Optimizing strategies in gastrointestinal surgery

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Summary and conclusions

In this thesis several aspects of abdominal surgery for benign and malignant diseases were highlighted. The aim of part I was to evaluate the clinical and functional outcome of abdominal surgery in patients with ulcerative colitis (UC) and familial adenomatous polyposis (FAP). In part II, the aim was to critically appraise the effects of the two new major developments in elective abdominal surgery.

Surgery for Ulcerative Colitis and Familial Adenomatous Polyposis (part I)

In chapter 1, a pilot study was performed to determine whether the type of approach, open or laparoscopic, and the order of devascularisation in laparoscopic colectomy, affects intestinal barrier function, local inflammatory response and clinical outcome. Twenty-two patients scheduled for laparoscopic colectomy were randomized to start with inferior mesenteric artery or ileocolic artery devascularisation. Eighteen patients scheduled for open surgery served as a prospective control group. To assess the intestinal barrier function release of intestinal fatty acid binding protein (I-FABP; marker of mucosal injury and ischemia) was measured pre- and postoperatively. Mesenteric lymph nodes were harvested to detect changes in RNA expression of genes encoding for inflammatory mediators using Multiplex Ligation Probe Amplification. After a right-sided start, excretion of I-FABP was significantly increased over time (P=0.002). In this group I-FABP levels were significantly increased on postoperative days 1 and 3 compared to preoperative values (P=0.011 and P=0.001, respectively). There were no differences in expression of inflammatory mediator-related genes or postoperative morbidity among the groups. This pilot study demonstrated that devascularisation started at the ileocolic artery during laparoscopic colectomy was associated with prolonged intestinal mucosal ischemia.

After a proctocolectomy with ileo-pouch anal anastomosis (IPAA) for ulcerative colitis (UC), patients are still at risk for the development of dysplasia and cancer in the pouch, the anastomotic site, or remaining rectal cuff. In chapter 2 the prevalence of dysplasia in UC patients who have undergone a proctocolectomy with IPAA and who demonstrated dysplasia or cancer in their resection specimen was assessed. Between 1988 and 2008, 290 patients with inflammatory bowel disease underwent a proctocolectomy with IPAA in the Academic Medical Center Amsterdam. A total of 64 patients with UC underwent surgery and had (indefinite for) dysplasia or carcinoma in their resection specimen. Forty-four patients (mean age 49 years) underwent surveillance pouch-endoscopy. The mean time between surgery and pouch surveillance was 8.6 (median 7.9, range 1-19) years. In 2 patients low-grade dysplasia was detected (4.5%). Based on this study the benefit of routine surveillance for dysplasia in the IPAA is uncertain.

A common complication after a proctocolectomy with IPAA is sexual dysfunction. This may have a large impact as most of the patients are young and sexually active. The most systematic physical reaction to sexual stimulation is an increase in vaginal vasocongestion, which can be assessed by vaginal pulse amplitude (VPA) using vaginal photoplethysmog-
raphy. Chapter 3 was designed to assess whether a proctocolectomy with IPAA was associated with autonomic pelvic nerve damage, as objectified with VPA during sexual stimulation (visual and vibrotactile), and with changes in subjective indices of sexual function, assessed with validated questionnaires. For 8 patients (median age 37) pre- and postoperative data was collected. VPA analysis showed a significant reduction in vaginal vasocongestion during sexual stimulation postoperatively, $P=0.012$. There were no differences in subjective sexual arousal and estimated lubrication during the experiment, and reported psychological and sexual functioning pre- and postoperatively. In conclusion, vaginal vasocongestion after IPAA was significantly reduced in this study. This indicates that IPAA in women is possibly associated with autonomic pelvic nerve damage or partial devascularisation of the vagina.

Most patients are young and in their reproductive years at the time of operation. In these patients, the optimal method of childbirth has yet to be determined. It is demonstrated that anal sphincter defects occur after vaginal deliveries. In patients with UC or FAP that have undergone or still have to undergo a proctocolectomy with IPAA, damage to the anal sphincter, pelvic floor or pudendal nerves will probably have more clinical impact at an earlier age compared to ‘normal’ women. A retrospective study was initiated, described in chapter 4, to evaluate the effect of vaginal delivery and its potential complications both before and after a proctocolectomy with IPAA on the pouch function. All women ($n=267$) who underwent a proctocolectomy with IPAA between January 1985 and November 2004 were retrospectively recruited from 3 academic medical centers in the Netherlands. Hundred seventy-two patients were available for analysis. Patients were asked about their pregnancies and risk factors for obstetric injury. Functional outcome was assessed by the colorectal functional outcome questionnaire. Median follow-up after pouch surgery was 7.2 (range 1.0–19.7) years. One hundred patients had at least one delivery; 86 of these 100 patients attempted a vaginal delivery of which 52 patients had an increased risk of obstetric injury according to the predefined risk factors. In patients with an increased risk of obstetric injury, ageing and longer follow-up appeared to be significant risk factors for impaired incontinence. Based on these results, patients with proctocolectomy with IPAA should be informed about the considerable risk of vaginal delivery on long-term pouch function.

**Enhanced Recovery After Surgery (part II)**

In chapter 5 the latest evidence of quality of life in patients after laparoscopic or open colorectal surgery was examined. After a systematic search 9 randomized clinical trials (RCTs) remained for analysis, comprising 2263 patients. Short- and long-term results of these 9 RCTs were described in 13 articles. Due to clinical heterogeneity, it was not possible to conduct a meta-analysis. Postoperative follow-up ranged from 2 days to 6.7 years. Four RCTs showed no significant differences in postoperative quality of life following open or laparoscopic colorectal surgery on short-term (1 to 12 weeks) or on long-term (3 months to 6.7 year) follow-up. The remaining 5 studies reported a better quality of life in favour of the laparoscopic group on a few quality of life scales at time points ranging from 1 week to 2 years after surgery. Based
on presently available high-level evidence, this systematic review showed no clinical relevant differences in quality of life on short- or long-term follow-up between open and laparoscopic colorectal surgery.

In chapter 6 another systematic review was performed of all RCTs and controlled clinical trials (CCTs) on laparoscopic versus open surgery within fast track perioperative care. Primary endpoints were primary and overall hospital stay, readmission rate, morbidity and mortality. Only 2 RCTs and 3 CCTs were eligible for final analysis, which reported on 400 patients. Data could not be pooled because of clinical heterogeneity. One RCT and one CCT stated a shorter primary hospital stay in the laparoscopic group of three and two days, respectively. In one RCT readmission rate was lower in the laparoscopic group; absolute risk reduction 21.4% and a number to treat of 4.7 patients. Another study showed a 23% difference in favour of the laparoscopic group with regard to morbidity, i.e. a number to treat of 4.4 patients. There were no significant differences in mortality rates. Based on this evidence, no conclusion could be made. So, whether laparoscopic surgery is still of added benefit when concurrently a fast track program is applied, remained a matter of debate.

To answer this question a multicenter randomized controlled trial of a 2 x 2 balanced factorial design was initiated at the Academic Medical Center. This study, presented in chapter 7, aimed to determine which perioperative treatment, i.e. laparoscopic or open surgery combined with fast track or standard care, was the optimal approach for patients undergoing segmental resection for colon cancer, and to investigate if either laparoscopy, FT care, or the combination of both is the main predictive factor for a faster postoperative recovery. Patients between 40 and 80 years of age, with an American Society of Anaesthesiologists grade of I, II or III, that were to undergo elective segmental colectomy for histologically confirmed adenocarcinoma or adenoma, and without evidence of metastatic disease were eligible. After informed consent patients were randomized to laparoscopic or open colectomy, and to fast track or standard care, resulting in four treatment groups. Patients, nursing and medical staff were informed about the applied care program, but blinded to type of intervention. In total 427 patients (mean age 66.5 years, 234 males) were randomized in 9 Dutch hospitals. Our primary endpoint was total postoperative hospital stay, including hospitalization period in case of readmission. Four hundred patients were available for analysis. Median total postoperative hospital stay was 5 days after a laparoscopic resection combined with fast track care, 7 days after an open/fast track treatment, 6 days after a laparoscopic/standard treatment, and 7 days after an open/standard treatment. Median postoperative hospital stay was similar to total postoperative hospital stay for all treatment groups, except for the open/fast track group in whom hospital stay was 6 days instead of 7 days. Linear regression analysis identified laparoscopy as the only independent factor to influence total postoperative hospital stay, i.e. a reduction of 21% (CI: 9-31%). FT care showed a trend, but the combination of both showed no additional benefit. Median postoperative hospital stay was significantly influenced by both, i.e. reduction of 20% (CI: 9-30%), and FT care, i.e. a reduction of 14% (CI: 10-20%). The combination of both did not add any benefit. Other secondary outcomes; overall morbidity,
reoperation rate, readmission rate, in-hospital mortality and in-hospital costs did not differ significantly among the groups. Logistic regression analysis showed that only laparoscopic resection resulted in a significantly lower overall- and major morbidity. The other endpoints were not significantly influenced by the different surgical regimens. Quality of life and patient satisfaction were similar. This study showed that a laparoscopic resection within a fast track perioperative care program is the optimal treatment for patients requiring a segmental colectomy for malignancy. If open surgery has to be performed, for example because of the lack of laparoscopic expertise or patient-related factors, then this should be embedded in a fast track protocol. In addition, laparoscopy was found to be the only significant independent factor to reduce postoperative hospital stay and morbidity.

As RCT’s comparing the effect on postoperative gastrointestinal motility are lacking a side-study of the LAFA-study was performed in Chapter 8. In this study it was evaluated which perioperative treatment, i.e. laparoscopic or open surgery combined with fast track or standard care, leads to faster recovery of the gut after colorectal surgery. Primary endpoints were colonic transit and gastric emptying. This was scintigraphically assessed from day 1 to 3. Colonic transit at day 2 and 3 was represented as geometrical center of activity (segment 0=small intestine, 1=proximal-, 2=distal colon, 3=toilet). Secondary endpoints were time to toleration of solid food and/or bowel movement, and time until (ready for) discharge. In total 93 LAFA patients participated. The median colonic transit at day 3 of patients undergoing laparoscopic/fast track care (2.6 (2.0-2.9)) was significantly higher, compared to the laparoscopic/standard (2.2 (1.6-2.5), \( P=0.044 \)), open/fast track (2.0 (1.6-2.4), \( P=0.010 \)), and open/standard care group (1.3 (1.0-1.5), \( P<0.001 \)). Median gastric retention did not differ between groups (\( P=0.61 \)). Multivariate regression analysis showed that both laparoscopic surgery and fast track care were significant independent predictive factors of improved colonic transit, resulted in significantly shorter time until toleration of solid food and bowel movement and recovered significantly faster. This study showed that laparoscopic surgery as well as fast track care result in a better recovery of the gut after colorectal surgery, leading to a more rapid clinical recovery. The optimal perioperative treatment with the fastest recovery of gastrointestinal function is laparoscopic resection embedded in a fast track program.

To even further assess why laparoscopic surgery combined with fast track care is the optimal treatment, another side-study of the LAFA-study was performed in chapter 9. In this study the effect on patient’s immune status and stress response after the 4 treatment combinations was evaluated. In each treatment group around 17 to 23 comparable patients were available for analysis. HLA-DR expression on monocytes is a measure for immune competence and was best preserved 2 and 24 hours after a laparoscopic/fast track treatment. Interleukin-6 is associated with postoperative complication rates and was significantly increased in the open/standard group at 24 hours and 72 hours postoperatively. C-reactive protein was significantly increased at all time points (1 hour, 2 hours, 24 hours and 72 hours) in the open/standard group. There were no differences regarding growth hormone level, prolactin level, cortisol level and rate of (infectious)complications between the groups. This study showed that im-
mune function is best preserved in patients having laparoscopic colectomy within a fast track program. Therefore, these data are supportive to chapter 7 & 8, in which an accelerated postoperative recovery was found in patients treated laparoscopically within a fast track program.

As illustrated by the previous chapters, implementation of fast track care is important, because it is associated with a shorter hospital stay and possibly less complications. In chapter 10 it was determined which baseline characteristics and/or which successfully achieved fast track elements are independent predictors of faster postoperative recovery in patients undergoing colonic resection for colon cancer. For this purpose data from the LAFA-study were used. During admission the fast track elements were prospectively evaluated per patient and scored whether or not successfully applied. In the fast track group there was a higher overall compliance to the preoperative and perioperative fast track elements (mean 9.7 elements out of 12; ranging from 52% to 97%) than to the postoperative elements (mean 2.9 elements out of 7; ranging from 30% to 66%). Some elements (no bowel preparation, thoracic epidural, forced body heating, removal of nasogastric tube, no abdominal drains) were also applied in standard care group as available evidence is so convincing, that it would have been unethical to withhold these in a trial setting. Two baseline characteristics and 2 fast track elements were found to be significant independent predictors on total postoperative hospital stay (THS); female sex was leading to a 15% (CI: 4-25%) reduction in THS, laparoscopic resection in a 15% (CI: 4-25%) reduction in THS, ‘normal diet at postoperative days 1, 2 & 3’ in a 30% (CI: 19-39%) reduction in THS, and ‘enforced mobilisation at postoperative days 1,2 & 3’ in 32% (CI: 20-41%) reduction in THS. In conclusion, evaluating only those fast track elements that were successfully achieved, showed that enforced advancement of oral intake, early mobilisation and laparoscopic surgery and female sex were independent determinants of early recovery.

Finally in chapter 11, the ultimate level of fast track care, namely day-care surgery, has been evaluated. The main goal of the fast track concept is to accelerate patient’s postoperative recovery resulting in a shorter hospital stay. Day-care surgery is a feasible option for some surgical procedures. In this prospective double-cohort study we evaluated the feasibility and desirability of 360° laparoscopic Nissen fundoplication (LNF) performed in day-care compared to a laparoscopic cholecystectomy (LC) in day-care. LC was chosen as cohort, because this procedure is performed routinely in day-care surgery. Twenty-two patients underwent LNF and 48 patients LC in day-care. After LNF, 21 out of 22 (95%) patients were discharged the same day. After LC, 45 out of 48 (94%) patients were discharged the same day. EQ-5D (a measure of health-related quality of life) and VAS scores were significantly worse after LNF in day-care (repeated measurements, P<0.0001 and P<0.0001). In a telephone survey 66.7% of the LNF patients preferred a short hospital stay over day-care surgery, compared with 30.9% after LC (P=0.011). In conclusion, LNF in day-care is feasible and safe, however postoperative pain scores were high and quality of life was diminished in comparison with LC. Since more than two-thirds of patients preferred short hospital admittance, conventional LNF can best be performed in a short-stay setting.