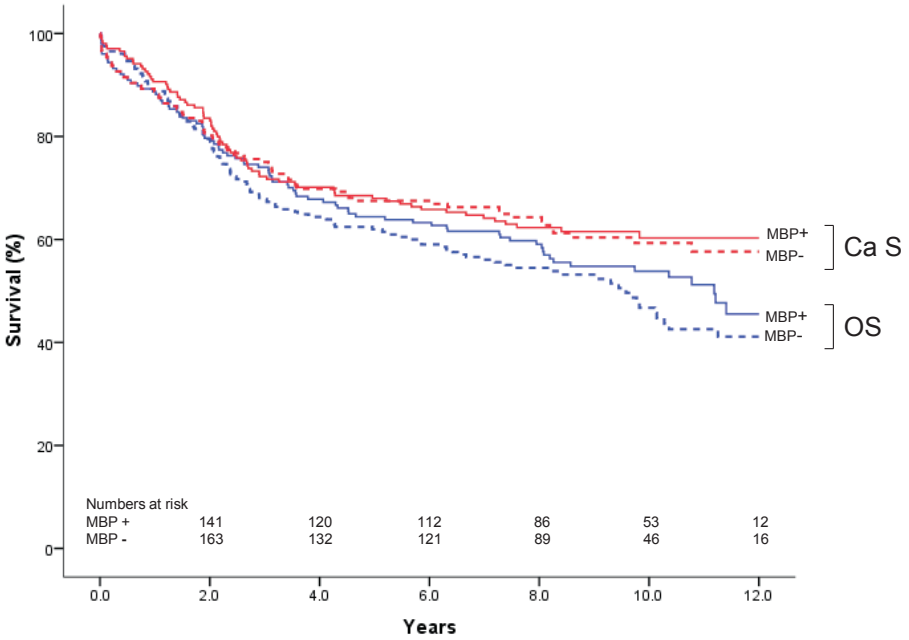

Fig. 2 Kaplan-Meier survival curves for overall survival (OS) and cancer specific survival (CaS) for patients treated with and without MBP before elective colorectal surgery for cancer.

Also within the separate Dukes' stages there were no significant differences in overall and cancer specific survival between the MBP arms (all p>0.31). Cox-regression analysis, allowing for age, gender, Dukes' stage and ASA classification also showed no significant differences between the two MBP arms (table 2). Further extension of the Cox-models with interaction terms to investigate whether the baseline characteristics influenced the difference between the two MBP arms showed no significant effect of any of the characteristics. Also the treatment center did not affect the survival outcomes.

Postoperative complication rates between patients treated with and without MBP are shown in table 3.

Table 2. Proportional hazards analyses for cancer related and all-cause mortality after potentially curative elective colorectal resection for cancer.

	Cancer related mortality			All-cause mortality		
	Hazard ratio Exp(ß)	95% CI	p-value	Hazard ratio Exp (ß)	95% CI	p-value
MBP						
no	1.00	-	-	1.00	-	-
yes	0.94	0.67-1.32	0.73	0.81	0.61-1.09	0.16
Gender						
Female	1.00	-	-	1.00	-	-
Male	1.14	0.81-1.61	0.46	1.23	0.91-1.65	0.17
Age						
≤60	1.00	-	-	1.00	-	-
61-70	1.10	0.64-1.91	0.73	1.28	0.80-2.05	0.30
>70	2.77	1.59-4.84	<0.001	2.56	1.60-4.11	<0.001
Dukes' stage						
A	1.00	-	-	1.00	-	-
B	2.67	1.20-5.91	0.02	1.57	0.95-2.61	0.08
C	6.91	3.12-15.28	<0.001	2.97	1.76-5.00	<0.001
D	41.01	17.60-95.58	<0.001	17.86	9.77-32.66	<0.001
ASA-classification						
I	1.00	-	-	1.00	-	-
II	1.11	0.67-1.85	0.68	1.38	0.89-2.14	0.15
III/IV	2.36	1.28-4.35	0.006	3.05	1.81-5.13	<0.001

Table 3. Complication rate after elective surgery for patients with colorectal cancer with and without preoperative MBP.

Complication	MBP+ (n=177)	MBP- (n=205)
Nr of patients with complications*	59(33%)	82(40%)
Anastomotic leakage	7(4%)	8(4%)
Wound infection	18(10%)	25(12%)
Urinary tract infection	12(7%)	18(3%)
Pneumonia	14(8%)	16(8%)
Intraabdominal abscess	6(3%)	9(4%)
Fascia dehiscence	2(1%)	6(3%)

* Patients can have more than one complication at a time.

Discussion

Sufficient evidence has shown that anastomotic leakage is associated with a higher prevalence of local recurrence and diminished long-term survival after elective colorectal cancer surgery[5-7]. Recent meta-analysis and systematic reviews show no difference in anastomotic leakage rate comparing MBP versus no MBP. Only Slim et al. published a meta-analysis in 2004 and

found significantly more anastomotic leakage after MBP (5.6% vs. 3.2%, p=0.032)[9]. However a more recent meta-analysis also by Slim et al. invalidates this outcome having added two large randomized controlled trials to their data and find no difference in anastomotic leakage rate between MBP and no MBP[2,8,10]. Other effects of MBP on postoperative complications have been thoroughly investigated presenting controversial results. Bucher et al. suggest that MBP is associated with structural alteration and inflammatory changes in the large bowel wall and that MBP is associated with higher postoperative morbidity rates in elective left-sided colorectal surgery[11,12]. This is supported by Bretagnol et al. who noted that MBP was associated with a significantly higher rate of infectious extra-abdominal complications[7]. Mean hospital stay was significantly longer for patients treated with MBP in both studies[11,13]. In contrast, authors of the French Greccar III trial demonstrated that rectal cancer surgery without MBP was associated with higher risk of overall and infectious morbidity rates and suggest continuing to perform MBP before elective rectal resection for cancer[14]. Contant et al. showed that MBP was associated with fewer intra-abdominal abscesses after anastomotic leakage compared to no MBP in elective colorectal surgery[8]. However both studies show no difference in anastomotic leakage rates. In summary this leaves us with controversial effects of MBP on anastomotic leakage and postoperative infection rates rendering the influence of applying or withholding MBP on survival in patients surgically treated for colorectal cancer remains unclear.

To date only one study compared long-term survival and surgical complications in patients who did and did not receive MBP[15]. Nicholson et al. retrospectively collected data of 1730 patients who underwent potentially curative colorectal cancer surgery. 1460 Patients were treated with MBP and 270 patients were not. Median follow-up was 3,5 (range 0,1-6,7) years. They found a 28% survival benefit in favour of patients treated with MBP (HR 0.72, 0.57 to 0.91) (p=0.005). However this survival advantage was no longer significant after adjustment for presentation for surgery (HR 0.85, 0.67 to 1.10) (P=0.220). This can be clearly explained due to the fact that patients undergoing emergency surgery are usually not treated with MBP and that the emergency setting is associated with poorer outcome[16,17]. The authors of this study conclude that neither postoperative complications nor long-term survival are improved by MBP in regards to colonic cancer. However this retrospective cohort study has several limitations. Their main conclusion was based on all-cause mortality and not on cancer-related mortality. In addition patients were not randomized between MBP and no MBP and the decision for applying MBP was solely made ad hoc by the medical staff prior to surgery, creating a potential source of bias.

The results of the underlying study show that MBP has no influence on all-cause and cancer related long-term survival in patients surgically treated for colorectal cancer with a median follow-up of 6.7 years. Adverse events relating to colorectal cancer survival would be expected within this time frame. These findings were expected as we found no difference

in anastomotic leakage and other postoperative morbidity rates between the MBP+ and MBP- groups in this study. One of the limitations of this study is the selection procedure. We selected patients from only 2 of 13 hospitals who participated in a previous randomized trial comparing the anastomotic leakage rate in patients treated with and without MBP[8]. By selecting patients only surgically treated for cancer we created an imbalance between MBP+ and MBP – (177 vs. 205 respectively) and a possible selection bias cannot be excluded. An additional limitation is that in 17 patients the cause of death could not be recollected. For these 17 patients cancer-related mortality was both calculated when deaths were presumed cancer-related and when left out. There were no differences between both calculations. Data is only shown when deaths were presumed cancer-related as this is most probable. As survival depends on many factors our study is underpowered. A large randomized trial would be preferable with long-term survival as primary endpoint in a cancer related patient group.
In conclusion, our results from a subgroup of a randomized trial suggest confirmation of our hypothesis that MBP has no influence on long term survival in patients surgically treated for colorectal cancer. However, more research is required to draw firm conclusions.

References

1. PR Fa-Si-Oen, C Verwaest, J Buitenweg, H Putter, JW de Waard, CJ van de Velde, et al. Effect of mechanical bowel preparation with polyethyleneglycol on bacterial contamination and wound infection in patients undergoing elective open colon surgery. Clin Microbiol Infect 2005;11:158-60.
2. Karem Slim, Eric Vicaut, Marie-Veronique Launay-Savary et al. Updated Systematic Review and Meta-Analysis of Randomized Clinical Trials on the Role of Mechanical Bowel Preparation Before Colorectal Surgery; Ann Surg 2009; 249, 2: 203-209
3. Guenaga KK, Matos D, Wille-Jørgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev. 2009;21(1):CD001544.
4. Pineda CE, Shelton AA, Hernandez-Boussard T et al. Mechanical bowel preparation in intestinal surgery: a meta-analysis and review of the literature. J Gastrointest Surg 2008;12:2037-2044.
5. Bucher P, Gervaz P, Soravia C et al. Randomized clinical trial of mechanical bowel preparation versus no preparation before elective left-sided colorectal surgery. British J Surg 2005; 92: 409-414.
6. Bucher P, Gervaz P, Egger JF, Soravia C, Morel P. Morphologic alterations associated with mechanical bowel preparation before elective colorectal surgery: a randomized trial. Dis Colon rectum 2005;49:109-112..
7. F Bretagnol, Y Panis, E Rullier et al. Rectal Cancer Surgery With or Without Bowel Preparation. Ann Surg 2010; 252:5: 863-868.
8. Bretagnol F, Panis Y, Rullier E, et al. Rectal cancer surgery with or without bowel preparation. The French Greccar III multicenter single-blinded randomized trial. Ann Surg 2010;252:863-868.
9. Caroline M E Contant, Wim CJ Hop, Hans Pieter van 't Sant et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial. Lancet 2007; 370:2112-17
10. Nicholson GA, Finlay IG, Diament RH et al. Mechanical Bowel preparation does not influence outcomes following colonic cancer resection. British J Surg 2011; 98: 866-871.
11. Kenneth G Walker, Stephen W Bell, Mathew JFX Rickard et al. Anastomotic leakage is Predictive of Diminished Survival After Potentially Curative Resection for Colorectal Cancer. Ann Surg 2004; Vol 240 no. 2: 255-259
12. McArdle CS, McMillan DC, Hole DJ. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. British J Surg 2005; 92: 1150-1154
13. Kube R, Mroczkowski P, Granowski, et al. Anastomotic leakage after colon cancer surgery: a predictor of significant morbidity and hospital mortality, and diminished tumour-free survival.
14. Slim K, Vicaut E, Panis Y and Chipponi J. Meta-analysis of randomized clinical trials of colorectal surgery with or without mechanical bowel preparation. Br J Surg 2004;91:1125-1130
15. B. Jung, L. Pahlman, P.O. Nystrom et al. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. Brit Journal Surg 2007; 94: 689-695
16. Cuffy M, Abir F, Audisio RA, Longo WE. Colorectal cancer presenting as surgical emergencies. Surg Oncol 2004;13:149-157.
17. Porta M, Fernandez E, Belloc J, et al. Emergency admission for cancer: a matter of survival? Br J Cancer 1998;77:477-484.

Chapter 8

General discussion and future perspectives

General discussion and future perspectives

Two large randomized trials by Contant et al. and Jung et al. prove with sufficient evidence that MBP does not reduce the risk of anastomotic leakage and infectious morbidity after colorectal surgery and may be safely abandoned. Jung et al randomized a total of 1505 patients between MBP and no MBP before open elective surgery for cancer, adenoma or diverticular disease of the colon. [1] They found no significant differences in terms of anastomotic healing or infection rate and advised MBP should be abandoned. Contant et al randomized 1431 patients between MBP and no MBP undergoing elective colorectal surgery for cancer, inflammatory bowel disease and benign causes for resection described in **chapter 2**. [2] Although they also found no differences in anastomotic leakage rates they did find significantly more intraabdominal abcesses after anastomotic leakage occurred in the no-MBP group compared to the MBP group (n=2 (0.3%) vs n=17 (2.5%), p=0.001). Despite the significant difference in incidence of intraabdominal abscesses between patients treated with MBP and without MBP Contant et al. indicated the lack of clinical significance as only 3 of 47 abscesses needed secondary surgical intervention. This raises the question whether we should expose large numbers of patients to the burden of MBP in order to prevent a relatively low incidence of intraabdominal abscesses which in most cases can be treated non-surgically. These two randomized trials provide the best level of evidence regarding MBP and colorectal surgery and both conclude MBP may be safely omitted.
However larger trials with stratification between diagnosis (cancer, IBD, benign) high and low rectal anastomosis and MBP versus an enema alone are called for. Due to the controversial results between overall, left-sided, low-anterior and rectal surgery concerning MBP and morbidity there is still a great deal of hesitance among surgeons to omit MBP in some specific cases such as rectal surgery. It will therefore be a challenge to include specific patients for larger trials in the future.

MBP and lower colorectal surgery

The two large randomized trials by Jung et al and Contant et al prove with sufficient evidence that MBP does not reduce the risk of anastomotic leakage and infectious morbidity after colorectal surgery. [1,2] However colorectal surgery is a broad term implementing surgery of both the colon and rectum. The question remains if colon and rectal surgery can be grouped regarding MBP or should they be considered two different surgical entities? Both trials did not differentiate between ileocolic, colocolic or colorectal anastomoses.[1,2] Guenega et al (2011) conducted a thorough review of MBP in regard to rectal surgery and even differentiated between studies comparing MBP to no MBP and MBP to just an enema. [3] Seven randomized studies contained patients treated with MBP and without MBP in rectal surgery described in this Cochrane review. None of these studies showed a significant difference in anastomotic leakage rates. [4-10]

The study with the largest number is the subgroup analysis described in **chapter 3** in this thesis.[5] It also failed to show any difference in anastomotic leakage rates and other septic complications. The shortcoming of this study is that it is a subgroup analysis and also underpowered and therefore inadequate for firm conclusions. The second largest study (the only non-subgroup study) is a randomized study performed by Bretagnol et al also comparing the outcome of 89 patients treated with and 89 patients treated without MBP [4]. They demonstrated that rectal cancer surgery without MBP is associated with a higher risk of overall and infectious morbidity rates. Although not statistically significant, they found a trend towards a twofold risk of anastomotic leakage (19% vs. 2%) and peritonitis (7% vs. 2%) in favor of the MBP group. They provide the best level of evidence in the area of MBP regarding low anastomosis. In addition they performed a subgroup analysis between high rectal cancer and mid/low rectal cancer and although numbers were small (data not shown) they found no heterogeneity and differences between groups. According to their results they rightfully conclude to continue to perform MBP before elective rectal resection for cancer, paying an important tribute to the ongoing debate on the use MBP. An interesting query would be if their results would have been any different had they compared patients treated with MBP to patients treated with just an enema instead of no preparation at all.[4] All five other studies are highly underpowered for reliable conclusions [6-10].

The subgroups of three studies comparing patients undergoing elective colorectal surgery who recieved either MBP or an enema were also incorporated in the 2011 Cochrane database systematic review by Guenega et al. [3][11-13] This resulted in a subtotal of 107 patients treated with MBP and 88 patients treated with an enema. No difference in anastomotic leakage rates were found after rectal surgery. Later Bertani et al. (2011) also performed a subgroup analysis and had randomized 73 patients between polyethylene glycol and a large volume glycerin enema versus a large volume glycerin enema alone in patients undergoing a low anterior resection. Although numbers are small (33 vs. 40) the incidence of surgical site infections and leakage was comparable.[14]

For the future a large randomized trial consisting of only patients undergoing rectal surgery divided into three groups should be conducted: patients receiving only MBP, patients receiving only an enema, and patients not receiving either of these two. This is hardly feasible due to the large numbers that would be needed for each group. In our opinion an enema seems rational prior to rectal surgery as this effectively cleans the bowel at the level of the anastomosis and will facilitate surgery at the time of transanal insertion of the stapling device for the creation of the rectal anastomosis without the detrimental effects of MBP. A randomized study comparing patients treated with MBP versus patients treated only with a single enema would be sufficient.

MBP in combination with a diverting ileostomy

A temporary diverting ileostomy is believed to reduce and prevent anastomotic leakage and septic complications in colorectal surgery. By diverting the faecal stream and keeping the anastomosis free and clean of faecal contamination, anastomotic leakage is prevented and when a leak does occur, septic complications are kept to a minimum. Two meta-analyses and one leading randomized clinical trial show the benefit of a diverting ileostomy in rectal surgery.[15-17] Both meta-analyses show that patients with a diverting ileostoma after low anterior resection had less clinically significant anastomotic leakages and a lower reoperation rate.

Chapter 3 addresses the value of a diverting ileostomy with or without MBP. Little is known about the effects of the remaining faeces in the large bowel after the application of a defunctioning ileostomy. That the remaining faeces in an unprepared colon could still jeopardize a distal colorectal anastomosis is a plausible yet unfounded theory. However, it is still a reason for many surgeons to persist in the use of MBP. The Dutch guidelines for acute diverticulitis (2012) state that a defunctioning ileostomy may mitigate the effects of anastomotic leakage but is of no use if the colon is filled with faeces.[18] Do they, in other words, discourage the use of a defunctioning ileostomy in an unprepared colon? Is on table lavage warranted when a defunctioning ileostomy is deemed necessary in an unprepared colon?

A survey among members of the Association of Coloproctology of GB & Ireland shows there is clearly no current standardization of bowel preparation amongst colorectal surgeons in the UK and the need for full preparation for a low anterior resection (LAR) remains controversial. Seventy-six per cent of respondents routinely defunctioned a LAR, and 74% of respondents believed that full MBP was required when doing so. Of the 144 surgeons who routinely defunctioned a LAR, 32 (22%) did not use full MBP, but 23 (72%) used enemas. A further four (8%) surgeons, who do not routinely use MBP for a LAR, commented they would perform an on-table lavage if they were going to fashion a defunctioning ileostomy.[19]

The subgroup analysis described in **chapter 3** does not show any difference in detrimental effects in the omittance of MBP in combination with a defunctioning ileostomy. However numbers are small and no firm conclusions can be drawn. A prospective randomized, controlled trial, comparing MBP with on-table lavage and no preparation for patients undergoing LAR with a defunctioning ileostomy, would provide valuable information to guide future practice. To our knowledge no studies address this controversy between no MBP and the appliance of a defunctioning stoma in literature.

MBP and short-term outcomes after anastomotic leakage

Some studies state that by diminishing the faecal load at the site of the anastomosis, the clinical sequelae of anastomotic leakage may be reduced. However, this has mainly been investigated in relation to a diverting ileostomy, and evidence that MBP has beneficial effects concerning the severity of an anastomotic leakage has not been put forth. [20-24]

Although MBP does not divert the faecal stream it is thought to reduce the faecal load at the site of the anastomosis through cleansing of the bowl before surgery. However the effects of MBP are only temporary compared to a diverting ileostomy. Studies investigating the effects of MBP on the clinical significance and consequences of an anastomotic leakage in colorectal surgery have not been reported. **Chapter 4** shows no difference in short term outcome between patients treated with and without MBP when confronted with anastomotic leakage. It is generally accepted anastomotic leakage occurs approximately on day 5-7 postoperatively and the remark can be made that the effects of MBP will have worn off by that time. It was criticized, for this reason, to be hardly surprising we found no differences between patients treated with or without MBP when leakage occurred. If we consider this righteous criticism then why did we for so long believe MBP may protect against anastomotic leakage as the effects will have worn off at the time of leakage. One can speculate MBP proposedly only protects against early leakages (day1-4) or was the rational for MBP perhaps that leakages generally occur earlier than day 5-7 and they only become symptomatic around day 5-7? In addition our data show no difference in time of onset of anastomotic leakage in patients treated with or without MBP. Perhaps this is the very reason MBP neither seems to decrease the incidence of anastomotic leakage rates nor does it seem to diminish the septic complications when leakage occurs. Contant et al already noted there were significantly more intraabdominal abcesses in patients with anastomotic leakage and not treated with MBP compared to patients treated with MBP (2 (0.3%) vs. 17 (2.5%), p=0.001) but did not regard this difference of any clinical relevance.[2] This clinical irrelevance is confirmed in more detail in this chapter.

MBP and laparoscopic colorectal surgery

Regarding laparoscopic colorectal surgery and MBP there are still many unanswered questions. Over time laparoscopic colorectal surgery has become common practice in elective colorectal surgery as it has shown to have superior short term effects compared to open colorectal surgery. [25-28] The influence of MBP on anastomotic leakage and septic complications has mainly been investigated for open surgery and only three trials mention the inclusion of laparoscopic colorectal surgery. [4,11,29]

It is reasonable to believe that the effects of MBP on anastomotic leakage and septic complications are not any different between patients with a laparoscopic or open approach. However, a prepared bowel may have a positive or negative influence on the exposure of the

surgical field and efficiency of the procedure. Four studies address the issue of the influence of MBP on the surgical field exposure and two are gynaecology orientated. [30-33]. Three conclude laparoscopic surgery could safely be performed without MBP and MBP has no beneficial influence on surgical difficulty, surgical times or surgical field of view. [30-32]
The difficulty of these studies is that the outcome measures are the evaluation of the surgical field by surgeons using a questionnaire giving these studies a very subjective character. In contrast Vlot et al. showed in an animal model that MBP increases working space by reducing bowel content and could be of benefit in challenging laparoscopic surgery.[33]
MBP may facilitate intracorporal anastomosis formation during laparoscopy. When creating an intracorporal anastomosis in an unprepared colon it may be challenging to remove any bowel contents at the site of the anastomosis. On the other hand, the risk of fluid bowel spillage in case of an inadequate cleansed bowel remains a matter of concern.
In conclusion it seems reasonable to believe that the effects of MBP on anastomotic leakage and septic complications are not any different between patients with a laparoscopic or open approach. However MBP should be considered when a surgeon needs to identify a small intraluminal lesion which is not preoperatievly marked or when an intra-operative colonoscopy might be necessary. Randomized trials are necessary to evaluate the beneficial effects of MBP in laparoscopic colorectal surgery using both questionnaires and hard data focussing for example on timing of the procedure, measuring small/large bowel circumference, working space, peroperative bowel spillage, peroperative complications, conversion rates etc. Without doubt this is challenging and large numbers are needed to show or exclude differences. **Chapter 5** shows at present there is no consensus between Dutch colorectal surgeons regarding MBP and laparoscopic colorectal surgery.

MBP and diverticulitis

Chapter 6 shows a subgroup analysis of patients derived from the randomized controlled trial (RCT) by Contant et al described in Chapter 2, who underwent elective surgical treatment for diverticulitis. [2] In the RCT by Contant et al diverticulitis was no risk factor for anastomotic leakage. However in literature elective surgery for diverticular disease is associated with major complications such as anastomotic leakage in 5-10% of patients and even with mortality (0-1%). [34] As the most common site for diverticulitis is the left-sided colon and because of the presence of an inflammatory component many colorectal surgeons may be hesitant in omitting MBP prior to surgery. However this subgroup analysis showed no benefit from MBP concerning anastomotic leakage or other septic complications. There may a selection bias as this study is a subgroup analysis of an earlier multicenter randomized trial. The inclusion period for the RTC by Contant et al was from 1998-2004. In this period it was still customary to undergo elective sigmoid resection after two attacks for diverticulitis. At present there is sufficient evidence that elective surgery to prevent recurrence and the

development of complications is inappropriate and should be used sparingly. [35-37] For the future a randomized trial is warranted including a MBP versus a no-MBP regime in semi-elective, or semi-acute complicated diverticulitis surgery cases when, as a rule, there is time for preoperative bowel preparation. Additionally, in this era laparoscopy for diverticulitis should be taken into account as this is much more likely to influence the outcome than MBP. [34, 38]
To date there are no other published data regarding MBP and elective colorectal surgery for diverticulitis

MBP and long-term survival
Anastomotic leakage is an independent prognostic indicator of poorer cancer-specific survival after potentially curative resection. [39-41]
In **chapter 7** we confirmed the hypothesis that MBP does not influence long-term survival in patients treated for colorectal cancer. This is not a surprising finding as we found no higher complication rate between the MBP+ group and the MBP- group. There are some obvious problems with this study. Firstly, there is potential to much bias given that patients from only 2 of 13 participating hospitals were included and patients groups were inequivalent due to the subgroup nature despite originating from a RCT cohort. Secondly, adjuvant and neo-adjuvant strategies or recurrence are factors much more likely to have an impact on the outcomes than whether or not MBP was used, especially since stage is known and stage IV patients are included. In our study we did not adjust for (neo-)adjuvant treatment. A potentially more interesting analysis would be to evaluate long- term outcomes in those patients alone with complications. There is only one study, a retrospective cohort study of 1730 patients, addressing the effect of MBP on long term survival. They also conclude long term survival is not improved by MBP in patients treated for colorectal cancer. [42]

General Conclusion

It is safe to conclude MBP may be omitted in elective colon surgery as shown by two large randomized trials. MBP and lower colorectal surgery remains a matter of debate as literature is controversial and sufficient evidence is lacking.

In an ideal the world the perfect preoperative MBP would consist of a reasonable small amount of fluid, not cause diarrhea, clean the bowel completely, decontaminate the bowel without creating an imbalance in intestinal flora , have no osmolitic effect draining valuable electrolytes, have no inflammatory effect on the bowel wall, consist of nutritional additives, with effects lasting over one week and would taste great, or none at all.

References

1. Jung B, Påhlman L, Nystrom PO, et al. Mechanical bowel preparation study group. Multicentre randomized clinical trial of mechanical bowel preparation in elective colonic resection. Br J Surg 2007;94:689-695.
2. CME Contant, WCJ Hop, HP van't Sant et al. Mechanical bowel preparation for elective colorectal surgery: a multicentre randomized trial. Lancet 2007;370:2112-17
3. Guenaga KK, Matos D, Wille-Jørgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev 2011:(9)CD001544.
4. Bretagnol F, Panis Y, Rullier E, et al. Rectal cancer surgery with or without bowel preparation. The French Greccar III multicenter single-blinded randomized trial. Ann Surg 2010;252:863-868.
5. Van't Sant HP, Weidema WF, Hop WC, et al. The influence of mechanical bowel preparation in elective lower colorectal surgery. Ann Surg 2010;251:59-63.
6. Burke P, Mealy K, Gillen P, Joyce W, Traynor O, Hyland J. Requirement for bowel preparation in colorectal surgery. Br J Surg 1994; 81: 907-10.
7. Miettinen RP, Laitinen ST, Makela JT, Paakkonen ME. Bowel preparation with oral polyethylene glycol electrolyte solution versus no preparation in elective open colorectal surgery: prospective, randomized study. Dis Colon Rectum 2000; 43: 669–75.
8. Santos JC, Batista J, Sirimarco MT, Guimaraes AS, Levy CE. Prospective randomized trial of mechanical bowel preparation in patients undergoing elective colorectal surgery. Br J Surg 1994; 81: 1673–76.
9. Jung B. Mechanical bowel preparation for rectal surgery (unpublished data). Personal communication to Cochrane Guenaga KK, Matos D, Wille-Jørgensen P. Mechanical bowel preparation for elective colorectal surgery. Cochrane Database Syst Rev 2011;21:CD001544.
10. Leiro F, Barredo C, Latif J et al. Mechanical preparation in elective colorectal surgery. Revista Argentina de Cirurgia 2008;95(3-4):154-167.
11. Moral MA, Aracil XS, Junca JB, Lopez LM, Tavira RH, Garnica IA et al. A prospective randomised controlled study on the need to mechanically prepare the colon in scheduled colorectal surgery. Cirurgia Espanola 2009;85(1):20-25.
12. Zmora O, Mahajna A, Bar-Zakai B, et al. Colon and rectal surgery without mechanical bowel preparation: a randomized prospective trial. Ann Surg 2003; 237: 363–67.
13. Scabini S, Rimini E, Romairone E et al. Colon and rectal surgery for cancer without mechanical bowel preparation: onecentre randomised prospective trial. World J Surg Oncology 2010;8:35-39.
14. Bertani E, Chiappa A, Biffi R, et al. Comparison of oral polyethylene glycol plus a large volume glycerine enema with a large volume glycerine enema alone in patients undergoing colorectal surgery for malignancy; a randomized clinical trial. Colorectal Dis 2011;13:327-34.
15. Matthiessen P, Hallböök O, Rutegård j, et al. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 2007; 246:207-214.
16. Hüser N, Michalski CW, Erkan M, et al. Systemic review and meta-analysis of the role of defunctioning stoma in low rectal cancer surgery. Ann Surg 2008;248:52-60.
17. Tan WS, Tang CL, Shi L, et al. Meta-analysis of defunctioning stomas in low anterior resection for rectal cancer. Br J Surg 2009;96:462-472.
18. http://www.heelkunde.nl/uploads/mu/22/mu22HtlbEpr-SLLyAdT5nQ/NVvH-richtlijn-Acute-diverticulitis-van-het-colon-2012.pdf
19. RJ Drummond, RM McKenna and DM Wright. Current practice in bowel preparation for colorectal surgery: a survey of the members of the Association of Coloproctology of GB & Ireland. Colorectal Disease 2011;13: 708–710
20. Dehni N, Schlegel RD, Cunningham C, Guiget M, Tiret E, Parc R. Influence of a defunctioning stoma on leakage rates after low colorectal anastomosis and colonic J pouch-anal anastomosis. Br J Surg 1998;85:1114-1117.

21. Marusch F, Koch A, Schmidt U, Geibetaler S, Dralle H, Saeger HD et al. Value of a protective stoma in low anterior resections for rectal cancer. Dis Colon Rectum 2002;45:1164-1171.
22. Gastinger I, Marusch F, Steinert R, Wolff S, Koeckerling F, Lippert H. Protectice defunctioning stoma in low anterior resection for rectal carcinoma. Br J Surg 2005;92:1137-1142.
23. Peeters KCMJ, Tollenaar RAEM, Marijnen CAM, Klein Kranenbarg E, Steup WH, Wiggers T, et al. Risk factors for anastomotic failure after total mesorectal excision of rectal cancer. Br J Surg 2005;92:211-216.
24. Poon RT, Chu KW, Ho JW, Chan CW, Law WL, Wong J. Prospective evaluation of selective defunctioning stoma for low anterior resection with total mesorectal excision. World J Surg 1999;23:463-467.
25. Breukink S, Pierie J, Wiggers T. Laparoscopic versus open total mesorectal excision for rectal cancer. Cochrane Database Syst Rev. 2006(4):CD005200.
26. Clinical Outcomes of Surgical Therapy Study Group. A comparison of laparoscopically assisted and open colectomy for colon cancer. N Engl J Med. 2004 May 13;350(20):2050-9.
27. Reza MM, Blasco JA, Andradas E, Cantero R, Mayol J. Systematic review of laparoscopic versus open surgery for colorectal cancer. Br J Surg. 2006 Aug;93(8):921-8.
28. Veldkamp R, Kuhry E, Hop WC, Jeekel J, Kazemier G, Bonjer HJ, et al. Laparoscopic surgery versus open surgery for colon cancer: short-term outcomes of a randomised trial. Lancet Oncol. 2005 Jul;6(7):477-84.
29. Bucher P, Gervaz P, Soravia C, et al. Randomized clinical trial of mechanical bowel preparation versus no preparation before elective left-sided colorectal surgery. Br J Surg. 2005;92:409-414.
30. Muzii L, Angioli R, Zullo MA, Calcagno M, Panici PB. Bowel preparation for gynecological surgery. Crit Rev Oncol Hematol. 2003 Dec;48(3):311-5.
31. Zmora O, Lebedyev A, Hoffman A, Khaikin M, Munz Y, Shabtai M, et al. Laparoscopic colectomy without mechanical bowel preparation. Int J Colorectal Dis. 2006 Oct;21(7):683-7.
32. SL Cohen, JI Einarsson. The role of mechanical bowel preparation in gynecologic laparoscopy. Reviews in Obstetrics & Gynecology 2011;4:28-31.
33. Vlot J, Slieker JC, Wijnen R, Lange JF, Bax KN. Optimizing working-space in laparoscopy: measuring the effect of mechanical bowel preparation in a porcine model. Surg Endosc. 2013 Jun;27(6):1980-5
34. Klarenbeek BR, Veenhof AA, Bergamaschi R, et al. Laparoscopic sigmoid resection for diverticulitis decreases major morbidity rates: a randomized control trial: short-term results of the Sigma Trial. Ann Surg 2009;249:218-24.
35. T Eglington, T Nguyen, S Raniga et al. Patterns of recurrence in patients with acute diverticulitis. Br J Surg 2010;97:952-957.
36. D Collins, DC Winters. Elective resection for diverticular disease: an evidence-based review. World J Surg 2008;32:2429-33.
37. S Janes, A Meagher and FA Frizelle. Elective surgery after acute diverticulitis. Br J Surg 2005;92:133-142.
38. M Levack, D Berger, P Sylla et al. Laparoscopy decreases anastomotic leak rate in sigmoid colectomy for diverticulitis. Arch Surg 2011;146:207-210.
39. Kube R, Mroczkowski P, Granowski D, Benedix F, Sahm M, Schmidt U et al. Anastomotic leakage after colon cancer surgery: a predictor of significant morbidity and hospital mortality, and diminished tumour-free survival. Eur J Surg Oncol 2010; 36: 120–124.
40. Walker KG, Bell SW, Rickard MJ, Mehanna D, Dent OF, Chapuis PH et al. Anastomotic leakage is predictive of diminished survival after potentially curative resection for colorectal cancer. Ann Surg 2004; 240: 255–259.
41. McArdle CS, McMillan DC, Hole DJ. Impact of anastomotic leakage on long-term survival of patients undergoing curative resection for colorectal cancer. Br J Surg 2005; 92: 1150–1154
42. Nicholson GA, Finlay IG, Diament RH et al. Mechanical Bowel preparation does not influence outcomes following colonic cancer resection. British J Surg 2011; 98: 866-871.

Chapter 9

Summary in English and Dutch

Summary

Surgical resection of a segment of the colon or rectum remains the cornerstone of treatment for patients with colorectal cancer or other indications for resection. For many decades mechanical bowel preparation (MBP) is used to clean the bowel of faeces prior to colorectal surgery with the aim of preventing clinical anastomotic leakage and limit faecal spillage during surgery. However the rationale behind MBP is merely a theory and has become more of a routine rather than evidence based practice. **Chapter 1** describes the role and types of MBP in colorectal surgery. Both the possible beneficial as detrimental effects are depicted. An overview of the literature is presented and demonstrates MBP is not supported by literature. **Chapter 2** contains one of the largest multicentre randomised trials with sufficient power to conclude MBP may be safely omitted in elective overall colorectal surgery.

Despite literature, surveys among colorectal surgeons show they are still reluctant in omitting MBP in lower colorectal surgey. This is mainly due to higher rates of anastomotic leakage and morbidity compared to colon surgery and the possibility of a diverting ileostomy. To many it seems irrational to divert the feacal stream with an ileostomy and still have a colon with remaining faeces that might jeopardize the anastomosis. In **chapter 3** the dillema of MBP and lower colorectal surgery with or without a diverting ileostomy are addressed. A subgroup analysis of the randomised trial mentioned in Chapter 2 was performed and did not show any differences in anastomotic leakage rates and other septic complications between patients with low anastomosis and treated with or without MBP. In addition, although numbers were small, we did not find any detrimental effects in omitting MBP in patients in which a diverting ileostomy was applied.

With regard to anastomotic leakage a distinction can be made between major and minor leakage. A major leak may be described as one of clinical significance (peritonitis, sepsis) often requiring surgical intervention. Minor leaks may be described as leaks confirmed by radiological studies but of no clinical significance and not needing any intervention. In **chapter 4** morbidity and mortality was investigated in the presence of anastomotic leakage in patients treated with and without MBP. We found no differences in mortality rate, initial need for surgical reintervention and extent of bowel contamination between groups. According to these results MBP does not seem to influence the course or outcome of a major anastomotic leak.

Chapter 5 describes the results of a questionnaire sent to Dutch colorectal surgeons enquiring about the implementation of MBP in laparoscopic colorectal surgery. This type of colorectal surgery adds another dimension to the role of MBP besides the assumed prevention of clinical anastomotic leakage and septic complications. It is believed MBP may have beneficial effects on the exposure of the operation field and on intestinal volume, possibly facilitating laparoscopic surgery. However, evidence to support this theory in literature is scarce. The

results of this survey show the indication of MBP is undefined and there is no consensus amongst colorectal surgeons in the Netherlands regarding the use of MBP in laparoscopic colorectal surgery.

Diverticulosis is an increasing benign colon entity in the Western world complicated by diverticulitis. Surgery for diverticulitis may be associated with higher morbidity than elective surgery for other diseases of the colon due to the additional infection and inflammation. In **chapter 6** we present a subgroup analysis of the RCT described in Chapter 2 concerning the influence of MBP on patients surgically treated for diverticulitis. No differences in anastomotic leakage and other septic complications were found in patients treated with MBP and without. Our results suggest MBP can safely be omitted in patients undergoing elective surgery for diverticulitis.

Chapter 7 evaluates the effects of MBP on long term survival in patients treated for colorectal cancer. Only one study in literature has addressed this matter (a retrospective cohort study) and concludes longterm survival is not improved in patients treated with MBP before colorectal cancer surgery. As surgeons have already started to omit MBP in daily practice based on literature we prefer to suggest withholding MBP has no negative effects on longterm survival in patients treated for colorectal cancer.

In conclusion this thesis shows that MBP can not only be safely omitted in overall colorectal surgery but further supports MBP having no positive effects in several subgroups including patients with lower colorectal surgery with or without a diverting ileostomy, with diverticulitis or with established anastomotic leakage. Finally it can be safely stated that survival is not compromized either.

Samenvatting

Chirurgische resectie van een deel van het colon of het rectum is nog steeds de hoeksteen van de behandeling van patiënten met een colorectaal carcinoom of andere aandoeningen van de dikke darm. Reeds decennia lang wordt mechanische darmvoorbereiding (MDV) toegepast om de darm te schonen van ontlasting voorafgaande aan chirurgie met als doel naadlekkage te voorkomen en spill van ontlasting tijdens de operatie te minimaliseren. Echter de ratio achter MDV is slechts theorie en is meer routine geworden dan evidence-based geneeskunde. **Hoofdstuk 1** beschrijft de rol en de verschillende soorten MDV bij colorectale chirurgie. Zowel de voor- als nadelen van MDV worden benoemd. Een overzicht van de literatuur wordt gepresenteerd waaruit blijkt dat de toepassing van MDV niet door de literatuur wordt ondersteund. **Hoofdstuk 2** omvat een van de grootste multicenter gerandomiseerde trials met voldoende power om te kunnen concluderen dat MDV veilig achterwege gelaten kan worden bij electieve colorectale chirurgie in de breedste zin.
Ondanks de literatuur laten enquêtes zien dat colorectale chirurgen nog steeds terughoudend zijn in het achterwege laten van MDV bij lage naden. Dit komt voornamelijk door het hogere aantal naadlekkages en morbiditeit vergeleken met meer proximale naden van het colon en de kans op het moeten aanleggen van een dubbelloops deviërend ileostoma. Voor velen is het tegenstrijdig om de ontlasting door middel van een dubbelloops ileostoma af te leiden met stroomafwaarts nog steeds een colon gevuld met ontlasting welke de naad nog in de vorm van lekkage in gevaar kan brengen. **Hoofdstuk 3** is gericht op het probleem van MDV en lage naden met of zonder dubbelloops deviërend ileostoma. Hiervoor werd een subgroup analyse verricht van de gerandomiseerde trial genoemd in Hoofdstuk 2 welke geen verschil liet zien voor naadlekkages en andere septische complicaties tussen patiënten met een lage naad die behandeld waren met of zonder MDV. Hoewel de aantallen klein waren, werden geen negatieve effecten van het achterwege laten van MDV gevonden bij patiënten, die een dubbelloops deviërend ileostoma hadden gekregen.
Met betrekking tot naadlekkages kan er een onderscheid gemaakt worden tussen ernstige en 'milde' vormen van naadlekkage. Een ernstige naadlekkage kan omschreven worden als een klinisch relevante naadlekkage (peritonitis, sepsis) welke meestal chirurgisch ingrijpen behoeft. 'Milde' naadlekkages kunnen omschreven worden als lekkages, die radiologisch bevestigd maar klinisch irrelevant zijn en geen behandeling behoeven. In **hoofdstuk 4** zijn de mortaliteit en morbiditeit onderzocht bij patiënten bij wie een naadlekkage is opgetreden en die behandeld zijn met en zonder MDV. Er waren geen verschillen in mortaliteit, noodzaak tot chirurgische re-interventie en contaminatie van het peritoneum tussen beide groepen. Volgens deze resultaten heeft MDV geen invloed op het beloop van colorectale naadlekkage. **Hoofdstuk 5** beschrijft de resultaten van een enquête verspreid onder Nederlandse colorectale chirurgen betreffende de toepassing van MDV bij laparoscopische colorectale

chirurgie. Laparoscopische darmchirurgie voegt mogelijk een nieuwe dimensie toe aan de rol van MDV, los van de veronderstelde beschermende invloed tegen naadlekkage en andere septische complicaties. Mogelijk heeft MDV een positief effect op het overzicht van het operatieterrein en op de omvang van de darm, hetgeen laparoscopische chirurgie kunnen vergemakkelijken. Echter bewijs voor deze effecten van MDV is vrijwel niet voorhanden in de literatuur. De resultaten van deze enquete laten zien dat er geen richtlijn en weinig consensus over de toepassing van MDV bij laparoscopische colorectale chirurgie bestaan.

Diverticulose is een veel voorkomende voornamelijk westerse darmaandoening en wordt niet zelden gecompliceerd door diverticulitis. Chirurgie voor diverticulitis gaat vaak door bijkomende ontsteking en infectie gepaard met een hogere morbiditeit dan electieve chirurgie voor andere aandoeningen van het colon. In **hoofdstuk 6** wordt een subgroup analyse van de RCT, zoals beschreven in Hoofdstuk 2, over de invloed van MDV op patiënten, die voor diverticulitis geopereerd werden. Er werden geen verschillen gevonden in aantal naadlekkages en andere septische complicaties tussen patiënten, die met en zonder MDV werden behandeld. Deze resultaten suggereren dat MDV veilig achterwege gelaten kan worden bij patiënten, die electief geopereerd worden voor diverticulitis.

In **hoofdstuk 7** worden de effecten van MDV op de lange-termijn overleving van patiënten, die geopereerd werden voor een colorectaal carcinoom, geëvalueerd. Slechts één studie uit de literatuur (retrospectieve cohortstudie) heeft zich op dit onderwerp gericht, waaruit geconcludeerd wordt dat de lange-termijn overleving niet beter wordt bij patiënten, die behandeld waren met MDV voorafgaande aan resectie. Gezien het feit dat chirurgen op basis van de literatuur reeds begonnen zijn om MDV in de dagelijkse praktijk niet meer toe te passen vonden wij het meer gepast om aan de hand van onze resultaten te suggereren dat het achterwege laten van MDV geen negatieve effecten heeft op de lange-termijn overleving.

Concluderend laat dit proefschrift niet alleen zien dat MDV veilig achterwege gelaten kan worden bij colorectale chirurgie in de breedste zin, maar ook geen positieve bijdrage levert met betrekking tot bepaalde subgroepen zoals van patiënten met colorectale chirurgie met een lage naad, met of zonder dubbelloops deviërend ileostoma, met diverticulitis en van patiënten geconfronteerd met een naadlekkage. Tenslotte heeft het achterwege laten van MDV ook geen negatieve invloed op de lange-termijn overleving bij colorectaal carcinoom.

Chapter 10

List of publications

List of publications

- **HP van 't Sant**, S Spronk, A Dees, WCJ Hop, PT den Hoed. De diagnostische waarde van kleuren-duplex-onderzoek bij arteriitis temporalis. NTvH Jaargang 15, nummer 2, februari 2006.

- **HP van't Sant**, CJC Braam, PT den Hoed. Liesbreuk straat. Medisch contact 61e jaargang februari 2006.

- **HP van 't Sant**, ND Bouvy, HJ Bonjer, WW de Herder, WCJ Hop, RA Feelders, RR de Krijger. The prognostic value of two different histopathological scoring systems for adrenocortical carcinomas. Histopathology 2007 Aug;51(2):239-45.

- **HP van 't Sant**, J Heisterkamp, DJ Bac, JW van der Sluijs, WF Weidema. Invaginatie veroorzaakt door een lipoom in het colon transversum bij een volwassene. NTvH Jaargang 16, nummer 1, januari 2007.

- **HP van't Sant**, Damhuis, PT den Hoed. Het voorkomen en vóórkomen van exploratieve thoracotomieën. NTvH Jaargang 16, nummer 4, juni 2007.

- CME Contant, WCJ Hop, **HP van't Sant**, HJM Oostvogel, HJ Smeets, LPS Stassen et al. Mechanical bowel preparation for elective colorectal surgery: a multicenter randomised trial. Lancet 2007;370:2112-17.

- de Meijer VE, **Van't Sant HP**, Spronk S, Kusters FJ, den Hoed PT. Reference value of transcutaneous oxygen measurement in diabetic patients compared with non-diabetic patients. J Vasc Surg. 2008 Aug;48(2):382-8.

- **Van't Sant HP**, Contant CME, Hop WCJ, Oostvogel HJM, Weidema WF. The Influence of Mechanical Bowel Preparation in Elective Lower Colorectal Surgery. Ann Surg 2010 Jan;25(1):59-63.

- **Van't Sant HP**, Contant CME, Hop WCJ, Oostvogel HJM, Weidema WF. The Influence of Mechanical Bowel Preparation in Elective Lower Colorectal Surgery. Letters to the Editor. Ann Surg 2010 Sep;252(3):575-576.

- **Van't Sant HP**, Weidema WF, Hop WCJ, Oostvogel HJM, Contant CME. Evaluation of morbidity and mortality after anastomotic leakage following elective colorectal surgery in patients treated with or without mechanical bowel preparation. Am J Surg 2011 Sep;202(3): 321-4.

- JC Slieker, **HP van 't Sant**, Vlot J, F Daams, FW Jansen, JF Lange. Bowel preparation prior to laparoscopic colorectal resection: what is current practice? J Laparoendosc Adv Surg Tech A. 2011 Dec;21(10): 899-903.

- **Van't Sant HP**, Slieker JC, Hop WC, Weidema WF, Lange JF, Vermeulen J, Contant CM. The influence of mechanical bowel preparation in elective colorectal surgery for diverticulitis. Tech Coloproctol. 2012 Aug;16(4):309-14.

- Kamman AV, **van 't Sant HP**, den Hoed PT, Vles WJ, van Well AME, Jonkman JGJ, van der Sluis JW. Vasculaire complicaties na claviculaosteosynthese. Ned Tijdschr Traum 2012(6):175-178.

- **Van't Sant HP**, Kamman AV, Hop WCJ, van der Heijden M, Lange JF, Contant CME. Mechanical bowel preparation has no influence on long-term survival in patients surgically treated for colorectal cancer.
  Accepted Am J Surg.

- **Van't Sant HP**, Lennox AF, Varcoe RL. Retrograde recanalization of internal iliac artery in a patient with buttock claudication: a case report. In progress.

Chapter 11

Dankwoord

Dankwoord

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Chapter 12

Curriculum vitae

Curriculum vitae

Hans Pieter van't Sant was born on the 29th of December 1977 in Gouda, the Netherlands. He spent his primary school period partly at the Casimir School in Gouda en partly at Mostyn House School in Neston, Cheshire, Great Britain. In 1996 he graduated from highschool (Gymnasium) at the Sint Jan's Lyceum in 's-Hertogenbosch. After this he entered medical school at the Erasmus University in Rotterdam and graduated in 2004. He started working as a surgical resident in the department of Surgery at the Ikazia Hospital in Rotterdam. In 2005 he started his surgical training in the same hospital part of Rotterdam School of Surgery. During this period the first steps towards the creation of this thesis were made under supervision of Dr CME Contant and Dr WF Weidema. In 2009 and 2010 he continued his surgical training at the Erasmus Medical Centre in Rotterdam. At the end of June 2011 he finished his surgical training. After a vascular surgery fellowship of 4 months at the Erasmus Medical Centre he worked as a fellow in vascular surgery from January 2012 to December 2012 at the Prince of Wales Hospital in Sydney, Australia. On his return to the Netherlands he worked as a fellow in vascular surgery in the Onze Lieve Vrouwe Gasthuis in Amsterdam for 15 months. On the 11th of May 2014 he became a Fellow of the European Board of Vascular Surgery. He is now a vascular surgeon at Reinier the Graaf Gasthuis in Delft.


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