Pre- and intraoperative gut irrigation and antibiotics in colorectal surgery : a clinical and experimental study

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Pre- and intraoperative gut irrigation and antibiotics in colorectal surgery

a clinical and experimental study

Proefschrift

ter verkrijging van de graad van doctor in de Geneeskunde
aan de Rijksuniversiteit Limburg te Maastricht
op gezag van de Rector Magnificus, prof. dr F. I. M. Bonke,
volgens het besluit van het College van Dekanen
in het openbaar te verdedigen in de aula van de universiteit
op vrijdag 24 november 1989
om 16.00 uur
door

Chander Mahabier

geboren in het district Nickerie in Suriname.

Promotores: Prof. dr C.P.A. van Boven
Prof. dr J.M. Greep

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Prof. H.A.F. Dudley (St. Mary's Hospital, London)
Prof. dr J.A. Gruwez (Katholieke Universiteit Leuven)
Prof. dr P.B. Soeters

'Bloom where you are planted'

To Mieke,
Shanti, Ratna and Kiran.
To the memory of my father and mother.

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Chapter 1

Aim of the study

Introduction

The use of antibiotic prophylaxis in elective colorectal surgery is now generally accepted [1] although the method of drug administration (oral or parenteral) and the duration are variable. A 24 hour prophylaxis (three doses) is most commonly used but some workers estimate that one single intravenous dose at the induction of anaesthesia would be sufficient [2].

Several antibiotics have been reported to be effective as prophylaxis in colorectal surgery. Although some surgeons claim that antibiotics active only against anaerobic bacteria provide adequate protection [3], it is commonly considered that drugs effective against the aerobic as well as the anaerobic colonic flora should be employed as prophylactic agents [4].

The adverse effect of faecal loading on the healing of colonic anastomoses has been reported in many clinical and experimental studies [5]. Bowel preparation, in order to get rid of the faecal mass in the colon, is generally claimed to be essential for the prevention of anastomotic leakage and postoperative septic complications (in combination with antibiotics) [6]. The studies on colorectal surgery reported in this thesis consist of a clinical and an experimental part.

Clinical study

Preoperative whole gut irrigation and antibiotics

Before 1979, oxytetracycline was used in the De Wever-Ziekenhuis, Heerlen, as prophylaxis in elective colorectal surgery, combined with a conventional bowel preparation using diets and laxatives for several days.

In 1979 a prospective randomized study was set up to evaluate the results of different antibiotics (including oxytetracycline) in combination with whole gut irrigation (WGI) as bowel preparation.

The aim was to compare the former policy of antibiotic prophylaxis with other combinations and to make the best choice for day to day use in the hospital.

Results of a prospective and randomized study in 212 patients are reported, as well as, additionally, those obtained in 215 patients who were treated with the regimen yielding the best results in the randomized study.

Intraoperative colon irrigation

Preoperative whole gut irrigation or other means of bowel preparation appeared to be difficult or impossible in patients with obstructing tumours.

A staged surgical procedure (including diverting colostomy, resection of the tumour at a second operation and closure of the colostomy at a third, or the use of the Hartmann

procedure) was the orthodox treatment for these patients. Intraoperative colon irrigation, permitting bowel preparation to a high standard during operation, enables the performance of a one-stage operation (primary resection and anastomosis) in patients with obstruction of the left colon, and was introduced in 1984. The experience and results with this procedure in 41 patients are reported.

Experimental studies

Evaluation of antibiotics

Animal experiments were carried out to investigate three clinically posed questions:

1. Is an evaluation of an antibiotic regimen for prophylaxis in an experimental animal model feasible, prior to its use in longlasting clinical trials?

The antibiotic regimens used in the clinical trial were also evaluated in an experimental intra-abdominal infection model [7] and the clinical and experimental results were compared. Several new antibiotics have been evaluated as prophylactic agents in colorectal surgery using this model.

Antibiotics and anastomotic healing

2. Is it safe to perform an anastomosis in the presence of infection provided antibiotics are given? Or, in other words: could antibiotics diminish the effect of perianastomotic infection and promote unimpaired anastomotic healing?

An experimental study was carried out using previously infected Vicryl[®] for the performance of the anastomosis. Bursting pressure measurements in the isolated colon containing the anastomosis at the 3rd and 7th day were used as parameters of anastomotic healing.

Acute colon decontamination

3. Can the colon be rapidly decontaminated by intraoperative lavage with povidone iodine?

Adequate serum levels of antibiotics and the reduction of the bacterial burden by whole gut irrigation with neomycin and metronidazole have been shown to be very effective in the prevention of septic complications in elective colorectal surgery [8].

During surgery of obstructing lesions of the colon an adequate level of antibiotics can easily be obtained by intravenous administration shortly before operation. No reduction of the colon flora, either with these antibiotics or by intraoperative colon irrigation, however, is to be expected.

In order to reduce the colon flora a method of acute colon decontamination was studied experimentally, and subsequently used in patients undergoing intraoperative colon irrigation.

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Part I

Review of the literature

Chapter 2

Bowel preparation for elective colorectal surgery

Bowel preparation: sense or nonsense?

The large bowel is heavily colonised by aerobic and anaerobic bacteria, the latter being 10,000 times more numerous. The most common aerobic organisms are *Escherichia coli* and *Enterococcus faecalis*, and the most common anaerobic bacteria belong to the species of *Bacteroides* and *Clostridium* [1]. During surgery, once the colonic wall is opened and faecal spillage occurs, sepsis almost invariably occurs unless appropriate antibiotic prophylaxis is given.

Wound infection after gastrointestinal operations is nearly always caused by endogenous bacterial flora contaminating the wound at operation [2]. The development of wound sepsis depends not only upon the species of bacteria inoculated into the wound but also upon their number. Experimental models suggest that direct inoculation of 10^6 organisms/ml is required to produce sepsis reliably, whereas if the number of organisms is $< 10^5$ /ml wound sepsis develops less often [3]. Thus, the greater the bacterial contamination the greater the risk and the higher the probability of sepsis [4].

Another finding of importance has been suggested by Rusca et al. [5]. In an experimental study it has been shown that bacteria which cause disruption of an anastomosis are probably seeded at the time of the creation of the anastomosis and do not leak out after the anastomosis has been performed.

Secondly, the presence of formed faeces in the intestinal tract proximal to a recently fashioned anastomosis poses a threat to that anastomosis. Therefore to leave an anastomosis, however carefully made, distal to a length of bowel loaded with formed faeces is to court disaster [6]. The dangers occur when bowel function returns after operation, for a bolus of hard faeces may become impacted at the anastomosis site. This will result in tension and ischaemia at the suture line, with the risk of anastomotic breakdown, leakage and gross faecal contamination of the abdomen.

Experimental and clinical investigations [7,8] emphasise the disastrous effect of faecal loading on colonic anastomoses, so causing postoperative septic complications.

Hence the purpose of preoperative large bowel preparation is to reduce the risk of faecal spillage and bacterial contamination of the abdomen during colorectal surgery. The risk cannot entirely be avoided, but the frequency and severity of bacterial spillage can be minimised by good operative technique and optimal bowel preparation.

There is a popular misconception that reduction in faecal residue (by bowel preparation) is associated with reduced counts of bacteria in the colon. Mechanical bowel preparation, however, will never decrease the number of residual microorganisms per ml of stool (concentration) in the colon at the time of operation and no decrease of postoperative complications is to be expected from this preparation alone [9,10,11].

Reducing colonic aerobic and anaerobic bacterial flora is achieved by using oral antibiotics [12] and is used by some workers to minimise the endogenous bacterial infection so that prophylactic antibiotics can more effectively combat the organisms invading the wound [13].

Irving and Scrimgeour in their recent publication [14] questioned the basic truisms of large bowel preparation in elective and emergency colorectal surgery. They described excellent results in 46 patients undergoing leftsided colonic resections and primary anastomosis without any bowel preparation. They argue that preoperative bowel preparation is time consuming, expensive, unpleasant to the patient and completely unnecessary! Provided a single dose of appropriate antibiotics is administered intravenously at the start of the operation, these workers claim that all forms of bowel preparation can be omitted.

The problem is that comparison of their results is scarcely possible because hardly any one else has used their methods. Secondly, the number of patients in their study is too small to be conclusive.

At one point their assumption has already been proven to be incorrect. Phillips et al. [15] (in the Large Bowel Cancer project), reported on a large number of patients (including 713 with obstructions) and noted a statistically significant difference in anastomotic leakage between patients without obstruction (6% leakage) and those who were indeed obstructed (18%). All underwent immediate resection and anastomosis without any bowel preparation.

The answer to the question concerning the sense or nonsense of large bowel preparation in elective colorectal surgery (with reference to the publication of Irving and Scrimgeour) can only be answered by prospective trials with sufficient and comparable groups of patients (degree of illness; staging of the tumour), with comparable operative technique (the use of one- or two-layer anastomoses; use of drains, defunctioning colostomy etc.) in whom the mechanical bowel preparation is studied as a single variable [16]. Such a trial will probably never take place for ethical reasons and the large number of patients required.

In view of the good results of optimal bowel preparation combined with perioperative antibiotic prophylaxis in elective colorectal surgery, it can be concluded that this basic surgical practice should not be violated.

Methods of bowel preparation

The ideal method of mechanical bowel preparation should completely empty the colon without distress to the patient. Such a method should be cheap, require a minimum of nursing time and not result in water and electrolyte imbalance. Ideally the colonic concentration of bacteria should be reduced to such an extent that systemic prophylaxis is not required and there should be no development of bacterial resistance or risk of superinfection. Unfortunately, no such ideal method exists. A balance, therefore, has to be struck between the desire of the surgeon to empty the colon of faeces and the degree of distress caused to the patient.

A number of different techniques can be used to clear the colon of faecal material. These include conventional bowel preparation with low or non residue diets, cathartics and enemata, whole gut irrigation (WGI), oral (mannitol or polyethylene glycol) bowel preparation and intraoperative colonic irrigation.

Conventional bowel preparation

This technique of bowel preparation has been used for many years [6]. It requires the admission of the patients to hospital 3-5 days before operation. A low residue diet is commenced, and this becomes a "fluid only" diet 1-2 days before surgery. Purgation with one of a variety of laxatives (senna, magnesium sulphate, castor oil etc.) is given for 2 days, followed by enemata and rectal lavage for 1 day [17].

This method provides excellent clearance of the colon, but it is exhausting for the patient, who comes to operation in a state of starvation; it also results in electrolyte loss [18]. It is time-consuming for the nurses and the patient and is expensive.

Elemental diets

Elemental Diets (Peptison^R; Nutrison^R) are designed to be absorbed totally within the small bowel so that no residue passes through the colon, while providing an adequate nitrogen and calorie intake for the patient.

It was thought that taking such a diet for several days preoperatively might provide the advantage of a low residue diet without the disadvantage of the starvation encountered with conventional bowel preparation. However, it has been found that such a diet neither empties the colon of faeces nor reduces the concentration of microorganisms within the colon [19].

The use of such diets has not gained great favour, but their value is that they maintain adequate preoperative nutrition in the debilitated patient [20].

Conventional bowel preparation and elemental diets both require considerable time in order to prepare the colon, and because of admission of patients to the hospital several days before operation to complete bowel preparation these methods are therefore also expensive. Within the last few years 3 methods of orthograde colonic lavage have been introduced in elective colorectal surgery: whole gut irrigation, oral mannitol bowel preparation and oral polyethylene glycol bowel preparation.

Whole gut irrigation (WGI)

Irrigation of the bowel with an electrolyte solution was first proposed for the treatment of cholera [21]. The technique was subsequently modified for use in preoperative bowel preparation [22,23]. The method of irrigation is described in chapter 4.

It provides excellent clearance of the colon (compared with conventional, elemental and mannitol bowel preparation) [24], with little fluid being left [25], and there is insignificant retention of water at the time of surgery.

There is negligible electrolyte imbalance [26] if an electrolyte solution is used for irrigation. Patient tolerance is good [27,28,29].

Oral mannitol bowel preparation

Mannitol bowel preparation depends upon the fact that mannitol, an oligosaccharide, is not absorbed. If given as a hypertonic solution (10-20%), it draws fluid into the lumen of the bowel by its osmotic action.

If an isotonic solution (5%) is given by mouth, the fluid is retained within the bowel [30].

The purgation is produced by irrigation of the colon with this fluid. The mannitol solution can be flavoured to the patient's taste and is then quite palatable to drink. On the day before operation, 200 g of mannitol diluted in 1 litre of water (20%), 2 litres (10%) of water or 4 litres of water (5%) is drunk over a 4-hour period. The main advantage of mannitol as compared to whole gut irrigation is that the use of a nasogastric tube and special toilet facilities are not required.

However many enteric microorganisms (*Escherichia coli*) ferment mannitol [31] and this results in increased postoperative septic complications, together with an increased risk of colonic explosion [32-36] due to hydrogen from bacterial fermentation. These are the reasons that its use is no longer recommended, despite the fact that addition of appropriate oral antibiotics to the mannitol bowel preparation diminishes the above-mentioned risks.

Bowel preparation with polyethylene glycol electrolyte solution

Polyethylene glycol (PEG), as an osmotic purgative, is comparable to mannitol but does not have the two above-mentioned side effects, as microorganisms cannot use it as a substrate. Since its introduction in 1980 [37] PEG has been used with balanced electrolyte solution [Golytely] for bowel preparation in patients undergoing colonoscopy or elective colorectal surgery [38-45]. It is usually suggested that an average of 4 litres should be sufficient to produce a clean colon. The advantage of this method therefore should be that there is no need for nasogastric intubation although some patients might still find it difficult to drink 4 litres within 4 hours. Therefore, some workers using PEG [46] introduce a nasogastric tube and irrigate not only with 4 litres but continue until the rectal effluent is totally clear.

One study compared whole gut irrigation with a balanced electrolyte solution against bowel preparation with PEG [47]. The authors prepared 15 patients with only 4 litres of PEG and another 15 with whole gut irrigation until a clear rectal effluent could be obtained. Only 4/15 patients prepared with PEG, as compared with all 15 prepared with WGI, had excellent or good cleansing results.

However, when the two different solutions were infused in a double-blind manner (as done in 40 patients) until the rectal effluent was clear, no significant difference in the amount of fluid needed was found. However, significantly less fluid retention occurred with PEG, but this appeared to be the only advantage.

Conclusions

- Until data from adequate controlled clinical trials prove the contrary, large bowel preparation before colorectal surgery should be considered essential.
- Whole gut irrigation, with balanced electrolyte solution or with polyethylene glycol until the rectal effluent is clear, is rapid, economical and well tolerated by patients. This method of bowel preparation is the best for its capacity to clean the colon.
- No reduction of bacterial colonic flora or decrease in postoperative septic complications is to be expected from bowel preparation alone.

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Chapter 3

Intraoperative colon irrigation

History

Many attempts have been made in the past to clean the colon or rectum during operation before performing a primary resection and anastomosis of the left colon.

In 1958, Windsberg [1] first reported a procedure for irrigating the colon. After mobilisation of the sigmoid and rectum, transsection took place distal to the obstructing tumour. The tumour and the colon were then eased over the left side of the operating table to gravitate toward a large pail outside the sterile field. A circulating nurse was then instructed to make a large opening in the bowel just above the obstructing carcinoma. Bowel contents then gushed out into the pail [fig. 1]. Gentle manipulating and milking of the proximal colon, from the caecum distally, completed the evacuation of nearly all fluid and faeces through the exteriorized limb. Hereafter resection was completed [fig. 2]. If necessary, a large calibre Levin tube was brought upwards into the bowel above the obstructing cancer and guided towards the right colon. The colon was irrigated through this tube without contamination.

Fig. 1: The exteriorized colon is shown hanging over the left side of the table with an opening made above the obstructing cancer, completing evacuation of bowel and eliminating all distention (from Windsberg et al. [1]).

Fig. 2: Wide resection completed (from Windsberg et al. [1]).

Fig. 3: The fully mobilized segment containing the growth is brought out of the abdomen with its end enclosed in a polyethylene bag (from Muir [2]).

Fig. 4: A 26 or 32 mm glass tube with side arm for irrigation is tied securely into the proximal end of the opened bowel (from Muir [2]).

Fig. 5: The Paul's tubing is compressed during irrigation, the bowel is lifted up and gentle manipulations used to break up the faecal mass (from Muir [2]).

Fig. 6: The bowel is lowered and its contents with the washings are milked into the Paul's tubing which carries them to the waste container beside the table (from Muir [2]).

Fig. 7: The Chaffin Sump drain used for rectal washouts (from Thow [3]).

fig. 7

In 1968 Muir [2] introduced a 26 or 32 mm glass tube [figs. 3 and 4] into the colon proximal to the obstructing tumour, through which irrigation could be performed [figs. 5 and 6].

Thow in 1976 [3] reported the use of the Chaffin Sump for intraoperative rectocolonic irrigation enabling him to perform a primary resection and anastomosis [fig. 7].

Subsequently in 1979, Rickett[4] used the obturating balloon colostomy (Torbay colostomy) in order to perform a one-stage resection with immediate anastomosis and to leave a colostomy which did not require to be closed. The device consisted of a rigid tube which was bent through 90 degrees. The bent position was incorporated in a soft rubber balloon which was inflated through a Luer connection valve side tube. A flange, secured in place by a screw cap, stabilized the tube in place [figs. 8 and 9].

Fig. 8: Obturating balloon colostomy -Torbay colostomy (from Rickett [4]).

Fig. 9: The device placed in the anastomosis, showing ligatures around the outside of the colon (from Rickett [4]).

fig. 8

fig. 9

fig. 10

fig. 11

Fig. 10: Colonic tube to protect the anastomosis after primary resection and anastomosis have been performed (from Hardy et al. [5]).

Fig. 11: The method used for intraoperative colonic cleansing in the experimental canine model (from Leiboff et al. [6]).

When the lesion lay between the transverse colon and the mid sigmoid, the device was placed at the site of the anastomosis. When the lesion was distal to the mid sigmoid point and had been excised, the obturating balloon was placed proximally in the transverse colon in order to defunction the bowel distally.

In the first case the device was removed after 7 days and in the latter case after 2-4 weeks. Following removal of the device, the colostomy site, after initial faecal discharge, healed spontaneously in 1-3 months.

Hardy et al. in 1985 [5], at first performed a primary resection and anastomosis in the unprepared bowel and thereafter introduced a colon tube through the anastomosis to the proximal colon for irrigation. At the end of the irrigation, the tube was withdrawn to a point proximal to the anastomosis and fixed to the perianal skin [fig. 10].

Leiboff et al. in 1985 [6] experimentally employed specially designed irrigating instruments including a colonic tube and a balloon-tipped rectal tube with a wide diameter lumen through which the colonic tube could be passed. Irrigation fluid was instilled via the colonic tube using a pump and the effluent was led away through the rectal tube [fig. 11].

The method of antegrade intraoperative colon irrigation which has gained wide use is Dudley's modification [7] of the irrigation procedure previously described by Windsberg and Muir.

Indications

Obstructions

Intraoperative colon irrigation has mostly been employed to clean the colon either when there is an obstructing carcinoma of the left colon (because of which preoperative whole gut irrigation is not feasible), or in emergency colorectal surgery [7]. The procedure has also been used with other non-malignant left-sided obstructions (e.g. anastomotic stenosis).

Diverticulitis

This is the second most frequent indication for performing intraoperative colon irrigation and creating a primary anastomosis after resection.

Non obstructing tumours

The procedure is also employed in non-obstructing tumours of the left colon when preoperative bowel preparation is not possible or when the colon appears at operation to be ill-prepared. The use of the rectal tube in these cases will enable the procedure to be carried out easily, without any spillage.

Perforations

In iatrogenic perforation (biopsies), traumatic wounds (gunshot; knife) or colonic perforation due to diverticulitis, intraoperative colon irrigation can easily be performed with the aid of the rectal tube after closing the perforation. After irrigation, resection and anastomosis can take place as in elective surgery.

The current management of civilian rectal injuries requires complete faecal diversion and presacral drainage of perirectal tissue to prevent fatal septic complications. The principles evolved from combat experience over the two World Wars and reduced the mortality of rectal wounds from 60% to approximately 20% during the Korean conflict [8].

Operative rectosigmoid washout to remove faecal debris became standard during the Vietnam war to further reduce pelvic infection [9-12].

Although the value of this manoeuvre in managing civilian rectal wounds has been questioned [13-27], primary repair is supported more and more [28].

Shannon et al. [22] showed an increase of septic complications in civilian rectal trauma managed without a rectal washout compared with groups in which a distal rectal washout was performed.

With the intraoperative colon irrigation technique, traumatic wounds of the left colon or rectum (gunshot, knife) can be managed safely as a one stage procedure.

After preliminary closure of the perforation, intraoperative colon irrigation and decontamination [see chapter 9] are performed with the aid of the rectal tube. Hereafter the closed perforation site is resected and anastomosed as a primary procedure in the optimally prepared colon. If closure of the perforation is not possible, colonic irrigation can take place using the irrigation drainage tube and rectal washout performed via the inbuilt irrigation canal of the specially designed rectal tube.

Fig. 12: Algorithm for the management of patients with major colonic haemorrhage (from Berry et al. [53]).

Major colonic haemorrhage

New indications for the use of intraoperative colon irrigation have been reported [29,30] in patients with major colonic bleeding in which the source is unclear despite the availability of modern diagnostic techniques such as selective angiography and isotope scintigraphy [31-51]. In these patients [fig. 12], intraoperative colon irrigation is performed during laparotomy using the rectal tube [53].

Colonic irrigation in such patients has been reported to be quite rapid (within 10 minutes), during which time 3 litres of fluid are sufficient to ensure complete clearance of the colon [29]. After the irrigation, the rectal tube is removed and a colonoscopy is then carried out by the endoscopist sitting between the legs of the patient (who lies in a Lloyd-Davies position). The passage of the colonoscope is assisted by the surgeon [fig. 13] who can also inspect the colon by transillumination. Localisation of the source of colonic bleeding is nearly always possible [53] and a partial colectomy, instead of the common blind (sub)total colectomy [54,55] can then safely be performed.

Fig. 13: Cut-away view of the caecal pole showing the Foley catheter inserted through the appendix and the colonoscope passed through the whole colon (from Scott et al. [30]).

Fistulae

In some patients with, for example rectovaginal fistulae there may be some practical objections to preoperative whole gut irrigation or other bowel preparations. After closing of the fistula during laparotomy, intraoperative colon irrigation can be carried out, preferably using the rectal tube.

Closure of a diverting colostomy

A few patients with a diverting left-sided colostomy have undergone this procedure [56]. The reason for performing intraoperative colon irrigation is mostly the ill-prepared colon at operation.

Volvulus

Volvulus of the left colon which can not be treated conservatively [57] necessitates a laparotomy. At operation, a simple retorsion or colopexy can be done if the colon itself appears to be healthy. Volvulus of the sigmoid however is reported to have a high recurrence rate, which suggest that elective resection would frequently prove necessary in any case [58-63].

With intraoperative colon irrigation, resection and primary anastomosis is feasible [64].

Contraindications

It is not suggested that intraoperative colon irrigation should be a routine procedure. Several factors pleading against the use of intraoperative colon irrigation and primary anastomosis are: cardiopulmonary instability; poor general condition; deficient nutritional state and immunosuppression. Local factors (intra-abdominally) are: advanced peritonitis; interloop abscesses and unhealthy or poorly vascularised bowel ends at resection.

Results in the literature

A review of the results from 1980 to December 1988 [7,29,56,64-9,70-3] using the intraoperative colon irrigation is listed in table 1. The indications for which this method has been used are displayed in table 2. Mortality due to anastomotic leakage is low, illustrating the safety of the method.

Table 1: Results in the world literature concerning intraoperative colon irrigation.

Author	Year	No. of patients	Mean age	Anastom. leakage	Wound-infect.	Deaths
Dudley (D)	1980	2	63	-	-	-
Radcliffe (R)	1983	64	?	2	5	2 (1)*
Alderi (A)	1985	24	?	1	-	? (0)*
Koruth (K)	1985	61	74	4	2	5 (1)*
Campbell (C)	1985	4	49.5	-	-	-
Scott (S)	1986	4	56	-	-	-
Eggert (E)	1986	9	71	-	-	1
Foster (Fo)	1986	15	76	2	2	2
Mourik van (M)	1986	15	70	-	-	3
Thomson (T)	1986	126	67.2	6	4	5(2)*
Pollock (P)	1987	41	79	-	2(13)**	7(0)*
Feng (Fe)	1987	5	61.8	-	-	-
Konishi (Kon)	1988	25	61.1	1	-	1(1)*
Totaal		395	66.2	16 (4.1%)	15 (3.8%)	26 (6.6%)

* death due to anastomotic leakage

** 13 minor wound infections

Table 2: Indications for intraoperative colon irrigation in the world literature.

Diagnoses	Authors														Total
	D	R	A	K	C	S	E	Fo	M	T	P	Fe	Kon	*	
Tumours(left colon)	2	50	24	47			6	7	8	106	41	5	21	317	
Diverticulitis		8					1	5		13				27	
Perforation		2		12			2		2					18	
Haemorrhage				2	4	4			1					11	
Closure of colostomy									4					4	
Volvulus		1						3					4	8	
Anastomotic stenosis		2												2	
Fistulae		1												1	
Others										7				7	
Total	2	64	24	61	4	4	9	15	15	126	41	5	25	395	

* for abbreviations of authors' names see table 1.

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Part II

Clinical studies

Chapter 4

Prophylactic antimicrobials and whole gut irrigation in elective colorectal surgery: a prospective randomised study

Introduction

Elective colon and, especially, rectal surgery is associated with a high incidence of postoperative septic complications. Most infections are endogenous and caused by dissemination of intestinal contents, either at the time of operation or as a result of anastomotic leakage [1]. It has been demonstrated that microorganisms spilled while the anastomosis is being created are able to destroy the anastomosis [1-3]. For this reason, optimal bowel preparation is mandatory and can be achieved either by a low residue diet with laxatives for several days, or by whole gut irrigation which takes only a few hours. Neither conventional bowel preparation [4-7] nor whole gut irrigation reduce the intramucosal flora of the colon, although they both reduce the faecal mass and the total number of intraluminal bacteria. An anti-infectious effect of whole gut irrigation alone is never to be expected [8-11].

Addition of antibiotics, either to minimise the concentration of bacteria in the colon or to achieve optimal serum and tissue levels at operation, is necessary and is common practice nowadays in elective colorectal surgery [12]. There are still controversies concerning the choice of drugs and the dosages and methods of administration.

Although prophylaxis against the anaerobic flora alone has been shown to be effective [13-16], it is generally accepted that any prophylaxis in elective colorectal surgery should cover both the aerobic and the anaerobic flora [17-23]. Both oral and parenteral administration of antibiotics have proved to be adequate for this [24-29].

The purpose of the present study was to evaluate the results of various antimicrobial regimens combined with whole gut irrigation and to make the best choice for use in our hospital.

Patients and methods

All patients admitted for elective colorectal surgery from July 1979 to December 1983 were divided at random into three groups. Each group underwent a bowel preparation (whole gut irrigation), but differed in the antibiotic used. The random code was broken and the study was stopped after 4.5 years by the independent observer because the complication rates in two groups appeared to be unacceptably high compared with the other group. Analysis of the results showed that reliable conclusions from this study could be drawn.

Patients with severe cardiac decompensation, renal insufficiency and obstructing tumours were not given whole gut irrigation and were therefore excluded from this study. Patients

with obstructing tumours received conventional bowel preparation or intraoperative colon irrigation [30]. Patients with ulcerative colitis or Crohn's disease and those admitted for emergency surgery were also excluded. Operations for closure of colostomies were not included.

All patients received the whole gut irrigation as described by Hewitt et al. [31] and Crapp et al. [32] on the day before operation. A nasogastric tube was placed in the stomach with the patient in a sitting position. The irrigant was warmed to 37°C with the help of a hemoheater. The bowel was irrigated under nursing supervision at a speed of 3 to 4 litres/hour until at least 10 litres had been given or the effluent was totally clear. To prevent symptoms of nausea, vomiting and distention, 10 mg mecloramide was given intramuscularly or intravenously to all patients prior to the irrigation and was repeated during the lavage procedure when necessary.

Prophylactic regimens

Three groups were formed and each patient was allocated to a particular group by drawing from a randomised sealed envelope a card which defined the prophylactic regimen to be used (table 1). The first group received 250 mg of oxytetracycline intravenously with the premedication and this drug was continued once daily for 5 days after the operation. This was the standard policy in elective colorectal surgery at that time and it was included in the trial.

Table 1: Antibiotic regimens of this study.

Group 1 (O)

Whole gut irrigation
oxytetracycline 250 mg iv. at premedication
oxytetracycline 250 mg im. once daily for 5 days

Group 2 (T-M)

Whole gut irrigation
metronidazole 2 g/oral after WGI
tobramycin 1.5 mg/kg iv with induction of anaesthesia
tobramycin repeated 8 and 16 hours post operatively
if operation >3 hours

Group 3 (N-M)

Whole gut irrigation
neomycin 1 g/litre and metronidazole 0.5 g/l in the
irrigation fluid from 6th litre onwards.

The second group received 2 grams of oral metronidazole after the whole gut irrigation but 12 hours before operation, followed the next day by tobramycin 1.5 mg/kg intravenously with the induction of anaesthesia. If the operation lasted for more than three hours, tobramycin was given at eight and sixteen hours postoperatively.

The third group received only neomycin (1 g/l) with metronidazole (0.5 g/l) in the irrigation fluid from the 6th litre onwards. All patients were irrigated with at least 10 litres, so every patient received at least 2.5 grams metronidazole and 5 grams of neomycin.

Exclusion after admission to trial

The number of patients entering the trial was 239. A total of 27 patients were excluded, 10 because no colon surgery was performed. Six patients were given other antibiotics 48 hours prior to surgery. The whole gut irrigation procedure had to be stopped in eight patients because of vomiting and in three patients because of collapse (table 2).

Table 2: Patient selection and reason for exclusion

	No. of patients
Entering the study	239
Excluded	27
Reasons for exclusion:	
No colon surgery performed	10
Other antibiotic used	6
WGI stopped because of:	
a. vomiting	8
b. collapse	3
Fulfilling the criteria	212

Observations

The wound was examined on the third and seventh days and on the day of discharge, by a resident unaware which prophylactic regimen had been followed. The last wound inspection took place at the first outpatient clinic visit, mostly four to six weeks after discharge. In the presence of wound infection aerobic and anaerobic cultures were taken. Blood cultures were taken when there were clinical grounds for suspecting septicaemia.

Colonic bacterial counts at operation

The bacterial flora in the groups were compared in 50 patients by taking swabs of the colon lumen at the proximal resection site during operation just before the performance of the anastomosis. *E. coli* and *B. fragilis* were counted and expressed as log₁₀ of the colon counts per ml.

Bacteriological methods

Swabs of colon contents and cultures from infected wounds were placed in Stuart's transport medium in 4 ml bijou bottles and fluid specimens were used to fill up other small screw-capped vials. All samples were taken without delay to the laboratory where they were cultured on the following media: sheep blood agar, Sabouraud agar and MacConkey agar plates (incubated in air), lysed sheep blood agar with Butzler's campylobacter supplement (incubated in a mixture containing 5% O₂, 10% CO₂ and 85% N₂), and supplemented anaerobic sheep blood agar containing 50 mg/l kanamycin, supplemented anaerobic horse blood agar (with nalidixic acid and Tween 80). All anaerobic cultures were incubated at 37°C in an anaerobic cabinet (Forma Scientific, USA) in an atmosphere of 85% N₂, 10% CO₂ and 5% H₂.

Definitions

Severe wound (S) infection: Wound infection was defined as severe in the presence of pus in the incision, often followed by further opening and drainage of the wound. Wounds opened on clinical grounds and containing pus were also allocated to this group.

Moderate wound (M) infection: Wound infection was regarded as moderate in the presence of erythema, painful induration or secretion with or without a positive culture. In this case hardly any surgical intervention was necessary to promote wound healing and no prolongation of hospitalisation or rehospitalisation was required.

Septicaemia was considered to be present only if micro organisms could be cultured from the blood.

In a *high anterior resection* the entire operation was conducted above the level of the pelvic peritoneal floor, the rectum itself was not mobilised, and the final anastomosis was between colon and a stump of upper rectum possessing a surrounding cuff of peritoneum.

In a *low anterior resection* the pelvic peritoneum was opened, the lateral rectal ligaments were divided and the rectum was lifted out of its sacral bed. The distal line of resection traversed the extraperitoneal rectum and the final anastomosis was between the sigmoid or descending colon and a low rectal stump without a peritoneal coat.

Operative procedure

The patients were operated on either by residents supervised by attending surgeons or by one of the senior surgeons themselves. All anastomoses were performed in two layers, with an inner continuous chromic catgut layer and an outer layer of knotted inverting Vicryl[®], except for the anterior resections where either a one layer continuous running suture of

chromic catgut or the Stapler apparatus was used. The anastomosis was covered with an omental flap whenever possible.

In low anterior resections two suction drains below the peritoneal reflections were used and brought out through separate stab wounds. In low anterior resections at least a catheter caecostomy was placed unless the surgeon felt that a diverting colostomy was necessary. The abdominal wound was closed in layers using knotted Vicryl^R or running monofilament Vicryl^R (PDS) for the fascia; the subcutis was not drained as a rule and was closed if necessary with knotted Vicryl^R. The skin was closed either by intracutaneous running monofilamentous Vicryl^R (PDS) or by knotted nylon. After abdomino-perineal resection of the rectum the proctectomy space was closed as a primary procedure over a sump drain, either placing omentum in the space or restoring the walls with peritoneum without creating an empty space.

All leftsided anastomoses were investigated on the 10th postoperative day with a gastrographin enema. Anastomotic leakages were divided into clinical, radiographical and radiographical plus clinical. The leakage was radiographical and clinical when symptoms of leakage occurred after the X-ray.

Statistics

Results were analysed using the X^2 test and the Student's t-test for small numbers, with the Rang test for comparing the duration of hospital stay.

Results

Patient population

The mean age, sex, preoperative diagnosis and the type of surgery performed in the several groups were comparable and showed no statistical differences (tables 3,4,5).

Table 3: Age; Sex distribution.

	Group 1	Group 2	Group 3	Total
Age <30:	2	1	2	5
31-40:	3	2	3	8
41-50:	6	5	9	20
51-60:	13	19	16	48
>60:	48	43	40	131
Total no. pat.	72	70	70	212
Male:	34	34	31	99
Mean hospital stay (days)				
a. uncomplicated	22.5	22.3	22.7	
b. complicated	46.7	43.8	24.8	

Table 4: Comparison of the diagnosis.

Diagnosis	Gp1 (O)	Gp2 (T-M)	Gp3 (N-M)	Total
Carcinoma of caecum/asc. colon	13	16	10	39
Carcinoma of transverse colon	5	5	6	16
Carcinoma of desc. colon	5	3	4	12
Carcinoma of sigmoid	15	10	12	37
Carcinoma of rectum	19	18	18	55
Sigmoid diverticulosis	10	13	13	36
Miscellaneous	5	5	7	17
Total number of patients	72	70	70	212

Table 5: Comparison of the operations.

Operations	Gp1 (O)	Gp2 (T-M)	Gp3 (N-M)	Total
Right hemicolectomy	13	16	10	39
Transv. colon resection	5	5	6	16
Left hemicolectomy	5	3	4	12
Sigmoid resection	12	8	7	27
Anterior resection	25	23	26	74
Abdomino-perineal resection	7	10	10	27
Miscellaneous	5	5	7	17
Total	72	70	70	212

Although more than 90% of the patients were older than 50 years, only in 5% (11 patients) did the whole gut irrigation procedure have to be stopped.

The procedure was well tolerated and the degree of emptiness of the colon was excellent to good in more than 90% of the patients. Postoperative wound infections after the various operations are listed in tables 6, 7 and 8 together with the organisms cultured.

Bacteriological results

The results of the intraoperative colonic bacterial counts are shown in figure 1 (page 56). In group 3 (where neomycin and metronidazole had been used in the irrigation fluid), a highly significant reduction of *E. coli* ($p < 0.001$) and *B. fragilis* ($p < 0.002$) occurred compared with group 1. Due to the small numbers of cultures in group 2 statistical comparison with group 3 is not adequately possible.

Wound infections

Wound infections in the group receiving oxytetracycline (table 6) were mostly caused by *Escherichia coli* and *Bacteroides fragilis*. Hardly any *Staphylococcus aureus* were cultured. In the second group receiving tobramycin and metronidazole (table 7) aerobic organisms (*E. coli*) were still often cultured from many wound infections, but the anaerobic bacteria (*B. fragilis*) were seldom present and could be found only in 3 cases. In the third group (table 8) anaerobic infections were abolished, and only in two patients were abdominal infections present, caused by aerobic bacteria. In all three groups, the perineal wound infection rate was high and in the third group (exogenous) *Staph. aureus* was often found.

A dramatic reduction of abdominal wound infection in group 3 (3.3%) occurred (table 9) when compared with group 1 ($p<0.002$) and also when compared with group 2 ($p<0.03$). No significant differences in perineal wound infection could be found, but because of the small numbers undergoing abdomino-perineal resections no conclusions could be drawn.

Table 6: Wound infections in group 1 related to the type of operation and organisms cultured.

Type of resection	Type of infection	Organism cultured	
		Aerobe	Anaerobe
1. sigmoid	abd. (S)	<i>E. coli</i> ; <i>Strept. faec.</i>	----
2. sigmoid	abd. (M)	<i>E. coli</i> ; <i>Strept. faec.</i> <i>P. mirabilis</i>	----
3. sigmoid	abd. (M)	<i>Strept. faec.</i>	<i>B. frag.</i>
4. sigmoid	abd. (M)	<i>E. coli</i>	----
5. abd.-perineal	abd.+perineal (S)	----	<i>B. frag.</i>
6. sigmoid	abd. (S)	<i>E. coli</i>	<i>B. frag.</i>
7. hemicolectomy R.	abd. (S)	<i>E. coli</i> ; <i>P. mirabilis</i>	<i>B. frag.</i>
8. hemicolectomy R.	abd. (M)	----	<i>B. frag.</i>
9. anterior	abd. (M)	----	----
10. hemicolectomy R.	abd. (S)	<i>Strept. sanguis</i>	<i>B. frag.</i>
11. abd.-perineal	perineal (S)	<i>P. mirabilis</i>	<i>B. frag.</i>
12. hemicolectomy L.	abd. (M)	----	----
13. anterior	abd. (S)	<i>E. coli</i> ; <i>Strep. faec.</i>	----
14. hemicolectomy L.	abd. (S)	<i>E. coli</i> ; <i>P. mirabilis</i>	----
15. anterior	abd. (S)	<i>E. coli</i>	<i>B. frag.</i>
16. abd.-perineal	perineal (S).	<i>E. coli</i>	<i>B. frag.</i>

S=severe, M=moderate infections

Table 7: Wound infections in group 2 related to the type of operation and organisms cultured.

Type of resection	Type of infection	Organism cultured	
		Aerobe	Anaerobe
1. partial colectomy	abd. (M).	----	----
2. colotomy	abd. (M).	----	----
3. hemicolectomy R.	abd. (M).	----	----
4. abd.-perineal	perineal (S).	<i>E. coli</i> ; <i>P. mirabilis</i>	<i>B. frag.</i>
5. abd.-perineal	perineal (S).	<i>P. mirab</i> ; <i>Strept.</i>	<i>B. frag.</i>
6. hemicolectomy R.	abd. (M).	<i>E. coli</i> ; <i>P. mirabilis</i>	----
7. abd.-perineal	abd.+ perineal (S).	<i>E. coli</i>	<i>B. frag.</i>
8. sigmoid	abd. (S)	<i>E. coli</i> ; <i>P. mirabilis</i> <i>Staph. aureus.</i>	----
9. sigmoid	abd. (M)	----	----
10. abd.-perineal	perineal (S)	<i>Staph. aureus.</i>	----
11. anterior	abd. (M)	<i>Strept. pyogenes.</i>	----
12. abd.-perineal	perineal (M)	<i>E. coli</i> ; <i>Haem. strept.</i>	----
13. anterior	abd. (M)	<i>E. coli</i> ; <i>Strept. agalact</i>	----
14. sigmoid	abd. (M)	<i>Staph. aureus</i>	----
15. transv.colon	abd. (M)	<i>E. coli.</i>	----
16. anterior	abd. (M)	----	----
17. hemicolectomy R.	abd. (M)	<i>Staph. aureus</i>	----

Table 8: Wound infections in group 3 related to the type of operation and organisms cultured.

Type of resection	Type of infection	Organism cultured	
		Aerobe	Anaerobe
1. abd.-perineal	perineal (M)	<i>Staph. aureus</i> ; <i>P. mirab.</i>	----
2. abd.-perineal	perineal+abd. (S)	<i>Staph. aureus</i> ; <i>E. coli</i> ; <i>P. mirab.</i>	----
3. abd.-perineal	perineal (M)	----	----
4. sigmoid	abd. (S)	<i>Staph. aureus</i> <i>Strept. faec.</i>	----

Table 9: Postoperative septic complications in the different groups.

Results	Group 1 (O)	Group 2 (T-M)	Group 3 (N-M)
Number of patients (N=212)	72	70	70
Abdominal wound infection (%) [W]	14/72 (19.4)	13/70(18.6)	2/70(2.9)
Perineal wound infection (%)	3/7 (42.9)	5/10 (50)	3/10 (30)
Overall anastomotic leakage (%) [L]	14/65 (21.5)	10/60 (16.7)	2/60 (3.3)
Septicaemia (%) [S]	8/72 (11.1)	6/70 (8.6)	0/70 (0)
W1 : W2 p>0.05	L1 : L2 p>0.05	S1 : S2 p>0.05	
W2 : W3 p<0.003	L2 : L3 p<0.02	S2 : S3 p<0.02	
W3 : W1 p<0.002	L3 : L1 p<0.002	S3 : S1 p<0.004	

Anastomotic leakage

The overall (clinical and radiological) anastomotic leakage rate in patients in whom a colo-colonic anastomosis was made (thereby excluding abdomino-perineal resections) was 14% in group 1, 10% in group 2 and 3.3% in group 3. The leakage rate in group 3 was much lower in comparison with group 1 ($p<0.002$) and was also significantly reduced when compared with group 2 ($p<0.02$).

Septicaemia

Septicaemia occurred in 8 patients in group 1 from whom aerobic organisms (mostly *E. coli*) as well as anaerobes were cultured. In the second group, septicaemia was only caused by aerobic bacteria and no anaerobes were cultured from the bloodstream. No septicaemia at all was observed in the third group. Statistically significant differences between groups 1 and 2 were not present.

Seriousness of wound infection and anastomotic leakage

Statistical significance hardly says anything about the gravity of a complication. In order to study their seriousness, wound infections and anastomotic leakages were subdivided. In group 1 seven patients had only wound infections, one patient had a wound infection and anastomotic leakage and two patients had a wound infection and septicaemia. Furthermore,

six patients had wound infections combined with anastomotic leakage and septicaemia (table 10). Most wound infections were severe, affecting the whole depth of the skin and, as shown in table 10, were accompanied by several other serious complications.

In the third group only four patients developed wound infections and they had no other accompanying complications.

Subdividing the anastomotic leakages (table 11) shows clearly that in groups 1 (7 patients) and 2 (4 patients) severe leakage occurred, whereas only two patients in group 3 had radiologically demonstrable leakages without clinical consequences.

Table 10: Wound infection and other complications.

	Gp 1	Gp 2	Gp 3
Wound infection alone	7	9	4
Wound infection together with:			
- anastomotic leakage	1	3	0
- septicaemia	2	2	0
- anastomotic leakage and septicaemia	6	3	0
Total number of patients:	16	17	4

Table 11: Anastomotic leakage subdivided.

	Gp 1	Gp 2	Gp 3
Anastomotic leakages (total number of patients)	14	10	2
Radiological leakage	7	6	2
Clinical leakage	3	3	0
Clinical and radiological leakage	4	1	0

Mortality

Three patients in the group receiving oxytetracycline died of septic complications (5 %), and two patients in the group receiving metronidazole and tobramycin died. All these patients had disruption of the anastomosis with intra-abdominal abscess formation. *Bacteroides fragilis* and *E. coli* were cultured from the bloodstream most often in the first group; in the second group all cases of septicaemia were caused by aerobic organisms. No death due to septic complications was noticed in the third group.

Postoperative hospital stay

The mean hospital stay (table 3) in the uncomplicated cases was comparable in the different groups. However, if complications occurred the hospital stay was doubled in the first two groups but was hardly influenced at all in the third one. This is of clinical importance although the hospital stay in group 3 just failed to reach a significant difference for $p < 0.05$ compared with the other groups.

Anterior resections

The percentage of patients with anterior resections who develop anastomotic leakage is known to be high and is associated with a high morbidity and a particularly high mortality [33]. In the present study all anterior resection anastomoses were investigated by a gastrographin enema on the 10th day. In the third group only two patients (2/26 = 7.7%) with low anterior resections had radiological signs of leakage in the absence of any clinical signs, whereas in groups 1 and 2 the leakage rates were 36% (9/25) and 26% (6/23) (table 12).

Table 12: Anastomotic leakage in patients with anterior resections (N=74)

Group	High	Low	N	Leakage	%leaks
1 (O)	19	6	25	9	36
2 (T-M)	12	11	23	6	26
3 (N-M)	14	12	26	2	7.7

1 : 2 $p > 0.05$

2 : 3 $p = 0.09$

3 : 1 $p < 0.02$

Prospective study group 1984-87

After finishing this trial we decided to use the regimen of group 3 (neomycin and metronidazole in the irrigation fluid) for all patients who were admitted for elective colorectal surgery in this hospital and who matched the criteria of the trial. All patients admitted from January 1984 to December 1987 were studied prospectively. The patients operated on (n=215) had all been admitted with carcinoma of the colon except for 31 patients who had diverticulosis and 14 patients operated for benign lesions (adenoma; fistula). The data collected from these patients once more confirmed the results of group 3 in the trial (tables 13 and 14).

Table 13: Diagnosis of patients admitted for elective colorectal surgery from 1984-87, undergoing whole gut irrigation and fulfilling the criteria for the trial.

Diagnosis	number of patients
carcinoma of caecum/ascending colon	47
carcinoma of transverse/descending colon	8
diverticulosis	31
carcinoma of sigmoid	37
carcinoma of rectum	78
miscellaneous	14
Total	215

Table 14: Elective colorectal operations from 1984-87 after whole gut irrigation with neomycin and metronidazole in the irrigation fluid and fulfilling criteria for the trial.

Type of resection	Pat.	Infection		Leakage	
		abd.	perin.	radiol.	clin.
hemicolectomy R. transverse colon and hemicolectomy L.	51	2			
sigmoid	16			1	
anterior:-high	35	1			1
-low	26	1			
abd.-perineal	62	2		3	
	25		8		
	215	6(2.8%)	8(32%)	4(2.1%)	1(0.5%)

Three radiographical leakages occurred and two patients had clinical evidence of leakage. The first patient had undergone left hemicolectomy in the past and was admitted again with a rectal carcinoma. After resection of the tumour the continuity of the bowel could only be restored by the interposition of an ileal loop. A clinical leakage occurred without wound infection or septicaemia. The second patient with symptoms of clinical leakage had been operated on for a "simple" excision of a polyp via a sigmoidotomy.

Eight moderate perineal wound infections (30%) were noticed, twice caused by *Staph. aureus* and twice by *E. coli*. Although no significant prolongation of the hospital stay occurred, it still has to be noted that the number of perineal infections was high (8 out of 25 rectum amputations). It is however comparable with the results of other workers [19, 34] who used the same definitions of wound infection and kept a prospective surveillance for its occurrence. *Bacteroides fragilis* was totally abolished and was never cultured from infected abdominal or perineal wounds (table 15).

The intraluminal stapler (ILS) was used in 51 of the 62 low and in 4 of the 26 high anterior resections. A diverting colostomy was performed in 15 of the low and in 4 of the high anterior resections. A tube caecotomy had been used in 33 of the low and in 6 of the high anterior resections; 14 low and 16 high anterior anastomosis were neither "protected" by a colostomy nor a caecotomy.

Table 15: Bacteriological isolates from abdominal and perineal wound infections in patients operated on from 1984-87.

	bacteria	
	abd. (n=6)	perineal (n=8)
<i>E. coli</i>		2
<i>B. fragilis</i>		
<i>Pr. mirabilis</i>		1
<i>Streptococcus sp.</i>		4
<i>Staph. aureus</i>	3	2
<i>Staph. epidermidis</i>	1	3
<i>Pseudomonas sp.</i>		4

Table 16: Bacteriological isolates from the abdominal and perineal wound infections of the trial.

Organisms isolated	Gp 1 (n=16)	Gp 2 (n=17)	Gp 3 (n=4)
<i>Escherichia coli</i>	9	7	1
<i>Bacteroides fragilis</i>	9	3	-
<i>Proteus mirabilis</i>	4	3	2
<i>Streptococcus sp.</i>	5	3	1
<i>Staphylococcus aureus</i>	-	4	3

Discussion

Whole gut irrigation is now widely used as a preoperative bowel preparation. Compared with the traditional mechanical enema preparation, whole gut irrigation is rapid, well tolerated and yields the best degree of emptiness of the colon in comparison with any available method up to now, thus preventing intraoperative spillage of faeces and infection of the anastomosis. Whole gut irrigation by itself does not give any protection against postoperative septic complications. Wound infection rates of 30 % [9] to 50 % [35] have been reported when whole gut irrigation has been used without antibiotics. After whole gut irrigation, fluid retention occurs. For that reason it is contraindicated in patients with severe cardiac decompensation, although overloading of the circulatory system cannot really be demonstrated.

With mannitol-containing irrigation fluid, the absorption of fluid is less [36] and the lavage procedure is shorter and better tolerated. Colonic explosions due to the formation of methane gas by anaerobic bacteria have been reported as a rare complication after the use of mannitol [37-39]. However, this fatal complication can be avoided by the use of oral antibiotics. Overgrowth of aerobic bacteria after preoperative bowel preparation is increasingly being reported [40-41]. For this reason the use of mannitol should not be recommended.

Whole gut irrigation with polyethylene glycol (Golytely) until a clear effluent is achieved, is a good alternative to mannitol or the balanced electrolyte solution. Its benefit is the lesser fluid absorption. Drinking of only 4 litres of polyethylene glycol however [44-53] has been reported to be inferior to the WGI procedure in obtaining a clean bowel [54].

In this study all patients received whole gut irrigation without mannitol. Although 90% of the patients were older than 50 years and several were more than 90 years old, the procedure was well tolerated and only in 5% (11 patients) did the whole gut irrigation have to be stopped because of vomiting and collapse. The cleansing of the colon in all three groups was comparable and was evaluated as excellent or good in more than 90% of the patients.

The dose of antibiotics was chosen arbitrarily and no special attention was paid to the level achieved in the serum or in the colon. The group receiving tetracycline was included in order to test the former standard policy. The two other antimicrobial groups contained agents which were effective against both aerobic and anaerobic flora. All the antimicrobial agents (except tobramycin) were prepared in the hospital pharmacy. Oxytetracycline appeared to be ineffective as a prophylaxis in this study, although it has been claimed in the past to be effective against aerobic and anaerobic bacteria. In the present study, its use failed to bring about adequate prevention of wound infection, septicæmia or anastomotic leakage.

Three patients died because of disruption of the anastomosis. A major part of the colonic flora appeared to be resistant to oxytetracycline. The rate of wound infections in the first two patient groups was high. In the second group 18.6% (13/70) of the patients developed abdominal wound infections, a figure higher than that reported after the use of metronidazole alone but comparable to the rates reported by workers employing a similar definition of wound infection [55-57]. Septic complications in this group were mostly caused by aerobic bacteria. The use of tobramycin in group 2 did not show any benefit as prophylaxis against the aerobic bacteria.

Two instances were found of septicaemia with aerobic micro-organisms and with disrupted anastomoses, resulting in the death of both patients. The incapacity of tobramycin to control aerobic infections has also been reported by others [58,59]. In the third group, *Bacteroides fragilis* was eradicated, no septic complications occurred and there were no deaths due to septic complications. This is comparable to the results of other workers [35,60-63] using oral neomycin and metronidazole. The differences in septic complications between the second and third groups were noted and were surprising. In both groups metronidazole was used orally, although in a different way, and only the use of tobramycin or neomycin was different. The first explanation of this difference could be the profound effect of neomycin and metronidazole in reducing the aerobic and anaerobic flora [19,64].

Comparison of the colonic cultures at operation with the microorganisms cultured from the wound infections [fig. 1 and table 16] shows a clear association between the species of bacteria isolated from the colon at operation and the species subsequently isolated from the postoperative wound infections and septicaemia. The lower the bacterial counts in the colon, the lower the septic complications proved to be. This might provide good evidence that these infections are caused by bacteria spilled into the wound from the bowel during the operation.

Fig. 1: *E. coli* and *B. fragilis* in the colon at operation. Cultures showing no growth are below the sensitivity of the bacteriological methods and are indicated under the hatched line ($< \log 2$).

It was never the policy to attempt to sterilise the colon, although sterile colonic cultures were found during operation in 25% (2/8) of patients in group 2 and in 45% (10/23) of those in group 3. Intramucosal bacterial culture or counting was not performed.

The influence of neomycin and metronidazole on the colonic microflora of volunteers receiving a normal diet has been investigated by Arabi et al. [65] who found that metronidazole alone had no influence on anaerobic faecal bacteria. Neomycin, on the other hand, was only effective against sensitive aerobes. However, the combination of neomycin and metronidazole profoundly reduced both the aerobic and the anaerobic bacteria [65].

Another study [35] comparing oral neomycin and metronidazole in a group of patients with conventional bowel preparation to those in a group receiving these antimicrobial agents in the irrigation fluid (as in our group 3), showed that the capacity for reducing the aerobic and the anaerobic flora was significantly higher in the irrigated group.

The superior results in group 3 compared with group 2 could not be explained by the probably higher serum levels of metronidazole due to the fact that more of this drug was given in the third group. It is debatable, however, whether higher serum levels are desirable and as shown in this study only little difference in anaerobic septic complications between groups 2 and 3 was found.

The results of this trial show that neomycin and metronidazole in the whole gut irrigation fluid are highly effective in preventing post-operative septic complications in elective colorectal surgery. From a practical point of view it appears to be very easy to administer neomycin and metronidazole, and there is no need to worry about the correct timing of the administration in order to achieve a high serum level at the time of operation. The cost of this method of prophylaxis was not more than \$ 6 per patient.

In particular the reduced length of hospital stay in patients with complications in group 3 compared with that in the two other groups reflected once more the adequacy of this prophylaxis.

Resistance development with this oral regimen has not been noticed, either in the trial or in the group studied prospectively in 1984-87. Neomycin is only used for whole gut irrigation. Metronidazole and neomycin were administered in a high dose for only a few hours, and were not used afterwards in the same patient. No systemic toxicity with metronidazole (which is maximally absorbed) was noted, and there was no local toxicity of neomycin, which is hardly absorbed at all.

Pseudomembranous colitis, a serious complication after oral or parenteral use of antimicrobials, was not recorded. Reports on this complication seem to differ according to the patient populations studied, and percentages from 0-10% have been mentioned [1,9].

Overgrowth of certain microorganisms after the oral use of antibiotics such as those in group 3 has been described but could not be detected in the present study, probably because of the very short duration and high dosage of the prophylaxis [40].

Staphylococcus aureus was cultured in the two groups with oral antimicrobials but was never cultured in the colon during operation.

All left-sided anastomoses in this study were investigated with gastrographic enemata. One might argue about the use of this method, but we had two reasons for performing it.

Firstly, comparison with the results by other surgeons [33] using the same method was possible. The second, and more important, reason was that a colostomy after a left-sided anastomosis was not required as a standard procedure. If an anterior anastomosis was made and found to be reliable (i.e. waterproof) or intact proximal and distal rings of the Stapler

apparatus were present, generally a colostomy was not performed except in extremely low resections. A catheter caecotomy was often carried out in such patients. Later in this study (Group 1984-1987), this caecotomy was omitted in 14 patients, relying on uneventful healing of the anastomosis in the presence of a totally empty bowel, due to adequate antibiotic prophylaxis and the use of normal surgical techniques.

Postoperatively, all patients received a liquid diet or Nutrison^R, until the performance of the X-ray.

In the absence of leakage, normal oral feeding was initiated and the caecotomy catheter removed. If a leakage was present, the residue-free diet was continued for another 10 days. With this policy, morbidity due to the presence and subsequent closure of a colostomy could be prevented in many patients.

Conclusions

- As a preoperative bowel preparation, whole gut irrigation is well tolerated, rapid, safe and economical and it has an optimal bowel cleansing capacity. It can be recommended as the best method currently available for pre-operative preparation in elective colorectal surgery.
- Very short term prophylaxis with neomycin and metronidazole in the irrigation fluid alone appears from this study to be by far the cheapest and does not give rise to systemic or local toxicity.
- Both good reduction in the concentration of the colonic microflora and adequate serum levels of metronidazole during operation were achieved. As a consequence it is highly effective in preventing wound infection and septicaemia. Most important of all, a dramatic reduction in anastomotic leakages is seen.

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Chapter 5

Intraoperative colon irrigation to permit left sided primary resection and anastomosis in the unprepared colon

Introduction

Faecal loading proximal to a colonic anastomosis increases technical difficulties and is a primary cause of anastomotic dehiscence [1]. In addition, contamination of the peritoneum and wound leads to increased sepsis. Preoperative irrigation of the colon has made it possible for the loaded but unobstructed colon to be mechanically prepared to a high standard [2].

However, the method is not applicable in about 20% of the patients in whom a growth may have considerably constricted the lumen of the bowel, and it is also inadequate in up to 20% of the patients without an obstruction, in whom optimal bowel preparation is not possible for several reasons.

Usually when faecal loading is found at operation because of obstruction of the left colon, either only a defunctioning colostomy is performed or the lesion is resected without an anastomosis.

Multiple operations may lead to increased complications and about 30% of the patients may never receive definitive treatment [3,4]. Especially, elderly patients with obstructing carcinoma and advanced local disease or metastases in the liver are particularly debilitated by the prolonged hospital stay and the accompanying stomal problems.

Intraoperative colon irrigation (a method for cleansing the colon at operation) as modified by Dudley in 1980 has been used in order to perform a primary resection and anastomosis in the left colon in patients who are unprepared (emergency surgery) or ill prepared (elective surgery). This method enables us to establish an "elective environment" at "non elective times".

In this chapter the experience and results of this method are reported.

Methods

Definitions

Large bowel obstruction: symptoms of constipation, pain and vomiting; the signs of abdominal distention and abnormal faecal distention of the gut or stenosis as shown by (contrast) radiography; at laparotomy findings of proximal bowel distention and oedema. Patients with simple loading of the proximal colon with faeces not removed by bowel preparation were not included.

Primary resection: removal of the cancer at the first operation, not necessarily with a synchronous anastomosis. *Staged resection:* removal of the cancer at a later operation other than the first (during which decompression, usually by a loop colostomy, had been performed).

Right colon: the colon proximal to the splenic flexure. The transverse colon is included with the right colon for practical purposes, because obstructing carcinoma in this region can be treated by an extended right hemicolectomy.

Left colon: the colon at or distal to the splenic flexure.

Surgical strategy

Definitive surgery for obstructing cancers of large bowel demands the presence of a qualified surgical team. Operations carried out in the middle of the night on mostly old and fragile patients, and with an inexperienced team, should be avoided if possible.

Two thirds of large bowel obstructions are closed-loop in nature because of a competent ileocaecal valve. However, these patients do not often constitute true emergencies in the sense that the patient need not to be rushed to the operating room within an hour or so of presentation. It is wise to take a more deliberate approach except in cases where peritonitis is present or there is a chance of perforation due to severe colonic distention.

Preoperative management

A nasogastric tube is inserted in all patients admitted with large bowel distention. At least a peripheral infusion is given on admission but a central infusion system, through which parenteral feeding and rehydration can take place, is introduced as soon as necessary. Care should be taken not to overfill the circulation. Assessment of the cardiovascular and metabolic state is necessary in order to judge the feasibility of the intraoperative irrigation procedure.

Confirmation of the diagnosis of organic obstruction, either by a gastrographin enema or by endoscopy, should always be done.

Operative technique

The first dose of broad spectrum antibiotic (tobramycin-metronidazole) is given intravenously at the induction of anaesthesia. If a process proximal to the splenic flexure is expected the patient is placed on his back with legs extended. If the lesion has been located distal to the sigmoid or in the rectum, the patient should be placed in an extended lithotomy position. The main advantage of this position is that access to the anus both for the wash-out and for introducing a stapling device or rectal tube is facilitated [5].

The operator stands to the left side of the patient. A midline incision from the xiphoid is carried down to the suprapubic area, skirting to the left side of the umbilicus. At the lower end the anterior rectus sheet is split right down to the peritoneum if adequate exposure is necessary. After the peritoneum has been opened, distended bowel will protrude in case of longstanding ileus. Before further exploration is undertaken, the colon is decompressed and gas is allowed to escape. For this purpose a 21 gauge needle is attached to a sucker and

Fig. 1: Colotomy for insertion of irrigation tube (from Radcliffe et al. [51]).

Fig. 2: Tube ileostomy and irrigation tube in situ (from Radcliffe et al. [51]).

inserted through a taenia in the transverse colon while pressure is applied to both flanks so as to force gas out of the ascending and descending colon. The needle point is kept in the gas bubble or it will soon become choked with faeces. If colonic distention is moderate, suction as alternative can be done after introduction of the Foley catheter necessary for the intraoperative irrigation.

Should the small bowel be distended, it is emptied by retrograde stripping into the stomach [6] and the contents withdrawn by a wide bore nasogastric tube.

Inspection of the abdominal organs is carried out with special attention to detection of liver metastases or other signs of incurability. The presence of these is an additional reason for a one-stage procedure. The lesion (usually an obstructing tumour) is mobilised at the choice of the surgeon. It is essential that the splenic flexure should be mobilised for if this is not done attempts to manipulate faeces past it may tear adhesions and cause splenic bleeding. The intestine is divided distally with the colon drawn laterally, and a slightly greater length of intestine than usual is cleared proximally and isolated between clamps.

A side opening is made in the bowel above the obstruction [fig. 1] and cannulated with a corrugated tube (anaesthetic gas scavenging tubing) which is secured with two strong encircling cotton tapes. Alternatively, the lesion can be resected and removed, minimising the chance of tumour cell spillage, and the irrigation drainage tube securely tied to the proximal cut end of the large bowel [fig. 2].

A long plastic bag is fixed to the distal end of the tube and is led to a bucket beside the operating table. The caecum is then mobilised. In the presence of the appendix a 14 Foley catheter is placed in the caecum through the amputated appendix stump. In the absence of the appendix a purse-string is made into the ileum 5 cm proximal to the ileocaecal valve and the Foley catheter introduced through a small ileotomy.

For colonic irrigation two three-litre bags containing Hartmann solution without antibiotics, (at 37°C) are connected to the Foley catheter. Before irrigation, a non-crushing clamp is placed on the terminal ileum to prevent reflux into the small bowel during lavage. As the colon fills with the irrigant, gentle colonic manipulation, breaking rigid contents with the

Fig. 3: Resection proximal to the irrigation drainage tube (from Radcliffe et al. [51]).

fingers, facilitates the transport of the colonic contents into the distal drainage system. Irrigation is carried out until the effluent is totally clear. At the end of this procedure mesenteric resection is completed if it has not been done already. The colon is divided between the two clamps placed proximal to the drainage tube, at a convenient site for the anastomosis [fig.3].

The Foley catheter can be removed but in most of the patients it is used as a tube caecostomy. Particular care is taken to make the caecostomy safe. The tube is secured in the caecum by a double purse-string seromuscular suture using Vicryl[®] 3x0. If Vicryl[®] 2x0 is employed for this purpose, then its removal after 10 days might appear to be difficult due to the strength of the thicker thread. The caecum is attached to the parietal peritoneum at at least four points by interrupted Vicryl[®] 3x0, picking up the seromuscular edge of the caecostomy.

The distal resection site is cleansed with 1% povidone iodine and the anastomosis made using either one-layer chromic catgut 2-0 or continuous seromuscular chromic catgut and inverting serosal Vicryl[®] 3-0. The anastomosis is tested for leakage by installation of methylene blue or povidone-iodine 1% through the rectal tube and placing a soft clamp proximal to the anastomosis. All anastomoses are covered with omentum when possible. If an anterior resection is planned during laparotomy, the omentum is lengthened in the beginning to judge its viability when the anastomosis is covered. Only if the anastomosis is located retroperitoneally (low anterior resections) are redon drains used as a routine. The operation finishes with introduction of a needle-jejunum catheter. The peritoneum with running Vicryl[®] 1-0; the fascia with interrupted Vicryl[®] 1-0 and the skin with interrupted nylon 4x0.

Postoperative management

The antibiotics, started preoperatively, are given twice more at intervals of 8 hours, unless the surgeon decides intraoperatively (due to spillage of faecal content or the presence of intra-abdominal septic sources) to continue them for a longer period.

Postoperative feeding with Peptison^R or Nutrison^R is commenced through the needle-jejunum catheter 24 hours after operation and is continued until the radiological control of the anastomosis. This is done on the tenth day in all patients with a left sided anastomosis.

The tube caecostomy is kept patent by flushing with 30 ml saline three times daily and is removed after the anastomotic integrity has been controlled radiographically and no leakage found to be present. Normal oral feeding is then started.

Early modifications to the technique

After intraoperative colon irrigation, some fluid remains in the colon. Leakage of this fluid rich in bacteria has to be prevented and therefore its removal is necessary. For this purpose the Foley catheter is connected to a CO₂ meter which is normally available in the operating theatre and used by the gynaecologist for abdominal distention before introducing the laparoscope. The CO₂ is blown (up to 30 mm Hg) through the colon and the majority of the fluid is removed by this gas stream.

A little fluid still remains in the descending colon but is removed by controlled suction through the Foley catheter. Due to the fact that faecal material has already been removed, the opening in the Foley catheter does not become choked. As a result an empty bowel (without the risk of peritoneal soiling) is achieved before the anastomosis is performed.

Patients

From July 1984 to December 1988 the intraoperative colon irrigation was employed in 41 patients for various reasons (table 1). In one patient, who had a diverting colostomy at the descending colon, a conservatively untreatable faecal impaction developed after contrast radiography had been performed. Three weeks later, and after many unsuccessful attempts to empty the colon, an intraoperative colon irrigation was performed and succeeded in relieving the faecal impaction [fig.4].

Not all patients admitted with obstruction were operated on in one stage after ICI. The presence of a surgeon familiar with the method and the suitability of the patients for the procedure were the limitations.

In the beginning, all operations were performed by one surgeon, but later on registrars also started employing this method under supervision. The operations performed are listed in table 2.

There were more females (25) than males (16), with an average age of 66 years. The three patients over the age of 80 were women (table 3).

Table 1: Diagnoses of patients undergoing intraoperative colon irrigation.

1. Obstructing left sided tumour	21
2. Non obstructing left sided tumour	9
3. Previous Hartmann procedure	2
4. Diverticulitis	3
5. Fistulae:	
recto-vaginal (diverticulitis)	1
ileo-sigmoid (Crohn's disease)	1
colon-right hip (divert; carc.)	1
6. Faecal impaction	1
7. Obstructive megacolon	1
8. Obstruction after Ripstein operation	1
<hr/>	
Total number of patients	41

Fig. 4: Patient with conservatively untreatable faecal impaction despite the presence of a diverting colostomy at the descending colon.

Table 2: Operations performed

1. Anterior resection	- high	11
	- low	6
2. Sigmoid resection		16
3. Left hemicolectomy		5
4. Reanastomoses Hartmann		2
5. Intraoperative colon irrigation (alone)		1
Total number of patients		41

Table 3: Age distribution of patients undergoing intraoperative colon irrigation.

Table 4: Type of anastomosis related to the operation.

Operations performed	number of patients	anastomoses		EEA Stapler
		one layer	two layers	
1. Anterior resection - high	11	5	5	1
- low	6			6
2. Sigmoid resection	16	9	6	1
3. Left hemicolectomy	5	3	2	
4. Reanastomoses Hartmann	2	1	1	
5. Intraoperative colon irrigation (alone)	1			
Total	41	18	14	8

Table 5: Stomata related to the type of operation.

Operations performed	number of patients	coeco-stomy	colo-stomy	none
1. Anterior resection - high	11	7	2	3
- low	6	4		2
2. Sigmoid resection	16	13		3
3. Left hemicolectomy	5	3		1
4. Reanastomoses Hartmann	2	2		
5. Intraoperative colon irrigation (alone)	1			
Total	41	29	2	9

Table 6: Complications related to the type of operation.

Operations performed	number of patients	wound infect.		anast. leakage		death	
		min.	maj.	rad.	clin.	cp	ca
1. Anterior resection - high	11	2		1		1	
- low	6	1					
2. Sigmoid resection	16		2		2	2	1
3. Left hemicolectomy	5						
4. Reanastomoses Hartmann	2	1					
5. Intraoperative colon irrigation (alone)	1						
Total	41	4	2	1	2	3	1
			14.6%		7.3%		9.8%

cp = cardiopulmonary

ca = carcinoma

Results

Intraoperative colon irrigation lasted from 20-80 minutes (mean 40 minutes) in which 7.4 litres (4-12 litres) was needed to achieve a clear effluent.

The average hospital stay in patients without a clinical anastomotic leakage was 19 days.

A total of 40 left sided anastomoses were made (table 4) using either a one- or a two- layer technique. All low anterior anastomoses were created with a EEA-stapling device. As an exception, one anastomosis was made with the stapling device after sigmoid resection. The general policy (being a teaching hospital with budgetary limitations) is not to perform a mechanical anastomosis if it can easily be made by hand.

Only two diverting colostomies were necessary in patients undergoing high anterior resections. Two colostomies were performed (second operations) for faecal diversion after clinical anastomotic leakages. In hardly any of the patients was a tube caecostomy made in order to decompress the anastomoses (table 5).

Moderate (minor) wound infections were noted in 4 patients but they healed without surgical intervention. Two severe (major) wound infections were noted.

In one of these patients, after a prolonged use of corticosteroids, a peristomal abscess developed and it had to be drained operatively. After the patient's discharge from the hospital and removal of the tube, a persisting fistula occurred which was treated operatively one year later after a laparotomy.

Fig. 5: Contrast radiography of the patient illustrating the fistula between the sigmoid and the right hip.

stage	with obstruction	without obstruction
A	-	1
B	8	3
C	11	1
D	5	1

Fig. 6: Dukes staging of 30 patients with carcinoma undergoing an intraoperative colon irrigation

The second patient developed a burst abdomen and although no abscess or pus was found at a second operation, this patient was assessed as having a major infection. Anastomotic leakage (table 6) occurred in 3 patients. In one of them (undergoing a high anterior resection) only a radiological leakage occurred without any clinical consequence. The first patient with a clinical leakage was operated on for an obstructing sigmoid carcinoma. At operation peritonitis carcinomatosa was detected and a palliative sigmoid resection performed, together with a tube caecostomy. A clinical leakage occurred and a diverting colostomy had to be made at the hepatic flexure. This patient died from a myocardial infarction 4 days after the second operation. The second patient with a clinical leakage was

a 65 year old female. A fistula between the colon and the right hip caused persisting fever and severe illness [fig.5]. At first an abscess at the right hip was drained operatively and this was followed by total parenteral nutrition in order to bring the fistula to rest. This conservative treatment had to be interrupted due to progressive deterioration of the patient. A laparotomy was performed and the sigmoid (including the fistula) resected, after which a two-layer anastomosis was created. Because of her extreme adiposity, and fearing the complications of a diverting colostomy, the surgeon performed a tube caecostomy. The anastomosis itself caused no technical problems although a clinical leakage subsequently occurred and a colostomy nevertheless had to be performed. She died 130 days after admission and at post-mortem examination an adenocarcinoma from the right hip was found, filling the whole pelvic region, surrounding the rectosigmoid and stenosing the ureters .

In total, four patients died (table 6), three from cardiopulmonary complications. The last one (as described above) died due to complications of widespread carcinoma together with clinical anastomotic leakage.

The Dukes staging of the 30 patients with carcinomata is shown in fig.6. More than half of the patients were in stages C or D.

Discussion

Management of the lesions of the right colon

For the management of obstructing lesions of the large bowel proximal to the splenic flexure (right colon), several preliminary operations can be employed prior to a resection. These are designed solely for the purpose of relieving obstruction.

Colonic decompression for non totally obstructing carcinomata (or in the case of Ogilvie's syndrome) is an option [7-9] especially in very ill patients in whom another decompression operation is not possible. Although in these cases the hazard of overinflation can be prevented by using carbon dioxide instead of non absorbable gases for safe decompression and for avoiding the devastating complications of perforation, an extremely skilled endoscopist ought to be available.

Caecostomy -tube, or (preferably) diverting- can be useful as a minor procedure for an obstructing growth near to the splenic flexure, where the surgeon does not wish to carry out an immediate extended right hemicolectomy and where a transverse colostomy will interfere with subsequent mobilization of the hepatic flexure if needed [10, 11].

Ileotransversostomy with the purpose of relieving obstruction by sidetracking faeces around the point of obstruction should only be used when there is an obstructing carcinoma of the ascending colon that is incurable because of extensive metastatic disease. If it is possible to resect and anastomose the colon as a primary procedure, this is better than ileotransversostomy [12, 13] both for the long term prognoses [14] and for palliation.

Nowadays, there is general agreement that where the obstruction is due to a growth in the right colon, hemicolectomy is the treatment of choice, even in the presence of a loaded ascending and transverse colon, as the anastomosis is fashioned between the ileum and a relatively empty distal colon [15-18].

Management of lesions of the left colon

For lesions at, or distal to, the splenic flexure (left colon), a staged surgical management is the orthodox treatment [19-25] including diverting colostomy at the first operation, resection of the tumour at a second and closing the stoma at a third operation.

The conviction that, whenever possible, the disease should be removed at the first operation is gaining more and more ground. Our policy is in full accordance with the statement of George Crile Jr. [26] discussing perforating lesions of the colon and the use of primary resection whenever possible: *'Most important is the elimination of the source of contamination. If this is done the patient has a better chance of recovery than he does following a small operation, which diverts the faecal stream. It is the disease, not the operation, which causes the death and it is the first responsibility of the surgeon to eradicate the disease'*. A Hartmann procedure or a Paul Mikulicz operation for left sided carcinomata or other colonic diseases offers a possibility of reaching this goal.

The mortality and, especially, the morbidity after the staged management [27] have encouraged surgeons from 1950 onwards to find ways of performing a primary resection and anastomosis.

However, the problem of an unprepared colon at operation and the general rule not to perform an anastomosis in the left colon in these cases still had to be solved.

Primary resection and anastomosis without any bowel preparation has been done in the past with some disastrous results [13]. Although a few good results have been reported in these cases [28], the general opinion of most surgeons is that a left-sided anastomosis should not be performed in an unprepared colon due to the unacceptably high anastomotic leakage rate and accompanying mortality [29]. To solve the problem of the unprepared colon in emergency surgery of the left colon, some authors introduced the "surgical colon preparation" removing the contaminated colon and performing an ileocolonic (rectal) anastomosis [30-37].

This is a well-conceived and satisfactory operation in some instances but has a few potential disadvantages: first, water absorption from the colon is quite drastically reduced and bowel motions tend to be semi-formed or loose and occur with increased frequency. Secondly, if the patient is elderly and there has been some loss of sphincter tone, he or she may have difficulty in controlling the altered faecal load. Thirdly, if an anastomotic leakage occurs [38] the patient is left with an ileostomy for the rest of his life.

In the literature only small series of functional results, mostly in young patients operated on for inflammatory bowel diseases (Crohn's disease, colitis), have been reported but larger series involving older patients treated in this way for cancer are necessary before acceptance of this method is justified. Kamm et al. [39] described the outcome of colectomy for severe idiopathic constipation in 44 women with a mean age of 34 years. Troublesome diarrhoea was seen in almost 30% of these patients.

Our opinion at present is that (sub)total colectomy can only be justified in patients with carcinoma if perforation of the caecum has occurred due to distention proximal to an obstructing tumour.

Indications and contraindications

The indications for using intraoperative colon irrigation before performing a one-stage operation are shown in table 1. It is not suggested that a one-stage operation with intraoperative colon irrigation should be a routine procedure although it is acceptable for most cases of left colonic obstruction provided that selection requirements and technical demands are met.

The general factors which influence any decision not to proceed with colonic irrigation and primary anastomosis include circulatory instability, poor general condition, deficient nutritional status and immunosuppression.

Primary anastomosis has especially to be avoided both in patients who have colonic resection in the presence of advanced peritonitis and interloop abscesses, and when the cut ends of the bowel appear unhealthy.

Two patients in this study with sigmoid resections developed clinical leakage, irrespective of the fact that the anastomoses had been technically easy to perform. Both these patients had peritonitis carcinomatosa. After this experience, and knowing the influence of tumours in the vicinity of an anastomosis on healing [40], performance of a primary anastomosis in these patients is not advised. Anastomoses in patients with liver metastases alone (without peritonitis carcinomatosa) did not show impaired healing.

Duration of the procedure

In this study it took 20-80 minutes (mean 40 minutes) to complete the peroperative lavage and this, added to the time required for the resection and anastomosis, meant that patients were anesthetized for between two and three hours.

It should be noted that in all these patients (except for 3 who were operated on immediately after admission) there was enough time to analyse the cardiopulmonary and nutritional states, and a considered preoperative judgement was almost always possible.

In the patients with a relatively stable circulatory state and in whom no intra-abdominal contraindications were present, the extra time for intraoperative colon irrigation was well spent because in a high percentage a further operation in these mostly elderly patients was avoided. With contemporary anaesthetic techniques, the additional time did not seem to expose the patients to any marked increase in risk.

Colostomy

Construction of a colostomy, even though this is considered a small operation, leads to a reduction in the quality of life in elderly patients [41,42]. In this study, a one-stage operation was possible and safe in all but one patient (in whom intraoperative colon irrigation had been used to get rid of conservatively untreatable faecal impaction).

Only two patients received a diverting colostomy. In most patients a tube caecostomy was used in order to decompress the anastomosis. However, the tube caecostomy could be omitted in patients in whom the anastomosis was above the peritoneal reflection, was created with sound surgical technique and was covered by omentum. In this study, using intraoperative colon irrigation and tube caecostomy a defunctioning colostomy could be avoided with reasonable safety. In difficult anastomoses a diverting colostomy may still be

the method of choice but this was employed only in two patients. As an alternative for a diverting colostomy, a transanal decompression [43], colonic bypass [44] or a transcaecal ileostomy as reported by Simpson and Srivastava [45] should be kept in mind.

Staged resection; mortality and morbidity

In general, obstruction is present in approximately 20% of all patients admitted for colonic carcinoma [46]. The chance of dying from obstruction is said to be between 20 to 30 %, irrespective of the operative policy [47]. In the older patients (>70 years) the chance of dying from obstruction (40%) is even higher [46].

Pollock et al. [48] reported a mortality of 44.7% (17 out of 38) after diverting colostomy had been performed with a view to a later resection of the obstructing lesions. The mortality was 33.3% in patients in whom a Hartmann or Mikulicz procedure had been performed.

Irvin et al. [49], in a retrospective analysis of 66 patients with malignant colon obstruction, noted a mortality rate of 38% within 30 days of operation. A prospective multicentre study of 444 obstructing left colon cancers [47] showed an in-hospital mortality of 24.3%.

Bakker et al. [50] reported a mortality rate of 37.3% (22 out of 59 patients) after the Hartmann procedure. The colorectal continuity in the surviving 37 patients was subsequently restored in only 12 patients leaving 25 patients with a permanent colostomy. Stomal necrosis or retraction occurred in 12 patients and leakage of the rectal stump in 3.

Wara et al. [22] in reporting the outcome of three-stage management of complicated diverticular disease of the sigmoid colon, showed that every step in the staged procedure had its own morbidity rate. Even if the complications were not serious, they debilitated the patient steadily and prolonged the course of the disease. Together with advanced age this may have been the main reason why an unexpectedly high proportion of patients (46 out of 83) did not reach the final stage of the planned treatment.

If the mortality percentage (mean 30%) after staged operation (including resection of the tumour and closing the colostomy) is compared with the mortality percentage (mean 10%) after intraoperative colon irrigation and the one-stage operation, the latter is always lower. This lower mortality percentage can be partially explained by the method of patient selection and therefore some of the results expressed might not be strictly comparable.

It is not the intention to question the feasibility or safety of staged management. On the contrary, the Hartmann procedure is still the method of choice for left sided colonic disease if there are contraindications to performing intraoperative colon irrigation followed by the one-stage operation. It is the excessively dogmatic adherence to the principles of a three-stage approach which is criticized, especially when a safe one-stage operation is possible.

In this study 4 out of 41 patients died (9.8%). This result with intraoperative colon irrigation compares unfavourably with the death rates 3% [51], 4% [52] and 3% [53] presented by some surgeons, but is comparable to the results of certain other workers [48,54], being 17.1% and 8.7% respectively.

Wound infection

The wound infection rate in this study was higher than that of other groups, but comparable with that of Pollock [48], who used the same definitions.

With the hypothesis that antibiotics administered intravenously at the induction of anaesthesia could not optimally combat the inoculation of organisms from the colon into the wound during surgery, a method of acute colonic decontamination was studied and recently introduced in this Institute. This technique is discussed in chapter 10.

New instruments have been developed in order to make the procedure even safer for most surgeons (Chapter 6).

Prognosis

Patients with obstructions have a poorer prognosis in the long term. As shown by the Large Bowel Cancer Project [47] (reporting the data of 713 patients with obstructive colon carcinoma) only 25 percent of patients with obstruction survived after 5 years compared to 45% in the non-obstructed group.

Fielding and Wells and other workers [4, 55,56] suggested that patients treated by primary resection might live longer. After primary and staged resections, they noted a survival of 50% and 25% respectively. Due to the small numbers of patients they studied (50 in all), their suggestion is not conclusive. Moreover, it is not supported by the findings of the Large Bowel Cancer Project, in which no significant difference in 5 year survival was found.

In our study more than half the patients operated on for obstructed carcinoma had advanced disease classified as Dukes C or D and this might reflect the poor outcome in these patients.

Conclusions

- The intraoperative colon irrigation procedure enables us to create an elective environment at "non elective" times in colorectal surgery, permitting a safe one-stage operation in most patients with obstructions of the left colon.

With the aid of the rectal tube, intraoperative colon irrigation can be performed easily in ill or unprepared patients with non obstructing lesions such as tumours, perforations or fistulae.

- If certain criteria are fulfilled, this procedure enables primary resection and anastomosis to be performed with low operative mortality- and complication rates.

It offers the patient:

- no stomal problems
- one-stage procedure with single hospitalisation
- shorter hospital stay with financial savings
- better quality of life (taking into consideration the short 5-year expectation in patients with obstructing carcinoma).

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Chapter 6

Development of new instruments and subsequent modifications to the intraoperative colon irrigation technique

A professional video film (VHS/U-matic) was made in order to demonstrate the technique of intraoperative colon irrigation as described in this chapter.

The use of the irrigation needle and drainage tube for obstructing lesions of the left colon is illustrated, as is the rectal tube for irrigation of the colon in non-obstructing disease. The method of intraoperative colon decontamination is also shown in this film.

Introduction

During the intraoperative colon irrigation procedure as described by Dudley in 1980 [1], leakage either at the site of the Foley catheter or at the site of the tube could not always be prevented. To overcome these problems, new instruments have been developed in order to make the procedure safer and easier to perform.

To minimise the bacterial inoculum during operation, a new method of intraoperative colon decontamination was studied experimentally and it is nowadays used.

New instruments

Irrigation needle

During intraoperative colon irrigation, the occurrence of leakage of intestinal contents at the site of the Foley catheter could not always be prevented. If the purse-string around the Foley catheter was too tight, then stenosis in the catheter occurred, decreasing the influx of irrigation fluid. On the other hand, if the purse-string was not tight enough leakage could occur during irrigation [fig.1].

An irrigation needle was developed, replacing the Foley catheter. The needle, which has an inner diameter of 3 mm [figs. 2 and 3] is introduced without a tomy with the aid of the trocar, preferably through the base of the appendix. In the absence of the appendix the needle can be brought in through the ileum or caput of the caecum after making a purse-string suture.

The needle is fixed on to the base of the appendix by simple tight ligation. To prevent slipping off, the needle is also fixed with this ligature [fig.4]. Because the needle is totally rigid hardly any leakage can occur after tight fixation.

Fig. 1: Probable leakage sites during the performance of the original intraoperative colon irrigation procedure.

Fig. 2: Schematic illustration of the irrigation needle with one or two Luer-lock connections.

Fig. 3: Irrigation needle with two Luer-lock connections with trocar.

Fig. 4: Irrigation needle introduced through the appendix and fixed by simple tight ligation.

Fig. 5: Schematic illustration of the irrigation rigid drainage tube in which the collapsible plastic bag is fixed so that leakage is almost impossible.

fig. 6

Fig. 6: The rigid drainage tube consists of 3 parts in which the collapsable plastic bag can be fixed without adhesive.

Fig. 7: The irrigation drainage tube.

Fig. 8: Fixation of the drainage tube at the proximal resected end and ligation with two cotton tapes. Colonic irrigation is carried out through the irrigation needle.

After introduction of the needle, the trocar is removed and the tap closed to prevent faecal spillage. Either one or two infusion systems can be connected to the needle for irrigation, depending on the presence of one- or three-litre plastic bags of Hartmann solution. If three-litre bags are available, one connection alone will be sufficient to perform a rapid irrigation.

Irrigation drainage tube

The second place where leakage could occur was the connection of the anaesthetic tubing, either at the site of its fixation to the colon or to the plastic bag [fig.1]. A special irrigation drainage tube has been developed, replacing the difficult to handle anaesthetic tubing. A very light totally non-collapsible material (Delrin^R) has been used to construct this tube. The collapsible plastic bag in the irrigation drainage tube is fixed without adhesive, in such a way that leakage at the site of the plastic bag is practically impossible [figs. 5, 6, 7 and 8]. Due to the fact that the tube is rigid and is furnished with grooves, tight ligation is feasible without any chance of the tube slipping off the colon during irrigation. The plastic bag is cut to the desired length and led to a bucket beside the table.

Fig. 9: The newly developed rectal tube.

Fig. 10: The balloon of the tube occludes the anus totally, preventing any spillage during intraoperative colon irrigation for non-obstructing lesions.

Fig. 11: Schema: Via the inbuilt irrigation canal in the tube instillation of cancericidal fluid, testing of the anastomosis or rectal washout is feasible.

Fig. 12: Intraoperative colon irrigation procedure in non-obstructing lesions, with the aid of the rectal tube.

Fig. 13: Transcaecal ileal diversion (from Simpson and Srivastava [2].

The rectal tube

In non-obstructing lesions of the colon in emergency surgery (tumours, perforation, massive colonic bleeding) or with ill-prepared non-obstructing lesions of the colon in elective surgery, the whole colon can be irrigated with the aid of the newly developed rectal tube [fig.9].

The non-sterile tube is introduced before the beginning of the operation and before placing the sterile towels. The balloon of the tube is insufflated with 50 ml air or water. It totally occludes the anus, preventing any perianal spillage of faecal contents during irrigation [fig.10]. The inner diameter of the tube (21 mm) facilitates the passage of gross faecal material without any hindrance. The distance between the balloon and the proximal opening of the tube is very short, preventing retention of faecal material. A plastic bag is fixed distally at the site of silicone rings in the tube, thus stopping the bag slipping off.

Instillation of cancericidal fluid (to kill exfoliated cancer cells in the lumen of the colon and to prevent anastomotic recurrence) and testing of the anastomosis with instillation of methylene blue or 1% povidone iodine are made feasible by the inbuilt irrigation canal in the tube [fig.11].

If necessary, the whole rectum can be cleaned using the irrigation canal. For this purpose an infusion system containing 1% povidone iodine is connected to the irrigation canal and a clamp placed distally on the rectal tube. If the rectum is filled with povidone iodine (in case of cleansing during operation faecal masses are broken with the finger by massaging the rectum), the clamp is loosened and faecal material led via the plastic bag to a bucket. This procedure can be repeated until the rectum is totally clean [fig.12].

The rectal tube can be used with the patient either in a supine or in a Lloyd-Davies position. If the patient is in a supine position, after introduction of the rectal tube this is led between the two blades of the urological table and will come out underneath, where it can be easily handled by the circulating nurse. The surgeon will have no hindrance from its presence during the operation.

Late modifications

Acute colon decontamination

A method of intraoperative colon decontamination was studied experimentally and introduced into the hospital.

Irrigation of the colon with 1% povidone iodine (Betadine ^R), was shown to decrease the aerobic and anaerobic bacterial flora including both *E. coli* and *B. fragilis* within 20 minutes (Chapter 9).

This method was easily applicable to the intraoperative colon irrigation procedure. After a clear effluent had been achieved, the colon was irrigated with one litre of 1% povidone iodine saline. This was made by mixing 100 ml of 10% povidone iodine with one litre of physiological saline from which 100 ml had been removed.

Careful surveillance of the patients receiving the acute colonic decontamination was undertaken, with special concern for the effects on the thyroid and on the bacterial counts at the anastomotic site, both before and after the povidone iodine irrigation. The preliminary results in the first group of patients were very promising .

Transcaecal ileal diversion

As shown in the clinical study using the intraoperative colon irrigation, only in two cases was a diverting colostomy used. In these cases the surgeon wanted to protect the anastomoses because of technical problems encountered during the operation.

An ingenious modification to "protect" the anastomosis has been reported by Simpson and Srivastava [2], and this can easily be incorporated in the intraoperative colon irrigation procedure in the following way:

After intraoperative colon irrigation, the tumour is resected and a primary anastomosis performed. If the anastomosis has to be protected, then the irrigation needle is removed. Appendicectomy is performed and a purse-string suture placed around the base of the appendix site. If appendicectomy had been performed previously, then a small incision is made in the caecal wall after placing a purse-string suture around the site of the incision.

A 22 or 24 French gauge Foley type inflatable catheter is negotiated via this lumen (appendix base or caecostomy incision) for a distance of at least 15 cm beyond the ileocaecal junction. This tube has been previously brought in through an incision in the anterior abdominal wall in the right iliac fossa, as with the tube caecostomy.

The patency of the lumen and the competence of the balloon of the catheter being checked beforehand, the balloon is inflated inside the terminal ileum just sufficiently to occlude the lumen of the ileum without causing ischaemia or undue pressure on the ileal wall.

The purse-string suture around the catheter in the caecal wall is then tightened. A second

purse-string suture around the catheter is made and the caecotomy site sutured to the lateral wall of the peritoneum so as to make a leakproof seal between the caecum and anterior wall [fig.13] as described with the tube caecostomy procedure. The tube is kept patent in the same way as the tube caecostomy. The patient is allowed only a liquid diet until removal of the catheter, which is done after confirmation of the integrity of the anastomosis (around the 10th day) by gastrographin enema.

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Part III

Experimental study

Chapter 7

Experiments on the efficacy of antibiotics used in induced intra-abdominal sepsis and their predictive value in colorectal surgery

Introduction

Intra-abdominal infections after colorectal surgery involve a complex microflora of both aerobic and anaerobic bacteria [1] from endogenous colonic microorganisms contaminating the adjacent tissue [2]. Prophylactic administration of antibiotics effective against aerobic and anaerobic bacteria is therefore the rule.

In clinical studies reporting the value of different antibiotic regimens as prophylaxis in colorectal surgery, the use of control groups receiving no antibiotics is accepted as being unethical [3].

Consequently the intergroup differences concerning postoperative septic complications are small and large numbers of patients are required for statistically significant conclusions to be drawn [4].

After such a trial had been finished (see chapter 4), questions arose about the need for an experimental model to test the predictability of these antibiotics.

Experimental infection in animal models offers an alternative for the testing of antimicrobial agents and has the advantage of allowing evaluation under controlled conditions. Furthermore, the study of untreated controls for the understanding of the pathological events that are associated with intra-abdominal contamination and subsequent infection is made feasible.

Several animal models for postoperative sepsis, peritonitis and abscess formation have been used for studying the efficacy of prophylactic antibiotics [1,5-7].

After a survey of the literature and a pilot study, a model of intra-abdominal sepsis closely approximating to the disease in humans (as described by Lahnborg et al. [8]) has been used to evaluate, in a similar way, the efficacy of the antibiotics which were studied in the clinical trial. Three new antibiotics whose use has been suggested in colorectal surgery were also tested.

The aim of this study was to evaluate the predictive value of such an experimental model in selection or rejection of antibiotics, prior to their application in longlasting trials in colorectal surgery.

Materials and methods

Animals

Male SPF-Brown Norway rats weighing 200-300 grams were obtained from the Centralised Experimental Animal Facilities of the State University of Limburg. All animals were specified pathogen free and housed in groups of 4 per cage and fed with beef food (table 1). Water was given ad libitum.

Table 1: Composition of beef food given to the animals in these experiments in order to change their colonic flora.

meat meal (78 % protein; 13 % fat)	56.0%
blood meal (88 % protein)	4.0%
soluble meat extract (88 % protein)	3.0%
animal fat	24.1%
vitamin; minerals, etc.	12.9%

According to this model all rats were given beef food starting 2 weeks before surgery and this was continued until the autopsy. By feeding the animals with meat instead of the rat chow diet, the intestinal flora was similar to that found in humans.

Operative procedure

Each rat was fasted for 24 hours before the surgical procedures and then anesthetized with ether. Clean but not sterile instruments were used.

The rats were shaved and a midline incision was made. A 2 cm segment of ileum 5 cm from the ileocaecal junction was isolated on its vascular pedicle, which was interrupted with a single Vicryl[®] ligature [fig. 1a]. To prevent unnecessary blood loss, the arcade of the ileum was ligated at the proximal and distal resection sites without interfering with the circulation of the anastomosis.

The intestine was then divided at each end of the two segments and intestinal continuity was re-established by knotting one layer everted end-to-end anastomosis of the two ends of the ileum with 6-0 Vicryl[®].

The defect in the mesentery was closed with two or three interrupted 6-0 Vicryl[®] sutures [fig. 1b]. The anastomosis was checked for leakage and patency before the intestine and devascularised segment of the ileum were returned to the abdominal cavity.

The abdominal wall was closed in two layers. The entire operation lasted 10-15 minutes.

Figs. 1a and 1b: Operative technique for creation of intra-abdominal sepsis in this study.

1= ligature around the vessels to the isolated ileal segment.

2= devascularised ileal segment which gradually became necrotic and subsequently served as the source of infection.

3= resected ileal ends to be anastomosed.

4= the continuity is restored by anastomosing the resected ileal ends with 6-0 Vicryl®.

5= mesentery closed to prevent internal herniation of the bowel.

Antibiotics

Six groups, each consisting of 12 animals, were formed non-selectively and each antibiotic was tested in a separate group.

Neomycin (1 gram/litre) and metronidazole (0.5 gram/litre) were given orally in 3 doses at 8 hourly intervals via a nasogastric tube 3 days before operation and continued for one day post operatively. Each dose contained 10 mg neomycin and 5 mg metronidazole.

The other antibiotics were given intravenously before the abdominal incision was made. Eight and sixteen hours postoperatively the same dose was administered subcutaneously. The control group received 3 ml of 0.9% sterile saline administered as mentioned above. The parenteral antibiotics given (per dose) were:

oxytetracycline	1.5 mg.
tobramycin	5 mg.
amoxycillin-clavulanate	100/20 mg.
ticarcillin-clavulanate	150/60 mg.
imipenem	10 mg.

Collection and processing of specimens from intra-abdominal exudate

Specimens taken with dry cotton-tipped sterile swabs and placed in Stuart medium were transported to the laboratory as soon as possible. All specimens were streaked on two blood agar plates and ten selective media. All manipulations of the anaerobic bacteria were carried out in an anaerobic glove box. The aerobic agar plates were incubated for 24 hours and aerobic plates for 48 hours at 37°C. The plates were then examined and different colony types isolated in pure culture and identified according to generally accepted microbiological methods.

Evaluation of the results

The following parameters were used for the evaluation of the efficacy of the antibiotics: mortality rate; time of death; number of abscesses; the presence of adhesions, peritonitis. Autopsy and bacteriological cultures from the abdomen were performed in all animals. The surviving animals (those not dying due to sepsis) were sacrificed 14 days after operation.

Results

Control group [fig. 2]

Within one day 8/12 (67%) rats died and all were dead within three days. All these animals showed typical signs of peritonitis and abscesses when they were autopsied. A polymicrobial flora mainly consisting of *E. coli*; *Proteus mirabilis*; *Streptococcus faecalis*; *Bacteroides fragilis* and *Clostridium perfringens* was recovered from the peritoneal exudate. All rats showed advanced interintestinal adhesions.

Neomycin-metronidazole

No rats in this group died of sepsis. One rat died 7 days after operation and autopsy showed an ileus due to anastomotic stenosis. No aerobic or anaerobic bacteria could be cultured from the abdomen at autopsy 14 days after survival. Hardly any adhesions were present.

Tobramycin-metronidazole

No animals died in the first 6 days but one died on the 7th day and two on the 8th due to sepsis. *E. coli*, *P. mirabilis* and *Strept. faecalis* were recovered from the peritoneal exudate. One rat died on the 13th day and ileus due to invagination of the anastomosis into the caecum was found at autopsy. No abscesses were found in these animals. Moderate adhesion formation was noted in the surviving animals.

Tetracycline

Within one day ten out of the 12 rats (83.3%) died. A mixed microflora with a predominance of *E. coli*, *P. mirabilis* and *B. fragilis* was found. The two surviving rats showed no abscesses at autopsy but gross intra-abdominal adhesion formation was found.

Amoxycillin-clavulanate(Augmentin^R)

No rats died. At autopsy insignificant adhesion formation was found and no abscesses were noted. Cultures of the abdominal cavity revealed no bacteria.

Imipenem

One of the animals died on the 4th day. Examination revealed an anastomotic dehiscence with abscess formation in the immediate vicinity of the anastomosis. Polymicrobial intestinal flora was cultured from this abscess.

Ticarcillin-clavulanate (Timentin®)

One animal died three days after operation. The surviving animals showed no significant adhesion formation and no abscesses were found at autopsy.

Fig. 2: Mortality rates in the rats in which no antibiotic prophylaxis has been given (control) and in those receiving the antibiotics indicated.

Discussion

In order to simulate the development of clinical conditions of intra-abdominal sepsis, a reproducible model [8] has been used. This model permits the study of both microbiological aspects and the healing of anastomoses. One important surgical aspect is the involvement of the anastomosis for the development of intra-abdominal infection. Feeding the animals with meat instead of rat chow diet causes the intestinal flora to resemble that in humans [9].

In pilot studies bacterial counts before and after beef food were performed. If the colonic bacteria in the sigmoid of rats with normal food is compared with that of humans, it is noticed that both are comparable except that the total numbers of aerobic (not the *B. fragilis*) and *Clostridium* species are significantly less present in these rats ($p < 0.05$ - independent t-test). These two species did increase after beef food. As a consequence, both floras (which were already comparable to a great degree before the beef food diet) became then fully comparable after this diet (table 2).

Nevertheless, if this infection model of progressive necrosis of the devascularised ileum was performed in rats without beef food, no mortality occurred. Our hypothesis is that through this unbalanced diet the general resistance of the rat decreases and enhancement of virulence of the colonic bacteria occurs. The mortality in the model used could not be explained by an increase in colonic flora counts alone. It is however useful as an experimental model for simulating intra-abdominal sepsis and approximating to the bacterial flora in the human colon.

Table 2: Colonic flora before and after beef food in 6 rats per group compared with the colonic flora in 6 humans (log 10 microorganisms/ml faeces) and their standard deviations.

Colonic flora	Rats		Humans
	without beef food	with beef food	
total aerobic	7.98 + 0.20	8.32 + 0.46	7.49 + 1.07
<i>E. coli</i>	7.16 + 0.49 [^]	8.01 + 0.37 [^]	7.01 + 1.14
<i>Enterococcus sp</i>	6.98 + 0.37	7.36 + 0.21	5.02 + 2.30
total anaerobic	9.89 + 0.19 * ^{^^}	10.33 + 0.26 ^{^^}	10.67 + 0.39 *
<i>B. fragilis</i>	8.59 + 0.56 &	9.41 + 0.40 &	9.06 + 0.45
<i>Clostridium sp.</i>	4.96 + 0.92 * ^{##}	6.52 + 0.46 #	5.33 + 0.70 **

Symbols indicate a statistical significance of at least $p < 0.05$

The administration of antibiotics in this study simulates the use of antibiotic prophylaxis in human colorectal surgery. In pilot studies, longer use of antibiotic did not result in a significant decrease in the mortality rate. Only reduced adhesion formation was noticed after 10 days administration of antibiotics. That is why the 24 hours antibiotic regimens seemed justified for studying their efficacy against aerobic and anaerobic bacteria in the experimental trial.

Oxytetracycline was used in the past for its alleged broad-spectrum effect against aerobic and anaerobic bacteria. In this experiment it failed to prevent mortality due to sepsis by these organisms. Although none of the animals, cagemates or progenitors had ever been treated with tetracyclines, most of the bacteria cultured appeared to be tetracycline resistant. The ineffectiveness of tetracycline for controlling aerobic and anaerobic septic complications has also been demonstrated in a clinical trial (Chapter 4).

Neomycin/metronidazole administration in this experiment yielded excellent results and none of the animals died of sepsis. This result is fully comparable to the clinical trial results using these agents.

Augmentin^R, Timentin^R and imipenem were shown to be equal and highly effective antibiotics against aerobic and anaerobic bacteria as claimed. Their use as prophylaxis or therapy in colorectal surgery trials seems justified according to these experimental results. Adhesion formation in this study proved to be directly proportional to the efficacy of antibiotics in controlling sepsis. The better the antibiotic worked, the lesser the degree of adhesion formation. This may indicate that bacterial infection plays an important role in the development of adhesions and that effective antibiotics may inhibit the development of adhesions.

Conclusions

- The model of Lahnborg et al. simulating intra-abdominal sepsis is suggested in studies for predicting the effectiveness of any antibiotics to be used in colorectal surgery. Exclusion or selection of antibiotics seems possible using this model.
- The mortality in this experimental model could not be explained by the increased count of colonic bacteria in animals given beef food. The unbalanced diet resulting in a decreased general resistance is probably the most important factor causing the deaths in this septic model.
- Oral administration of neomycin and metronidazole appeared to be very effective in preventing mortality and adhesion formation. The same results were accomplished using parenteral Augmentin^R, Timentin^R or imipenem.
- Antibiotics effective against the major colonic bacteria seemed to decrease the extent of intra-abdominal adhesion formation.

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Chapter 8

The influence of antibiotics on colonic anastomosis in rats: evaluation by bursting pressure measurement

Introduction

From the earliest days of surgery, colonic anastomotic leakage has been the source of considerable morbidity and mortality and various factors are now known to influence the healing of colonic anastomoses [1-3]. Although technical failure may occur, there are a number of factors to be considered including malnutrition [4], protein depletion [5], trauma [6], blood loss [7] and metabolic impairment [8].

Similarly, there are known to be a number of local factors which may lead to disruption of an anastomosis: sepsis [9], faecal loading [10], foreign bodies [11] and ischaemia [12].

In experimental studies [13] it has been demonstrated that disruption of an anastomosis occurs by spillage of bacteria during the performance of the anastomosis and not afterwards. Experiments performed in an attempt to find factors minimizing the postoperative septic complications has provided evidence that antibiotics could favourably modify the healing of an anastomosis [14,15].

The aim of this study was to investigate the influence of antibiotics on the healing of colonic anastomoses in the absence and presence of faeces or infection.

The questions posed were:

1. Does optimal bowel preparation (including antibiotics) result in better healing of colon anastomoses?
2. Could antibiotics prevent the impaired healing of an anastomosis in the presence of infection? This was assumed to be the most important question which had to be answered.
3. What is the influence of antibiotics on perianastomotic adhesion formation?

The phenomenon of adhesion formation after bowel anastomosis in an intra-abdominal septic model was reported in a previous study (Chapter 7).

In the following study we wished to record the presence of adhesions conforming to a specific protocol and to study the influence of antibiotics on them. The bursting pressure of the left colon containing the anastomosis was used as a parameter for healing.

Materials and methods

Animals

Specific pathogen-free Brown Norway rats that weighed approximately 200 to 300 grams were obtained from the Centralised Animal Facilities of the State University of Limburg.

Housing

On delivery the animals were numbered and assigned at random to one of the experimental groups. Rats were housed in stainless wire cages, 4 per cage and acclimatised to the laboratory conditions (temp. 22° C and a 14 hours day/ 10 hours night cycle) for 2 weeks before the beginning of the experiments.

Diet

All rats received beef food beginning 2 weeks before surgery, and were maintained on the same diet throughout the experiments. Rats are known to be relatively resistant to infections and to have an ability to heal their intestine that is well beyond that of humans. Even peritonitis does not carry the same hazards in rats as it does in many humans.

Antibiotics

Amoxycillin-clavulanate (Augmentin^R) containing 100/20 mg per dose was administered intravenously before the laparotomy was made. Eight and sixteen hours postoperatively this dose was repeated subcutaneously. Augmentin^R has proved to be an effective agent against aerobic and anaerobic colonic bacteria in an experimental intra-abdominal septic model (Chapter 7).

Infected anastomoses

In order to study the influence of antibiotics on an anastomosis infected with a specific bacterium, non-monofilamentous (woven) Vicryl^R 5-0 was incubated for 24 hours in a bottle containing a fresh culture of *E. coli*. This infected Vicryl^R was used to perform the anastomoses in groups 4 and 5.

Bowel preparation

At the beginning of this study whole gut irrigation (and, later, intraoperative colon irrigation) was used as a bowel preparation to achieve a clean colon before the creation of the anastomosis in the groups in which this was required.

Whole gut irrigation (WGI)

The rats were fasted for 24 hours, weighed and anaesthetised with ether. When the animal was well anaesthetised, a cannula was inserted via the oesophagus until it reached just into the stomach [16]. The animal was then fixed on to a plate with a built-in heating system maintained at 34⁰ C. The skin of the cervical area was shaved and disinfected with 1% povidone iodine before making a longitudinal incision of about 2 cm along the trachea. The oesophagus was presented by blunt dissection, after which a tourniquet was placed around it to fix the cannula inside. This proved to be necessary to prevent aspiration of the gastric contents during the infusion of the irrigation fluid. After the wound had been covered with gauze soaked in a sterile 0.9% solution of saline, the WGI began. Starting gently with 0.5 ml per minute irrigation was increased gradually to a steady state level of 4 ml per minute. The irrigation fluid was preheated to 34⁰ C to prevent substantial loss of heat by the animal during the procedure. The irrigation fluid contained 6.00 g NaCl, 0.75 g KCl and 2.94 g NaHCO₃ per litre sterile water; the pH was 8.3. At the end of the procedure the tourniquet was removed, the wound was sutured with biodegradable material and the rat was placed in warm surroundings for reconvalescence. All rats were irrigated until the effluent was totally clear.

Intraoperative colon irrigation (ICI)

Because of the problems (see discussion) encountered with whole gut irrigation, a new method of rapid colonic cleansing (Chapter3) was used in groups 4 and 5. Comparison of WGI and ICI concerning their influence on the healing of colonic anastomoses was made in pilot studies in which no difference at all in bursting pressure was noted between the two methods.

Study groups

Five groups containing 24 rats each were formed at random. Group 1 (control group) received no bowel preparation and no antibiotics. In group 2 WGI was used as bowel preparation; no antibiotics were administered. All rats in group 3 underwent WGI and received antibiotics as well. In group 4 intraoperative colon irrigation was performed as bowel preparation but previously infected Vicryl^R was used to perform the anastomosis and no antibiotics were given. In group 5 infected Vicryl^R was used, but antibiotics were given too.

Fig. 1: Principle of the technique of measurement of the bursting pressure in the colon containing the anastomosis.

*Fig. 2 a and b: Apparatus and practical set up for measurements of bursting pressure .
1= apparatus constructed by the Physiological Laboratory of the State University of Leiden.*

2= infusion pump, which infused water at a desired rate.

3= pressure transducer.

4= writer.

Bursting pressure (BP)

The principles of the technique of measurement of bursting pressure are illustrated in fig.1. The technique is used mainly for the measurement of the mechanical strength of anastomoses in the gastrointestinal tract: the anastomosis is tested in a standard length of intestine by inflation with water or air until leakage through the bowel wall starts to occur: the intraluminal pressure is recorded at the moment of rupture.

For measuring the bursting pressure of the colonic anastomosis in this study an apparatus constructed by the Physiological Laboratory of the State University of Leiden [8] was used, with permission of Prof. dr A. Zwaveling.

The 5 cm part of the colon with the anastomosis in the middle was removed, any pellets of faeces were carefully milked out of each segment and the colon was fixed on two hollow needles. One needle was connected to an infusion pump, which infused water at a desired rate. The other needle was connected to a pressure transducer which was, in turn, connected to a writer that reported the pressure graphically. Before the infusion pump was switched on, the whole system was filled with water and calibrated [fig. 2a, b]. With the pump switched on, water was infused at a standard rate. The pressure in the system (and colon) was raised steadily until leakage occurred through the anastomosis or the bowel wall. This was recorded graphically [fig.3].

Bursting pressure was defined as the pressure at which water leaks first appeared or complete rupture of the anastomosis occurred. Measurements were made on the 3rd and 7th days postoperatively and the bursting wall tension was calculated from the product of bursting pressure and the radius of the intestine at the point of rupture, according to the Law of La Place, as reported by Nelsen and Anders [17].

Student's test was used in the statistical analysis of the results of the bursting pressure measurements, as described by Fisher [18].

Fig. 3: Example of graphical illustration of the bursting pressure measurement (gauge= 100 mm Hg). After a slow increase a sharp drop in pressure is noticed as the colon starts leaking.

The operation

All operations were performed immediately after the bowel preparation under ether anaesthesia. Clean but not sterile instruments were used. After shaving, a 4 cm long midline abdominal incision was made. The colon was divided with scissors 3 cm above the

Fig. 4: Performance of the anastomosis in the colon using 5-0 Vicryl[®] interrupted everting sutures.

peritoneal reflection. Care was taken not to disturb the circulation of the anastomosis. The colon was anastomosed with one layer of approximately 8 interrupted everting sutures through all layers using Vicryl[®] 5-0 [fig.4]. The abdomen was closed in one layer with a 3-0 running Mersilene[®] suture.

Autopsy procedure

Half of the rats in each group were killed with an overdose of ether on the 3rd day and the rest of the animals were sacrificed on the 7th day. The abdomen was opened and adhesions present were noted as reported by Mol [19]:

- O = no adhesions, or a thin fibrin coat at the mesenteric side of the anastomosis
- +
- ++ = adhesions involving not more than half the surrounding of the anastomosis [fig. 5]
- +++ = more than a half of the surface of the anastomosis is surrounded by adhesions
- ++++ = massive, often circular adhesions around the anastomosis and in the vicinity involving other organs (walling-off by adjacent healthy tissue) [fig. 6].

Fig. 5

Fig. 6

Fig. 5: Example of grade ++ perianastomotic adhesion formation.

Fig. 6: Example of grade ++++ perianastomotic adhesion formation.

The whole colon was removed; adhesions were cut from their surroundings, attempts being made not to exert any traction on the anastomosis.

Five cm of the left colon with the anastomosis in the middle were excised for measurements. The bursting pressure was measured in an adjacent piece of the remaining colon of equal length, in order to quantify the bursting pressure in the normal colon of that group [figs. 7 a and b].

Fig. 7 a and b: Bursting pressure measurement in the normal colon (a) and in the colon containing the anastomosis (b), which in this case shows leakage near to, but not in, the anastomosis.

Results

The results of bursting pressure measurements of the colonic anastomoses are shown in table 1.

Nine rats in group 4 (infected anastomosis without antibiotics) died within 3 days due to sepsis from the infected Vicryl[®]. The bursting pressure was measured on the 3rd day in 7 animals in this group and on the 7th day in 8 of them.

Bursting pressure measurements on the 3rd day in all groups appeared to be very disappointing. In 8 of the 53 surviving rats the anastomosis broke down during attempts to remove the whole colon carefully. In 12 animals (divided over the several groups) no pressure at all could be recorded. In the remaining 23 animals only very low bursting pressures, varying from 5 to 30 mm Hg, were noted.

On this day the anastomoses appeared to have virtually no strength and therefore these results have not been analysed statistically.

An increase of the bursting pressure on the 7th day was seen in the groups given antibiotics but this was not statistically significantly different from the other groups (independent t-test). No differences at all were registered in bursting pressure of the normal colon in the various groups, as expected (table 1).

Table 1: Bursting pressure in normal colon of the rats and in the colon containing the anastomosis on the 7th day.

Groups	Bursting pressure (mm Hg)		
	no.	normal colon	anastomosis
1 (WGI-/ANT-)	12	321.7 ± 49.4	197.5 ± 10.4
2 (WGI+/ANT-)	12	295.8 ± 50.8	189.2 ± 13.9
3 (ICI+/ANT+)	12	347.5 ± 22.3	205 ± 19.5
4 (ICI+/ANT-/INF+)	8(4†)	291.7 ± 47.5	189.2 ± 12.4
5 (ICI+/ANT+/INF+)	12	294.2 ± 36	197.8 ± 7.9

WGI +/- = with(+) or without(-) whole gut irrigation
 ICI +/- = with(+) or without(-) intraoperative colon irrigation
 ANT +/- = with(+) or without(-) antibiotics
 INF +/- = with(+) or without(-) infected anastomosis

The most striking difference on the 7th day was the gross appearance of the anastomoses. Animals receiving no antibiotics in which an infected anastomosis had been used (group 4) showed the presence of numerous adhesions. The whole anastomosis was mostly sealed off by omentum, small bowel, bladder and seminal vesicles [fig. 6], whilst in rats receiving antibiotics (groups 3 and 4) the anastomoses were surrounded by only a few friable adhesions, or none at all ($p < 0.05$).

Table 2: The degree of perianastomotic adhesion formation (grades 0 to +++) in the different groups 7 days after resection and anastomosis of the left colon.

Groups	no.	grade				
		0	+	++	+++	++++
1 (WGI-/ANT-)	12		3	7	2	
2 (WGI+/ANT-)	12	1	6	4	1	
3 (ICI+/ANT+)	12	9	3			
4 (ICI+/ANT-/INF+)	8(4†)				1	7
5 (ICI+/ANT+/INF+)	12	7	4	1		

0 = no adhesions at all

++++ = massive perianastomotic adhesions

Statistical analysis of the groups (Kruskal-Wallis tests):

1 vs 2 = not significant

1 vs 3 = $p < 0.05$

4 vs 5 = $p < 0.05$

2 vs 4 = $p < 0.05$

Discussion

In the beginning of this study, WGI was used as the method to obtain a colon totally free of faeces, as described by Ruys et al. [16]. The procedure lasted for about 2-3 hours using 200-300 ml fluid. As a method of colonic cleansing (in order to perform an anastomosis in a faeces-free colon) this method appeared to be time-consuming and during our learning phase several rats died after whole gut irrigation.

Confronted with this problem, the intraoperative colon irrigation (ICI) was introduced in animals. This appeared to be a very easy method to use, giving a totally empty colon within 10 minutes. No rats at all died while this method was being used and it is proposed as the method of choice. It can also be used in experiments with other animals in which a totally clean colon is required, for example, for anastomotic studies.

Several parameters for studying anastomotic healing have been suggested including:

- a. clinical leakage [20, 21]
- b. radiological leakage [22]
- c. bursting pressure [23-26]
- d. tensile strength [27, 28]
- e. collagen content [29-35]
- f. microvascular study [36]
- g. (scanning electron) microscopy [37, 38]
- h. oxygen tension [39].

Encouraged by the findings of others [8,40,41,42] it was decided to use the bursting pressure as a parameter of anastomotic healing, but it did not appear to be useful due to the problems with perianastomotic adhesion formation.

Bursting pressure measurements on the third day proved to be useless as a parameter of anastomotic healing. As observed by others [22,43] the strength of an anastomosis during the first three days depends wholly upon the strength of the suture material and the tissue holding it.

In pilot studies more than half of the twelve colonic specimens ruptured through the normal colon rather than through the anastomosis during bursting pressure tests on the 10th postoperative day. Only in a few rats was this the case on the 7th day. Leakage on this day occurred mostly at the anastomosis and not in the normal colon. Therefore this day was chosen for measuring bursting pressure.

It has been suggested by this study that in case of small leakages (or if anastomotic healing is impaired for some reason), any decrease in bursting pressure could then be completely masked by adhesion formation. The more the anastomotic healing is impaired, the more adhesion formation or sealing off by healthy tissue will occur. This hypothesis has been supported by histological studies [44] and it agrees with the findings of other workers [45, 46].

In an early phase of healing as shown by Jiborn [47] lower bursting pressures will be noticed in the cases of increased adhesions and uneventful healing, but if the bursting pressure is measured on a later date (7th day) no differences between impaired and

unimpaired anastomotic healing will be noticed, due to the firmness of organized adhesions. This is in conformity with our findings.

If the colon is pulled out of the abdomen for bursting pressure measurements, even the most careful removal of these adhesions from the anastomosis will damage it. The bursting pressure will not then reveal the real strength caused by the healing of the anastomosis but will be a product of healing and iatrogenic artefacts.

On the other hand, if the adhesions are left attached to the anastomosis as in this study (by cutting the anastomosis carefully from the surrounding tissues without using any traction) then the bursting pressure will not really illustrate the anastomotic healing but will be influenced by the degree of "sealing off".

Bursting pressure differences reported by studies [8,25] comparing anastomotic healing in different groups of animals (eg. tumour-bearing and non tumour-bearing animals from irradiated and non-irradiated rats) are probably not as much influenced by adhesion formation as is the case with fully comparable groups (concerning nutritional, immunological and metabolic states) in which an infection model is used as in this study.

After this study was finished, a silastic cylinder sheet 2 cm in length and 1 cm in diameter was constructed, cut open along one side in the length and fixed loosely around the anastomosis in order to study healing without interference with adhesions.

Surprisingly [48] the sheet was recognized as a foreign body, dramatically incorporated into the surrounding tissue, and, in a few cases, had perforated into the colonic lumen by the 7th day.

The hazardous effect of wrapping anastomoses with sheets (in dogs) have been reported by Ravitch [49,50]. In his study, all anastomoses which had been wrapped with polyethylene sheets broke down. The most reasonable explanation appeared to be that in anastomoses not prepared by antibiotics there was considerable bacterial contamination of the anastomotic area. If the anastomoses were then isolated from the protective defences of the peritoneum by interposed foreign material, infection around the suture line would result, progressing to necrosis, leakage and fatal peritonitis.

Other writers have reported [13] that perforated sheets may prevent this complication. Reports of omentectomy or regimens of promethazine and dexamethasone [51] for inhibition of adhesion formation should be tested for their merits, on condition that they do not disturb anastomotic healing.

Although it is suggested by this study that antibiotics in combination with an optimal bowel preparation did not result in any improvement in anastomotic healing, this conclusion is not correct due to the degree of adhesion formation and its interference with the bursting pressure in impaired anastomotic healing. Safe methods for isolating the anastomosis from adhesions should be investigated before the performance of bursting pressure studies to evaluate anastomotic healing in infection models. Articles on this subject using bursting pressure as "the" parameter of anastomotic healing - and totally ignoring the problems of adhesion formation - should be read with scepticism.

Conclusions

- The bursting pressure is unreliable as a parameter for the study of anastomotic healing in fully comparable groups of rats using an infection model, unless the (infected) anastomosis can be studied in complete and safe isolation from adhesion formation.
- Intraoperative colon irrigation as a procedure for obtaining a totally clean colon for studies in experimental animals appears to be rapid, highly effective, safe, easy to use and thus preferable to whole gut irrigation.
- The only effect of antibiotics in this study was the significant inhibition of adhesion formation, especially in animals where an infected anastomosis was used.

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Chapter 9

Acute intraoperative decontamination of the colon: an experimental study

Introduction

Colorectal operations are associated with a high incidence of septic complications [1]. Most infections are endogenous and caused by spillage of intestinal contents at the time of operation [2].

Attempts to reduce this high incidence of infection should therefore be directed to the reduction of faecal mass by evacuation of the colon, decontamination of the bowel [3], by adequate levels of an appropriate antibiotic at the time of bacterial invasion during operation [4] and a meticulous operative technique [5]. This goal has been achieved in elective colorectal surgery either by preoperative whole gut irrigation with neomycin and metronidazole in the irrigation fluid [6,7] or by whole gut irrigation with preoperative intravenous administration of antibiotics.

In emergency colorectal surgery, e.g. for diverticulitis, obstructing carcinoma, ischaemic bowel disease or trauma, intraoperative irrigation of the colon [8] has been practised. With this procedure the faecal mass in the colon is optimally removed, but it has only a minor effect on the faecal bacteria during operation.

Antimicrobials administered during these emergency operations (mostly obstructing carcinomata) can attain adequate tissue concentration but due to the lack of time no reduction of the flora in the lumen of the colon can be expected.

As a consequence, more infection has been noted after these operations compared with elective colorectal surgery, even when patients with an already contaminated abdomen (trauma, perforation) are excluded.

The aim of this study was to find a method for rapid decontamination of the colon which was easily applicable to the intraoperative colon irrigation procedure.

Polyvinyl pyrrolidone iodine (povidone iodine, PVP-I) has been shown to be a safe and effective broad spectrum bactericidal agent and is known to exert its action rapidly [9-15]. Its use was therefore studied. Secondly, the influence of oxygen on the colon flora was studied. After the intraoperative colon irrigation procedure, some fluid still remains in the colon. In order to prevent spillage during operation most of this fluid is removed by blowing the colon through with CO₂ gas which is normally available in the operating room. Instead of blowing through with CO₂, oxygen was chosen in these experiments because of its toxicity to obligately anaerobic bacteria, which are the major constituent of the colonic flora.

At first, in-vitro studies were performed to test whether a rapid and significant reduction of colonic microorganisms could be achieved with a 1% povidone iodine solution (a 1:10 dilution of the commercial 10 % concentration). Then the antibacterial effect of povidone iodine and oxygen on the flora in the colonic walls of rats was examined in an in-vivo study.

Materials and methods

In-vitro studies

The povidone iodine 10 % stock solution used was: Betadine lot X 870506 (Dagra-Pharma BV, Diemen).

Faeces were obtained from four healthy volunteers and from four rats. The rats were sacrificed for this purpose and faeces was removed from the descending colon and sigmoid.

Data derived from experimental pilot studies showed that after intraoperative colon irrigation a reduction of more than 2 logarithms of the microorganisms in the colon occurred, due to both the removal of the faecal mass and to dilution. In order to obtain a good comparison with the in-vivo study in which the colon irrigation was performed, it was decided to dilute the faeces in the in-vitro study by a factor of 100.

The influence of metronidazole and neomycin on the faecal flora was examined as a comparison in order to evaluate the speed of reduction of the bacterial flora by these antimicrobials in the irrigation fluid used in the colon lavage procedure.

Three faecal suspensions of 0.5 g from each volunteer or rat were diluted in pre-reduced anaerobic sterilised diluent (pH= 7.2) so that 45 ml mixture was obtained.

Thereafter, 5 ml saline was added to the 45 ml mixture in the control group, giving a final dilution of 1:100.

In the PVP-I group, 5 ml of 10% PVP-I was added instead, providing a concentration of 1% PVP-I in the test solution.

In the antimicrobial group, 5 ml of solution containing neomycin (1000 mg/l) and metronidazole (500mg/l) were added instead. The procedure is shown schematically in fig. 1. All suspensions were kept at 37°C under anaerobic conditions during the experiments. After thorough mixing, 0.5 ml aliquots of each suspension were processed for subsequent determination of surviving organisms at 10, 20, 30, 60 minutes and 24 hours after injecting the test solution. Within each set 0.5 ml aliquots of the saline control were taken at the same interval to eliminate any effect that the order of processing might have on the bacterial counts.

Fig. 1: Schematic illustration of the in-vitro experiment.

In-vivo study

Specific pathogen free-BN rats, ranging in weight from 300-400 grams, were obtained from the Centralised Animal Facilities of the State University of Limburg. Preoperatively, all rats had free access to water and irradiated food rat chow (Hope farms, Woerden, The Netherlands). The animals were separated at random into three groups, each of 9 rats. None of the rats had received antibiotics before or during the experiments. All rats underwent an intraoperative colon irrigation with saline.

Technique of the intraoperative colon irrigation

The rats were anaesthetised with ether. After shaving and disinfection of the skin, a distal median laparotomy was made and only the caecum luxated above skin level. A purse-string suture was made in the caecum and a button-probe with a Luerlock connection introduced. Saline warmed up to 37°C was aspirated into a 60 ml syringe. A small vascular clamp was placed on the ileum to prevent reflux of fluid and the colon was irrigated with the saline solution until the effluent was totally clear. In the PVP-I group, this was followed by irrigation of the colon with 60 ml of 1% PVP-I.

The procedure lasted only 10 minutes and 120-180 ml saline was necessary to achieve a clear effluent. In the oxygen group, after the irrigation, the colon was blown through with 100% oxygen at 44 mm H₂O pressure for 5 minutes. After the irrigation, the button-probe was removed and the caecotomy closed with the purse-string suture (Vicryl[®] 2-0). The abdomen was closed in one layer, including skin and peritoneum, with a continuous running suture. Twenty minutes after the irrigation, all rats were sacrificed with an overdose of ether and the abdomen was reopened by cutting the running suture.

A 3 cm segment of the descending colon was excised, immediately placed in an anaerobic transport bottle and processed within 5 minutes in an anaerobic glovebox for aerobic and anaerobic quantitative cultures.

Bacteriological methods

The excised descending colon was homogenised and thoroughly mixed with 9 parts pre-reduced anaerobic saline (PRAS) diluent (saline with 0.05% cysteine HCl) using a turrax mixer. All homogenates in the in-vivo and the in-vitro studies were serially diluted tenfold (10¹⁰) and an aliquot of 0.036 ml of each dilution was spread over the surface of plates using a spiral plater (Spiral System Model B, Lameris, Utrecht, The Netherlands).

The facultative aerobic microflora was quantitated, presumptively identified and grouped by plating the dilution 10¹⁰ on to selective and differential plates. Five per cent sheep blood agar (Oxoid CN 55) was used for the total count of facultative aerobes; Levine agar (Oxoid CM 69) for counting coliforms. All plates were incubated for 48 hours at 37°C under atmospheric conditions before counting.

For the total obligatory anaerobe counts dilutions 10¹⁰ were inoculated on Wensinck medium [16]. A selective medium containing bile salts and aesculin was used for the quantitation of the *Bacteroides fragilis* group [17]. All plates for anaerobes were incubated

in an anaerobic glovebox at 37° C in an atmosphere containing 10% H₂, 10% CO₂ and 80% N₂. The plates were counted after 48 hours and after one week. Colony counts were expressed as the 10 logarithm per gram of colon faeces. Microbiological data were analysed by Student's t-test.

Results

In-vitro studies

Bacterial counts before and after exposure of the human faeces to PVP-I and neomycin/metronidazole are shown in fig. 2.

Treatment with 1% PVP-I resulted within 10 minutes in elimination of all aerobic and anaerobic microorganisms (p<0.002) except for clostridia and the bacilli. The action of PVP-I on spores seemed to be much weaker as has been reported by others [18]. Killing of the clostridia occurred after longer exposure.

Treatment with neomycin and metronidazole showed only a slow reduction in the anaerobic organisms and no effect at all on the aerobic flora within 60 minutes. The influence of 1% PVP-I and the antimicrobials on the colonic flora of the rat were the same as on human faeces. Due to the irradiation of the food given preoperatively, to the rats, *Bacillus* spp. were eliminated and the action of PVP-I on them could not be tested.

Fig. 2: Mean and standard deviations of the total aerobic and anaerobic counts after in-vitro exposure of human faeces to povidone iodine or antibiotics.

Fig. 3: Mean and standard deviation of the total aerobic and anaerobic counts after in-vivo exposure of rat faeces to povidone iodine or antibiotics.

In-vivo studies

The microbiological data are summarised in fig. 2. Separate cultures and counts of *B. fragilis* and *E. coli* were done, in order to study the in-vivo effects of PVP-I and oxygen on these most important pathogens in colorectal surgery. Saline had no effect. Exposure of the colonic flora after the colon irrigation to the PVP-I for 20 minutes in the manner described resulted in a dramatic reduction in the number of *B. fragilis* ($p < 0.0001$). From six of the nine specimens no *B. fragilis* could be cultured ($< \log 2$), (table 2).

The influence of PVP-I on the total aerobic flora (table 1) was more pronounced than on the total anaerobic flora, although both were significantly ($p < 0.001$) reduced compared to the control group. This was also the case with *E. coli*.

In the group treated with oxygen no reduction in the colon flora was noticed (table 1).

Table 1: Mean and standard deviations of the total aerobic, anaerobic, *E. coli* and *B. fragilis* counts (log CFU/g colon wall) 20 minutes after exposure to saline, PVP-I and oxygen.

Microorganisms	Saline	PVP-I	Oxygen
total aerobic	6.00 + 0.58 ^a	2.91 + 0.59 ^b	5.93 + 0.86 ^c
total anaerobic	7.01 + 0.50 ^d	4.09 + 0.72 ^e	6.74 + 0.72 ^f
<i>E. coli</i>	5.57 + 0.63 ^g	2.63 + 0.72 ^h	4.89 + 1.02 ⁱ
<i>B. fragilis</i>	5.82 + 0.78 ^j	2.09 + 0.20 ^k	5.61 + 1.08 ^l

a vs b: p = 0.0001 a vs c: p = 0.81
 d vs e: p = 0.0001 d vs f: p = 0.37
 g vs h: p = 0.0001 g vs i: p = 0.11
 j vs k: p = 0.0001 j vs l: p = 0.65

Table 2: Mean total aerobic, anaerobic, *E. coli* and *B. fragilis* counts 20 minutes after in-vivo exposure to saline, povidone iodine and oxygen.

Discussion

Even high levels of appropriate antibiotics do not effectively prevent wound infection in colorectal surgery when there is massive bacterial contamination from the unprepared intestine [4]. In the present study we have suggested that also in emergency surgery, after an intraoperative irrigation of the colon with 1% PVP-I, a rapid and significant reduction of the total aerobic and anaerobic bacteria could be brought about, with a profound effect on *Bacteroides fragilis* which are among the most important anaerobic species.

Oxygen, on the contrary, exerted no effect at all on the bacteria and the expected influence on the anaerobic flora was not realised. Because the obligately anaerobic bacteria are susceptible to oxygen, the idea arose during the in-vivo experiments of using oxygen instead of CO₂ as a additional means of reducing the anaerobic flora.

No preliminary in-vitro study with oxygen had been carried out and no probable dangers which oxygen could cause in the operating room had been investigated. If oxygen appeared to work, the safety of its use in this way would have to be studied but due to the results of the in-vivo experiments no such study was necessary.

Complete sterilisation of the colon is not feasible by any of the commonly used methods for bowel preparation in colorectal surgery and was also not achieved with the PVP-I irrigation procedure. It should be noticed that only the colon is irrigated and return of the normal flora (apart from growth of the bacteria present in the colon wall) will occur due to passage of the small bowel contents as soon as peristalsis starts again.

All aliquots taken from the stock solutions were serially diluted tenfold (10¹⁰) before spreading them over the surface of the plates for the aerobic and anaerobic cultures. These diluted aliquots of PVP-I (0.0001%) were previously tested and found not to be inhibitory to any of the challenge organisms. Due to the degree of dilution the iodine was inactivated and therefore neutralisation (for example, with sodium thiosulphate) was not necessary [19].

PVP-I lavage for antegrade whole gut irrigation as preoperative bowel preparation has been used in elective surgery [20]. However, significant bacterial reduction in combination with adequate tissue levels of antibiotic can be reached safely with metronidazole and neomycin in the irrigation fluid during the whole gut irrigation [7] which makes this method superior. There is now little controversy about the use of solutions of PVP-I as abdominal irrigations during surgery. In the literature more benefit [10,11,21-25] than disadvantage [26-29] has been reported with this procedure.

In the present study we used the 1% PVP-I concentration (1:10 dilution of the 10% stock solution) because this solution has been used in clinical practice for abdominal irrigation.

Secondly, increased antibacterial activity of dilute preparations of povidone iodine solutions has been demonstrated by Berkelman et al [30]. A maximal bactericidal action was noticed between 1% and 0.01% PVP-I (1:10 and 1:1000 dilutions of the stock solution). The hypothesis in their article was that with dilution the non-complex-bound iodine increased, and this was responsible for the killing activity.

Gottardi [31, 32] and others [33] showed that, starting from a commercially available 10% solution, the content of non-complex-bound iodine initially increased as the dilution increased, reaching a maximum value at about 0.1% strength solution (1:100 dilution) and falling again on further dilution.

With the results of these two studies a good correlation between the microbicidal activity and the content of non-complex-bound iodine (I_2) could be reproduced.

The concept that the microbicidal activity of PVP-I solutions must be attributed to the effect of the non-complex-bound iodine is thereby reinforced and nowadays generally accepted [34,35].

The safety and efficacy of bowel irrigation with PVP-I has been demonstrated by animal experiments and also in man, where it has been used as an enema. Also segments of human colon have been treated this way [13, 14, 19, 36, 37]. However PVP-I at 5% or 10% concentration has been used in nearly all these studies.

Thirdly, dilute solutions of PVP-I (1%, for example) showed also decreased mucous membrane irritation and decreased toxicity. In their experiment with 10% PVP-I enemas in dogs Orsay et al. [38] noted an excessive mucous discharge and erythema which disappeared when 5% PVP-I was used.

Irritation tests performed on the cornea of rabbits once more demonstrated better tolerance of the more dilute PVP-I solution [35].

Moreover, it has been suggested that the irritation/toxicity of the PVP-I depends on the total iodine concentration (which decreases in diluted PVP-I) and not from the non complex-bound iodine (which increases with dilution [35]).

Generally no bacterial resistance against povidone iodine occurs after repeated use [39, 40]. Bacterial resistance to PVP-I after 25 years of use as a broad spectrum antiseptic has only been reported in 2 publications [41, 42]. *Pseudomonas cepacia*, in some case protected by organic or inorganic materials, seemed to be pseudoresistant. PVP-I exerts its bacterial action by oxidation and rapid binding of the non-complex-bound I_2 to bacterial proteins [4,10,43,44] and due to this mechanism overgrowth of organisms resistant to antimicrobials is highly improbable.

The influence of 1% PVP-I on thyroid function is well established [24, 45-52]. After abdominal irrigation with PVP-I, an increase in serum iodine has been noted and transient alterations of the T4 and TSH (without any toxic effects) have been found. However, these values return to normal within a few weeks in adults.

Neonates, however are more susceptible to PVP-I. After prolonged use in infants with omphalocele, 3 cases of povidone iodine-induced hypothyroidism have been reported to date [53-55]. Although there are no reports in the literature of permanent hypothyroidism in infants following the use of iodine-containing antiseptics, their use in neonates is not advocated [56].

PVP-I has been well tolerated in iodine hypersensitive [44] patients, although its use in these patients should not be encouraged.

Experimental investigations have demonstrated that PVP-I did not interfere with anastomotic healing [38] and, on the contrary, antiseptic irrigation of the rat before and after surgery has been shown to produce a significantly lower percentage of cases with colonic dehiscence [57].

An additional benefit of the use of PVP-I in colorectal surgery might be its cytotoxic effect on tumour cells.

Umpleby et al. [58] compared cytotoxic agents used intraluminally to prevent suture line recurrence following resection of the large bowel for cancer. They showed that PVP-I was

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Chapter 10

Protocol for the treatment of colonic disease in elective and emergency surgery

(see also chapter 3)

Elective colorectal surgery

(see algorithm)

All patients admitted for colorectal surgery are organised to undergo a whole gut irrigation with neomycin and metronidazole in the irrigation fluid, provided that the contraindications are taken into account.

Whole gut irrigation is not feasible in those patients admitted with obstruction and intraoperative colon irrigation through the irrigation drainage tube is performed instead.

Preoperative bowel preparation is not possible in a small proportion of patients because of refusal or other contraindications, or is found at operation not to have been satisfactory. Intraoperative colon irrigation with the rectal tube is easily performed, especially if no obstructions are present.

An (extended) right hemicolectomy is the method of choice in obstructing lesions of the right colon without any bowel preparation.

Non-elective colorectal surgery

For obstructing lesions of the right colon the procedure to be followed is the same as that in elective colorectal surgery.

Most of the obstructing lesions of the left colon can be handled by the intraoperative colon irrigation using the irrigation drainage tube if certain criteria are fulfilled.

With non-obstructing lesions intraoperative colon irrigation can be carried out using the rectal tube, after which resection and anastomosis are performed as in elective colorectal surgery.

For volvulus of the left colon, in which conservative treatment has failed and operation is mandatory, intraoperative colon irrigation is feasible either with the irrigation drainage tube or the rectal tube (depending upon the quality of the colon).

A (sub)total colectomy is only justified in cases of toxic megacolon or if perforation in the caecum has occurred due to distension in the presence of a left sided obstructing tumour.

COLORECTAL SURGERY

Summary and conclusions

Chapter 1

The aims of the studies presented in this thesis are reported briefly in this chapter.

Chapter 2

The sense or nonsense of bowel preparation is discussed especially in view of the opinions of some workers that bowel preparation is probably unnecessary. Several methods of preoperative bowel preparation are discussed with their pros and cons.

Conclusions

- Until data from adequate controlled clinical trials prove the contrary, large bowel preparation should be considered essential before colorectal surgery .
- Whole gut irrigation with balanced electrolyte solution or with polyethylene glycol until the rectal effluent is clear, is rapid, economical and well tolerated by patients. This method of bowel preparation is the best for its capacity to clean the colon.
- No reduction of bacterial colonic flora or decrease in postoperative septic complications is to be expected from bowel preparation alone.

Chapter 3

A historical review is given of attempts to clean the colon during operation in order to perform a primary resection and anastomosis. It resulted at last in the method as described by Dudley, nowadays used as the method of intraoperative colon irrigation. As indications for this procedure are mentioned: obstructing carcinomata, diverticulitis, perforations, major colonic haemorrhage, fistulae, closure of a colostomy and sometimes volvulus. Contraindications to this procedure concern the suitability of the patient and local factors such as abscess or bowel ischaemia after resection.

The results reported in the literature up to December 1988 are shown in tables 1 and 2.

Chapter 4

The results of three prophylactic antimicrobial regimens combined with whole gut irrigation (WGI) were evaluated in 212 patients undergoing elective colorectal surgery. Three groups were formed at random. The first group (72 patients) were given intramuscular oxytetracycline just before surgery; the second group (70 patients) received oral metronidazole and intravenous tobramycin. The third group (70 patients) received only metronidazole and neomycin in the irrigation fluid. All patients were prepared by WGI on the day before surgery, and the procedure was well tolerated in 95% of them. In 5% the irrigation had to be stopped and the patients were excluded from this study.

Abdominal wound infection occurred in 19.4% (14/72) in group 1, in 18.6% (13/70) in group 2 and in 2.9% (2/70) in the group 3 patients. The occurrence of septicaemia (group 1: 11% (8/72); group 2: 9% (6/70); group 3: 0%) and the overall frequency of anastomotic leakage (group 1: 22% (14/72); group 2: 17% (10/70); group 3: 3% (3/70) were both significantly reduced in group 3 compared with groups 1 and 2.

Anastomotic leakage in all patients (N=74) undergoing anterior resection was investigated radiographically on the 10th day. A highly significant reduction in the total anastomotic leakage rate was achieved in group 3. This rate was 7.7% (2/26), compared with 36% (9/25) in group 1 and 26% (6/23) in group 2.

After this trial had been finished, all patients admitted for elective colorectal surgery underwent WGI with metronidazole and neomycin in the irrigation fluid. The results in 215 patients studied prospectively with this regimen once again confirmed the data from group 3. It is **concluded** that very short term antimicrobial prophylaxis with neomycin and metronidazole in the irrigation fluid alone appears to be very effective in reducing wound infections and septicaemia, and -most important of all- yields a dramatic reduction in anastomotic leakage.

Chapter 5

In this chapter the experience and the results with the intraoperative colon irrigation are reported. Forty-one patients with a mean age of 66 years underwent intraoperative colon irrigations for various reasons, followed by resection and primary anastomosis of the left colon. A protective diverting colostomy was used in only two patients with technically imperfect low anterior anastomoses. Uneventful anastomotic healing occurred in all patients, except in two with peritonitis carcinomatosa who developed clinical leakages. In total, four patients died, three from cardiopulmonary complications and one due to the complications of widespread carcinoma together with anastomotic leakage.

Conclusions

- The intraoperative colon irrigation procedure enables us to create an elective environment at "non elective" times in colorectal surgery, permitting a safe one-stage operation in most patients with obstructions of the left colon.
- If certain criteria are fulfilled, this procedure enables primary resection and anastomosis to be performed with a low mortality and complication rate. It offers the patients:
 - no stomal problems
 - one-stage procedure with single hospitalisation
 - shorter hospital stay with financial savings to the community
 - better quality of life.

Chapter 6

Some new instruments were developed in order to increase the safety and ease of the procedure. With these instruments the intraoperative colon irrigation procedure could be performed without any spillage at all, as discussed in this chapter and shown in a video film.

Chapter 7

The aim of this study was to evaluate the antibiotics used in the clinical trial (chapter 4) in a similar way in an experimental septic model. The question posed was: Can a useful selection or rejection of antibiotic prophylaxis in colorectal surgery be done with this model prior to its application in longlasting clinical trials? The intra-abdominal septic model described by Lahnborg et al. was used for this purpose. Some new antibiotics whose effectiveness in colorectal surgery have been claimed were also tested. Rats, given beef food to change their intestinal flora (which then became comparable with that of humans), were used. Six groups, each containing 12 animals, were formed non selectively and each antibiotic was tested in a separate group. The following parameters for the evaluation of the efficacy of antibiotics were used: time of death, number of abscesses, presence of adhesions, peritonitis. All surviving animals were sacrificed on the 14th day and intra-abdominal assessment of the parameter was done.

The ineffectiveness of oxytetracycline for controlling aerobic and anaerobic septic complications was demonstrated in this model (which was also the case in the clinical study). Neomycin/metronidazole, Augmentin^R, Timentin^R and imipenem were shown to be highly effective for use as prophylaxis.

Conclusions

- The model of Lahnborg et al. simulating intra-abdominal sepsis has been suggested for predicting the effectiveness of any antibiotic to be used in colorectal surgery. Exclusion or selection of antibiotics seems possible using this model.
- The mortality in this experimental model could not be explained by the increased count of colonic bacteria in animals given beef food. The unbalanced diet, resulting in a decreased general resistance, is probably the most important factor causing the deaths in this septic model.
- Oral administration of neomycin and metronidazole appeared to be very effective in preventing mortality and adhesion formation. The same results were accomplished using parenteral Augmentin^R, Timentin^R or imipenem.
- Antibiotics effective against the major colonic bacteria seemed to decrease the extent of intra-abdominal adhesion formation.

Chapter 8

The main question posed in this study was: could antibiotics prevent the impaired healing of an anastomosis in the presence of infection?

Five groups containing 24 rats each were formed at random. Group 1 received no bowel preparation and no antibiotics. In group 2 whole gut irrigation (WGI) was used as bowel preparation but no antibiotics were given. All rats in group 3 underwent WGI and received antibiotics. In group 4 intraoperative colon irrigation (ICI) was performed as bowel preparation. Previously infected Vicryl^R was used to perform the anastomoses. No antibiotics were given. In group 5 infected Vicryl^R and antibiotics were used.

Bursting pressure (BP) measurement was chosen as a parameter of anastomotic healing.

No intergroup statistical differences in BP were noted and one might conclude that antibiotics did not influence the anastomotic healing. It is shown that this conclusion is not correct due to the influence of adhesion formation on the BP.

Conclusions

- The bursting pressure is unreliable as a parameter for the study of anastomotic healing in fully comparable groups of rats using an infection model, unless the (infected) anastomosis can be studied in complete isolation from adhesion formation.
- ICI as a procedure for obtaining a totally clean colon is safe, rapid and easier to perform than WGI in animal experiments.
- Antibiotics inhibit adhesion formation ($p < 0.05$).

Chapter 9

Even high level of appropriate antibiotics do not prevent wound infections in colorectal surgery when there is massive bacterial contamination from the unprepared intestine.

In this experimental study, methods for decontaminating the colon during the intraoperative colon irrigation procedure were investigated in-vitro and in-vivo.

Polyvinyl pyrrolidone iodine (PVP-I) has been shown to be a safe and effective broad spectrum antibacterial agent and is known to exert its action rapidly. Therefore this agent was tested for its capacity to decontaminate the colon. Secondly, the influence of oxygen on the anaerobic colonic flora was investigated.

In-vitro studies: Faeces obtained from four healthy volunteers and from four rats were exposed to PVP-I and neomycin/metronidazole.

In-vivo studies: Three groups of rats, each containing of 9 animals, were separated at random. All rats underwent intraoperative colon irrigation with saline. In the control group only intraoperative colon irrigation was performed; in the PVP-I group after saline irrigation, the colon was irrigated with 60 ml of 1% PVP-I. In the oxygen group after irrigation, the colon was blown through with 100% oxygen for 5 minutes. Twenty minutes after the procedure a 3 cm segment of the descending colon was excised and prepared for aerobic and anaerobic cultures.

In-vitro studies: Treatment with 1% PVP-I resulted within 10 minutes in elimination of nearly all aerobic and anaerobic microorganisms ($p < 0.002$). Treatment with metronidazole and neomycin showed a slow reduction in the anaerobes, but no effect at all on the aerobic flora within 60 minutes.

In-vivo studies: Significant rapid reduction ($p < 0.0001$) of the total colonic flora occurred after irrigation with 1% PVP-I. In the group treated with oxygen, no reduction in the colon flora was noticed.

Conclusion

PVP-I (1%) in combination with the intraoperative colon irrigation, did appear to be highly effective for acute colon decontamination.

Chapter 10

The lesions learned from clinical and experimental studies reported in this thesis and which are important for the clinical practice of colorectal surgery are summarised in the algorithm in this chapter.

Samenvatting en conclusies

In **hoofdstuk 1** worden de doelstellingen van dit proefschrift ('Pré- en intra-operatieve darmlavage en antibiotica in de colorectale chirurgie: een klinisch en experimenteel onderzoek') in het kort besproken.

Op basis van literatuurstudie wordt in **hoofdstuk 2** de zin van pré-operatieve darmvoorbereiding besproken. De mening van sommige onderzoekers, dat darmvoorbereiding niet nodig is, wordt kritisch getoetst. Verschillende methoden voor pré-operatieve darmvoorbereiding worden inclusief hun pro's en contra's besproken.

De **conclusies** hieruit getrokken luiden als volgt:

- Totdat het tegendeel bewezen is door gecontroleerde, klinische, prospectieve studies moet pré-operatieve darmvoorbereiding in de colorectale chirurgie essentieel geacht worden.
- Totale darmlavage met een uitgebalanceerde electrolyt-oplossing of met polyethyleenglycol totdat het effluent helder is, is snel, economisch en wordt goed verdragen door de patiënt. Deze methode van darmvoorbereiding geniet de voorkeur, gezien haar vermogen om het colon te reinigen.
- Vermindering van de bacteriële darmflora en van post-operatieve infecties ten gevolge van darmvoorbereiding alleen, is niet te verwachten.

In **hoofdstuk 3** wordt een historisch overzicht gegeven van de pogingen om het colon te reinigen tijdens de operatie ten einde een primaire resectie en anastomose uit te voeren. Deze resulteerde tenslotte in de methode zoals die door Dudley beschreven is en die tegenwoordig in gebruik is als dé methode voor intra-operatieve colonlavage. Als indicaties voor deze procedure worden genoemd: obstruerende carcinomen, diverticulitis, perforaties, massaal bloedverlies uit het colon, fistels, sluiten van een colostomie en soms volvulus.

Contra-indicaties bij deze procedure hebben betrekking op de algehele klinische toestand van de patiënt en op lokale factoren zoals een abcessen of slechte vascularisatie van het colon na resectie.

In de tabellen 1 en 2 (p. 32-33) wordt een overzicht gegeven van de resultaten met deze methode in de literatuur tot 1 januari 1989.

In **hoofdstuk 4** worden de resultaten van drie profylactische antimicrobiele methodes, gecombineerd met totale darmlavage, prospectief geëvalueerd bij 212 patiënten, die electieve colorectale chirurgie ondergingen. Drie gerandomiseerde groepen werden gevormd. De eerste groep (72 pat.) kreeg vlak voor de operatie intramusculair oxytetracycline. De tweede groep (70 pat.) kreeg oraal metronidazole en intraveneus tobramycine. De derde groep (70 pat.) kreeg alleen metronidazole en neomycine in de spoelvloeistof.

Alle patiënten ondergingen pré-operatief een totale darmlavage. Deze werd door 95% goed verdragen. Bij 5% moest het spoelen om diverse redenen worden gestopt, waarna deze patiënten werden uitgesloten van dit onderzoek.

Abdominale wondinfectie kwam voor bij 19,4% (14/72) van de patiënten in groep 1, bij 18,6% (13/70) ervan in groep 2 en bij 2,9% (2/70) ervan in groep 3. Sepsis (groep 1: 11% (8/72); groep 2: 9% (6/70); groep 3: 0%) en het optreden van naadlekkage (groep 1: 22% (14/72); groep 2: 17% (10/70); groep 3: 3% (3/70)) waren beide significant verminderd in groep 3 vergeleken met de groepen 1 en 2.

De anastomosen bij alle patiënten (N=74) die een anterieure resectie ondergingen, werd op de 10e dag röntgenologisch onderzocht. In groep 3 werd een hoog significante vermindering van het totaal aantal naadlekkages bereikt namelijk 7,7% (2/26), vergeleken met 36% (9/25) in groep 1 en 26%(6/23) in groep 2.

Na het beëindigen van dit onderzoek, ondergingen alle patiënten, die voor electieve colorectale chirurgie opgenomen werden, een totale darmlavage met metronidazole en neomycine in de spoelvlloeistof. De resultaten bij 215 patiënten, die prospectief bestudeerd werden met deze methode, bevestigden nog eens de resultaten van groep 3.

Geconcludeerd wordt, dat antimicrobiele profylaxe met neomycine en metronidazole in de spoelvlloeistof heel doeltreffend blijkt te zijn voor het verminderen van wondinfectie, sepsis en -het allerbelangrijkste- een aanzienlijke vermindering oplevert van het aantal naadlekkages.

Hoofdstuk 5 bevat de ervaringen met en resultaten van intra-operatieve colonlavage. Eenenvertig patiënten met een gemiddelde leeftijd van 66 jaar ondergingen om diverse redenen intra-operatieve lavage, gevolgd door resectie en primaire anastomose van het linker colon. Slechts bij twee patiënten met een technisch onvolkomen lage anterieure anastomose werd een "beschermende" anus praeternaturalis aangelegd.

Bij alle patiënten vond een normale genezing van de naad plaats, behalve bij twee met peritonitis carcinomatosa. Zij kregen een klinische lekkage. In totaal overleden vier patiënten, drie door cardiopulmonaire complicaties; een patiënt aan de gevolgen van uitgebreide tumormetastasen en tevens naadlekkage.

Conclusies:

- Met behulp van de intra-operatieve colonlavage hoeven de meeste patiënten met een obstructie van het linker colon maar één keer geopereerd te worden.
- Als aan bepaalde criteria voldaan is, kan primaire resectie en anastomose worden uitgevoerd met een laag mortaliteits- en complicatiepercentage.

De voordelen voor de patiënt zijn:

- geen complicaties van een stoma;
- eenmalige operatie en ziekenhuisopname;
- korter verblijf in het ziekenhuis, wat een financiële besparing voor de gemeenschap betekent;
- een kwalitatief beter leven.

In **hoofdstuk 6** wordt een drietal nieuwe instrumenten besproken die ontwikkeld zijn ten einde de veiligheid en het gemak van de procedure te verbeteren. Met deze instrumenten kon de intra-operatieve colonlavage uitgevoerd worden zonder enige 'spilling', zoals in dit hoofdstuk is besproken. In een videofilm wordt de techniek van de intra-operatieve colonlavage met behulp van deze instrumenten gedemonstreerd.

Hoofdstuk 7 omvat de beschrijving en de resultaten van een onderzoek dat tot doel had de antibiotica, die in het klinische onderzoek werden gebruikt, op gelijke wijze in een experimenteel infectiemodel te evalueren. De vraagstelling luidde: is met dit model selectie of uitsluiting van antibiotica mogelijk, voordat deze in langdurige klinische studies als profylaxe worden toegepast? Voor dit doel werd gebruik gemaakt van het intra-abdominale infectiemodel, zoals beschreven door Lahnborg et al. Ook werden enkele nieuwe antibiotica getest, waarvan in de colorectale chirurgie beweerd wordt dat zij doeltreffend zijn. Er werd gebruik gemaakt van ratten, die 'beef food' kregen om hun darmflora te veranderen, zodat deze vergelijkbaar werd met die van mensen. Er werden a-select zes groepen gevormd, elk bestaande uit 12 dieren. Elk antibioticum werd in een afzonderlijke groep onderzocht.

De volgende parameters voor de evaluatie van de effectiviteit van de antibiotica werden gebruikt: tijdstip van overlijden, aantal abscessen, aanwezigheid van verklevingen en/of peritonitis. De overlevende dieren werden op de veertiende dag intra-abdominaal geëvalueerd op de aanwezigheid van abscessen, adhesies of peritonitis. In dit model werd de ineffectiviteit van oxytetracycline aangetoond, voor wat betreft het onder controle krijgen van aerobe en anaerobe infectieuze complicaties. Hetzelfde was het geval in het klinische onderzoek. Neomycine/metronidazole, Augmentin^R, Timentin^R en imipenem bleken bijzonder doeltreffend als profylaxe.

Conclusies

- Met het model van Lahnborg et al. bleek het mogelijk te zijn de effectiviteit van antibiotica te voorspellen, die als prophylaxe in de colorectale chirurgie gebruikt zouden kunnen worden.
- De mortaliteit in dit experimentele model kan niet verklaard worden door het toegenomen aantal darmbacteriën. Het onevenwichtige dieet, waarvan een verminderde algemene weerstand het gevolg is, is waarschijnlijk de belangrijkste factor waardoor de sterfgevallen in dit infectieus model veroorzaakt werden.
- Orale toediening van neomycine en metronidazole bleek bijzonder effectief te zijn, wat betreft het verminderen van mortaliteit en adhesies. Dezelfde resultaten werden bereikt met het gebruik van Augmentin^R, Timentin^R of imipenem.
- De mate van intra-abdominale adhesievorming bleek verminderd te worden door antibiotica die ook effectief waren tegen een groot deel van de darmbacteriën.

In **hoofdstuk 8** is een onderzoek beschreven, waarvan de belangrijkste vraagstelling was: kunnen antibiotica een ongehinderde genezing van de anastomose bewerkstelligen in geval van een lokale infectie?

Vijf groepen, elk bestaande uit 24 ratten, werden 'at random' gevormd. Groep 1 kreeg noch darmvoorbereiding, noch antibiotica. In groep 2 werd totale darmlavage gebruikt als darmvoorbereiding, maar er werd geen antibiotica toegediend. Alle ratten in groep 3 ondergingen totale darmlavage en kregen antibiotica. In groep 4 werd intra-operatieve colon lavage toegepast als darmvoorbereiding. Geïnfecteerd Vicryl^R werd gebruikt voor het maken van de anastomosen. Er werd geen antibiotica gegeven. In groep 5 werd én geïnfecteerd Vicryl^R én antibiotica gebruikt. Het meten van de 'bursting pressure' (BP) werd gekozen als parameter voor het genezen van de anastomose. Er werden geen statistische verschillen in de BP tussen de groepen genoteerd en men zou geneigd zijn te concluderen, dat antibiotica geen invloed hebben op genezing van de anastomose. Aangetoond wordt, dat deze conclusie niet juist is door de invloed van adhesievorming op BP.

Conclusies

- De 'bursting pressure' is onbetrouwbaar als parameter voor het bestuderen van de genezing van een anastomose in volledig vergelijkbare groepen ratten, bij het gebruik van een infectie-model, tenzij de (geïnfecteerde) anastomose geheel afgezonderd van adhesievorming bestudeerd kan worden.
- In dierexperimenten is de intra-operatieve colon lavage als methode voor het verkrijgen van een totaal schoon colon veilig, snel en bovendien eenvoudiger uit te voeren dan de totale darmlavage.
- Antibiotica verhinderen adhesievorming ($p < 0,05$).

In de colorectale chirurgie biedt zelfs een hoge antibioticaspiegel geen adequate preventie tegen wondinfecties, indien er bacteriële contaminatie plaatsvindt vanuit de onvoorbereide darmen. In deze experimentele studie werden *in-vitro*- en *in-vivo*-methoden onderzocht om het colon te decontamineren tijdens de operatie. Het is bekend, dat polyvinylpyrrolidone-jodium (PVP-J) een veilig en doeltreffend breed spectrum bactericide middel is en dat het snel werkt. In **hoofdstuk 9** werd PVP-J onderzocht op zijn vermogen het colon te decontamineren. Bovendien werd de invloed van zuurstof op de anaerobe darmflora nagegaan.

In-vitro onderzoek: faeces, verkregen van vier gezonde vrijwilligers en van vier ratten, werd blootgesteld aan PVP-J en neomycine/metronidazole.

In-vivo onderzoek: drie groepen ratten, elk bestaande uit 9 dieren, werden "at random" samengesteld. Alle ratten ondergingen intra-operatieve colonlavage met fysiologisch zout. In de controlegroep werd alleen intra-operatieve colonlavage uitgevoerd. In de PVP-J groep werd, na het spoelen met fysiologisch zout, het colon nagespoeld met 60 ml 1% PVP-J. In de zuurstofgroep werd het colon, na spoeling, gedurende 5 minuten doorgeblazen met 100% zuurstof. Twintig minuten na deze handeling werd een 3 cm lang segment van het colon descendens geëxciëerd en geprepareerd voor een aerobe en een anaerobe kweek.

In-vitro onderzoek: Behandeling met 1% PVP-J resulteerde binnen 10 minuten in de eliminatie van nagenoeg alle aerobe en anaerobe micro-organismen ($p < 0,002$). Behandeling met metronidazole en neomycine liet na 60 minuten een langzame afname van de anaeroben zien, doch had geen enkel effect op de aerobe flora.

In-vivo onderzoek: er deed zich na spoelen met 1% PVP-J, een significante en snelle vermindering voor ($p < 0,0001$) van de totale darmflora. In de groep die behandeld werd met zuurstof werd geen reductie van de darmflora bemerkt.

Conclusie

1% PVP-J bleek, in combinatie met intra-operatieve colonlavage, een bijzonder effectief middel te zijn voor wat betreft acute decontaminatie van het colon.

In **hoofdstuk 10** is het algoritme voor de chirurgische behandeling van colonaandoeningen opgenomen. Dit protocol is gebaseerd op de lessen geleerd uit de klinische en experimentele studies die in dit proefschrift beschreven worden en die van belang zijn voor de colonchirurgie.

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