Colorectal Anastomotic Leakage: New perspectives

Freek Daams

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1

Introduction

1.1 Colorectal anastomotic leakage.

Adapted from: Colorectal anastomotic leakage: Aspects of prevention, detection and treatment.
Daams F, Luyer M, Lange JF.
World J Gastroenterol. 2013 Apr 21;19(15):2293-7.

Introduction

According to the nationwide Dutch Colorectal Surgical Audit, 9097 patients underwent a resection of the colon or rectum (6263 colonic resections, 2494 rectum resections and 340 double tumours in 2011)[1]. Of them, 6718 patients (73,8%) were operated with a colorectal anastomosis with or without deviating stoma. Overall, colorectal anastomotic leakage (CAL) occurred in 463 patients (6,9%, 6,5% after colon resection, 9,2% after rectum resection).

	Colon		Rectum	
	<75 yrs	≥75 yrs	<75 yrs	≥75 yrs
Resections (%)	10249 (59%)	7246 (41%)	5076 (72%)	1933 (28%)
Anastomotic Leakage (%)	666 (7,4%)	449 (7,3%)	310 (11,4%)	55 (8,1%)

Table 1. Number of colon and rectum resections in the Netherlands in 2011 and percentage anastomotic leakage. Adapted from "DSCA jaarrapportage 2011, clinicalaudit.nl

Morbidity in these patients is dramatically increased opposed to patients without CAL and frequently consists of re-operations, radiological interventions and a permanent stoma in up to 56% of the cases[2 3]. Despite the publication of numerous studies investigating risk factors, surgical techniques and prevention of CAL, this incidence and the concomitant burden for patients, surgeons and healthcare systems have yet not been decreased.

Definition

Definition of CAL is challenging. Most authors consider CAL as some form of inflammation or abscess in the presence of wound dehiscence at the anastomotic site. Elements of severity of peritonitis, purulent or fecal discharge and fistula are not consistently described. Bruce et al showed in 2001 out of 49 studies on lower gastrointestinal anastomosis, 29 studies described their definitions, while these showed large differences[4]. Most of the studies used water soluble contrast study (X-ray or CT) to confirm the leakage. The International Study Group of Rectal Cancer defined CAL as a defect of the intestinal wall integrity at the colorectal or colo-anal anastomotic site (including suture and staple lines of neorectal reservoirs) leading to a communication between the intra- and extraluminal compartments[5]. A pelvic abscess close to the anastomosis was also considered CAL. Furthermore, a grading

system was introduced by the Study Group for leakage of rectal anastomosis based on therapeutic consequences. Although this enables future comparability of studies, it does not seem particularly helpful as a clinical treatment guideline.

Causes and risk factors

Since many risk factors are established for CAL, its cause is probably multifactorial. When CAL occurs in the very early postoperative phase (POD 1-5), iatrogenic failure is very likely. Insufficient suturing or stapling and too much tension on the anastomosis could be the underlying mechanism, since during the first postoperative five days the integrity of the anastomosis largely depends on suture or stapling material since collagenolysis exceeds production of the collagen matrix[6]. Impaired woundhealing usually results in leakage from POD 3 – 12. In normal healing, a fibrous cap forms over the serosal aspect of the anastomosis. This precipitates pluripotent fibroblast ingrowth leading to contraction, differentiation and regeneration of the anastomotic site[7]. Factors leading to impaired wound healing amongst many are impaired perfusion and subsequent ischemia, local inflammation, diabetes, smoking, alcohol abuse, obesity, medication, (i.e. steroids, NSAIDs) and age[8]. Interestingly, above mentioned factors for impaired woundhealing are also well documented risk factors for leakage. Furthermore other patient factors as well as surgery related factors are described to increase the risk of leakage, such as male gender, longer duration of operation, preoperative transfusion, high calciumscore, contamination of the operative field, preoperative radiotherapy and timing during duty hours[9-12]. Increasingly, aspects of case volume for rectal surgery are discussed in respect to postoperative complications. Asteria et al. described case volume per centre < 20 is correlated to CAL[13]. In line with this finding, Biondo and co authors described in their study over 1046 emergency colorectal resection that CAL occurred less frequent in patients who were treated by specialized colorectal surgeons[14]. Recently, risk factor studies have also been undertaken for laparoscopic colorectal surgery, identifying BMI, tumour distance from the anal verge, tumour depth, and pelvic outlet as independent predictors for increased operative time and morbidity after laparoscopic total mesorectal excision[15]. Furthermore, ASA III/IV patients and longer operative time are risk factors for CAL after laparoscopic colorectal surgery [16].

Surgical technique

Currently, the only way to prevent CAL is to renounce from restorative surgery. This is justified when the estimated risk of CAL in an individual patient exceeds

the population risk, when expected postoperative functional results are very poor or when the preoperative condition of the patient does not allow coping with the inflammatory response to a potential leakage. Recently, Dekker et al. validated a risk scoring system in which preoperative and intraoperative factors were included[17]. As a predictor, the Colon Leakage Score (CLS) had an excellent area under the curve of the receiver-operating characteristics curve (AUC 0.95, 95%CI 0.89 – 1.00), and an odds ratio of 1.74 (95%CI 1.32 – 2.28). This scoring system enables the identification of high risk patients intraoperatively and could help the surgeon to decide not to restore continuity or to deviate.

Reduction of the rate of clinical leakage of the rectal anastomosis is achieved by a defunctioning stoma as is shown by Matthiessen et al in 2007[18]. Recently however, a Dutch study showed that the increase of defunctioning stomas (from 57% during the Dutch TME trial to 70% in 2011 according o the Dutch Surgical Colorectal Audit) has not led to a decrease in CAL[19]. Therefore, deviating stomas should probably be reserved for patients with a predicted high risk of leakage.

When the evidence that is available for the hand-sewn anastomosis is evaluated, it can be concluded that an inverting single layer continuous suture technique with slowly absorbable monofilament material seems preferable[20]. Strong evidence lacks for other important aspects as distance from the suture to the edge of the anastomosis, distance between the sutures, layers included in the suture, suture tension and the optimal configuration. The highest level of evidence exists for the equality regarding to CAL of stapling versus hand sewn anastomosis, without evidence for one technique being superior to the other[21]. Concluding from the above mentioned statements, currently stapling techniques might be of preference since the technique is uniform and easy to learn, making it ideal for comparing results between hospitals and surgeons and for teaching young surgeons. Other surgical aspects of prevention of CAL include a tensionfree anastomosis, the absence of peritonitis and techniques of endoluminal sealing (Figure 1).

However, no clear importance can be attributed for these aspects in current literature.

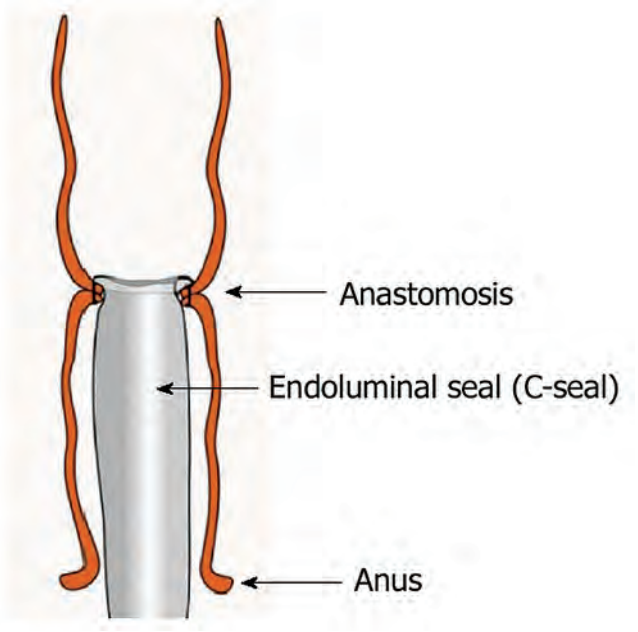

Figure 1. C-seal. Endoluminal biodegradable anastomotic cover. Printing with permission of Dr. K. Havenga, Universitair Medisch Centrum Groningen

Although literature is not anonymous, all surgeons agree that meticulous care of regional perfusion must be taken in order to prevent ischemia of the anastomosis[22-24]. Intraoperatively this is assessed routinely by inspection of the vitality of the bowel and palpation of the mesenteric vessels. Local ischemia of the anastomosis could be caused by tightened sutures that are placed very close to each other. The advantage of good anastomotical apposition opposed to the induced local ischemia was never before the subject of an experimental study. Part 2 of this thesis describes two experimental studies on the importance of apposition and local perfusion of the anastomosis. Furthermore, the additional exposure to risk of CAL in the case of misplaced stomas prior to treatment of locally advanced and recurrent rectal cancer will be discussed in this chapter. Furthermore, two papers are included that review all the available current literature of the surgical aspects of the creation and sealing of the colorectal anastomosis.

Early detection

CAL typically becomes clinically apparent between the fifth and the eighth postoperative day, but many exceptions exist, with one study even reporting a mean of the twelfth postoperative day for the diagnosis of CAL[25]. Clinical signs of systemic inflammatory response syndrome, fever, ileus and pain are frequent but have low positive predictive value for CAL, when observed separately. The interval between surgery and clinical onset suggests a preclinical phase in which non-clinical methods could be used to predict CAL. Many investigators acknowledge that early detection could lead to early treatment and improve patient outcome[26-29]. In the search for an early predictor, biochemical, radiological and clinical tools have been tested in studies, including CRP measurement, drain fluid analysis, a clinical leakage risk score (Figure 2) and water soluble contrast enema.

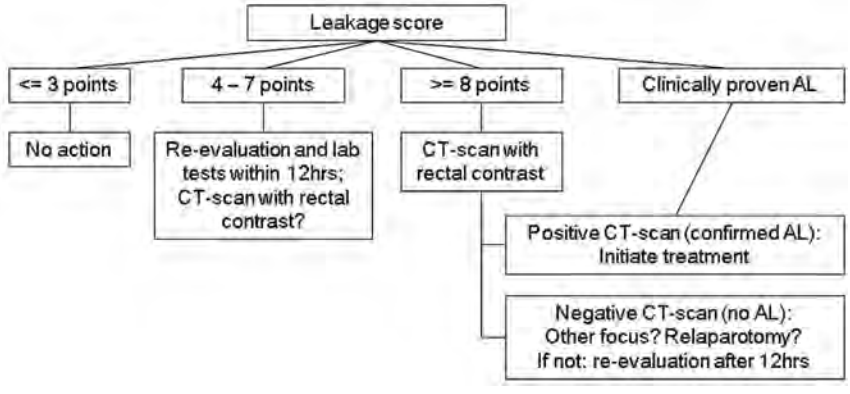

Figure 2. The Dutch Leakage Score. According to the points attributed to the patients on the basis of clinical symptoms, treating doctors can follow this diagnostic flowchart. Reprinted from: Eur J Surg Oncol. 2009 Apr;35(4):420-6)

Part 3 provides a review on all the available techniques for early detection of CAL and their diagnostic value. Furthermore, in this chapter the value of microdialysis of the peritoneal cavity as detection method for CAL is described.

Treatment

When facing and treating patients with CAL, surgeons have to take into account many different aspects, i.e., age, health status and current clinical condition of the patient, extent of dehiscence, time between operation and reoperation, indication of primary resection, presence of diverting stoma and localisation of the anastomosis. These variables lead to individualisation of treatment strategies and incomparable

outcome. However, surgeons believe that the anastomosis can be repaired rather than dismantled[30]. This seems to have paved the way for a trial in which besides mortality and morbidity, preservation of the anastomosis could be one of the endpoints. Part 4 provides an overview of the occurrence and appearance of CAL in a population of patients with locally advanced and recurrent rectal cancer. Additionally, it conveys the results of a national questionnaire among gastrointestinal surgeons surveying the current practical approach to CAL.

Quality of life

In contrast to the short term consequences of CAL, long term effects (>2yrs) have not been extensively described in current literature. From an oncologic perspective, some authors have described that the occurrence of CAL can lead to a higher systemic and local recurrence rate and lower cancer related survival for colorectal cancer[31 32]. Others found a decreased overall survival but did not observe a worse cancer related outcome[33]. A study on long term effects of colorectal resections on health related quality of life (HRQoL) showed that survivors of rectal cancer have similar HRQoL compared to healthy subjects[34]. How this is affected by CAL has not been studied extensively. HRQoL could be negatively influenced by repetitive surgery, prolonged hospitalisation, unintended permanent stomas etc. Some specific aspects of HRQoL have been studied. Bittdorf et al investigated aspects of fecal continence[35]. In their study patients after CAL did not show worse continence function compared to a non-CAL control group shortly after surgery. A small study by Nesbakken however showed that patients after CAL experienced impaired long term anorectal function, compared to control patients[36]. Riss et al. have investigated long term HRQoL in terms of pelvic organ function after CAL in colorectal patients using a matched control group[37]. They found worse urinary function in patients after CAL but not increased rates of fecal continence or sexual dysfunction. In Part 5 a study is described in which HRQoL of patients after CAL was assessed with a mean follow up of 9.7 yrs after primary surgery. These patients were compared to a group of patients after colorectal surgery, matched for age, gender, type of surgery and follow up.

Objectives of this thesis

CAL is a serious complication that has great clinical impact on patients, putting surgeons in dilemmas of prevention, diagnosis and treatment. Many aspects of CAL like etiology remain unclear. This thesis was performed to search for answers to the following questions.

1. What is the effect of local ischemia on healing of colorectal anastomosis?
2. What is current best practice for creation of colorectal anastomosis?
3. What is current best practice for creation of an emergency stoma?
4. What role do sealants play in the gastrointestinal anastomosis?
5. What is best practice of early detection of CAL?
6. Which strategies are considered by surgeons for the treatment of CAL?
7. What are the long term effects of CAL on health related quality of life?

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2

Surgical technique

2.1 Influence of local ischemia on anastomotic healing in mice

Local ischemia does not influence anastomotic healing, an experimental study
Daams F, Monkhorst K, vd Broek J, Slieker JC, Jeekel J, Lange JF.
Eur Surg Res. 2013 Mar 27;50(1):24-31

Abstract

The role of local ischemia in the pathogenesis of colorectal anastomotic leakage (AL) is not known. This study investigates the role of local ischemia caused by sutures in an experimental colonic anastomosis model. 36 Mice were assigned to three types of anastomosis all using running sutures, in the first group 5 stitches were, in the second 12 stitches were used and in the third group at least 30 stitches were used. After 7 days the mice were re-operated and signs of AL were scored and coronal coupes of the anastomosis were histologically analysed. Distribution of weight was not significantly different between the three groups. Mortality was 44% and not significantly different between the groups (group 1: 5/12, group 2: 4/12, group 3: 7/12, p=0.72). Faecal and purulent AL were observed in 6 animals in group 1, 2 in group 2, and 3 in group 3 (group 1: 50%, group 2: 17%, group 3: 25%, p=0.19). The distance between the two colonic edges (group 1: 0.51 microm; group 2: 1.34 microm; group 3: 0.53 microm, p=0.18), the diameter of the lumen at the site of the anastomosis (group 1: 2.92 microm; group 2: 4.06 microm; group 3: 3.2 microm, p=0.9) and the largest diameter of the lumen proximally to the anastomosis (group 1: 2.05 microm; group 2: 3.1 microm; group 3: 2.6 microm, p=0.25) were not different between the groups. Histological parameters of wound healing were not significantly different for the three groups. In this mice study no macroscopic and microscopic differences were observed between colon anastomosis with 5 stitches versus 12 and >30 stitches. This might indicate that local ischemia does not negatively influence colonic wound healing.

Introduction

Anastomotic leakage (AL) is a major complication in colorectal surgery and leads to significant morbidity and mortality [1]. Prevention of this dreaded complication has been investigated with regard to different surgical aspects, including amongst many others deviating ileostomy, routine draining and sealing of the anastomosis [2-5]. When surgical anastomotical technique is closely looked at, a recent review by Ho et al. illustrates that both a superior construction as well as a superior technique lack [6]. Regional colonic perfusion is a well studied subject and has shown to have many different anatomical variations [7]. Many authors agree that meticulous care of regional perfusion must be taken in order to prevent ischemia of the anastomosis, although literature is not anonymous. Komen et al showed superior perfusion of the anastomosis in rectum resection using a "low-tie" technique, preserving the left colonic artery [8]. Vignali et al showed a positive correlation between decrease in regional perfusion and AL although a recent retrospective study of Lehmann showed no increased risk of AL after sacrificing the complete inferior mesenteric artery [9, 10]. Next to this, an experimental study in rats showed no decreased bursting pressure of colon anastomosis in rats, after the colon was pedicled and had shown reduced oxygenation [11].

The role of local anastomotic ischemia on anastomotic healing is equally unclear. Monitoring micro perfusion intraoperatively is possible by visible light spectroscopy and seems to predict postoperative AL, although a recent review concludes that this and many other similar techniques for monitoring micro perfusion are far from ideal and need further research before clinical implementation [12, 13]. Disruption of local micro perfusion by staples induces necrosis due to the small interstaple distance, not withstanding the fact that this does not lead to worse results compared to hand sewn anastomosis [14]. Paradoxically, in the hand sewn anastomosis many surgeons would take great care not to tie sutures too tight in order to prevent local ischemia and subsequent necrosis. To elucidate the effect of local ischemia on colonic anastomotic healing this study was set up in a hand sewn experimental colonic anastomosis model.

Methods

Animals

From previous research from our own group (Komen et al. 2009), it is known that anastomotic leakage is induced in 44% of the murine population, using 5 sutures for the colon anastomosis. It was hypothesized that this percentage would be reduced

to 25% when more sutures would be applied. Using a standard deviation of 12,5% and a desired power of .80 a sample size of 7 animals per group was needed. To compensate for expected non AL-related deaths, 5 additional mice per group were added. Consequently 36 male C57B6 mice were used for this experiment. Animal age was 2 months and their weight varied from 25 to 30gr. All animals were operated after an acclimatization period of 7 days. Animals were kept per 4 animals in cages, in which a 12hr light/dark cycle, room temperature and normal humidity were maintained. There was free access to unlimited water and commercial chow. The local animal ethical committee approved the study (DEC reference 105-09-14).

Surgical considerations

All animals were operated under isoflurane anaesthesia at day 1. The abdomen was shaved and entered through a midline laparotomy. The colon was transversely divided 1-2 centimetres distally to the ileocecalvalve, taking great care that the mesentery was not damaged. In group 1 the colon was anastomosed in an end-to-end running fashion using 5 stitches of monofilament nonresorbable 8-0 wire (Dafilon, Braun, Germany), in group 2 12 running stitches were used and in group 3 a minimum of 30 running stitches was used, in group 1 leading to approximately 1.25 mm distance between sutures, in group 2 0.5 mm/suture and in group 3 0.2 mm/suture (Figure 1). All anastomosis were constructed in an everting full thickness fashion.

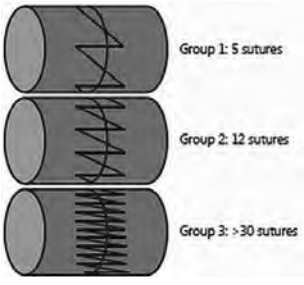

Figure 1. Distribution of sutures over the anastomosis.

The abdominal wall and skin were closed independently using a braided 5-0 running suture (Safil, Braun, Germany). After the operation the animals were kept under a heating lamp and received 2ml of 0.9% sodium subcutaneously. Mice were weighed daily from day 2 till day 6. At day 7, general anaesthesia was achieved using isoflurane and a relaparatomy was performed. Great care was taken dissecting the anastomosis from its adhesions. The anastomosis was resected together with an adjacent 2 cm of colon and mesentery. Animals were terminated by cardiac transsection at the end of the operation.

Macroscopic findings

After 7 days relaparotomy was performed and macroscopic findings, such as abscesses, adhesions or gross AL, were documented. In case of preliminary death section was performed and cause of death was reported. Macroscopic findings, such as abscesses or faecal contamination of the peritoneum were documented during relaparotomy. An abscess was defined as a well contained collection of pus in the direct vicinity of the anastomosis; faecal leakage was defined as diffuse presence of faeces in the presence of a dehiscence of the anastomosis. Both entities were considered AL and represented the primary endpoint of the study.

Histological examination

Directly after excision, the anastomosis was fixed in formalin and within two days embedded in paraffin. Per animal 2 coronal coupes were made (Figure 2) and examined by the same pathologist (KM).

Histology parameters included presence of inflammatory cells (lymphocytes, polymorph neutrophils), fibroblasts, necrosis, muscular and epithelial regrowth, collagen fibres. Every parameter was scored in an ordinal fashion (none = 1, mild = 2, moderate = 3, severe = 4). Microscopically the apposition of the two bowel segments was measured as well as the thickness of the fibrotic cap that covered the anastomosis.

Statistics

All data was analysed using SPSS. Data were presented as mean values with standard deviation. For non-parametric ordinal and nominal samples the Kruskal-Wallis test was used for comparing the three groups, no post hoc analysis was performed. Pearson's test was used for correlation. P-value < 0.05 was considered significant.

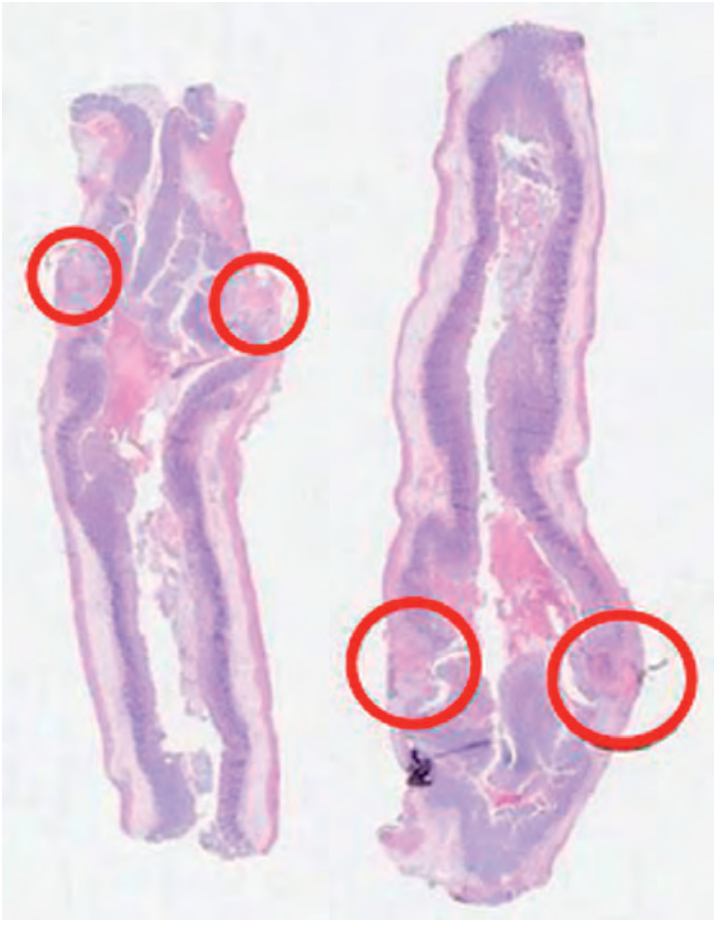

Figure 2. Coronal samples of the murine colon. Circles indicate the anastomosis.

Results

Macroscopy

All animals experienced a certain amount of weight loss, those surviving until relaparotomy showed an increase in weight from day 5. Distribution of weight was not significantly different between the three groups (Figure 3).

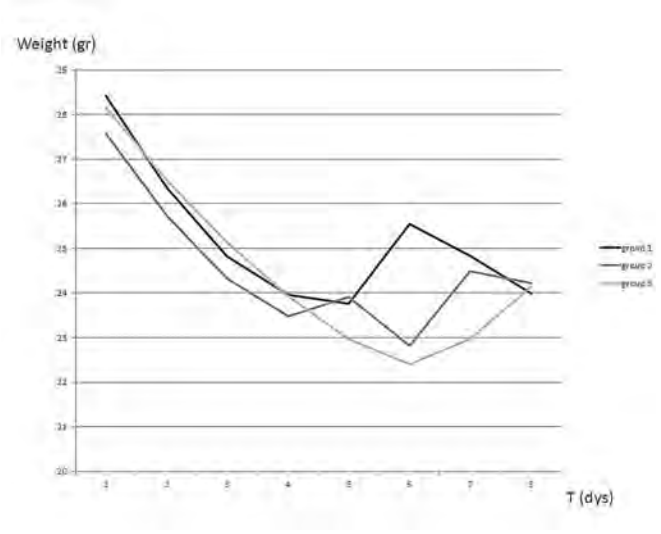

Figure 3. Weight distribution over time of the three groups.

16 Of 36 mice (44%) died before the end of the experiment. Mortality was not significantly different between the groups (group 1: 5/12, group 2: 4/12, group 3: 7/12, p=0.72, Table 1). In 6 animals (6/36, 17%) faecal leakage occurred. Incidence of faecal leakage was not significantly different between the groups (group 1: 3/12, group 2: 2/12, group 3: 1/12, p=0.56, Table 1) did not differ. Faecal leakage is significantly correlated to death in group 1 and group 2 but not in group 3 (group 1: 3/5, 60%, r=0.68, p=0.01; group 2: 2/4, 50%, r=0.63, p=0.03; group 3: 1/7, 14%, r=0.3, p=0.3). Abscesses were found in 3 animals in group 1 (3/12, 25%), zero in group 2 (0/12, 0%), en 2 in group 3 (2/12, 17%), which was not significantly different (p=0.56, Table 1). Abscesses as a cause of death were observed in zero animals in group 1 (0/5, 0%), zero animals in group 2 (0/4, 0%) and 1 in group 3 (1/7, 14%), with no significant correlations to mortality in all groups. When scores for faecal and purulent leakage were added, AL was observed in 6 animals in group 1, 2 in group 2, and 3 in group 3 (group 1: 50%, group 2: 17%, group 3: 25%, p=0.19).

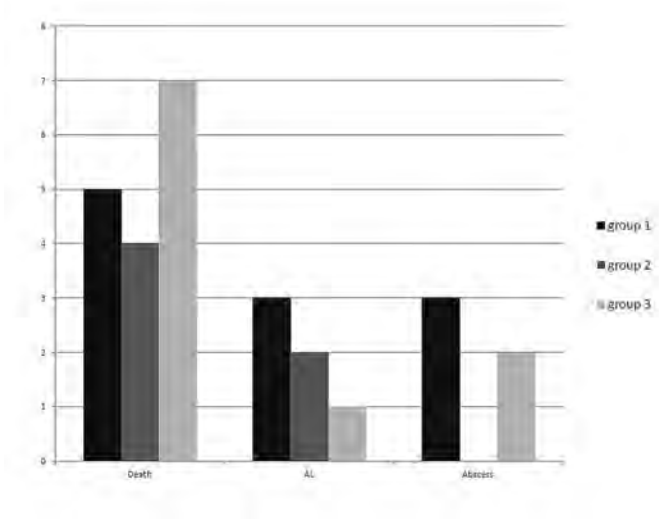

Table 1, Outcome of animals. Death, leakage and abscess formation.

Other causes of death included ileus due to herniation of small bowel (n=1), ileus due to anastomotic stenosis (n=1) and diffuse purulent peritonitis in the absence of anastomotic dehiscence (n=1). In 6 mice the cause of death could not be identified, none of these animals had abnormalities intra-abdominally.

For 20 surviving animals microscopic analysis was performed. Microscopically measurements of the anastomosis were carried out. These include the distance between the two colonic edges (group 1: 0.51 microm; group 2: 1,34 microm; group 3: 0,53 microm, p=0.18), the diameter of the lumen at the site of the anastomosis (group 1: 2.92 microm; group 2: 4.06 microm; group 3: 3.2 microm, p=0.9) and the largest diameter of the lumen proximal to the anastomosis (group 1: 2.05microm; group 2: 3.1 microm; group 3: 2.6 microm, p=0.25).
As depicted in (Figure 4), healing of the everting anastomosis occurred by formation of a fibrotic cap.

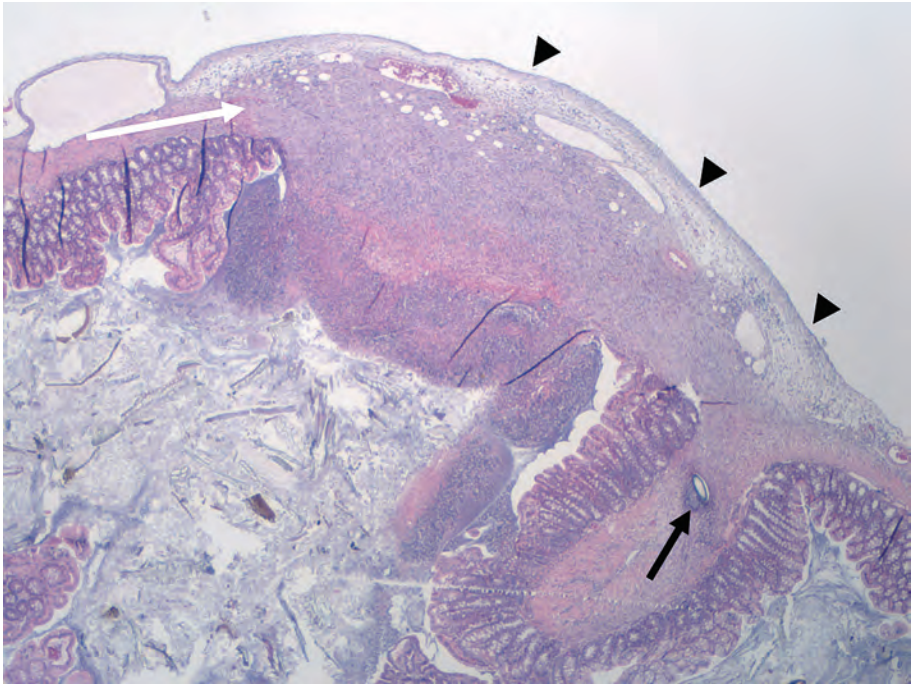

Figure 4. Close up of anastomosis. The fibrotic cap (black arrowheads) covering the anastomosis. Initiation of fibroblast ingrowth from the submucosal layer can be seen (white arrows) as well as the suture (black arrow).

This cap forms a matrix for fibroblasts, which derive from the submucosal layer as seen in figure. The thickness of this fibrotic cap was not significantly different between all groups (group 1: 0.49 microm; group 2: 0.44 microm; group 3: 0.33 microm, p=0.67). Underneath this sheet practically all animals had microabscesses with diameters varying from 1 to 4.5 microm.

For histological parameters of wound healing results are not significantly different for the three groups. Median score for all groups for necrosis was 'none', inflammatory cell infiltration was 'severe', infiltration of fibroblasts was 'severe' and collagen formation was 'moderate'. Early re-epithelialisation was observed in all groups to a 'moderate' extend; no significant differences were seen between all groups.

Discussion

Ischemia plays a role in colonic AL and can be divided into local ischemia at the very anastomotic site and regional ischemia. This study shows that increased local ischemia by disturbance of microcirculation due to a large abundance of sutures at the site of a colorectal anastomosis in mice, does not lead to increased AL or decreased wound healing. Furthermore, compared to the control group of 12 sutures (group 2) and a leakage group of 5 sutures (group 1), group 3 did not show differences in microscopic evaluation of inflammatory reaction, fibroblast proliferation and re-epithelisation. A few arguments can be made for these findings. Primarily, during the first 1-4 days of anastomotic wound healing mature collagen degrades under the influence of matrix metalloproteinases (MMP's) [15]. Colonic anastomoses are weak during those first days and apposition of the wound edges depends largely on the suture holding capacity of the collagen. Thus in the first few days many sutures would be advantageous. Secondly due to disturbance of microcirculation, necrosis would be more pronounced between sutures and colonic edges in the group 3. Necrosis leads after 24 hours to a subsequent inflammatory reaction. Since in our study we sacrificed the animals after 7 days, no necrosis of any importance could be observed in all groups. There was no difference in the amount of inflammation between the groups. Re-epithelisation starts at day 3-5 and could be observed in our groups without any difference between the groups. Probably this is explained by the fact that full epithelial regrowth is predominantly determined by the distance between the mucosa on either side of the colonic edges, which was not different between the groups [16].

In our study the same patterns of wound healing at day 7 could be observed as in previous studies with a rat model such as absence of necrosis, appearance of fibroblast bridging of the anastomosis and inflammatory cell infiltration (lymphocytes and polymorph neutrophils) [17]. Although in humans it is common practise to perform hand sewn anastomosis in an inverting fashion, in mice it is practically impossible due to the small size of the colon [18]. Therefore in this study anastomosis were performed in an everting fashion. In contrast to humans, in experimental studies everting anastomosis cause more adhesions, but less stenosis and comparable leakage rates [19]. Local ischemia was not quantified in our study, nevertheless, it was objectified that the intersuture interval was much smaller in group 3 than in group 1. Waninger et al showed that in rats a smaller intersuture distance lead to improved apposition compared to a large interval (1,5mm vs. 2,5mm). In our study this corresponded to group 2 and group 1 respectively [20]. More sutures per mm

theoretically lead to even better apposition. In our study this could not be observed, since the width between colonic wound edges did not differ significantly at day 7. This could be explained by the fact that at that time wound apposition is not determined anymore by the sutures but rather by the fibrotic cap and infiltrating myofibroblasts that induce wound contraction. Other factors influencing apposition might be of importance, as tension-free position of the anastomosis, the length of the anastomosis and the configuration. It is arguable that a tension-free, wide side-to-side anastomosis has better apposition than a strained end-to-end anastomosis, regardless of the amount of suture that is used or the applied tension on the wire.

In our study there was a significant mortality. Only partly this was caused by AL, which developed in 9 animals, 7 of these animals died. Previously our group has shown that creating a colonic anastomosis in mice using 12 sutures led to AL in 11%, corresponding with the present study(17%) [21]. By reducing the amount of sutures and therefore reducing the apposition but also preserving the microcirculation, the current study shows an increase in leakage up to 50%, again corresponding to previous research [21]. Creating very tight apposition and disruption of microcirculation by many sutures in group-30, the incidence of AL was 25%, without negative influence on histological features of the anastomosis. According to this data, it seems that apposition is more important in colonic healing, than the microcirculation at the anastomotic site, with fibrous tissue healing occurring mainly perianastomotically. These findings support the development of new anastomotic techniques of maximal apposition like sealing or gluing with or without staples or sutures.

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2.2 Influence of local ischemia on anastomotic healing in rats

Small intersuture distance does not negatively influence colorectal anastomotic healing
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Submitted J. of Gastrointestinal Surgery

Abstract

Local ischemia induced by sutures is commonly regarded as a factor that influences anastomotic healing negatively. As a consequence in sutured anastomosis this principle might result in large intersuture distance and loose apposition taking care not to disrupt local perfusion. This study was set up to investigate the influence of the intersuture distance on anastomotic healing. 141 Male Wistar rats were divided in two groups. In group 1 both colorectal anastomoses were created using 12 sutures, in group 2 >30 sutures were used. After 2, 4, 7, 14, or 28 days after the primary operation, anastomotic bursting pressure (ABP), intraabdominal adhesions and anastomotic leakage and stenosis were measured. Furthermore microscopic evaluation was performed. During sacrifice at day 7, adhesions around the proximal anastomosis of group 2 had a significant higher Zühlke-score (group 1: 1.9, group 2: 2.7, p = 0 .044) than the adhesions of group 1. Microscopic scoring of the anastomosis showed significantly higher scores for acute inflammation (group 1: 2.75, group 2: 3.40, p = 0.023) and necrosis (group 1: 1.50, group 2: 2.47, p = 0.011) after 2 days in group 2. No differences were seen for anastomotic leakage, ABP, stenosis and the other microscopic parameters at all time points. This study shows that increased numbers of sutures in colorectal anastomosis caused more necrosis and an increased acute inflammatory reaction after 2 days. However, anastomotic healing was uneventful.

Introduction

During construction of a colorectal anastomosis, surgeons pay careful attention to its vascularisation as poor perfusion predisposes for anastomotic leakage[1]. Anastomotic ischemia can be assessed by visualisation and palpation of the mesenteric vessels, the aspect of the serosal surface of the colonic edge and gross bleeding of the site of the anastomosis[2]. Objective measurement of the perfusion of the anastomosis has been shown to be feasible, using Doppler, near infrared and visible light spectroscopy and laser fluorescence angiography[1,3,4]. Although promising in terms of standardisation and comparison of anastomotic perfusion, neither correlation of impaired perfusion with anastomotic leakage (AL) nor cut-off values exist for these techniques. Secondly, although previous studies have shown detrimental effects of reduced perfusion on anastomotic healing[5,6], other studies do not identify reduced regional perfusion as risk factor for AL[7,8]. Lastly, even when regional perfusion of the anastomosis is optimal, local ischemia might be induced by stapling or by sutures. Although many surgeons are trained according to the dogma that the anastomotic healing occurs in between the separate stitches, this statement has been seemingly proven wrong with the successful introduction of stapling techniques that allow virtually no space between the staples. Until recently little research had been performed on the balance between local anastomotic ischemia and concomitant necrosis induced by sutures on the one hand and approximation and apposition of the anastomotic edges on the other. A previous study from our group showed in a murine model that smaller intersuture distances did not lead to AL induced by local ischemia[9]. Therefore it was concluded that apposition is probably more important than preventing local ischemia. Since these conclusions were based on a small group of small animals and anastomoses were created in an everting fashion and analysed at just one single time point, this study was designed to further translate these results towards the human situation.

Methods

Animals

141 male Wistar rats were used for this experiment. Animal age was at least 2 months and their average weight was 375gr. All animals were operated after an acclimatization period of at least 7 days. Animals were kept per 2 animals in individually ventilated cages, in which a 12hr light/dark cycle, room temperature and normal humidity were

maintained. There was free access to unlimited water and commercial chow. The local animal ethical committee approved the study (DEC reference 105-11-10).

Surgical considerations

All animals were operated under general anaesthesia (isoflurane 2%, FiO2 60%) at day 1, additionally 0,05 mg/kg buprenorfine was administered subcutaneously. The abdomen was shaved and entered through a midline laparotomy. The descending colon was transversely divided 3,5 - 4cm proximally to the peritoneal reflection, taking care that the mesentery was not damaged. Two small swabs were introduced transanally, were guided in the proximal anastomotic edge and served as canula over which the anastomosis was created. When this proximal anastomosis was finished, an additional anastomosis was performed in the same manner approximately 1cm proximally to the peritoneal reflection. In group 1 both anastomoses were performed in an end-to-end running fashion using 12 stitches of monofilament nonresorbable 8-0 wire (Dafilon, Braun, Germany), in group 2 >30 stitches were used. This led to approximately 1.5mm distance between sutures in group 1 and 0,6mm in group 2. All anastomoses were constructed in an inverting fashion (Figure 1).

The abdominal wall and skin were closed independently using a braided 5-0 running suture (Safil, Braun, Germany). After the operation the animals were kept under a heating lamp and received 5ml of 0.9% sodium subcutaneously. The weight and wellness of the animals were closely monitored until termination of the experiment. Animals were sacrificed at 2, 4, 7, 14, or 28 days after the primary operation. Before sacrifice, a relaparatomy was performed under isoflurane general anaesthesia. Great care was taken dissecting the anastomosis from its adhesions, which were scored according to Zühlke's grading system (Appendix 1)[10].

Grade	Observation
0	No adhesions
1	Filmy adhesions: easy to separate by blunt dissection; no vascularization
2	Stronger adhesions: blunt dissection possible but partly sharp dissetion possible (beginning of vascularization)
3	Strong adhesions: lysis possible but sharp dissection only; clear vascularization
4	Very strong adhesions: lysis possible by sharp dissection only (organ strongly attached with severe adhesions and damage of organs hardly preventable)

Appendix 1. The Zühlke grading system for peritoneal adhesions.

Standard scoring of signs of macroscopic AL (evident faecal leakage or juxta-anastomotic abscesses) or stenosis was performed. The proximal anastomosis was resected and anastomotic bursting pressure (ABP) was performed on this section, according to the method described in a previous study from our group[11]. Bursting pressure was not measured in the animals that were sacrificed at day 28 since after more than 20 days no difference between the groups was expected[12]. The distal anastomosis was taken out for pathological analysis, since the anastomosis would be unaffected by the measurement of the ABP. Animals were euthanized at the end of the operation.

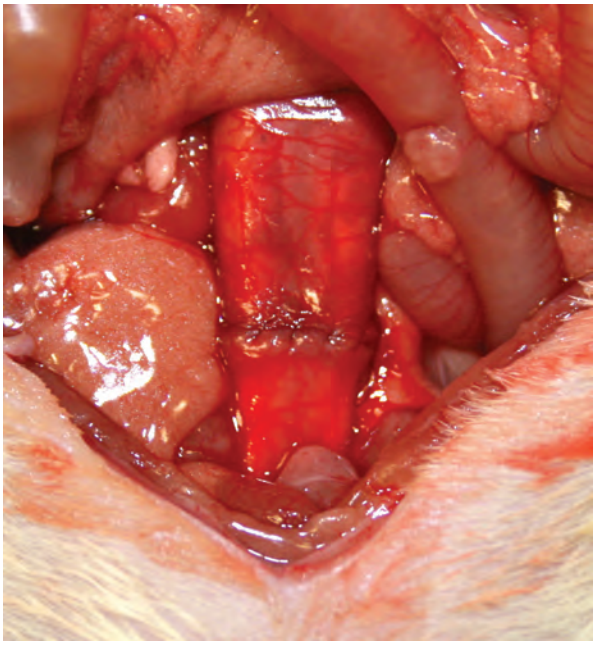


Figure 1. Inverting colorectal anastomosis in a rat, using 12 sutures.

Histological examination

Directly after excision, the distal anastomosis was fixed in formalin and embedded in paraffin within two days. Per anastomosis, 2 coronal coupes were made and examined by the same pathologist (KM). Histological parameters included the presence of acute inflammatory cells (neutrophilic granulocytes), chronic inflammatory cells (lymphocytes and monocytes), fibroblasts, necrosis, muscular and epithelial regrowth and collagen fibres (Figure 2). Every parameter was scored in an ordinal fashion (none = 1, slight= 2, mild = 3, severe = 4).

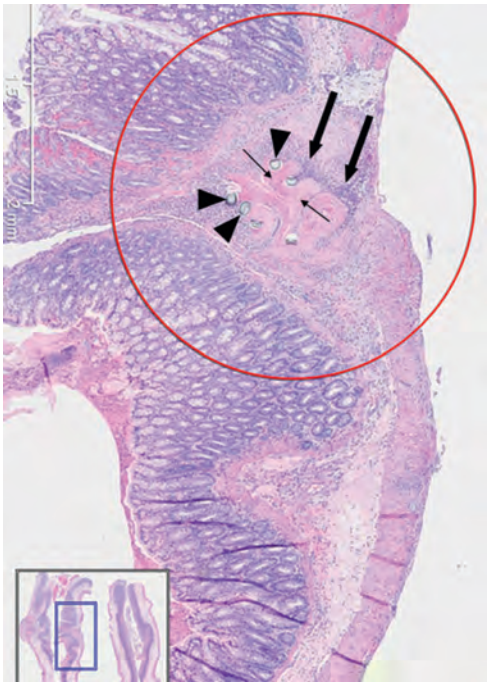


Figure 2. Microscopic evaluation was carried out on coronal slides. A red circle indicates the anastomotic site. The sutures (arrow heads) and necrosis (small arrows) as well as surrounding acute inflammatory reaction (large arrows) are clearly visible.

Statistics

All data was analysed using SPSS. Data were presented as mean values with standard deviation for continuous data. For nominal samples the Chi²-test was used. For continuous and ordinal data the Mann-Whitney-U-test was used. When >2 groups were compared, the Kruskal Wallis test was used. P-value < 0.05 was considered significant.

Results

Group 1 vs. group 2

During sacrifice at day 7, adhesions around the proximal anastomosis of group 2 had a significant higher Zülhke score than the adhesions of group 1 (group 1: 1.9; group 2: 2.7; p = 0 .044). No significant differences between both groups were found for AL, anastomotic stenosis, and juxta-anastomotic adhesions at the other points in time (Table 1).

	2 days			4 days			7 days			14 days			28 days		
	group 1	group 2	p	group 1	group 2	p	group 1	group 2	p	group 1	group 2	p	group 1	group 2	p
weight at sacrifice (mean; gram)	379	382	p = 0.920	352	361	p = 0.421	372	384	p = 0.474	416	392	p = 0.126	367	366	p = 0.825
macroscopic anastomotic leakage															
proximal (n / total)	0 / 12	0 / 16	n.p.	1 / 14	3 / 14	p = 0.280	1 / 16	2 / 11	p = 0.332	0 / 11	0 / 16	n.p.	0 / 17	0 / 12	n.p.
distal (n / total)	0 / 12	0 / 16	n.p.	1 / 14	2 / 14	p = 0.541	0 / 16	0 / 11	n.p.	0 / 11	1 / 16	p = 0.398	0 / 17	0 / 12	n.p.
anastomotic stenosis															
proximal (n / total)	3 / 12	0 / 16	p = 0.067	0 / 14	1 / 14	p = 0.309	0 / 16	0 / 11	n.p.	0 / 11	2 / 16	p = 0.223	0 / 17	0 / 12	n.p.
distal (n / total)	4 / 12	6 / 16	p = 0.820	6 / 14	6 / 14	p = 1.00	6 / 14	6 / 14	p = 0.332	1 / 11	3 / 16	p = 0.488	3 / 17	2 / 12	p = 0.945
juxta-anastomotic adhesions															
proximal (mean; mean Zühlke score)	0.66 1.2	0.69; 1.6	p = 0.971 p = 0.593	1.2 1.2	1.4 1.8	p = 0.568 p = 0.055	1.8 1.9	2.5 2.7	p = 0.090 p = 0.044	2 2	1.9 1.9	p = 0.834 p = 0.655	1.3 1.9	1.4 2.1	p = 0.745 p = 0.948
distal (mean; mean Zühlke score)	0.33 1	0.77 1.1	p = 0.173 p = 0.593	1 1.1	1.8 1.5	p = 0.130 p = 0.90	1.3 1.6	1.6 2.2	p = 0.524 p = 0.091	1.7 2.2	1.9 2.2	p = 0.607 p = 0.607	1.5 1.6	1.7 1.8	p = 0.646 p = 0.949
ABP (mean; mmHg)	63	67	p = 0.790	68	50	p = 0.285	190	156	p = 0.336	222	247	p = 0.190			

Table 1. Macroscopic parameters. n.p. = Not possible, ABP = Anastomotic Bursting Pressure

When ABP was measured for both groups, no significant differences were found (Chart 1). No difference between group 1 and 2 was found for weight at all time points.

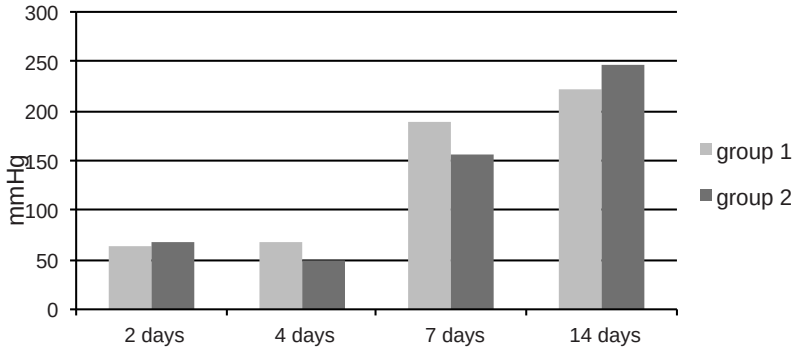
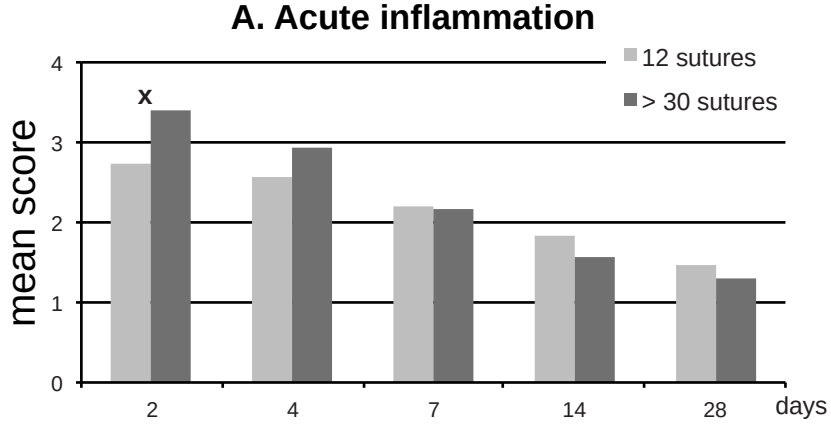


Chart 1. Anastomotic bursting pressure.

Microscopic scoring of the anastomosis showed significantly higher scores for acute inflammation (group 1: 2.75; group 2: 3.40; p = 0.023) and necrosis (group 1: 1.50; group 2: 2.47; p = 0.011) after 2 days in group 2, no other parameters showed significant difference between the two groups at this and the other points in time (Chart 2).



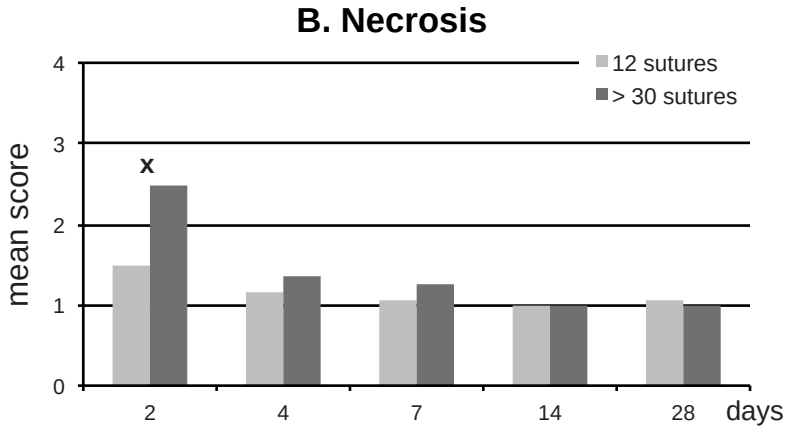
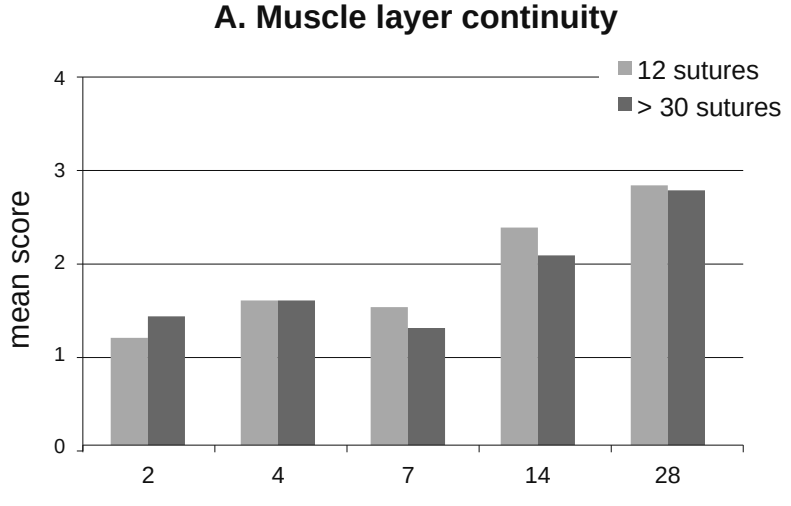


Chart 2 . Microscopic parameters for anastomotic healing. A. Acute inflammation, B. Necrosis. X = significantly different.

Changes over time

Over time both groups showed a significant higher bursting pressure after day 4 ($p < 0.001$ for both groups 1 and 2; (Chart 1)). Microscopic evaluation revealed a significantly lower score for acute inflammation ($p < 0.001$ for both groups 1 and 2) and necrosis ($p < 0.001$ for both groups 1 and 2) over time in both groups (Chart 2). Both groups showed significantly higher scores for muscle layer continuity ($p < 0.001$ for both groups 1 and 2) and epithelisation ($p < 0.001$ for both groups 1 and 2 (Chart 3)).



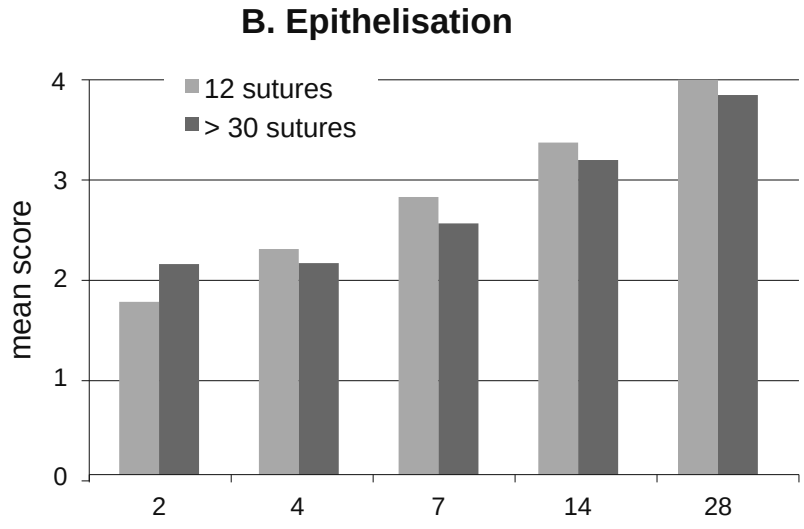
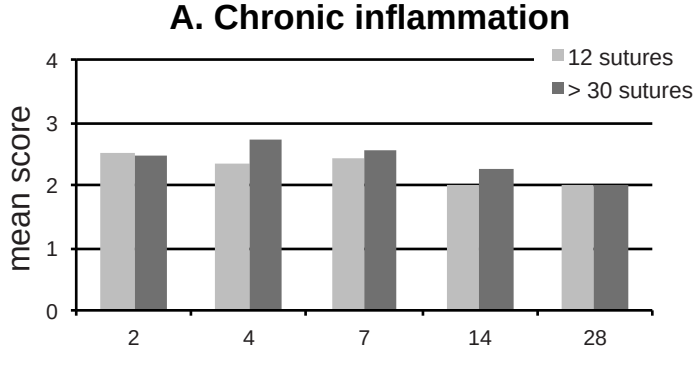


Chart 3. Microscopic parameters for anastomotic healing. A. Muscle layer continuity, B. Epithelisation.

The scores for chronic inflammation were significantly lower at the later time points in group 2, but not in group 1 (group 1: $p = 0.06$; group 2: $p = 0.01$ (Chart 4A)). In both groups fibroblasts were present with a significant peak around 7 days after which a reduction was seen ($p < 0.001$ for both groups 1 and 2; Chart 4B). A similar pattern over time was seen for collagen scores in both groups albeit those highest values were measured at day 14 (Chart 4C).



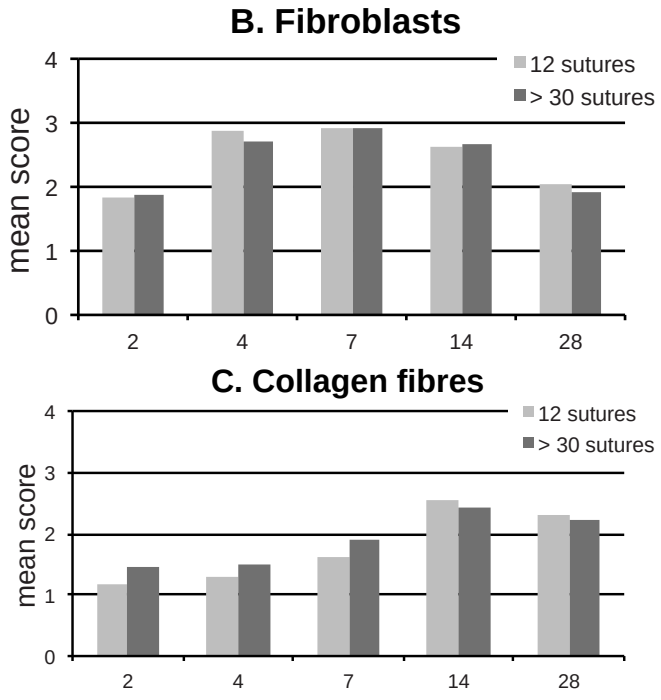


Chart 4. Microscopic parameters for anastomotic healing. A. Chronic inflammation, B. Fibroblasts, C. Collagen fibres.

Discussion

This study shows that very small intersuture distance resulting from an increased number of sutures in experimental colorectal anastomosis caused more necrosis and an increased acute inflammatory reaction after 2 days. However, this study also shows that in both groups a similar pattern of anastomotic healing occurred. This pattern was characterised by an acute inflammatory response, followed by proliferation of fibroblasts peaking at day 7 and collagen fibres at day 14. Remodellation of the anastomosis occurred after day 14 with reduction of acute and chronic inflammation and reduction of fibrosis and collagen, while muscle layers and epithelisation reached complete continuity. These observations are in line with previous literature, showing fibrinous covering of the serosal side of the anastomosis in normal anastomotic wound healing[13].

Local perfusion between sutures (or staples) seems to be, based on these findings, of less importance than regional perfusion as has been shown by others[3,14,15]. This supports the formerly established finding that during the first days of anastomotic healing, the anastomotic strength mostly relies on strong watertight apposition

supported by sutures or staples. Although an acute inflammatory process, mostly located at the serosal side of the anastomosis, accompanies colorectal anastomotic healing, these micro abscesses do not seem to impair anastomotic healing. Muscle layer continuity and reepithelisation reach their maximum at day 28.

These results correspond with the result of a previous study by our group showing that anastomosis created with > 30 sutures did not manifest inferior healing capacities compared to anastomosis with 12 or 5 sutures in a murine model after 7 days[9]. The current study does not only support these findings in a larger number of animals of a higher species, but also showed that over time the healing properties of both group showed the same pattern of reduction of necrosis and inflammation. This anastomotic necrosis was seen at day 2 as small necrotic patches of tissue in the direct proximity of the suture. Inflammation was seen both in abundance as a reaction to improper suturing such as eversion of the colonic edges, but also in a lesser extent in well apposed inverting anastomoses that still allowed microscopic leakage of bowel content. This implicates that a limited amount of acute inflammation is part of normal anastomotic wound healing and that inversion of the anastomosis helps to restrict it.

In human colorectal surgery, inversion of the hand-sewn anastomosis is supported by level 1B evidence from 1970[16]. Just as many different types of suture bites lead to exclusion of the mucosa and subsequent inversion, also the increase of amount of sutures contributes to proper inversion of the whole length of the anastomosis. Fear of disruption of the microcirculation by many sutures is not supported by this study.

In conclusion, this study rejects the surgical dogma that colorectal anastomotic healing occurs in between the sutures and that surgeons should take care not to place their sutures too close to the other. The study shows that although more necrosis and inflammation were present after 2 days in the rats with > 30 sutures per anastomosis, this did not lead to worse anastomotic healing properties. As a consequence adding extra sutures in case of doubtfully large intersuture spaces is better than avoiding them.

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2.3 Review of technique for creation of colorectal anastomosis

Systematic review of the technique of colorectal anastomosis
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JAMA Surgery 2013 Feb;148(2):190-201

Abstract

Many different techniques of colorectal anastomosis have been described in search for the technique with the lowest incidence of anastomotic leak. A systematic review of leakage rates of techniques of handsewn colorectal anastomosis was conducted, to provide a guideline for residents and promote standardization of its technique. Clinical and experimental articles on colorectal anastomotic techniques and ananstomotic healing published in the past 4 decades were searched. We included evidence on suture material, suture format, single- vs double-layer sutures, interrupted vs continuous sutures, handsewn vs stapled and compression colorectal anastomosis, and anastomotic configuration. In total, 3 meta-analyses, 26 randomized trials, 11 nonrandomized comparative studies, 20 cohort studies, and 57 experimental studies were found. Results show that, for many aspects of the technique of a hand-sewn colorectal anastomosis, evidence is lacking. A single-layer continuous technique using inverting sutures with slowly absorbable monofilament material seems preferable. However, in contrast to stapled and compression colorectal anastomoses, the technique for hand-sewn colorectal anastomoses is non-standardized with regard to intersuture distance, suture distance to the anastomotic edge, and tension on the suture. We believe detailed documentation of the anastomotic technique of all colorectal operations is needed to determine the role of the hand-sewn colorectal anastomosis.

Introduction

Construction of a colorectal anastomosis is a hallmark of surgical training. However, although surgical residents can refer to key publications with evidence based conclusions for many topics, mere imitation of an experienced surgeon traditionally is considered the basic source for the technique of hand-sewn colorectal anastomosis. The large variety of anastomotic techniques is one of the main difficulties in the interpretation of the literature. Anastomotic leakage (AL) following colorectal resection is a major problem of surgical care, with an incidence between 3-19%[1-4]. Although accurate prediction of risk is impossible, certain factors are known to contribute to AL, including surgeon-related factors (e.g. increased incidence of AL in a colorectal anastomosis constructed after hours[5], and the positive role of specialization on complications in colorectal surgery[6]) and patient-related risk factors (e.g., the inverse relationship between the height of colorectal anastomosis from the anal verge and the leak rate[7-12]). Decades of research have resulted in many studies investigating different techniques for constructing colorectal anastomosis in search for the safest method. Appreciating the conclusions from this extensive research is essential for the quality of colorectal surgery and for the resident being trained in colorectal surgery. Our aims were to perform a systematic review of all aspects of the technique of hand-sewn colorectal anastomosis, and compare hand-sewn with mechanical colorectal anastomosis to provide a guideline for residents and to promote standardization of the technique.

Methods

Search strategy

A literature was searched using Medline, Embase, and Cochrane databases for studies between Janueary 1, 1970 and February 1, 2011, using the key words presented in the eFigure (http://www.jamasurg.com). The search was restricted to articles published in English, Dutch and French. References in the selected publications were searched for additional studies.

Study selection

Clinical as well as experimental studies were selected to address several aspects of the technique of hand-sewn colorectal anastomosis. These included:

1. Suture material
2. Suture format (size of suture bites, in-between distance of bites, suture tension, configuration of the bite, and inverting versus everting sutures)
3. Single- vs double-layer colorectal anastomosis
4. Interrupted vs continuous sutures
5. Hand-sewn vs stapled colorectal anastomosis
6. Hand-sewn vs compression colorectal anastomosis
7. Configuration of colorectal anastomosis (end-to-end (ETE), end-to-side (ETS), side-to-end (STE), side-to-side (STS), length of the side-limb, length of the enterotomy)

Inclusion criteria for clinical studies

Only clinical articles comparing 2 or more colorectal anastomotic techniques with regard to clinical AL were considered relevant. When only 1 comparative study was available on a particular subject, clinical cohort studies were added to the selection. Results were analysed only if the study groups and results were clearly described with proper statistical analysis.

Inclusion criteria for experimental studies

Experimental articles were selected when comparing 2 or more colorectal anastomotic techniques together with objective measurements for anastomotic healing: AL, anastomotic bursting pressure (ABP), anastomotic breaking strength, histologic results, or collagen concentration. When 2 studies were reported by the same institution, either the better quality study or the most recent publication was included. As with clinical studies, results were analysed only if the study groups and results were clearly described with proper statistical analysis. However, the lack of statistical analysis of histological findings in experimental studies was accepted.

Exclusion criteria

Because the healing of small-bowel anastomoses is different and the incidence of AL lower compared with large-bowel anastomoses, studies including both procedures without differentiating the results and statistical analysis were excluded. Ileocolic anastomoses after right hemicolectomy or ileocecal resection represent healing of

the colon, and were therefore included. Studies reporting radiological AL without distinction of clinical AL were excluded, as were studies reporting only on emergency operations, children, and colo-anal anastomosis or pouches. Results of experimental studies measured directly after the construction of colorectal anastomosis were not taken into account because these do not reflect anastomotic healing.

Data extraction for clinical studies

Two physicians (J.C.S. and F.D.) entered data in a database following standard protocols. Seven factors were considered for clinical studies. These included:

- First author and year of publication
- Level of evidence (following the Centre of Evidence Based Medicine, University of Oxford)
- Study design
- Number of patients
- Location of anastomosis in gastrointestinal tract
- Definition of outcome by the authors (AL, clinical AL, radiological AL)
- Results and statistical analysis

Data extraction for experimental studies

Six factors were considered for experimental studies. These included:

- First author and year of publication
- Study design
- Number of animals per group
- Species
- Outcome factors for anastomotic healing (AL, ABP, breaking strength, histology, or collagen-concentration)
- Results

Results

The literature search identified 6168 articles. 1443 articles remained after duplicates were removed. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyeses) flowchart in figure 1 shows the selection of studies: 117 studies were included in the systematic review.

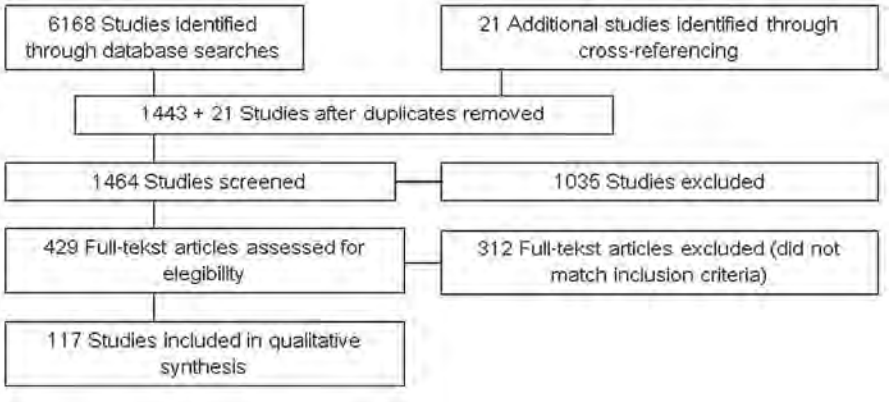

Figure 1. The PRISMA flow-chart: selection of relevant studies.

Included studies and their characteristics are listed in table 1,2,3,4,5,6 and 7, together with all results of outcome measures. The results per research question are summarized herein.

1. Suture material

Decades ago, several materials such as silk, linen, catgut, polyglactin 910, and nylon were commonly used for colorectal anastomosis. Today most gastrointestinal anastomoses, including colorectal anastomosis, are constructed with polydioxanone sutures. Ten experimental studies were included[13-22] (Table 1). Results show that absorbable sutures compared with non-absorbable or slowly-absorbable sutures cause more tissue reaction[16, 17, 20], one study showing absorbable sutures dissolve too rapidly, influencing anastomotic strength[16]. Multifilament compared to monofilament sutures cause more tissue damage and easier adherence of material within the interstices of multifilament sutures[14, 15, 18, 19], providing a basis for infection[23]. Surprisingly, experimental studies on healing of colorectal anastomosis constructed with polydioxanone sutures are scarce; only two studies were included, finding equal ABP and histology between polydioxanone and polyglycolic acid[13, 15]. Non-comparative

experimental studies that did not match the inclusion criteria for the present review have shown that polydioxanone sutures possesses all aspects considered important: monofilament, little histological reaction, slowly-absorbable with long preservation of strength, and low adherence of bacteria to the material[23-26].

Source	Level	No. of cases	Outcome	Results
Clinical				
Gillatt '87 28	1b (RCT)	57pt, colorectal	Clinical AL	AL: PDS 0% (n=30); silk 3,7% (n=27). NS
Clark '77 27	1b (RCT)	194pt, colon	Clinical and radiological AL	24% AL catgut(n=99) vs 8.4% AL polyglycolic acid(n=95). Significant
Experimental				
Andersen '89 13		196 rats	Histology	Polyglactin 910 vs PDS. Equal histologic results at days 7 and 56.
Foresman '89 15		160 rats	ABP	Polyglyconate vs PDS. No significant difference in ABP at days 0-7-14-21-42.
Lord '78 18		30 rats	Histology of the submucosa	Rough surface vs smooth surface. Rough surface (catgut, braided silk, polyglycolic acid) most damage to submucosa. Polyethylene terephthalate coated with polytetrafluoroethylene better, polypropylene best histologic results.
Orringer '77 20		84 dogs	Histology	Silk vs polypropylene vs wire: silk most inflammation, polypropylene less inflammation, wire least inflammation at days 4-7-10-14.
Munday '76 19		44 rats	ABP, histology	Catgut vs polyglycolic acid. Equal ABP and histology at day 7.
Deveney '77 14		60 dogs	Breaking strength, histology	Catgut vs chromic catgut vs polyglycolic acid vs polyglactin 910: equal strength and equal histologic results at day 4-7-14.
Hastings '75 16		127 dogs	Breaking strength, histology, collagen	Absorbable vs nonabsorbable sutures : Absorbable: less breaking strength at day 14-28, equal collagen at day 120, worse histolologic results at day 120.
Letwin '75 17		28 dogs	Histology, ABP	Double layer anastomoses 'chromic catgut-silk' vs 'polyglycolic acid – polyglycolic acid': catgut-silk significantly more suture reaction and lower ABP at day 7.
Pasternak '07 22		85 rats	Breaking strength	Doxycycline (MMP-i) coated sutures vs control carrier-coated sutures: higher breaking strength in doxycycline sutures at day 0-3.
Pascual '08 21		40 rats	AL, ABP	Polyglactin 910 with mesenchymal cells vs polyglactin 910: no difference in AL, no difference in ABP, fewer adhesions in polyglactin 910 with mesenchymal cells at day 4-7-14-21.

Table 1. Included studies and their characteristics (AL= anastomotic leakage, histol= histology, ABP= anastomotic bursting pressure, bstrenght= breaking strength, coll= collagen, blflow= blood flow). NIR= not included in this review (in case a supplemental subgroup was also studied, outside the topic of this review, NS: not significant.

New possibilities of sutures coated with mesenchymal stem cells and doxycycline were explored in 2 experimental studies with promising, but not yet convincing results[21, 22].

Two included randomized clinical trials (RCTs) on suture material fail to achieve a unanimous conclusion, because of the small number of patients included and the different suture materials tested that are rarely used today[27, 28].

In conclusion, on the basis of experimental studies, non-absorbable or slowly absorbable monofilament sutures seem to be the suture of choice for colorectal anastomosis. However there is no level 1 evidence to confirm this hypothesis.

2. Suture format

a. Size of suture bites

Since Lembert[29] described the construction of intestinal anastomoses in dogs using suture bites with 5mm distance to the cut edge nearly 2 centuries ago, this aspect seems to have become less clear in surgical literature. One experimental study was found for this systematic review that investigated the difference in anastomotic strength in rats with sutures placed between 3mm and 1.5mm from the cut edges. Results showed lower breaking strength for small bites, measured at day 2[30]. One RCT by Greenall et al. reporting on the distance of the suture to the wound edge matched the inclusion criteria. They randomly allocated patients to have bowel sutures placed either 5 or 10mm from the cut edges, with no significant differences in AL[31]. Because it is not possible to extrapolate the distances used in a rat model to the clinical situation, we can only conclude from one level 1b RCT that distances of 5 and 10mm from the cut edge will probably give adequate results.

b. In-between distance of bites

Lembert described in 1826 an in-between distance of approximately 1cm between sutures[29]. One experimental study conducted by Waninger et al. investigating the distance between sutures in rats was included in our review. It concluded that a small distance between sutures (1.5mm) improves apposition compared with a large distance (2.5mm)[32]. Neither clinical comparative studies nor cohort studies were found. Again, distances in a rat model are difficult to extrapolate to the patient. Because clinical studies on this topic are lacking, no precise maxim can be distilled from the literature.

Source	Level	No. of cases	Outcome	Results
Size of suture bites - clinical				
Greenall '79 31	1b (RCT)	100pt, colon	Clinical AL	Suture bite 5mm AL 4% (n=50) vs 10mm 6% AL(n=50), NS
Size of suture bites - experimental				
Hogstrom		80 rats	Breaking strength	1.5mm vs 3.0mm distance from wound edges: less breaking strength 1.5mm at day 2.
In-between distance of bites - experimental				
Waninger		432 rats	Histology	2.5mm vs 1.5mm suture distance: 1.5mm better histology.
Suture tension - experimental				
Waninger		432 rats	ABP, histology	No tension vs moderate tension vs high tension on knot: moderate tension better histology, and higher ABP at day 4. No tension: higher ABP at day 7.
Configuration of the bite - clinical				
Leslie '03 37	2b (cohort)	484pt, colon	Clinical AL	Interrupted serosubmucosal stitches: 0.2% AL.
Pye '96 38	2b (cohort)	214pt, colorectal	Clinical AL	Interrupted serosubmucosal stitches: 0.5% AL.
Carty '91 39	2b (cohort)	421pt, colorectal	Clinical AL	Interrupted extramucosal stitches: 2.1% AL.
Lafreniere '8540	2b (cohort)	134pt, colorectal	Clinical AL	Interrupted full thickness (modified Gambee): 0% AL.
Motson '84 41	2b (cohort)	92pt, colon	Clinical AL	Interrupted full thickness (mattress suture): 4.4% AL.
Configuration of the bite experimental				
Krasniqi '09 36		73 rats	Histology	Serosubmucosal (Halsted) vs full tickness (Gambee) vs posterior Gambee/anterior Halsted stitch: better macroscopic and microscopic histology with full thickness.
Houdart '83 35		210 rats	Histology	Extramucosal vs full thickness stitch: equal histology.
Inverting versus everting - clinical				
Goligher '70 52	1b (RCT)	70pt, colon	Clinical AL	AL: 2.9% inverting(n=35) vs 28.6% everting(n=35), significant.
Inverting versus everting – experimental				
Ortiz '75 44		88 rats	AL, histology	Inverting vs everting: no AL, slower healing and equal adhesions with everting.
Irvin '73 47		93 rabbits	AL, ABP, histology	Inverting 1layer vs inverting 2layer vs everting: more AL, lower ABP, and delayed mucosal union with everting.
leDouarec '72 51		65 rabbits	Histology	Direct (everting) vs intraluminal (inverting) sutures: direct more severe inflammation, intraluminal better histological repair.

Table 2. Included studies on suture format.

c. Suture tension

In routine clinical practice, 2 undefined schools of thought seem to exist: the first believes that sutures should be tightened to prevent dehiscence of the anastomosis, and the second considers that sutures should be applied more loosely, allowing maximal perfusion of the cut edges. Again only one rat study[32] investigated this, with moderate tension giving the best histological and microangiographic results. Whether tension on knots could influence the incidence of AL in a clinical setting has not been investigated for interrupted or continuous suturing. On the basis of the literature evaluated in the present review, nothing can be concluded on the proper tension on the thread or on the knot.

d. Configuration of the bite

Historically, all opinion leaders proposed their own configuration of gastrointestinal sutures. Anatomical apposition of all layers promoting primary healing was thought to be important. These days, most surgeons will use a simple through-all-layers technique. From ex vivo studies it is known that sutures through the mucosal layer do not contribute to anastomotic strength[33, 34].

The present review included 2 experimental studies on rat colon, comparing histological results of full-thickness sutures to serosubmucosal sutures. Houdart et al. found no histological differences[35], but Krasniqi et al. found better histological results for full-thickness sutures with equal anastomotic strength[36]. No comparative clinical studies were found on the configuration of the bite. Because of this lack of evidence, we have included cohort studies, reporting low rates of AL for both serosubmucosal and full-thickness suture formats (AL 0% - 4.4%) [37-41].

We can only conclude, using scarce level 2b evidence from the cohort studies evaluated, that both serosubmucosal as full-thickness suture seem to provide low rates of AL. It is clear that the configuration of the suture bite is considered of little interest in studies regarding AL.

e. Inverting vs everting sutures

Since the publication of Lembert[29], surgeons generally have advocated an inverting technique of gastrointestinal anastomosis because it is believed that protruding mucosa will lead to AL. However, in the 1960s, 2 clinical studies showed good healing of everting anastomoses with a low incidence of AL[42, 43]. Between 1960 and 1970, these 2 non-comparative studies were followed by many experimental publications comparing everting with inverting techniques. They failed to achieve

a unanimous conclusion on anastomotic healing; however they were consistent in showing that everting anastomoses cause more adhesions but less stenosis[44-51]. All 3 experimental studies published after 1970 included in this present review seem to show improved anastomotic healing for inverted anastomoses[44, 47, 51]. The only clinical study matching the inclusion criteria was a RCT[52] showing a 5-fold increased incidence of AL in patients receiving an everting colorectal anastomosis compared to those receiving an inverting colorectal anastomosis. No cohort studies matching our inclusion criteria were found. Therefore, on the basis of available experimental and level 1b clinical studies, there seems to be an advantage of inverting over everting colorectal anastomosis; nonetheless level 1a evidence is lacking.

3. Single- vs double-layer colorectal anastomosis

The technique developed by Lembert[29] and later modified by Czerny[53] is based on a double-layer inverting anastomotic technique. In the 19th and the greater part of the 20th centuries, this was the criterion standard for gastrointestinal anastomosis; in the second half of the 20th century, however, the single-layer anastomosis regained attention through the favorable results obtained by Halstead, Gambee, and Gambee et al.[54-56]. The 13 included experimental studies come to the same conclusion: double-layer anastomoses are inferior to single-layer anastomoses because of increased inflammation and diminished circulation[47, 57-68]. One RCT matched the inclusion criteria, showing no significant differences in AL between single- and double-layer colorectal anastomosis in 92 patients[69].

This RCT conducted a subgroup analysis of 25 low colorectal anastomosis, finding a significantly higher incidence of AL in colorectal anastomosis created with the double-layer technique. None of the 3 non-randomized comparative studies included in this review found a significant difference in AL between the 2 techniques[65, 70, 71]. In conclusion, these results, added to the knowledge that single-layer anastomoses take significantly less time to construct and are less costly[72], are in favor of single anastomoses, on the basis of level 1b evidence.

4. Interrupted vs continuous sutures

The question whether to use interrupted or continuous sutures arose when single layer anastomoses became common practice. Six experimental studies were included, showing equivocal results: better serosal apposition[73] and blood flow in continuous sutures[74], with equal results on ABP and histologic examination[35, 75-77]. Randomized controlled trials investigating interrupted and continuous sutures for colorectal

Source	Level	No. of cases	Outcome	Results
Clinical				
Everett '75 69	1b (RCT)	92pt, colorectal	Clinical AL	AL: 5% 1layer(n=40); 4.8% 2layer(n=52), NS
Ceraldi '93 70	2b (nonrandomized)	84pt, colon	Clinical AL	AL: 6.8% 1layer(n=44); 9.5% 2layer(n=21), NS
Fielding '80 71	2b (nonrandomized)	1466pt, colon	Clinical AL	AL: 12% 1layer(n=458); 13.5% 2layer(n=968), NS
Reichel '75 65	2b (nonrandomized)	408pt, colorectal	Clinical and radiological AL	AL: 10.3% 1layer(n=320); 10.3% 2layer(n=88), NS
Experimental				
Athar '96 66		18 dogs	Breaking strength	1layer more strength, 2layer less adhesions and smaller diameter anastomosis.
Langer '96 64		26 rabbits	AL, ABP	Steroid model, 1layer vs 2layer (vs stapled, NIR): equal AL, 2layer higher ABP.
Templeton '85 60		40 dogs	AL, ABP, histology, collagen	1layer vs 2layer (vs 2xstapled, NIR): 0 vs 30% AL, histology worse for 2layer, equal ABP and collagen.
Yesilkaya '85 61		20 dogs	Collagen	1layer vs 2layer: lower collagen in 2layer.
Graffner '84 59		18 pigs	AL, breaking strength, histologoy, blood flow	1layer vs 2layer (vs stapled, NIR): No AL, equal breaking strength, more inflammation and less blood flow 2layer.
Wheeless '83 68		81 dogs	Blood flow	1 layer (Gambee) vs 2 layer (vs stapler, NIR): 1 layer higher blood flow.
Schillaci '79 62		30 dogs	ABP, collagen	1layer vs 2layer (vs sleeve, NIR): equal ABP and collagen.
Chung '87 63		30 dogs	Blood flow	Different handsewn vs stapled anastomoses: 2layer more reduction of blood flow.
Langer '75 57		80 dogs and rats	Histology, blood flow	1layer vs 2 layer: 2layer delayed recovery, more ulceration and stenosing, delayed revascularisation.
Reichel '75 65		360 dogs	AL, ABP, histology	1layer vs 2layer: no AL, equal ABP, histology worse in 2layer.
Irvin '73 47		93 rabbits	ABP, histology, collagen	1layer vs 2layer (vs everting, NIR): equal ABP, collagen, and histology.
Herzog '73 67		200 rats	Breaking strength, blood flow	1layer better vascularisation and higher bursting strength.
McAdams '70 58		116 dogs	Histology	1layer (Gambee) vs 2layer (Czerny-Lembert). More inflammation 2layer.

Table 3. Included studies on single- versus double-layer anastomosis.

anastomosis are lacking; therefore, only 1 small, nonrandomized, comparative clinical study finding no significant differences was included[78], and noncomparative cohort studies were selected on continuous and interrupted suturing finding equally low

leakage rates[38, 72, 79-92]. Clinical and experimental studies have not concluded that one technique is superior to the other, and a high level of evidence is lacking (limited here to level 2b); however from a technical and time-consuming point of view a continuous suture is preferable over interrupted sutures for creating colorectal anastomosis.

Source	Level	No. of cases	Outcome	Result
Clinical				
Deen '95 78	2b (nonrandomized)	53pt, colon	Clinical AL	AL: 3.8% continuous(n=26) ; 3.8% interrupted (n=27), NS
Volk '11 92	2b (cohort)	463pt, ileocolonic	Clinical AL	AL:3.1% AL continuous
Law '99 86	2b (cohort)	500pt, colorectal	Clinical AL	AL:1.4% AL continuous
AhChong '96 79	2b (cohort)	93pt, colorectal	Clinical AL	AL:2.2% AL continuous
Flyger '95 81	2b (cohort)	105pt, colon	Clinical AL	AL:1.0% AL continuous
Max '91 88	2b (cohort)	1000pt, colorectal	Clinical AL	AL:1.0% AL continuous
Sarin '89 90	2b (cohort)	65pt, colon	Clinical AL	AL:6.2% AL continuous
Harder '88 82	2b (cohort)	143pt, colon	Clinical AL	AL:0.0% AL continuous
Bailey '84 80	2b (cohort)	100pt, colorectal	Clinical AL	AL:0.0% AL continuous
Thomson '93 91	2b (cohort)	200pt, colorectal	Clinical AL	AL:2.0% AL continuous
Pramateftakis '10 89	2b (cohort)	276pt, colorectal	Clinical AL	AL:2.5% AL interrupted
Pye '96 38	2b (cohort)	213pt, colorectal	Clinical AL	AL:0.5% AL interrupted
Huguier '82 83	2b (cohort)	105pt, colorectal	Clinical AL	AL:3.8% AL interrupted
Khubchandani '82 85	2b (cohort)	112pt, colorectal	Clinical AL	AL:4.5% AL interrupted
Matheson '81 87	2b (cohort)	168pt, colorectal	Clinical AL	AL:4.2% AL interrupted
Jonsell '78 84	2b (cohort)	165pt, colorectal	Clinical AL	AL:8.5% AL interrupted
Experimental				
Shandall '85 74		40 rabbits	Blood flow	Continuous vs interrupted: continuous sign lower blood flow.
Houdart '83 35		210 rats	Histology	Extramucosal continuous vs extramucosal interrupted vs continuous. Equal histology at day2-180.
Jiborn '78 77		64 rats	Collagen	Continuous vs interrupted vs control : continuous lower collagen metabolism until day4.
Jiborn '78 76		71 rats	ABP	Continuous vs interrupted vs control : equal ABP at day4 and 7.
Jiborn '78 75		71 rats	Breaking strength	Continuous vs interrupted vs control. Equal breaking strength at day4 and 10.
Delaitre '77 73		83 rabbits	Histology	Continuous vs interrupted: continuous more mucous evagination, and better apposition (from 1 day to 3months).

Table 4. Included studies on interrupted versus continuous sutures

5. Hand-sewn vs stapled colorectal anastomosis

After the introduction of stapled colorectal anastomosis in the 1980s, both techniques have become prevalent, without defined indications but for the lower rectal anastomoses. Most surgeons apply both techniques, although often with a personal preference.

Thirteen RCTs[93-105] and 3 meta-analyses were included[106-108]. Lustosa et al. published a Cochrane meta-analysis of 9 RCTs conducted between 1981 and 1991. In this group of 1233 patients, there was no difference in mortality, AL, strictures or reoperation between stapled and handsewn colorectal anastomosis[107]. An earlier meta-analysis, conducted in 1998 combined 13 RCTs concerning patients with colorectal anastomosis, and found similar results: no significant differences in AL or mortality[108]. The Cochrane review conducted by Choy et al. included studies on colorectal anastomosis after right hemicolectomy.

Source	Level	No. of cases	Outcome	Result
Clinical				
Choy '07 106#	1a (meta-analysis)	955pt, ileocolic	Clinical AL	AL: 1.1% stapled(n=357); 3.8% sutured(n=598), NS
Lustosa'01 107*	1a (meta-analysis)	1233pt, colorectal	Clinical AL	AL: 6.3% stapled(n=622); 7.1% handsewn(n=611), NS
MacRae '98 108^	1a- (meta-analysis)	2256pt, colorectal	Clinical AL	AL: odds ratio stapled vs handsewn 0.89 (CI 0.58-1.29), NS
Fingerhut '95 100*^	1b (RCT)	159pt, colorectal supraperitoneal	Clinical AL	AL: 0% stapled(n=85); 0% handsewn(n=74), NS
Docherty '95 96^#	1b (RCT)	625pt, colorectal	Clinical AL	AL: 4.5% stapled(n=330); 4.4% handsewn(n=321), NS
Fingerhut '94 99*^	1b (RCT)	113pt, left colon	Clinical AL	AL: 3.7% stapled(n=54); 8.5% handsewn(n=59), NS
Sarker '94 105*^	1b (RCT)	60pt, rectum	Clinical AL	AL: 0% stapled(n=30); 6.7% handsewn(n=30), NS
Kracht '93 102*^#	1b (RCT)	268pt, colorectal	Clinical AL	AL: 8.8% stapled(n=137); 12.2% handsewn(n=131), NS
Friend '90 101^	1b (RCT)	239pt, left colon	Clinical AL	AL: 3.5% stapled(n=114); 8.8% handsewn(n=125), NS
Cajozzo '90 95^	1b (RCT)	48pt, colorectal	Clinical AL	AL: 8.3% stapled(n=24); 4.2% handsewn(n=24), NS
Elhadad '90 97*	1b (RCT)	272pt, colorectal	Clinical fistula	AL: 8.3% stapled(n=139); 11.5% handsewn(n=133), NS
Gonzalez '87 104*^	1b (RCT)	113pt, rectum	Clinical AL	AL: 10.9% stapled(n=55); 10.3% handsewn(n=58), NS
Everett '86 98	1b (RCT)	94pt, left colon	Clinical AL	AL: 0% stapled(n=44); 4% handsewn(n=50), NS
McGinn '85 103*^	1b (RCT)	118pt, low colorectal	Clinical AL	AL: 12.1% stapled(n=58); 3.3% handsewn(n=60), significant
Brennan '82 94^	1b (RCT)	100pt, colorectal	Clinical AL	AL:10% stapled(n=50); 6% handsewn(n=50), NS
Beart '81 93*^	1b (RCT)	70pt, colorectal	Clinical AL	AL: 2.9% stapled(n=35); 2.9% handsewn(n=35), NS

Source	Level	No. of cases	Outcome	Result
Clinical				
Resegotti '05 115	2b (nonrandomized)	122pt, ileocolic crohn	Clinical AL	AL: 2.0% stapled(n=51); 14.1% handsewn(n=71), significant
Anwar '04 110	2b (nonrandomized)	100pt, ileocolic malign	Clinical AL	AL: 0% stapled(n=41); 0% handsewn(n=59), NS
Smedh '02 113	2b (nonrandomized)	42pt, crohn	Clinical AL	AL: 0% STS stapled(n=20); 0% ETE handsewn(n=22), NS
Sielezneff '01 112	2b (nonrandomized)	116pt, sigmoid diverticular disease	Clinical AL	AL: 0% stapled(n=49); 0% handsewn(n=67), NS
Montesani '92 114	2b (nonrandomized)	533pt, colorectal	Clinical AL	AL: 28.5% stapled(n=28); 3.1% handsewn(n=505), significant
Scher '82 111	2b (nonrandomized)	242pt, colon	Clinical AL	AL: 2.3% stapled(n=87); 2.6% handsewn(n=155), NS
Adloff '80 109	2b (nonrandomized)	51pt, rectum	Clinical AL	AL: 7.7% stapled(n=26); 8% handsewn(n=25), NS
Experimental				
Singer '04 119		20 pigs	ABP, histology, collagen	Steroid-model. Equal ABP and collagen, inflammation worse for hand-sewn at day4.
Senagore '92 118		42 pigs	ABP, histology, blood flow, collagen	Equal ABP, histology, blood flow, and hydroxyproline.
Kent '92 125		20 dogs	ABP, histology	Handsewn: higher ABP, equal histology at day3 and 5.
Jansson '91 116		30 pigs	AL, breaking strenght, blood flow, collagen	Handsewn vs stapled (vs glued, NIR): no AL, equal breaking strength, blood flow and collagen.
Dziki '91 124		24 dogs	ABP, histology, collagen	Handsewn: higher ABP at day4, better histology, equal collagen.
Julian '89 123		56 dogs	Blood flow	Equal vascularisation at day3 to 13.
Kozol '88 120		8 dogs	Histology (edema)	No significant differences in edema at t=28h.
Chung '87 63		30 dogs	Blood flow	Tight stapling: less blood flow; adjusted stapling: better blood flow than hand-sewn.
Graffner '84 59		18 pigs	AL, breaking strength, histology, blood flow	1layer vs 2layer vs stapled: no AL, more necrosis stapled, equal blood flow and breaking strength.
Moss '84 121		10 dogs	ABP	Stapled higher ABP at day4.
Buchmann '83 122		8 dogs	Histology	Equal histology at day4. Stapled more fibrosis at 2,3,6 months.
Wheeless '83 68		81 dogs	Blood flow	1layer (Gambee) vs 2layer vs stapled: stapled higher blood flow than 1 and 2layer.
Polglase '81 117		24 dogs	AL, histology	Equal AL, handsewn more narrowing, stapled more ulcerative gap.

Table 5. Included studies on hand-sewn versus stapled anastomosis.
*indicates a RCT also included in the meta-analysis of Lustosa, # indicates a RCT also included in the meta-analysis of Choy, ^ indicates a RCT also included in the meta-analysis of MacRae.

This review showed significant less overall AL in the stapled group; however when clinical AL was used as the only outcome measure, this difference did not reach statistical significance[106]. An interesting subgroup analysis made by Friend et al.[101] found more AL in handsewn colorectal anastomosis when the anastomoses made by residents were separately analyzed. Their conclusion was that stapling seems to have an advantage in less experienced hands. Of 7 included nonrandomized cohort studies included in this review, 5 found no superiority of one technique[109-113]. Two studies found significantly more AL in stapled compared with hand-sewn anastomoses[114, 115]. However, one of these had significantly more patients with corticosteroids in the stapled group[115], while the other included 505 hand-sewn compared with 28 stapled colorectal anastomoses[114]. Thirteen experimental studies included herein found results approximately similar to in the clinical setting: no significant differences in AL, with equal or higher ABP in stapled colorectal anastomosis [59, 63, 68, 116-125].
In conclusion, the field of hand-sewn vs stapled colorectal anastomosis has been well studied. On the basis of level 1a evidence, no superiority of stapled over hand-sewn colorectal anastomosis exists.

6. Hand-sewn vs compression colorectal anastomosis

Denans described the first technique to create intestinal anastomoses by compression in 1827[126], followed by other devices, such as the Murphy button in 1892[127]. Today the biofragmentable anastomotic ring, made of absorbable polyglycolic acid, is used most often. Four included experimental studies show that compression colorectal anastomosis leads to acceptable healing and strength[128-131]; 6 included RCTs provide equivalent conclusions, finding no significant differences between hand-sewn and compression colorectal anastomosis [132-137]. Also, noncomparative clinical cohort studies including up to 1360 patients have reported incidences of AL between 0,7% and 5%[138-141]. Although few gastrointestinal surgeons routinely use compression colorectal anastomosis, it seems a safe method. On the basis of 6 level 1b studies, no superiority of compression over hand-sewn colorectal anastomosis exists when comparing leak rates.

Source	Level	No. of cases	Outcome	Results
Clinical				
Pahlman '97 137	1b (RCT)	100pt, colon	Clinical AL	AL: 4% BAR(n=50); 2% handsewn(n=50), NS
Gullichsen '92 135	1b (RCT)	150pt, colon	Clinical AL	AL: 2.5% BAR(n=79); 4.2% handsewn 2layer(n=71), NS
Bubrick '91 134	1b (RCT)	782pt, colorectal	Clinical AL	AL: 3% BAR(n=395); 3% handsewn(n=283); 4% stapled(n=104), NS
Dyess '90 136	1b (RCT)	59pt, colon	Clinical AL	AL: 0% BAR(n=27); 0% handsewn(n=16); 0% stapled(n=16), NS
Cahill '89 132	1b (RCT)	202pt, colorectal	Clinical AL	AL:2% BAR(n=101); 8.2% handsewn(n=85); 6.3% stapled(n=16), NS
Corman '89 133	1b (RCT)	438pt, colon	Clinical AL	AL: 2.7% BAR(n=222); 2.5% handsewn(n=162); 1.9% stapled(n=54), NS
Experimental				
Bundy '93 129		36 dogs	ABP	BAR vs handsewn vs stapled: handsewn higher ABP at day3, equal ABP at day7.
Gullichsen '93 131		42 dogs	Histology	BAR vs handsewn vs stapled: more edema and inflammation BAR at day1 and7.
Smith '88 128		40 dogs	AL	Radiotherapy model. 2 sizes BAR vs handsewn vs stapled: BAR 1.5mm more AL, other groups equal.
Maney '88 130		178 dogs	AL, ABP, histology	BAR vs EEA vs handsewn: no AL, equal ABP, equal histology.

Table 6. Included studies on hand-sewn versus compression anastomosis.

7. Configuration of colorectal anastomosis

Source	Level	No. of cases	Outcome	Result
Clinical				
Brisinda '09 144	1b (RCT)	77pt, rectum	Clinical AL	AL: 29.2% ETE(n=37); 5.0% ETS(n=40), significant
Tsunoda '09 145	1b (RCT)	40pt, rectum	Clin AL + stump leakage	AL: 5% short limb(n=20); 10% long limb(n=20), NS
Experimental				
Willis '06 143		18 dogs	Perfusion	Stapled ETE vs stapled STE (vs Jpouch, NIR): ETE better blood flow compared with STE.
Sailer '00 142		32 pigs	Blood flow	ETE vs STS (vs small pouch vs large pouch, NIR): equal blood flow.

Table 7. Included studies on configuration.

Studies regarding the configuration of the afferent and efferent ileal, colonic or rectal loops are heterogeneous in patient selection and configuration, and often concentrate on stapled pouches for very low anastomoses with outcome variables other than AL. Only 2 experimental studies matched the inclusion criteria; one study found

no difference in blood flow between ETE or side-to-side anastomosis after rectal resection in pigs[142], and the other found better blood flow in ETE compared with side-to-end anastomosis after rectal resection in dogs[143]. The included RCTs are also scarce: one on ETE versus end-to-side finding more AL in ETE[144], and the other on the optimum side limb for side-to-end colorectal anastomosis found no difference between 3cm- and 6cm sized limbs[145]. No studies investigating the ideal length of the enterotomy were identified.
It is difficult to draw a conclusion out of this small amount of studies; there is one level 1b study showing a lower incidence of AL with end-to-side colorectal anastomosis and one level 1b study indicating that a 3-cm or a 6-cm side limb does not affect the incidence of AL.

Conclusion

In the clinical setting, healing of colorectal anastomosis is obscured from direct postoperative inspection. When AL occurs, diagnosis can be made only after the patient has become ill, making it a feared complication with high morbidity and mortality[1, 4, 146-148]. This systematic review of all aspects of hand-sewn colorectal anastomosis and the comparison of handsewn to mechanical anastomosis provides an overview on the existing colorectal anastomotic techniques combined with the available scientific evidence on anastomotic healing. Evaluation of studies on colorectal anastomosis with clinical AL as outcome measure and proper statistics produced very little level 1 evidence for all aspects of handsewn colorectal anastomosis. Nevertheless, we can formulate a conclusion using experimental results combined with clinical results for many aspects: the single-layer continuous suture technique by an inverting technique with slowly absorbable monofilament material seems preferable on the basis of level 1b evidence. However, for the other aspects of the technique, such as how far to place the suture from the anastomotic edge, the intersuture distance in relationship to the distance to the edge, which layers to include in the bite, how high the tension on the suture should be, and through what configuration the anastomosis should be made, surgeons probably rely on their teachers and instinct rather than on scientific evidence. Large cohort studies that are available, describing low rates of AL for the used anastomotic technique might indicate that dedicated, high-volume colorectal surgery has a role in lowering the incidence of AL because of a surgeon's familiarity with a certain technique.

Considering mechanical colorectal anastomosis, level 1a evidence indicates that stapling and hand-sewn anastomoses give equal results with regard to clinical AL, and level 1b evidence determines that compression and hand-sewn colorectal anastomosis have similar AL rates. In contrast to all possible variations that exist when sewing an anastomosis by hand, the technique of a stapled anastomosis is much more uniform in the hands of surgeons. This could lead to standardizing colorectal anastomosis, and prevent the nonscientific practice of the preferences of individual surgeons from being handed down from teacher to student without documentation of their exact properties and incidence of AL.

We can conclude from this review that, until now, hand-sewn colorectal anastomosis is constructed following a largely non-defined technique. The circumstances of RCTs do not reflect daily practice; therefore routine detailed documentation of anastomotic technique of all colorectal operations will be instrumental in formulating a definite conclusion on the role of the unstandardized hand-sewn colorectal anastomosis.

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2.4 Review of sealants in gastrointestinal surgery

Sealants in gastrointestinal anastomosis: a systematic review
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Abstract

Anastomotic leakage (AL) in gastrointestinal (GI) surgery remains a major problem. Research has been performed on the use of surgical glues as GI anastomotic sealants for various anastomotic configurations. No clear overview has yet been presented on the use of sealants in GI anastomosis. This systematic review aims to provide a clear overview of recent experimental and clinical research on the sealing of different levels of GI anastomosis. Medline and Embase databases were searched for clinical and experimental articles published after 2000. Articles were included only if a tissue adhesive around a GI anastomosis was used to prevent anastomotic leakage. Results were categorized according to level of anastomosis, glue category and level of evidence. In total 50 studies were included, of which 16 on humans. Four studies were included on esophageal anastomosis, 13 on gastric anastomosis, 5 on pancreatic anastomosis, 8 on ileal anastomosis and 20 on colorectal anastomosis. The use of fibrin glue and cyanoacrylate glue has been the main focus of glue research for the sealing of GI anastomosis. Using these glues seems effective in protecting the ileal anastomosis and also in gastric/bariatric surgery. Results for sealing esophageal and pancreatico-digestive anastomoses remain inconclusive, as is the case for colonic anastomoses. Further research should concentrate on the clinical evaluation of promising experimental results as well as on new types of tissue adhesives. This field of research may benefit from a more systematic approach with comparable methodology between researchers.

Introduction

Each year, millions of gastrointestinal (GI) anastomoses are created worldwide. Anastomotic leakage (AL) after the creation of a bowel anastomosis remains an important complication in GI surgery. Despite years of research, incidence of AL remains high, varying from 3% after ileal anastomosis to 20% after esophageal and colorectal anastomosis, with subsequent mortality rates as high as 20% [1-3].

Surgical adhesives have been gaining popularity in various fields of clinical practice, especially for skin closure. There are various categories of tissue adhesives, each with their own adhesive properties and uses [4]. Basically, a tissue adhesive forms bonds with its substrate ensuring sufficient adhesion. These bonds can either be chemical, of which covalent bonds are the strongest, or physical, including hydrogen bonds or van der Waals forces [5]. Furthermore, the total strength of the glue bond depends on the balance between interaction within the glue (cohesion) and between the glue-substrate interface (adhesion).

Except for external use, tissue adhesives can also be of use intracorporeally; already various glues are being used in (cardio-)vascular surgery, plastic surgery and increasingly in surgery of the GI tract [6-7]. By using these adhesives as sealants for GI anastomosis, enhancing standard anastomotic technique, AL might be prevented or reduced and its clinical symptoms ameliorated.

Numerous research projects have been undertaken to assess the applicability of available sealants in GI surgery; however no recent literature provides the surgical community with an up-to-date and clear overview on the progress in this field. Despite years of research on the topic of anastomotic sealing, it remains challenging to draw clear conclusions about the usefulness of glue as an anastomotic sealant. This is due to the heterogeneic nature of the performed experiments, especially with regard to glue categories used, glue dosage, type of anastomosis performed, choice of animal model and inconsistent results between researchers.

This systematic review includes recent information on all types of anastomotic configurations in the GI tract and provides a means to discover similarities and make comparisons between different levels of anastomosis. In this review an overview is provided on all available clinical and experimental research concentrating on the use of surgical adhesives as bowel sealants, presented by level of GI anastomosis and category of adhesive used.

Methods

This systematic review was performed according to the PRISMA guidelines [8]. A literature search was performed on the 12th of May 2011, including all relevant articles since January 2000. The search was performed in EMBASE and MEDLINE databases, and articles were screened by two independent researchers in a standardised manner. Articles were included only if these addressed a tissue adhesive applied around a gastrointestinal anastomosis to prevent AL or to decrease leakage related complications. Review articles were excluded. For clinical studies, the level of evidence (following the Centre of Evidence Based Medicine, University of Oxford) was extracted. The following search strategy was used:

(((anastom*[tw] OR Anastomosis, Surgical[mesh])
AND (Gastrointestinal Tract[mesh] OR gastrointest* OR gastric*[tw] OR intestin*[tw] OR colorect*[tw] OR colon[tw] OR rectum[tw] OR rectal[tw] OR esophag*[tw] OR oesophag*[tw] OR duoden*[tw])) OR Biliopancreatic Diversion*[tw] OR Esophagoplast*[tw] OR Esophagostom*[tw] OR Gastrectom*[tw] OR Gastroenterostomy[mesh] OR Gastroenterostom*[tw] OR Jejunoileal Bypass*[tw] OR Pancreaticoduodenectom*[tw] OR Pancreaticojejunostom*[tw]
) AND (adhesive*[tw] OR seal*[tw] OR Glue*[tw] OR Gluing[tw] OR Tissue Adhesives[mesh]) AND (2000[pdat]:2011[pdat]) AND english[lang]

Results

After the selection process described in Figure 1, 48 articles were included in this review.

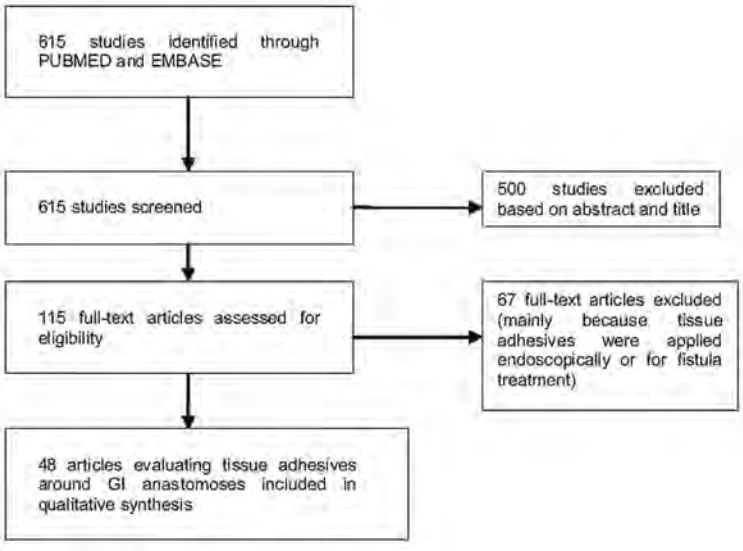

Figure 1. PRISMA-flowchart for selection of relevant studies.

An overview of all tissue adhesives, as mentioned in the included articles, is provided in Table 1.

Sealants in esophageal surgery

Experimental

Fibrin Glue/ Cyanoacrylate

The role of sealing in esophageal surgery has been investigated experimentally by Yurtcu *et al.* [9]. In this rabbit study three glues/healing agents, including fibrin glue (FG) and cyanoacrylate glue (CA), were applied on an esophago-gastric anastomosis. No AL was observed in any of the study groups and CA showed superior histological scores and higher bursting pressure when compared to the other groups. In a similar study by the same authors CA proved successful in the closure of esophagocutaneous leakage [10].

Cyanoacrylate glues:		
Manufacturer	**Trade name**	**Composition**
Ethicon (J&J; USA)	Dermabond	2-octyl-cyanoacrylate
	Omnex	2-octyl-cyanoacrylate
B.Braun (GER)	Histoacryl Blue	n-butyl-2-cyanoacrylate
GEM Italia (IT)	Glubran 2	n-butyl-2-cyanoacrylate and methacryloxysulfolane
Adhezion medical (USA)	Surgiseal	2-octyl-cyanoacrylate
GluStitch Inc. (CAN)	GluSeal	2-octyl-cyanoacrylate
Henkel (GER)	Pattex	Ethyl-2-cyanoacrylate
Polyethylene glycol:		
Manufacturer	Trade name	Composition
Covidien (FR)	Duraseal	Polyethylene glycol, trilisine amine and blue dye
	Duraseal Xact	Idem, with N-hydroxy succinimide
Baxter (USA)	Coseal	Polyethylene glycol, hydrogen chloride and sodium phosphate-sodium carbonate
Genzyme Biosurgery Inc. (USA)	Focalseal-L	Polyethylene glycol, acrylate-capped poly-L-lactide and polytrimethylene carbonate
Other categories:		
Manufacturer	Trade name	Composition
Cardial SA (FR)	GRF glue	Gelatin-resorcinol-formaldehyde glue
Geister GmbH (GER)	Gluetiss glue	Gelatin-resorcinol-glyoxal glue
Biomet (USA)	GPS system for PRP glue	Platelet rich plasma (PRP)
Cryolife (USA)	BioGlue	Glutaraldehyde-albumin glue
Mundipharma GmBH, (GER)	Polydione-liposome (PVP-1)	Elemental iodine and polyvinylpyrrolidone (polydione) + liposome hydrogel
Cohera medical Inc. (USA)	TissuGlu	Urethane adhesive (lysine derived)

*not marketed for medical use

Table 1. Tissue adhesives.

Other categories

No other glue categories have been used in the field of experimental esophageal anastomotic research.

Clinical

Fibrin Glue

Two clinical trials have been conducted to demonstrate the use of FG sealing in esophageal surgery. Level 1b evidence is derived from a randomized controlled trial (RCT) performed by Upadhyaya *et al*. In this study the application of FG (Tisseel) to end-to-end esophagostomies for esophageal atresia was investigated [11]. The Tisseel

group showed significantly less leakage and strictures compared to the control group. A case-control study by Saldana *et al.* showed significant reduction of AL after FG sealing of 14 esophagectomies with colonic interposition [12]. No clinical studies were found on regular esophagectomies in adults.

Cyanoacrylate/ other categories

No other glue categories have been used in the field of clinical esophageal anastomotic research.

LOE*	Author / year	Model	N	Tissue adhesive	Methods	Outcome
-	Yurtcu / 2010 10	Rabbit	24	CA (Glubran 2) FG (Beriplast)	Esophageal anastomosis	+
1b	Upadhyaya / 2007 11	Clinical (RCT)	52	FG (Tisseel)	Esophageal anastomosis	+
3b	Saldana / 2009 12	Clinical	38	FG (Quixil)	Colonic interposition	+

Table 2. Sealants in esophageal surgery

* = level of evidence

Sealants in gastric/bariatric surgery

Experimental

Fibrin Glue

Experimentally, numerous studies have been conducted in this field. FG sealing was evaluated in two studies. In a pig model of leaking gastrojejunostomy, Bonanomi *et al.* and Nguyen *et al.* independently showed improvement of the leakage rate after FG sealing when compared to unsealed controls [13-14] .

Cyanoacrylate

The use of CA was tested in one study. Weiss *et al.* reported that the sealing of gastrojejunal anastomosis in a rat model with cyanoacrylate was as safe as an unsealed anastomosis [15].

Other categories

In an *ex-vivo* pig study, Nandankumar *et al.* reported that the use of glutaraldehyde-albumin glue (BioGlue) to reinforce complete and incomplete circular stapled gastrojejunostomies resulted in significantly increased anastomotic bursting pressure (ABP) [16].

Clinical

Fibrin Glue

Clinical evidence is derived from 9 studies, including one level 1b randomized controlled trial and six level 2b prospective cohort studies, all on the use of FG. Silecchia *et al.* performed the only randomized multicentre study, showing no difference in AL after (laparoscopic) Roux-en-Y- gastric bypass ((L)RYGB) with anastomotic FG sealing [17]. Liu *et al.* found, in their nonrandomized case-control study that patients in which the gastrojejunal anastomosis was sealed with FG after RYGB developed significantly less AL than the unsealed controls [18]. One prospective study by Efthimiou *et al.*, in which 474 patients undergoing LRYGP received FG sealing of gastro-jejunal anastomosis and gastric staple line, also showed no effect of sealing on the incidence of AL. However, they found that FG use is associated with an increased clinical inflammatory response mimicking AL [19]. Three observational uncontrolled studies showed low prevalence of AL after the use of FG in laparoscopic gastric bypass (Sapala *et al.* 0% (0/738)[20], Cottam *et al.* 1.6% (2/126)[21], Raquel *et al.* 2% (2/100)[22]). Retrospectively, Fullum *et al.* reported 3 leaks in 760 LRYGB performed by one single surgeon using FG to seal every staple line [23].

Cyanoacrylate

No studies on the use of CA have been performed in this field.

Other categories

One case report on the use of autologous platelet gel (APG) in 10 morbidly ill patients undergoing LRYGP reported positive effects of APG on the incidence of surgical complications, including AL [24].

Sealants for pancreatic anastomosis

Experimental

Fibrin Glue/ Cyanoacrylate

No experimental studies were performed on FG or CA sealing.

Other categories

Experimentally, Argyra *et al.* performed a study on ten pigs in which a sutureless pancreaticojejunal anastomosis (PJ) with polyethylene glycol glue (PEG) was created [25]. They concluded that in their series the use of PEG was technically feasible, prevented anastomotic dehiscence and did not interfere with the wound healing