Chapter 9

C-reactive protein in predicting postoperative complications Are there differences in open and minimally invasive colorectal surgery? A randomized clinical trial

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Submitted
ABSTRACT

In search of improvement of quality control in the postoperative phase, C-reactive protein (CRP) is increasingly being studied as an early marker for postoperative complications in major abdominal surgery. Several studies reported an attenuated immune response in minimally invasive surgery, which might affect interpretation of postoperative CRP levels. The present study assessed CRP as a predictor for major postoperative complications in patients undergoing open and minimally invasive colectomy.

Subgroup analysis from a randomized clinical trial including patients with non-metastasized colorectal cancer. Patients were randomized between open and laparoscopic segmental colectomy. In a subgroup of 79 patients standard postoperative measurements of CRP were collected routinely preoperatively and 1, 2, 24 and 72 hours after surgery.

Seventy-nine patients were randomized, being 37 patients in the open group and 42 patients in the laparoscopic group. Major complications occurred in 19% of laparoscopic procedures and 13.5% of open procedures (p = 0.776). In uncomplicated cases, CRP levels were significantly lower 24 and 72 hours after laparoscopic resection. No differences in CRP were observed stratified for surgical technique in patients with major complications.

C-reactive protein can be applied as a marker for major postoperative complications in both open and minimally invasive colorectal surgery. Decreased surgical trauma in laparoscopy leads to lower postoperative CRP levels in patients with an uncomplicated postoperative course. Inflammation in major complications exceeds the effect of primary surgical trauma, and no differences in CRP levels are observed stratified for surgical technique. Future research should aim to assess the role of standardized postoperative CRP measurements.
INTRODUCTION

Over the past decades, medical care for patients undergoing colorectal surgery has improved significantly with Fast-Track peri-operative care and minimally invasive surgical techniques. Minimally invasive techniques have proven to be superior to conventional open techniques in colorectal surgery regarding short-term outcomes, such as improved postoperative recovery and a reduced postoperative systemic immune response with possible concomitant inhibitory effect on tumor spread and metastasis. Long-term outcomes are similar in both groups.

Major complications after colorectal surgery, requiring invasive treatment, are reported in up to 20% of patients. In search of improvement of quality control in the postoperative phase, C-reactive protein (CRP) is increasingly being studied as both an early marker for postoperative complications, as well as a safe discharge criterion.

Several studies have assessed the use of CRP as an early marker for postoperative complications following colorectal surgery. In some studies procedures with open and minimally invasive techniques were both included, whereas correction was omitted. Other studies included only open procedures or only minimally invasive procedures, with similar results.

If the inflammatory and immune responses are attenuated in minimally invasive procedures in comparison to open procedures, this might affect interpretation of postoperative CRP levels and could imply a different cut-off or correction should be applied for CRP as a marker for complications. A recent meta-analysis showed no differences in CRP levels between open and minimally invasive surgery in patients that suffered postoperative complications. The study did suffer from selection bias, since gastric and oesophageal resections were only performed open, whereas gastric bypass was only performed laparoscopically. Additional evidence is necessary.

Aim of the present study was to compare the value of C-reactive protein as a predictor of major postoperative complications in patients undergoing open versus laparoscopic colorectal surgery within the context of a randomised trial in which routinely CRP was measured to exclude bias.

MATERIALS & METHODS

Patients

Patients with histologically confirmed malignancy or adenoma planned for elective segmental colectomy with curative intent were eligible. Patients had to be between 40 and 80 years of age and have an American Society of Anaesthesiologists grade below IV. Exclusion criteria consisted of a previous midline laparotomy, emergency surgery
and patients who were to receive a planned stoma. Patients with immune depressant
disease or medication were also excluded. Upon obtaining informed consent patients
were randomized between open or laparoscopic colectomy. This study is a substudy
from the LAparoscopy and/or FAst track multimodal management versus standard care
(LAFA-trial). The design and primary results of the trial were previously published \(^1, 33\). Patients were included from the VU University Medical Center and Academic Medical
Center, Amsterdam, Netherlands.

Recorded data regarding baseline characteristics included age, gender, BMI, co-
morbidities and American College of Anaesthesiologists (ASA) classification. Recorded
clinical parameters included indication for operation, type of surgery, duration of
surgery, clinical parameters, performed CT-scans, complications according to Clavien-
Dindo classification and mortality.

Complications were graded according to a modified Clavien-Dindo classification,
which grades complications according to the necessitated treatment \(^34, 35\). Minor
complications, consisted of grade I and II, encompassing complications that require
pharmaceutical treatment (i.e. antibiotics) and wound infections, treated by opening
the wound at the bedside. Major complications consisted of grade III to V, encompassing
all complications that require invasive treatment (i.e. percutaneous drainage or reopera-
tion), ICU admission and even leading up to death. Mortality was defined as in-hospital
mortality.

All patients received perioperative prophylactic intravenous antibiotics and throm-
boprophylaxis according to local protocol. Treatments of major complications were
classified as reoperations, radiological interventions such as percutaneous drainage and
intensive care admission.

**Design**

Patients included in the LAFA-trial were randomized between laparoscopic or open
segmental colectomy and fast-track or standard postoperative care in a 2 by 2 balanced
factorial design. The study was conducted in accordance with the principles of the
declaration of Helsinki and approved by local medical ethics review boards (protocol
NTR222).

In a subgroup of 81 patients standard postoperative measurements of CRP Blood
samples for C-reactive protein analysis were collected routinely preoperatively and 1,
2, 24 and 72 hours after surgery. C-reactive protein samples were analyzed by immu-
noturbidimetric methods, using the BM/Hitachi 705 (Boehringer, Mannheim, Germany).
Due to logistic reasons standardized CRP measurements were only available for patients
operated in the VUmc or AMC hospital in the Netherlands, being 81 patients.

All patients received similar postoperative diagnostic work-up for complications.
Patients had daily assessment of clinical parameters (i.e. heart rate, blood pressure,
temperature, pain, ileus). Upon clinical deterioration additional biochemical testing was performed (regardless of the standardized testing). Imaging was performed with

**Statistical analysis**

Statistical analysis was conducted in SPSS version 19.0 (SPSS Inc. Chicago, IL, USA). Continuous variables with normal distributions were presented as means and standard deviations. Medians and interquartile ranges were used as a central tendency for continuous variables with abnormal distributions. Categorical data were expressed with percentage frequencies. Comparison between the open and minimally invasive group was conducted with Student’s T-test or Mann-Whitney-U as appropriate for continuous variables. Chi-square tests were used for comparison of categorical data. A value of p < 0.05 was considered statistically significant. Backward stepwise logistic regression techniques were applied to determine predictors for major complications and in order to assess effect-modification by surgical technique. This study was assessed and approved by the medical ethical committee of the VU Medical Centre. Informed consent was waived due to the observational nature of the study.

**RESULTS**

Eighty-one patients were assessed for eligibility. Two patients were excluded since they declined extra blood sampling due to needle-phobia. Seventy-nine patients were randomized in the VU University Medical Center and Academic Medical Center. Thirty-seven patients were randomized to an open procedure and 42 patients were randomized to a laparoscopic procedure. The trial also balanced for standard or Fast Track postoperative care, indicating 19 patients were operated laparoscopically and received postoperative Fast Track care. The other 23 patients that were operated laparoscopically received standard postoperative care. In the open group 17 patients received Fast Track care and 20 patients received standard care. Due to the design in a 2x2 factorial model no confounding is expected by postoperative care. Baseline characteristics are depicted in table 1. No statistically significant differences were observed for patient characteristics. 94,7 % of samples were collected and analysed on time, taking into account accrual times as described in the study protocol. Missing values were mainly caused by delay and arrival of samples outside the predetermined time interval, these samples were therefore not analysed.
All patients underwent elective segmental colectomy for cancer. No differences were observed for type of colectomy. Duration of surgery was significantly longer and blood loss was significantly less in the laparoscopy group (p<0,001). In one patient the procedure was converted to an open colectomy because of bulky tumour with ingrowth in

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Open (n)</th>
<th>Minimally invasive (n)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>37</td>
<td>42</td>
<td></td>
</tr>
<tr>
<td>Gender, male (%)</td>
<td>26 (69 %)</td>
<td>23 (62,2 %)</td>
<td>0,52</td>
</tr>
<tr>
<td>Age, years (mean ± SD)</td>
<td>66,3 ± 12</td>
<td>66,7 ± 9,7</td>
<td>0,858</td>
</tr>
<tr>
<td>Body mass index (BMI) mean ± SD</td>
<td>25,8 ± 4,3</td>
<td>25,3 ± 3,3</td>
<td>0,593</td>
</tr>
<tr>
<td>ASA-classification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>9 (24,3 %)</td>
<td>14 (33,3 %)</td>
<td>0,497</td>
</tr>
<tr>
<td>II</td>
<td>24 (56,8 %)</td>
<td>24 (57,2 %)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>6 (16,2 %)</td>
<td>4 (9,5 %)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>1 (2,7 %)</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Comorbid disorders</td>
<td>27 (73 %)</td>
<td>29 (69 %)</td>
<td>0,702</td>
</tr>
</tbody>
</table>

Operative details

Surgery type

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Open (n)</th>
<th>Minimally invasive (n)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Right hemicolecetomy</td>
<td>20 (54,1 %)</td>
<td>15 (35,7 %)</td>
<td>0,469</td>
</tr>
<tr>
<td>Transversectomy</td>
<td>1 (2,7 %)</td>
<td>3 (7,1 %)</td>
<td></td>
</tr>
<tr>
<td>Left hemicolecetomy</td>
<td>3 *8,1 %</td>
<td>5 (11,9 %)</td>
<td></td>
</tr>
<tr>
<td>Sigmoid resection</td>
<td>11 (29,7 %)</td>
<td>14 (33,3 %)</td>
<td></td>
</tr>
<tr>
<td>Rectum resection</td>
<td>2 (5,4 %)</td>
<td>5 (11,9 %)</td>
<td></td>
</tr>
</tbody>
</table>

Duration of surgery, min (mean ± SD) = 130 (98 - 173) 191 (160 - 220) <0,001

Blood loss = 230 (150 - 400) 80 (0 - 150) <0,001

Postoperative complications

<table>
<thead>
<tr>
<th>Category</th>
<th>Open (n)</th>
<th>Minimally invasive (n)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated</td>
<td>28 (75,7 %)</td>
<td>29 (69 %)</td>
<td>0,473</td>
</tr>
<tr>
<td>Minor complication</td>
<td>4 (10,8 %)</td>
<td>5 (11,9 %)</td>
<td>0,776</td>
</tr>
<tr>
<td>Major complication</td>
<td>5 (13,5 %)</td>
<td>8 (19,1 %)</td>
<td></td>
</tr>
</tbody>
</table>

Hospital stay (median days (IQR))

<table>
<thead>
<tr>
<th>Category</th>
<th>Open (n)</th>
<th>Minimally invasive (n)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated</td>
<td>6 (4 - 9)</td>
<td>4 (3 - 7)</td>
<td>0,011</td>
</tr>
<tr>
<td>Minor complication</td>
<td>10 (8 - 19)</td>
<td>14 (7 - 16)</td>
<td>0,998</td>
</tr>
<tr>
<td>Major complication</td>
<td>18 (11 - 72)</td>
<td>23 (13 - 40)</td>
<td>0,943</td>
</tr>
</tbody>
</table>

30-day mortality = 1 - 0,284
CRP in open and minimally invasive abdominal surgery

the abdominal wall. Analysis was performed according to the intention to treat principle and this patient was analysed in the laparoscopy group.

**Postoperative complications**

Complications were observed in 27,8% of patients. Major complications were observed in eight laparoscopy patients (19,1 %) and in five patients who underwent an open procedure (13,5 %). Minor complications were observed in 11,9% of laparoscopic procedures and 10,8 % of open procedures. No differences in complication rates were observed for open and laparoscopic procedures (p = 0,776). An overview of complications is depicted in table 2. In uncomplicated patients admission duration was significantly shorter. Hospital stay was significantly longer in complicated patients and did not differ between open and laparoscopic procedures, as depicted in table 1.

**C-reactive protein**

CRP data was collected routinely preoperatively (baseline) and 1, 2, 24 and 72 hours postoperatively. CRP data were compared for open and laparoscopic techniques, and in order to check for confounding also stratified for postoperative care, being standard or Fast Track. No differences in CRP levels were observed between the different postoperative care groups (all p>0.08).

Data were stratified for patients with major complications in comparison to patients with no or minor complications, as depicted in figure 1. In concordance with previous analyses CRP levels were significantly lower in patients who underwent a laparoscopic

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**Table 2: Overview of all postoperative complications. Cardiac complications occurred after the fifth postoperative day in both affected patients.**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Open</th>
<th>%</th>
<th>Minimally invasive</th>
<th>%</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>37</td>
<td></td>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anastomotic leak</td>
<td>3</td>
<td>8,1%</td>
<td>3</td>
<td>7,1%</td>
<td>0,872</td>
</tr>
<tr>
<td>Surgery</td>
<td>2</td>
<td></td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous drainage</td>
<td>1</td>
<td></td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolonged postoperative ileus</td>
<td>2</td>
<td>5,4%</td>
<td>6</td>
<td>14,3%</td>
<td>0,192</td>
</tr>
<tr>
<td>Surgery</td>
<td>-</td>
<td></td>
<td>3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound/stoma problem</td>
<td>3</td>
<td>8,1%</td>
<td>2</td>
<td>2,5%</td>
<td>0,543</td>
</tr>
<tr>
<td>Surgery</td>
<td>-</td>
<td></td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-abdominal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pneumonia</td>
<td>2</td>
<td>5,4%</td>
<td>2</td>
<td>4,8%</td>
<td>0,896</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>2</td>
<td>5,4%</td>
<td>2</td>
<td>4,8%</td>
<td>0,896</td>
</tr>
</tbody>
</table>
procedure. When stratifying analysis for major complications versus no or minor complications results depicted lower CRP values in minimally invasive patients with no or minor complications at 24 and 72 hours after surgery (p < 0.05). No differences in CRP levels were observed between laparoscopic and open procedures in patients with major complications (all p-values > 0.5). Receiver Operator Characteristic (ROC) curve analysis for CRP levels 72 hours postoperatively as a marker for major complications revealed an area under the curve of 0.674 (95% confidence interval 0.506 – 0.842). By determining the Youden-index the optimal cut-off was determined at CRP levels of 140 to 150 mg/L. A relatively small number of events prevented more precise determination of the cut-off.

**Logistic regression analysis**

Logistic backward stepwise regression analysis was performed with major complications as outcome. Laparoscopic and open surgery, and the CRP levels 72 hours postoperatively on POD 3 as a marker for complications were entered in the model. Correction was applied for sex, age and ASA-classification. The model is depicted in table 3. No interaction was observed between the CRP levels and open or laparoscopic surgical technique. No effect-modification or confounding was observed after correction for any of the added
variables. In the final model, after backward stepwise logistic regression with a 0.1 limit for removal, only the CRP levels 72 hours after surgery remained as a significant predictor for major postoperative complications.

**DISCUSSION**

Regardless of the applied surgical techniques, open or minimally invasive, postoperative CRP levels can be used to predict or rule out major postoperative complications. In this randomized clinical trial comparing open and minimally invasive colorectal surgery, CRP levels in patients with an uncomplicated postoperative course or minor complication, were significantly lower in the minimally invasive group at 24 and 72 hours postoperatively, whereas in patients with major complications no differences were observed for CRP levels between the two different surgical approaches. Correction with backward stepwise logistic regression techniques further emphasized there was no effect-modification or confounding by surgical approach in the relationship between CRP levels and major postoperative complications. The determined cut-off was similar to a previously determined optimal cut-off based on a pooled analysis of 1427 patients and may be applied in both open and laparoscopic segmental colectomy. 21.
The differences in CRP levels between open and minimally invasive surgery in patients with an uncomplicated or minor complicated postoperative course can be explained by the differences in the amount of operative trauma, leading to lower levels of acute phase proteins such as CRP and interleukin-6\textsuperscript{26,36}.

Interestingly, no differences were observed in CRP levels stratified for operative approach in patients who suffered a major complication, indicating the inflammatory reaction following major complications surpasses differences in surgical trauma. These results underpin the use of postoperative CRP levels as a marker for complications, regardless of surgical approach. These results may indicate that major complications such as leakages might be developing earlier than we think, as their consequences may be observed as early as the first postoperative day. A recent meta-analysis supports our findings; in absence of complications, CRP levels were lower in patients that underwent minimally invasive surgery compared to open surgery. As stated in the introduction this study suffered from selection bias\textsuperscript{37}. Indicating the importance of the prospective randomised evidence here presented.

Postoperative hospital stay was also significantly shorter in minimally invasive surgery for patients with an uncomplicated postoperative course (p=0.011), this is in concordance with available literature\textsuperscript{1,20}. Baseline characteristics in this population were similar in both groups. When correction is applied for surgical technique, as depicted in the regression table, no statistically significant effects on postoperative CRP levels are observed.

CRP is a well-established marker for inflammation and has been studied as a predictor of postoperative complications, ranging from analysis of solely anastomotic leak to analysis of all complications. Interestingly, multiple studies that assessed postoperative CRP included patients that were operated using both minimally invasive approach as well as conventional open approach, without applying correction for surgical approach\textsuperscript{22-25}. Only one study assessed both surgical techniques separately and found CRP levels were lower following minimally invasive surgery, although data was not stratified for adverse events\textsuperscript{38}. The here presented study depicts similar results, but also portrays how the inflammation due to major complications exceeds the differences in CRP levels caused by surgical approach alone.

This study was performed as a sub study of the LAFA-trial, which investigated differences between both laparoscopic or open segmental colectomy and fast-track or standard care. By using randomized data selection bias was omitted. CRP levels were measured routinely and less than ten percent of CRP data was missing due to clinical delay. In many observational studies CRP levels are only determined on demand, implicating bias. A prospective clinical trial is underway from our department in order to assess the role of standardized CRP measurements in a postoperative Quality Control algorithm for prediction of complications and as a safe discharge criterion\textsuperscript{39}. 

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In conclusion, C-reactive protein can be applied as a marker for major postoperative complications in both open and minimally invasive colorectal surgery. Reduced amount of surgical trauma in minimally invasive surgery leads to lower postoperative CRP levels in patients with an uncomplicated or minor complicated postoperative course. Huge inflammatory response in major complications exceeds the effect of primary surgical trauma, and no differences in CRP levels are observed stratified for surgical approach, open or minimally invasive. Future research should aim to assess the role of standardized CRP measurements in patients undergoing major abdominal surgery.
REFERENCES


