Selective decontamination of the digestive tract in elective gastrointestinal surgery
Roos, Daphne

Citation for published version (APA):

General rights
It is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), other than for strictly personal, individual use, unless the work is under an open content license (like Creative Commons).

Disclaimer/Complaints regulations
If you believe that digital publication of certain material infringes any of your rights or (privacy) interests, please let the Library know, stating your reasons. In case of a legitimate complaint, the Library will make the material inaccessible and/or remove it from the website. Please Ask the Library: http://uba.uva.nl/en/contact, or a letter to: Library of the University of Amsterdam, Secretariat, Singel 425, 1012 WP Amsterdam, The Netherlands. You will be contacted as soon as possible.
CHAPTER 8
Summary, conclusions and future perspectives
SUMMARY

The aim of this thesis was to evaluate the role of Selective decontamination of the digestive tract (SDD) in elective gastro-intestinal (GI) surgery on postoperative infectious complications. Mortality, hospital stay and cost-effectiveness were also analysed. This thesis also will provide an overview of the clinical applicability of SDD in elective GI surgery.

SDD was introduced in 1983 in Intensive care medicine as a new technique for infection prevention and has shown to decrease morbidity and mortality significantly in this group of patients. As one of the founders of the concept of SDD, Stoutenbeek also advised the use of SDD in patients undergoing surgery, because postoperative infectious complications after elective gastrointestinal surgery remained high, up to 28% after colorectal surgery, in spite of optimal perioperative care and the use of systemic antibiotics. The most common infections, are nosocomial infections and occur after 48 hours after admission to the hospital. They are mostly caused by Gram-negative bacteria from the patients digestive tract. To decrease the incidence of these infections, perioperative SDD was introduced on the surgical ward of the OLVG in 1999, in patients who underwent colorectal surgery.

Chapter 2 describes the results of a retrospective analysis of prospectively collected data of 162 patients who were admitted to the surgical ward for elective colorectal surgery in a three year period. Of these patients, 76 (47%) received SDD (polymyxine B sulphate 100mg, tobramycine 80mg and amphotericine B 500mg (PTA)) 4 times daily, which was preferably started 1 to 2 days before surgery. The control group consisted of 86 (53%) patients who were not treated with SDD. Both groups received identical systemic antibiotics peri-operatively. In the SDD group, more patients underwent a (low) anterior resection. The SDD was started before surgery and continued for at least 3 days after surgery in 47 (62%) patients. There were 6 patients (7.9%) with infectious complications (mainly urinary tract infections and pneumonae) in the SDD group compared with 17 patients (19.8%) in the control group (p=0.031). Infectious complications and anastomotic leakage together were evaluated as “the combined primary endpoint”. The incidence of the combined endpoint was 8 (11%) in the SDD group versus 22 (26%) in the control group (p=0.014). There was no difference in mortality or hospital stay. Multivariate analysis showed that no-SDD, age above 60 years and diabetes were independent predictors of postoperative complications.

Because the SDD in this retrospective study was given randomly, according to the surgeon’s prevalence, the results of this study might have been influenced by bias. Therefore in 2003 a randomized, double blinded, placebo controlled trial was a initiated, to further evaluated the previous results. In chapter 3, 289 patients were randomized and analysed, undergoing elective gastrointestinal surgery in a 5-year period, including upper and lower GI procedures. To correct for an expected difference in number of upper and lower GI surgery, patients were classified into 4 groups; Group A included patients undergoing esophageal and gastric surgery, group B Hepato-Pancreateo-Biliary (HPB) surgery, group C
colectomies, and group D rectal resections. Most patients however underwent colorectal surgery. Patients were randomized between SDD and placebo, which was given 4 times daily, 1 to 2 days before surgery and continued until normal bowel movements were achieved or at least for 3 days after surgery. All patients received systemic antibiotics perioperatively. To determine if patients had an infection before surgery, a preoperative culture of sputum and urine was collected at the outpatients clinic. On the operating room, a rectal culture was taken to determine if decontamination had occurred.

Optimal trial medication was administered in 82 (57.3%) patients in the SDD group and 87 (59.6%) in the placebo group, with a median of 19 doses in the SDD group and 20 doses in the placebo group. In the SDD group a significantly lower rate of postoperative infectious complications was found; 28 (19.6%) in the SDD group, versus 45 (30.8%) in the placebo group (p = 0.03). The incidence of anastomotic leakage was significantly lower in the SDD group than in the placebo group, 9 (6.3%) versus 22 (15.1%) respectively. There was no significant difference in hospital stay or mortality. Among the patients with anastomotic leakage, age was higher (71 versus 59) but hospital stay was shorter (21 versus 33 days) in the SDD group compared to placebo. This RCT showed a relative risk reduction in postoperative infectious complications of 36% and a NNT of 9. Also a 58% relative reduction of anastomotic leakage was found. Based on these findings, we advised to consider perioperative SDD for patients undergoing GI surgery, starting 3 days before surgery and continue SDD until normal bowel movements are achieved.

Although the effect of SDD on morbidity and mortality in ICU patients seems to be clear, only 30% of all Dutch ICU’s currently use it. We suspected that the use of SDD on the surgical ward would even be less adopted. In chapter 4 a point prevalence study was conducted to investigate the use of SDD, perioperative antibiotics and mechanical bowel preparation (MBP) in elective GI surgery in the Netherlands. An online questionnaire was sent to GI surgeons of 86 (8 academic and 78 peripheral) hospitals. The response rate was 74%; 6 academic centres and 58 peripheral hospitals were included. Twenty hospitals (31.1%) applied SDD exclusively in their ICU’s. Only 4/64 (6.3%) hospitals applied SDD on the surgical ward. There was a difference in indication of SDD between these hospitals; 2 hospitals prescribed SDD in GI surgery, one primarily in hyperthermic intraperitoneal chemotherapy (HIPEC) procedures and one exclusively in liver transplantations. Systemic antibiotics during GI surgery were administered in all Dutch hospitals, although only 59.4% applied the AB approximately 30 minutes before surgery according to Dutch guidelines. In 81.3% a cephalosporin was used, in 76.6% it was combined with metronidazole. Strikingly, 90.6% still used MBP before surgery, mainly for left sided (open or laparoscopic) colorectal surgery and transanal endoscopic microsurgery (TEMI). For upper GI surgery, no MBP was given. In conclusion, perioperative SDD in elective GI surgery is seldom applied on Dutch surgical wards and only subscribed when the hospital ICU used it too. Perioperative antibiotics are administered to late in 40.6% and MBP is still used in left-sided colorectal surgery in almost all Dutch surgical wards.
With the current economic crisis, reduction in healthcare costs are more important than ever. The cost-effectiveness of SDD on the ICU has been described in literature and showed lower costs in patients who received SDD. In **chapter 5** the population from our RCT was used to calculate the incremental cost-effectiveness ratio for SDD versus placebo as the difference in mean total costs (in euro) divided by treatment effect. The aim of this study was to objectify the costs in patients who were admitted to the surgical ward and scheduled for elective GI surgery. Furthermore this study also analysed if the reduction in postoperative infectious complications from our previous RCT lead to lower costs. All surgical procedures, re-interventions (i.e. relaparoscopy/laparotomy or radiological interventions) and laboratory data were summarized during one year of follow up. Also costs from consultation of an other specialist, including the use of diagnostics, were recorded. SDD reduced the costs by EUR 2,604 per patient, resulting in a cost-effectiveness acceptability of SDD of ≥92%. This was mainly due to reduction of the costs of hospitalization.

As mentioned before, the use of SDD in the ICU is extensively evaluated and reported in literature, but not many RCT’s have been conducted on the use of SDD in elective GI surgery. Also, the administration of perioperative SDD is not widespread accepted in GI surgery. In **chapter 6** a systematic review of the literature and meta-analysis was presented which compared the effect of perioperative SDD in elective GI surgery with systemic antibiotics to systemic antibiotic prophylaxis alone. The primary outcome was infectious complications and anastomotic leakage. Secondary outcome was hospital stay and mortality. Medline, Embase and the Cochrane Central register of Controlled trials were used, and identified 1660 potentially relevant articles of which 38 studies were retrieved for more detailed evaluation. Eight studies with a Jadad score > 3 were eligible for inclusion in the systematic review, including a total of 1668 participants. Most of the RCTs were conducted and published before 2007 and therefore ERAS protocols were not yet included in these trials. Of 1668 patients, 828 received preoperative SDD with perioperative intravenous antibiotics, while 840 patients only received perioperative intravenous antibiotics with or without an oral placebo. All systemic antibiotics had a Gram-negative coverage. Only three trials described the continuation of oral decontamination after surgery. Infectious complications were reported in 5 studies: 77(9%) patients with SDD versus 118 (14%) patients in the control group (p = 0.002). Wound infections were described in 6 trials with a decrease in the SDD group (4.2% versus 8.8%). Anastomotic leakage was less in the SDD group (2.3% versus 5.2%) (p = 0.002).

Separate analysis of the subgroups “upper” and “lower” GI surgery was conducted and showed that SDD reduced infectious complications in both subgroups without difference in effect. Hospital stay did not differ between groups ( p =0.19) but was only mentioned in two trials. Mortality rates, described in three trials, were not significantly different between groups ( p = 0.27). We concluded that the use of perioperative SDD decreased infectious complications after elective upper and lower GI surgery. Future trials are needed to analyse a potential effect of perioperative SDD on mortality and hospital stay and to evaluate the effect of SDD next to the introduction of the enhancement recovery protocols.
The aim of our study described in chapter 7 was to analyse the results of cultures taken during our RCT and determine their correlation with cultures taken of postoperative infections. As mentioned earlier 289 patients undergoing elective gastrointestinal surgery, were randomly assigned to receive SDD or placebo (143 versus 146 patients respectively). In the outpatient clinic preoperative diagnostic samples of sputum and urine were collected, to determine preoperative infections. All patients received systemic antibiotics during surgery. On the operating room, rectal swabs were taken to objectify the state of decontamination. Adequate decontamination was defined as absence of growth of Gram-negative bacteria and yeasts. If a postoperative infectious complication was suspected, a culture was taken from wound, blood, urine or sputum or from the abdominal cavity during surgery. Patients were treated for infections according to hospital protocol. Preoperative urinary cultures were taken in 244 (84%) patients. In 9% there was a urinary tract infection present (14 in the SDD group versus 9 in the placebo group). Of all patients with sputum cultures, 90% showed no growth. Per-operative rectal cultures were obtained in 198 patients, 99/143 (69%) in the SDD group and 99/146 (67%) in the placebo group. In the SDD group, 64/99 (65%) was adequately decontaminated. Of these patients, 51 did not develop infectious complications (79.7%). In 50% of the cases, the bacteria found in diagnostic cultures were similar to those found in the peroperative rectal cultures. SDD reduced peroperative carriage of Gram-negative bacteria and yeasts, which resulted in no Gram-negative postoperative infections in the successfully decontaminated group of patients. One third of the patients was not adequate decontaminated, therefore optimization of preoperative SDD is required.

CONCLUSION

Perioperative SDD with perioperative systemic antibiotics reduces postoperative infectious complications and anastomotic leakage in elective gastrointestinal surgery, compared with systemic antibiotics alone. The administration of SDD is uncommon in the Netherlands and only used for GI surgery if the ICU of those hospital advocates SDD too. SDD needs to be administered in adequate doses over a sufficient period of time to achieve adequate decontamination, that means a reduction in peroperative carriage of Gram-negative bacteria and yeasts, which results in less Gram-negative postoperative infections. In practice this means that SDD needs to be started 3 days before elective surgery (which can be done at home) and continued until normal bowel movements have been achieved and/or normal intake is guaranteed. The bad taste of SDD needs to be explained by the attending surgeon. SDD can simply be prepared in every hospital pharmacy and lowers total costs.
FUTURE PERSPECTIVES

Today, the influence of intestinal microbiota on the health system is becoming more and more acknowledged.\textsuperscript{10} It is becoming increasingly evident that the complex bacterial population of the digestive tract forms an ecosystem that plays an important role in different diseases. Age, diet and health status of the host affect the composition of microbiota and several diseases are associated with changes in the composition of gut microbiota (‘the intestinal microbiome’), including metabolic diseases, inflammatory bowel diseases and obesity and diabetes.\textsuperscript{11-13} The composition of bacteria, involve the immune system as well as the colonic mucin structure. Of course, it is not yet clear if the changed composition of flora are a cause of a consequence of a disease.\textsuperscript{14}

Microbiota (e.g. Bacteroides) that produce carcinogenic metabolites, are associated with colorectal carcinogenesis\textsuperscript{15} and upper GI diseases, including benign upper GI diseases and gastric cancer.\textsuperscript{16} On the other hand, Fecal microbiota transplantation (FMT) can be used as a therapy for recurrent Clostridium difficile infection (CDI).\textsuperscript{17,18}

The amount of microorganisms in the intestine outreach the number of cells in the human body. Gene sequencing techniques are able to identify the genoma in microbiota.\textsuperscript{19-21} Maybe in the future, this development will lead to identification of patients that are more susceptible for specific diseases by using their stool as a diagnostic and perhaps prognostic tool.

Most importantly, anastomotic leakage is a major complication after GI surgery and does not only cause discomfort to the patient, but can also lead to sepsis, reintervention, ICU admittance, prolonged hospital stay and even death. While bacteria play an important role in the development of anastomotic dehiscence, by causing local inflammation at the suture line with intramural abscess formation and necrosis\textsuperscript{22}, perioperative SDD seems to decrease anastomotic leakage. Prevention of anastomotic leakage is important, because it has been shown in the literature that leakage is associated with diminished survival and a higher prevalence of local recurrence of tumor.\textsuperscript{23}

Although the reduction in perioperative endotoxaemia by SDD is mainly studied in cardiac surgery\textsuperscript{24}, preventing or decreasing perioperative endotoxaemia by perioperative SDD is also an important topic, while bacterial endotoxins lead to metastatic tumor growth in experimental tumor models because they increase tumorcell adhesion.\textsuperscript{25}

The SELECT trial (NL 2011-002211-28) is a multicenter RCT which compares SDD with placebo in elective colorectal surgery. The primary outcome is anastomotic leakage, the secondary endpoint is long term oncological outcome. This trial has been started in the end of 2012 and will hopefully give answers to these important topics.
REFERENCES

10. Marcel Levi, Darmflora, Medisch Contact 18 april 2013, 68 nr.16, blz 856.
SUMMARY, CONCLUSIONS AND FUTURE PERSPECTIVES


