Annals of Medicine and Surgery 35 (2018) 44–50

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.elsevier.com/locate/amsu

Bilirubin, urobilinogen, pancreas elastase and bile acid in drain fluid. The GBUP-study: Analysis of biomarkers for a colorectal anastomotic leakage

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ARTICLE INFO

Keywords:
Anastomosis
Colorectal surgery
Anastomotic leak
Predictive diagnosis
Anastomotic leakage

ABSTRACT

Purpose: A colorectal anastomotic leakage (CAL) is a major complication after colorectal surgery and leads to high rates of morbidity and prolonged hospital stay. The study aims to evaluate the benefit of using bilirubin, urobilinogen, pancreas elastase and bile acid in the drain fluid (DF) as a predictive marker for the CAL.

Methods: From June 2015 to October 2017 100 patients, who underwent left hemicolectomy (LH), sigma resection (SR), high anterior resection (HAR), low anterior resection (LAR) or reversal of Hartmann's Procedure (ROHP) were included in this monocentric non-randomized prospective clinical trial. During the first four postoperative days (POD) the concentration of bilirubin, urobilinogen, pancreas elastase and bile acid in the DF was measured.

Results: In total 100 patients were recruited. 17 were excluded due to intraoperative decisions to conduct a protective stoma. 6 patients had a CAL. The patients of the control group (n = 77) and the patients who suffered from a CAL (n = 6) had no increased concentration of urobilinogen and pancreas elastase in the DF. The concentration of bile acid in the DF of the patients who suffered from a CAL differed from those of the control group on the 4th POD (p = 0.055).

The concentration of bilirubin in the DF of the patients who suffered from a CAL significantly differed from those of the control group on the 1st POD (p = 0.031) and on the 3rd POD (p = 0.041).

Conclusion: Bilirubin and bile acid in the DF may function as a predictive marker for a CAL.

1. Introduction

A CAL is a major complication after colorectal surgery and leads to high rates of morbidity, reoperation, intervention and a prolonged hospital stay [1]. The International Study Group of Rectal Cancer defined in 2010 the CAL following anterior resection of the rectum as a defect of the intestinal wall integrity at the colorectal or colo-anal anastomotic site, which allows a connection between the extra- and intraluminal space. The authors differentiated between three grades of severity; grade A is a CAL requiring no active therapeutic intervention, grade B is a CAL requiring active therapeutic intervention without reoperation and grade C is a CAL requiring a reoperation [1]. The mortality rate lies between 10% and 20% [2]. Moreover a CAL has a negative impact on the long-term cancer specific survival and recurrence rate [3].

Several studies have been carried out to circumscribe the risk factors for developing a CAL. In summary considered risk factors are: rectal resection, smoking, alcohol abuse, high body mass index (BMI), the male gender, treatment with steroids, radiotherapy and chemotherapy, a high American Society of Anesthesiologists (ASA) score, cardiac and vascular diseases, duration/length of surgery and emergency surgery [6–10].

The diagnosis of a CAL is mostly made between the 5th and 13th POD due to unspecific clinical signs and symptoms, which can mimic less serve infections (wound, urinary tract) [11–14]. In literature the computer tomography of the abdomen is described as being a sufficient

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https://doi.org/10.1016/j.amsu.2018.09.008
Received 17 June 2018; Received in revised form 29 August 2018; Accepted 12 September 2018

diagnostic approach to detect a CAL [11].

Viable predictive clinical diagnostics to detect a CAL are currently subject of research and due to morbidity and high rate of mortality urgently required. An endoscopic approach to treat small leaks would allow treatment without major surgery. We have therefore performed a prospective pilot study to evaluate the viability of the bilirubin, urobilinogen, pancreas elastase and bile acid concentration in drain fluids as a predictive marker. Pancreas elastase, bile acid and bilirubin as well as its metabolites like urobilinogen were excreted by bowel movement. We postulate that these metabolic products can leave the intraluminal space through the anastomotic leak. As in the beginning the leak is naturally a small one, we assume that pancreas elastase, bile acid, bilirubin and urobilinogen are detectable in the drain fluids even before the CAL is felt as abdominal pain due to peritonitis.

2. Methods

At Helios Hospital Berlin-Buch, Germany, the GBUP-study ("Gallensäure, Bilirubin, Urobilinogen, Pankreaselastase"-Studie) was conducted as a monocentric non-randomized prospective clinical trial from June 2015 until October 2017. The study was registered in the German Clinical Trial Register (DRKS-ID: DRKS00009738; https://drks-neu.uniklinik-freiburg.de/drks) and was approved by the medical ethical committee in accordance with the ethical standards of the Helsinki Declaration of 1975 in March 2015. All patients gave informed consent.

2.1. Inclusion criteria

Patients undergoing (open/laparoscopic) left hemicolectomy (LH), (open/laparoscopic) sigmoid resection (SR), (open/laparoscopic) high anterior resection (HAR), (open/laparoscopic) low anterior resection (LAR), (open/laparoscopic) reversal of Hartmann's Procedure (ROHP) or (open/laparoscopic) colectomy (CT) were included.

Oncologic resections as well as resections for inflammatory disease and ischemic colitis were involved.

2.2. Exclusion criteria

Being under 18 years of age or pregnancy were criterions for exclusion. Patients who did not receive a drain as well as patients who got a protective ileostomy or colostomy were excluded.

2.3. Surgical approach

The surgical procedure and the technique for conducting the anastomosis (stapled/hand sewn) were left to the surgeon's discretion. The patients were operated by laparotomy or laparoscopy. All patients received preoperative antibiotic prophylaxis and an intra-abdominal drain.

To obtain the DF, a drain was placed at the anastomosis and was left in place during the first four postoperative days. We used the KapillardrainD12© (Dahlhausen, Köln, Germany) as a passive drainage systems.

When patients felt disturbed by the drain in terms of pain, movement limitation or paresthesia, it was removed earlier than planned.

2.4. Drain fluid

The DF was depleted once a day with intervals of 24 h, respecting rules of sterility.

2.5. Determination of bilirubin, urobilinogen, pancreas elastase, and bile acid

The determination of the total bilirubin, urobilinogen, pancreatic elastase and bile acid concentration was done via routine clinical chemistry assays. Total bilirubin was measured by using the third generation Bilirubin Total assay on a Cobas© c501 system (Roche Diagnostiscs, Mannheim, Germany). Urobilinogen was determined with a semi quantitative Combur© 10 test strip (Measurement: negative: < 17 µmol/l; normal: 17–68 µmol/l; +: 68–135 µmol/l; ++: 135–203 µmol/l; +++ > 203 µmol/l). The Urisys© 1100 analyzer was used (Roche Diagnostiscs, Mannheim, Germany). The pancreatic elastase was measured by using a standard ELISA assay (ScheBo Pancreatic Elastase 1, ScheBo Biotech, Gießen, Germany) and bile acids by using an enzymatic Thio-NAD assay (Fifth Generation Bile Acid Assay, Labor + Technik, Berlin, Germany).

2.6. Definitions

The endpoint of the GBUP-study was the CAL. According to the recommendation of the International Study Group of Rectal Cancer in 2010, a CAL is defined as a defect of the intestinal wall at the anastomotic site which allows a connection between the extra- and intraluminal space. Radiologic confirmation of a CAL was defined as an extravasation of endoluminal contrast agent and/or significant perianastomotic air on computed tomography. The endoscopic confirmation of a CAL is defined as the visual detection of the leak.

Interventions to treat the CAL included the endoscopic negative pressure wound therapy, antibiotic therapy and the surgical approach disconnecting or sewing the anastomosis, constructing a new anastomosis via loop ileostomy or by conducting a colostomy via ROHP. Postoperative mortality is defined as the death of a patient within 30 days after surgery.

2.7. Data collection

Demographic data of the patients (age, ASA-score, BMI, gender), type of operation, postoperative complications, and follow-up data were collected through a standardized case record form. In the event of a CAL, the postoperative day of diagnosis, the diagnostic approach for detection and the treatment was documented.

2.8. Follow-up

To detect a CAL after the discharge from our hospital all patients were contacted after the 15th and 30th POD by phone or by mail.

2.9. Statistics

In order to compare the baseline data (age, gender, type of operation etc.) between the CAL and the no CAL groups, mean, standard deviation, minimum, maximum and median were calculated for continuous variables. Four categorical variables cross-tables were calculated.

Normality of continuous variables was tested with the Shapiro-Wilk-test. In case of normally distributed continuous variables t-tests for independent groups were used to compare the CAL-/no CAL-groups, otherwise Wilcoxon-tests were used. In case of categorical variables Fishers exact test was used.

A p-value < 0.05 was regarded as statistically significant.

Due to the small group of CAL of this investigation, no multivariate analysis was carried out. For the same reason as for the tests of differences (bilirubin and bile acid) at the 1st – 4th POD no alpha-correction was done.

All statistical analyses were carried out using R 3.2.1 ("World famous astronaut"). The sample size calculation was done by using PROC POWER in SAS 9.4.