Study Protocol

Effects on omission of NSAIDs in the standard analgesic regimen on the consumption of opioids after elective laparoscopic colorectal cancer resection in an ERAS setting. A prospective single-center cohort study.

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Background:

Many standard analgesic regimens after colorectal cancer surgery includes a NSAID in combination with paracetamol and other non-opioid analgesics. Concerns about a risk of cardiovascular and renal impairment and the possible association with anastomotic leaks have questioned the rationale of NSAID use in the postoperative period and the need for possible alternatives[1–5]. In our department of colorectal cancer - surgery we decided to remove NSAIDs from the standard analgesic package from 1th of April 2016 without other analgesic substitution. This change might imply deterioration of the enhanced recovery program with an increase in the use of opioids and side effects that might cause a longer length of stay. In addition, recent studies are relaunching ibuprofen as a chemo-preventive of colorectal cancer [6,7] thus leaving the colorectal surgeon in doubt whether NSAIDs are beneficial or harmful to our patients.

Objective:

The aim of the present study is to investigate the short- and long-term outcomes before (+ ibuprofen) and after (- ibuprofen) April 1 st 2016.

Methods

Design

A prospective, consecutive single-center cohort-study.

Study population

Patients undergoing elective laparoscopic colorectal cancer resection at Zealand University Hospital, before and after 1st. of April 2016 are eligible for the study. Patients with a preoperative use of opioids within the last 3 months, undergoing a palliative resection or had a surgical complication leading to reoperation in general anesthesia will be excluded. Palliative resection is defined as patients with symptomatic metastatic colorectal cancer that undergoes resection of the primary tumor with the aim to relieve symptoms such as obstruction, bleeding or perforation.

Before April 1st. 2016 all patients, regardless of cardiovascular morbidity or kidney disease, received ibuprofen 400 mg in combination with paracetamol 1000 mg four times a day in the postoperative period and until admission. After April 1st the patients only received paracetamol. If the standard analgesic regimen was insufficient, patients in both groups were treated with intravenous, subcutaneous or oral opioids defined as drugs within the ACT-code (Anatomical Therapeutic Chemical Classification System) N02A. The department has a well-implemented Enhanced Recovery After Surgery (ERAS) program with a standardized management of the perioperative course and discharge with no other changes in the program in the study period.

Demographic and perioperative data including length of stay and postoperative complications within 30 days will be collected from the national prospective database of the Danish Colorectal Cancer Group. According to the exclusion criteria all patients with a registered surgical complication clavien dindo ≥3b will be excluded. The postoperative medical complications are categorized in the database in: Stroke, acute myocardial infarction, aspiration, pneumonia, heart failure, lung embolism, respiratory insufficiency, kidney failure, sepsis, deep venous thrombosis, arterial embolism and “other medical complication”. The medical

complications are also graded according to the clavien-dindo classification system. Daily postoperative opioid consumption until discharge, readmissions within 30 days, colorectal cancer recurrence or all-cause mortality are retrospectively collected from the electronic patient journal system (EPIC/OPUS).

Blood samples of creatinine and C-Reactive Protein are collected with one baseline preoperative sample (within 30 days before the operation) and postoperative day 1 to 7. Most patients will be discharged 2 to 3 days after the operation. Creatinine will be analyzed as a delta value of the baseline and the postoperative maximum serum creatinine value. In the analysis of CRP we will compare the postoperative in-hospital peak-value[8,9].

Troponine I is a biomarker of MINS (myocardial injury after non-cardiac surgery) that was measured in the study period on postoperative day 1 to 4 or until discharge. Troponine I values will be categorized in < 15, 15-45 and >45[10].

Study outcome

The primary outcome measure is changes in opioid use between the two groups (+/- NSAID), calculated as oral morphine equivalent (omeq) doses in mg. The secondary outcome measures are length of stay, postoperative medical complications within 30 days, changes in postoperative troponine I and creatinine, colorectal cancer recurrence and all-cause mortality. Colorectal cancer recurrence is defined as a local recurrence of cancer or a colorectal metastasis diagnosed >120 days after surgery.

A subgroup analysis of the primary outcome with patients who underwent a laparoscopic resection (including robotic assisted surgery) as well as a subgroup analysis excluding all patients with a surgical complication will be done.

Power calculation

The sample size calculation was based on non-parametric testing regarding the primary outcome. The minimally clinically relevant change in opioid consumption between the two groups was estimated to 25 % with a standarddeviation of 37.5 oral morphine equivalent (omeq). To detect a difference with a power of 80 % and an error alpha of 0.05 the total sample size was estimated to 502 patients – 251 patients in each group.

Statistical analyses

Data will be analyzed using non-parametric tests. For dichotomous data Chi-square/Fishers exact test will be used and quantitative data will be analyzed using the Mann-Whitney test.

Data permissions

Permission to enter the patient history was granted at The Danish Patient Safety Authority with ref.no. 3-3013-2746/1 23th of November 2018.

Permission to store data safely electronically was granted from the Data Surveillance Council (Datatilsynet – Region Sjælland) with ref.no. 18-000315/115.

Publication

The results will be published in an international scientific paper.

Research group

M.D. Stine Ydegaard Turiño (corresponding author) syt@regionsjaelland.dk

M.D., Ph.D. Jens Ravn Eriksen[1] jeer@regionsjaelland.dk

M.D. Steffen Kirstein Brisling[1] skbr@regionsjaelland.dk

Med.Sc.D. Ismail Gögenur[1] igo@regionsjaelland.dk

M.D, Ph.D. student Rasmus Vogelsang[1] rvo@regionsjaelland.dk

Department of Surgery, Zealand University Hospital, Lykkebækvej 1, DK-4600 Koege, Denmark.

Budget

There are no expected expenses of the study.

Time schedule

The data will be collected and analyzed during 2020 and the final article will be ready for publication in 2021.

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