

Ansgar Michael Chromik
Frank Endter
Waldemar Uhl
Arnulf Thiede
Hans Bernd Reith
Ulrich Mittelkötter

Pre-emptive antibiotic treatment vs 'standard' treatment in patients with elevated serum procalcitonin levels after elective colorectal surgery: a prospective randomised pilot study

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A. M. Chromik · W. Uhl ·
U. Mittelkötter
Department of General Surgery,
University Hospital of Bochum,
Bochum, Germany

F. Endter · A. Thiede · H. B. Reith
Department of Surgery,
University Hospital of Würzburg,
Würzburg, Germany

U. Mittelkötter (✉)
Surgical Department,
University Hospital of Bochum,
Gudrunstrasse 56,
44791 Bochum, Germany
e-mail: u.mittelkoetter@klinikum-
bochum.de
Tel.: +49-2345090
Fax: +49-234-5092203

Abstract *Background:* Procalcitonin (PCT) is regarded as a specific indicator of bacterial infection. Infectious complications in patients after colorectal surgery are a common cause of morbidity and mortality. The aim of this study was to investigate (a) whether PCT could serve as a negative predictive marker for postoperative complications and (b) whether, in patients with elevated PCT levels, a pre-emptive treatment with the third-generation cephalosporin ceftriaxone is superior to an antibiotic treatment starting later on the appearance of clinical signs and symptoms of infection. *Patients and methods:* By screening 250 patients with colorectal surgery, we identified 20 patients with PCT serum levels more than 1.5 ng/ml on at least 2 of the first 3 postoperative days. The remaining 230 patients were followed-up for the occurrence of infectious complications. The 20 patients with elevated PCT were included in a prospective randomised pilot study comparing pre-emptive antibiotic treatment with ceftriaxone vs standard treatment. *Results:* The

negative predictive value of PCT for systemic infectious complications was 98.3%. In patients receiving pre-emptive antibiotic treatment (ceftriaxone), both the incidence and the severity of postoperative systemic infections were significantly lower compared to those in a control group (Pearson's χ^2 test; $p=0.001$ and $p=0.007$, respectively). Major differences were also observed with respect to duration of antibiotic treatment and length of hospital stay. *Conclusions:* PCT is an early marker for systemic infectious complications after colorectal surgery with a high negative predictive value. A significant reduction in the rate of postoperative infections in patients with elevated PCT serum concentrations was achieved by means of pre-emptive antibiotic treatment.

Keywords Procalcitonin · Fast-track colorectal surgery · Infectious complication · Postoperative monitoring · Pre-emptive antibiotic therapy

Introduction

Postoperative infections complications are a serious clinical problem in patients after elective colorectal surgery [1–4]. They are divided into local wound infections and systemic infectious complications. Local wound infections (epifascial or subfascial) occurred in the 'pre-antibiotic era' in up

to 50% of patients, but nowadays, the use of perioperative antibiotic prophylaxis has reduced the incidence to about 10% or less [5–7]. Systemic infectious complications comprise primary complications as peritonitis and abscess formation (mostly due to anastomotic insufficiency) and secondary complications as pneumonia, urinary tract infection and other infections [8, 9]. Indications for antibiotic

prophylaxis are wounds belonging to the clean-contaminated and contaminated category. Single-dose applications are at least as effective as multiple-dose regimens. Antibiotics selected should cover both aerobic and anaerobic bacteria [10–12]. Regimens commonly used are second- or third-generation cephalosporins±metronidazole [6, 7, 13, 14].

There are several inflammatory laboratory markers, like tumor necrosis factor (TNF)- α , interleukin (IL)-1, IL-6 and C-reactive protein (CRP), but they are non-specific for infection and can be caused by conditions like pancreatitis, burns, trauma or acute lung injury [15].

Serum procalcitonin (PCT), consisting of 116 amino acids and being produced in the C cells of the thyroid gland, has been proposed as a marker of microbial, i.e. bacterial, fungal and parasitic infection [16–18]. In healthy humans PCT baseline levels are low (<0.1 $\mu\text{g/l}$), but PCT baseline levels increase significantly (>1.5 $\mu\text{g/l}$) in individuals with severe bacterial infectious complications like meningitis [19, 20], systemic inflammatory response syndrome (SIRS) and sepsis [21–24], pneumonia [25, 26] or with neutropenia-associated fever [27].

Furthermore, PCT seems to be of diagnostic value for detecting postoperative infectious complications after different types of surgery [28]. It was shown that PCT could serve as an early predictive marker for the clinical course of septic complications after some kind of abdominal surgery [29, 30].

In this study, we sought to determine

- whether PCT could be useful as a negative predictive marker for systemic infectious complications in patients after colorectal surgery and

Table 1 Inclusion and exclusion criteria for the prospective randomised trial: pre-emptive antibiotic treatment vs standard treatment

Inclusion criteria	Exclusion criteria
Elective colonic surgery	Perioperative antibiotic prophylaxis of more than 24 h duration
Preoperative PCT serum level less than 1.0 ng/ml	Seizure disorder
Postoperative PCT serum level more than 1.5 ng/ml on 2 of the first 3 postoperative days	Pregnancy or lactation
Perioperative antibiotic prophylaxis of less than 24 h duration	Known hypersensitivity to cephalosporins
Age 18–90 years	Renal failure
Written informed consent for participation	Positive serology for HIV
	Primary immune deficiency
	Current cytostatic or immunosuppressive medication
	Treatment with an investigational new drug within the last 30 days

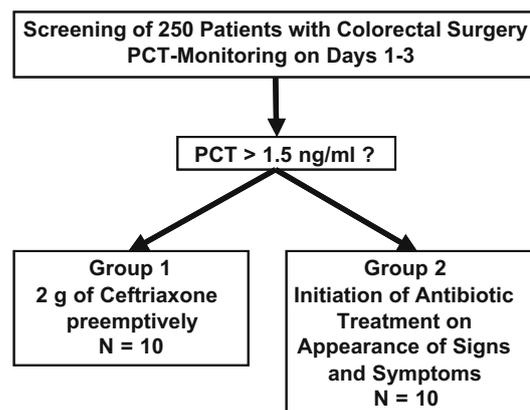


Fig. 1 Study design for the prospective randomised trial: pre-emptive antibiotic treatment vs standard treatment

- whether patients with PCT serum levels more than 1.5 ng/ml might benefit from an earlier initiation of antibiotic treatment (i.e. pre-emptive therapy) with the third-generation cephalosporin ceftriaxone compared to a control group receiving an antibiotic later based on the appearance of clinical signs and symptoms of infection.

Table 2 Prospective randomised trial: pre-emptive antibiotic treatment (group 1) vs standard treatment (group 2)

	Group 1 (n=10)	Group 2 (n=10)
Sex ratio (male/female)	6:4	5:5
Age (years) median (range)	62 (38–82)	70 (62–89)
Height (cm) median (range)	170 (151–184)	171 (151–178)
Weight (kg) median (range)	72.5 (51.0–85.0)	66.5 (36.0–103.0)
Type of surgery		
Rectum resection	3	0
Sigma resection	3	5
Sigma and rectum resection	0	1
Reposition of anus praeter	1	1
Right hemicolectomy	2	3
Transversectomy	1	0
PCT more than 1.5 ng/ml on day 1	10	10
PCT more than 1.5 ng/ml on day 2	10	10
PCT more than 1.5 ng/ml on day 3	5	8
PCT more than 1.5 ng/ml on 2 successive days	10	10
Clinical signs/symptoms of infection on days 1–3	0	1

Baseline patient characteristics, type of surgery and procalcitonin (PCT) serum levels on days 1–3 after operation

Patients and methods

At the surgical department of the University Hospital of Würzburg (Germany), 250 patients with elective colorectal surgery were included in the study, which was approved by the medical ethics committee of the University Hospital of Würzburg. The first part of the study included a screening of all patients for elevated PCT in the postoperative period. During the second part of the study patients with elevated PCT were enrolled in a prospective randomised trial for pre-emptive antibiotic treatment.

Preoperative period

On admission to the hospital the medical history of each patient was recorded, and a comprehensive physical examination [including chest X-ray and electrocardiogram (ECG)] and basic serum haematological and biochemical tests were performed. Additionally, PCT serum levels were determined preoperatively by use of an immunoluminometric assay, which measures serum PCT within 1 h (Brahms Diagnostica, Berlin, Germany). Only patients with a preoperative PCT serum value of at most 1.0 ng/ml were included in the study, as this cut-off value is considered as normal for a healthy out-patient population (Brahms Diagnostica). Preoperatively, all patients received an enema for bowel preparation. Perioperatively, patients received 2 g cefotiam plus 500 mg metronidazole.

Screening for elevated PCT

The first 3 postoperative days PCT serum levels of all patients were measured. All other medical interventions, concomitant medications, adverse effects and infectious complications were recorded in a case record form.

Patient selection for the randomised trial

Patients who showed elevated postoperative PCT serum levels more than 1.5 ng/ml on 2 of the first 3 postoperative days were checked for the eligibility criteria (as indicated in Table 1) to the prospective randomised trial for pre-emptive antibiotic treatment.

Patients fulfilling the inclusion and exclusion criteria were randomly assigned to either group 1 (pre-emptive antibiotic treatment) or group 2 (standard treatment).

Randomised trial: pre-emptive antibiotic treatment

After randomisation on postoperative day 3 all group 1 patients received a pre-emptive antibiotic therapy of 2 g ceftriaxone as an intravenous infusion over 30 min once a day starting on postoperative day 3. The group 2 patients were closely monitored and received antibiotic treatment according to the standard of the hospital, i.e. only in cases that clinical signs and symptoms of infection appeared (Fig. 1).

Table 3 Prospective randomised trial: pre-emptive antibiotic treatment vs standard treatment

No.	Procedure	Wound infection	Systemic infectious complication	Antibiotic treatment
1	Rectum resection	None	None	Ceftriaxone (4 days)
2	Rectum resection	None	None	Ceftriaxone (7 days)
3	Sigma resection	None	None	Ceftriaxone (5 days)
4	Sigma resection	Epifascial	None	Ceftriaxone (5 days)
5	Reposition of anus praeter	None	Anastomotic insufficiency with peritonitis, severe sepsis requiring surgical revision on seventh postoperative day. MOF and exitus letalis on 22nd postoperative day	Ceftriaxone (6 days); further escalation with metronidazole, ampicillin, vancomycin, imipeneme, fluconazole and tobramycin
6	Right hemicolectomy	None	None	Ceftriaxone (5 days)
7	Sigma resection	None	None	Ceftriaxone (4 days)
8	Rectum resection	None	Anastomotic insufficiency with peritonitis on eight postoperative day requiring revision and colostomy	Ceftriaxone (11 days); further escalation with metronidazole, piperacillin, compactam and tobramycin
9	Right hemicolectomy	None	None	Ceftriaxone (4 days)
10	Transversectomy	None	Urinary tract infection	Ceftriaxone (5 days)

Clinical data for group 1 (pre-emptive antibiotic therapy)

MOF Multi-organ failure

In both groups the antibiotics were applied until clinical and laboratory signs of infection had disappeared for at least 2 days. Patients were prematurely excluded from the study on the occurrence of severe adverse events or other medical conditions, protocol violations, requirement of drugs listed under the exclusion criteria or on withdrawal of their informed consent.

The main objective of this trial was to determine the incidence of postoperative infectious complications (primary end point) in both groups. Postoperative infectious complications comprise local wound infections and systemic infectious complications as peritonitis/abscess formation due to anastomotic insufficiency, nosocomial pneumonia and urinary tract infections. Secondary end points of the study were postoperative mortality attributed

to infectious complications, determination of leucocyte count and body temperature, duration of antibiotic treatment and length of hospital stay.

Data were computed with SPSS software, release 12.0 (SPSS Inc., Chicago, IL, USA). In the present study, we sought to test the hypothesis that the incidence of infections in group 1 would decrease or remain constant against the alternative that the incidence would increase in each group. To compare results of both study groups we used Pearson's χ^2 test, Fisher's exact test and *t* test as appropriate. Continuous, normally distributed data are expressed as arithmetic mean (\pm SD), and other quantitative data are expressed as median (range). *P*<0.05 was considered to be statistically significant.

Table 4 Prospective randomised trial: pre-emptive antibiotic treatment vs standard treatment

No.	Procedure	Wound infection	Systemic infectious complication	Antibiotic treatment
1	Right hemicolectomy	None (fulfilling SIRS criteria)	None	None
2	Sigma resection	Epifascial	None	Ceftriaxone (8 days)
3	Reposition of anus praeter	None	Small-bowel leakage with peritonitis requiring surgical revision twice	Cefotaxime (4 days); further escalation with metronidazole, ampicillin and ceftriaxone
4	Sigma resection	None	Nosocomial pneumonia with Sepsis. Exitus letalis due to cardiac insufficiency 1 week after transferring to rehabilitation centre	Piperacillin and sulbactam (8 days)
5	Right hemicolectomy with partial resection of urinary bladder	None	Urinary tract infection	Cefotaxime (5 days)
6	Sigma resection	None	Anastomotic insufficiency with peritonitis requiring surgical revision with terminal colostomy	Cefotaxime and metronidazole (4 days); further escalation with piperacillin, sulbactam and tobramycin
7	Sigma resection	Epifascial	None	None
8	Sigma and rectum resection	None	Anastomotic insufficiency with formation of stool-fistula	Ceftriaxone and metronidazole (4 days); further therapy with imipenem and metronidazole (5 days)
9	Sigma resection	None	Anastomotic insufficiency with peritonitis requiring surgical revision on the seventh postoperative day. Exitus letalis on the eight postoperative day due to sepsis with MOF	Cefotaxime, metronidazole and tobramycin (3 days)
10	Right hemicolectomy	None	Anastomotic insufficiency with peritonitis on the eight postoperative day requiring surgical revision. Nosocomial pneumonia severe sepsis with MOF and exitus letalis on the 33rd postoperative day	Ceftriaxone, metronidazole and ampicillin (7 days); further escalation with piperacillin, sulbactam, tobramycin and clindamycin

Clinical data for group 2 (standard therapy)

Diagnostic value of PCT screening

With the data obtained during the postoperative screening for PCT (first part of the study) and the randomised trial (second part of the study), the diagnostic value of PCT screening was estimated by calculating the negative predictive value.

Results

Screening for elevated PCT

During an 18-month study period we screened a total of 250 patients with elective colorectal surgery for PCT serum levels on the first 3 postoperative days. The screening group consisted of 132 men (mean age 67.6 years) and 118 women (mean age 62.2 years). We identified 20 patients with PCT levels more than 1.5 ng/ml on at least 2 of the first 3 days after operation who met also the other inclusion criteria.

Of the remaining 230 patients, 16 developed postoperative local wound infections (7.0%), which were cured without any further surgical intervention or antibiotic treatment. Systemic infectious complications were observed in 4 of the 230 patients (1.7%) (2 pneumonia, 1 urinary tract infection and 1 lethal peritonitis due to anastomotic insufficiency). Thus, the negative predictive value was 93.0% for local wound infections and 98.3% for systemic infectious complications.

Randomised trial: pre-emptive antibiotic treatment

Patient characteristics were comparable between the patients of the two treatment arms (Table 2). There were also no significant differences with respect to underlying diseases and risk factors (data not shown). Detailed data about the type of surgery, clinical course and outcome for each patient of the two study groups are indicated in Tables 3 and 4.

There was no significant difference in the incidence of local wound infections which occurred in two out of ten patients in group 1 and one out of ten patients in group 2 (Table 5). All wound infections were epifascial and did not require any further invasive surgical therapy or antibiotic treatment.

In group 1 postoperative systemic infectious complication occurred in three out of ten patients, and in group 2, postoperative systemic infectious complication occurred in seven out of ten patients (Table 5). The difference in the incidence was statistically significant, i.e. $p=0.001$ (Pearson's χ^2 test) and $p=0.003$ (Fisher's exact test). In group 2 one patient developed two systemic infectious complications (anastomotic insufficiency with peritonitis and nosocomial pneumonia), which means there occurred eight systemic

Table 5 Prospective randomised trial: pre-emptive antibiotic treatment (group 1) vs standard treatment (group 2)

Infection and severity	Group 1 (n=10)	Group 2 (n=10)
Incidence of local wound infections	1/10	2/10
Epifascial	1	2
Subfascial	0	0
Incidence of systemic infectious complications	3/10	7/10*
Patients with more than one systemic infectious complication	0/3	1/7
Type of systemic infectious complication observed		
Anastomotic insufficiency with peritonitis	2	4
Pneumonia	0	2
Small-bowel leakage with peritonitis	0	1
Urinary tract infection	1	1
Total	3	8
Severity of sepsis/SIRS [31]		
SIRS	1	1
Sepsis	0	4
Severe sepsis	1	2
Septic shock	0	1
Total	2	8**
Patients requiring catecholamines	1/10	6/10***

Incidence and severity of infectious complications in both study groups

* $p=0.001$ (Pearson's χ^2 test), $p=0.003$ (Fisher's exact test)

** $p=0.007$ (Pearson's χ^2 test), $p=0.023$ (Fisher's exact test)

*** $p=0.019$ (Pearson's χ^2 test)

complications in seven patients. Major differences were also observed in the severity of postoperative infections. Two patients in group 1 and eight patients in group 2 met the commonly applied SIRS/sepsis criteria [31] ($p=0.007$ using Pearson's χ^2 test and $p=0.023$ using Fisher's exact test). One patient in group 1 and six patients in group 2 required catecholamines ($p=0.019$ using Pearson's χ^2 test and $p=0.057$ using Fisher's exact test).

Assessment of postoperative mortality attributed to infectious complications revealed that in group 1, one patient with anastomotic insufficiency died 3 weeks after operation due to diffuse peritonitis. In group 2 three patients died (two with diffuse peritonitis and one with nosocomial pneumonia) as indicated in Tables 3 and 4. Determinations of leucocyte count and body temperature showed no differences between the groups (data not shown).

The levels of serum PCT concentrations are shown in Table 6. In both groups values on day 1 were almost identical but declined profoundly in group 1 over the next 9 days, probably due to the early administration of ceftriaxone. In the control group serum levels fluctuated much prominently and stayed higher over time. The

Table 6 Prospective randomised trial: pre-emptive antibiotic treatment (group 1) vs standard treatment (group 2)

Treatment day	Group 1 ^a		Group 2 ^b	
	Mean (±SD)	Median (range)	Mean (±SD)	Median (range)
1	2.10±1.95	1.40 (0.60–6.70)	1.90±1.50	1.43 (0.50–5.50)
2	1.18±0.99	0.90 (0.30–3.00)	1.97±2.32	0.95 (0.20–7.30)
3	1.09±1.24	0.50 (0.20–4.00)	3.20±3.98	1.50 (0.46–12.80)
6	0.93±1.23	0.40 (0.20–4.00)	8.05±20.95	1.05 (0.17–67.50)
9	0.69±0.73	0.35 (0.10–2.20)	0.79±0.55	0.80 (0–1.60)
14	1.63±1.36	1.65 (0.40–2.80)	0.61±0.47	0.55 (0–1.30)

Postoperative PCT serum levels (nanograms per millilitre) in both study groups

^aNine patients on days 1, 2, 3 and 6; eight patients on day 9 and four patients on day 14

^bTen patients on days 1, 2, 3 and 6; nine patients on day 9 and eight patients on day 14

duration of antibiotic treatment was 5.5 days (median, range 4–20 days) in group 1 and 9 days (median, range 3–16 days) in group 2, but the difference was not statistically significant ($p=0.274$). Length of hospital stay in group 1 was 18 (median, range 10–49 days) vs 30 days in group 2 (median, range 9–82 days), but the difference did not reach level of significance ($p=0.057$).

Discussion

Postoperative infectious complications in patients after colorectal surgery are associated both with high rates of morbidity and mortality and high treatment costs. These patients require after-operation intensive care for several days, but early clinical manifestations indicative of infectious complications are often subtle or non-existent. Physicians cannot base the diagnosis upon classical signs and symptoms of infection, like body temperature, CRP, leucocyte or platelet count, so there is undoubtedly a need for specific laboratory markers to discriminate patients truly infected from those who are not and to confirm a timely diagnosis.

Procalcitonin is a well-established indicator of bacterial, fungal and parasitic infections in patients with septicaemia, meningitis, pneumonia and urinary tract infection [16, 22, 32–34]. There is growing evidence that PCT could also serve as a predictive marker for postoperative infectious complications [28], but specific reference ranges have to be considered depending on the type of surgical intervention. Minor aseptic interventions cause lower postoperative PCT values than major abdominal or thoracic surgery [35, 36]. In one series with 33 patients after major abdominal surgery, including intestinal resection, a PCT cut-off value of 1 ng/ml had a sensitivity of 70% and a specificity of 81% in the prediction of infectious complications 24 h postoperatively [37].

Only two studies showed that PCT could serve as an early predictive marker for the clinical course of septic complications after colorectal surgery [30, 37]. One prospective clinical study enrolling 70 patients after

elective colorectal and aortal surgery focused on the early prediction of infectious complications by postoperative monitoring of PCT. In the study population PCT levels on the first postoperative day were closely related to infectious complications [30]. In our study, we measured the course of PCT serum levels in 250 patients after colorectal surgery during the first 3 postoperative days. PCT serum levels under 1.5 ng/ml on 2 of the first 3 postoperative days appeared to be highly effective as a negative predictive marker for systemic infection complications, as the negative predictive value was 98.3%. In contrast to systemic infectious complications the negative predictive value for local wound infections was 93.0%, indicating the reduced capability of PCT in the prediction of such non-systemic complications.

We did not measure routinely postoperative CRP levels in the study population because postoperative CRP levels are, in our opinion, inferior to serum PCT in the early detection of postoperative complications. One major drawback of CRP is the elevation due to the operative trauma itself, which does not allow differentiating between operative trauma and early infectious complications. Another drawback of CRP is the longer half-time.

In the second part of our pilot study we tried to find indications for the appropriateness of a pre-emptive antibiotic treatment in patients at risk of postoperative infections and with PCT serum levels more than 1.5 ng/ml on at least 2 of the first 3 days after operation.

Only three patients (30%) of group 1 receiving ceftriaxone as a pre-emptive treatment showed infectious complications compared to seven out of ten (70%) patients in group 2 (receiving treatment according to hospital standard). Differences both in the incidence of postoperative infections and their severity were statistically significant. The low number of patients is a clear limit to our pilot study. Nevertheless, our preliminary data support the view that a significant reduction in the rate of postoperative infections is achievable in patients with elevated PCT serum concentrations and with early pre-emptive antibiotic therapy. The study results need confirmation by including a higher number of patients for the identification of patient

subgroups who might benefit from PCT monitoring and pre-emptive antibiotic treatment.

Our data also suggest that treatment costs could be reduced. The length of hospital stay in group 1 was 18 days (median) compared to 30 days (median) in the control group, although the difference was not yet statistically significant. The risk to develop postoperative infections seems to be much lower in patients with PCT serum levels less than 1.5 ng/ml. These patients may have the option of an earlier discharge from hospital. Recent clinical pathways for fast-track colorectal surgery allow time points for discharge from the hospital as early as postoperative day 4 or 5 [38, 39]. Against the background of fast-track colorectal surgery a standardised postoperative PCT screening could provide a useful tool in identifying patients

at risk for systemic infectious complications and thus reduce readmission rates.

Conclusions

Procalcitonin is an early marker for systemic infectious complications after colorectal surgery with a high negative predictive value. For fast-track colorectal surgery it could serve as a tool for identifying patients at risk for developing systemic infectious complications. Pre-emptive antibiotic treatment of patients with elevated PCT serum concentrations with the third-generation cephalosporin ceftriaxone resulted in a significant reduction of postoperative infectious complications.

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