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Procalcitonin-Based Therapeutic Strategy to Reduce Antibiotic Use in Patients after Cardiac Surgery: A Randomized Controlled Trial

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SUMMARY

Introduction Procalcitonin (PCT) is a thyroid gland prohormone, and its serum concentration is elevated in systemic bacterial infections. The diagnostic cut-off value of PCT in patients early after cardiac surgery remains unclear.

Objective We investigated whether procalcitonin-guidance could reduce antibiotic usage safely.

Methods The prospective study included 205 patients who underwent open heart surgery. The patients were randomly assigned for procalcitonin-guided antibiotic treatment (PCT-group; n=102) or standard care (standard group; n=103). On the basis of serum procalcitonin concentrations, usage of antibiotics was encouraged (PCT≥0.5 ng/mL) or discouraged.

Results A relative risk of antibiotic exposure in the standard group compared with the PCT-group was 3.81 (95% CI=2.03-7.17; p<0.0001). The mean cost of antibiotics per patient in procalcitonin group was €193.3±636.6 vs. €372.1±841.1 (p=0.206) in the standard group, while the mean cost per hospital day was €8.0±18.4 vs. €17.8±36.3 (p=0.028). We found that non-infectious complications occurred in 40/102 vs. 41/103 (p=0.592) while infections appeared in 5/102 vs. 22/103 (p=0.001) cases. A statistically significant difference was observed in the treatment of urinary infections between PCT-group and standard group; 1/102 vs. 9/103 (p=0.016). In the PCT-group, the ICU stay was 5.74±11.49 days and in the standard group 6.97±11.61 (p=0.812). The hospital stay was 12.08±11.28 vs. 12.93±10.73 (p>0.05) days, respectively. Mortality rates were equal in both groups of patients (p=0.537).

Conclusion Procalcitonin-guided antibiotic treatment is safe and can significantly reduce the cost of postoperative care. Additionally, the antibiotic use during immediate postoperative course should be timely controlled and limited to documented bacterial infections.

Keywords: procalcitonin; antibiotics; inflammatory mediators; cardiac surgery

INTRODUCTION

Procalcitonin (PCT) is a 14-kDa protein encoded by the Calc-I gene along with calcitonin and katacalcin [1]. Blood concentrations of procalcitonin are increased in cases of systemic inflammation, especially when this is caused by bacterial infection. Studies of its behaviour in patients with bacterial sepsis have led to the proposal that it is a useful marker for systemic bacterial infection, with greater specificity and sensitivity than acute phase proteins such as C-reactive protein (CRP), D-dimer, elastase, interleukins etc. [2].

At present, the mechanisms of procalcitonin induction are not fully understood. The sources of procalcitonin are the thyroid gland, immunocompetent cells [3, 4], cells of the neuroendocrine system [5] and human adipocytes upon inflammatory stimulation [4]. Upon infection, circulating procalcitonin concentrations are also increased in thyreoidectomized patients, suggesting the existence of non-thyroidal sources of inflammation and sepsis-mediated procalcitonin [6, 7].

Several studies have contributed to the use of procalcitonin as a diagnostic marker for severe sepsis and septic shock after cardiac intervention [8]. Over the last decade, investigators underscored the specificity of the procalcitonin test in cardiac surgery in comparison to other surgical interventions (abdominal surgery, vascular interventions on major blood vessels, ablative surgery etc.) [9]. However, the diagnostic cut-off value of procalcitonin in patients early after cardiac surgery on cardiopulmonary bypass (CPB) remains unclear [8, 10]. Since operated patients often manifest a systemic inflammatory response (SIRS) independently of whether a bacterial infection is present, procalcitonin is useful in guiding treatment and avoiding delayed or unnecessary antibiotic therapy. For optimal antibiotic use, rapid and accurate differentiation of clinically relevant bacterial infection following open heart surgery is crucial. Inappropriate use of antibiot-

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ics is believed to be the main cause of nosocomial infections and reduction of antibiotic use is fundamental in combating the increase of antibiotic-resistant bacteria.

OBJECTIVE

Biomarkers, namely procalcitonin and CRP, when used in combination with a good clinical evaluation, provide useful information in the diagnosis of infection. The aim of this study was to perform serial measurements of procalcitonin concentrations to identify bacterial infection in early postoperative period in patients needing antimicrobial treatment. We investigated whether procalcitonin-guidance could reduce antibiotic use in patients subjected to the open heart surgery safely.

METHODS

Patients

This study was a prospective, randomized controlled trial comparing routine use of antimicrobial therapy with procalcitonin-guided antimicrobial treatment for patients subjected to open heart surgery. After obtaining approval from the Ethics Committee and written informed consent from each patient, this study included 205 consecutive patients (65 women, 140 men) scheduled to undergo open heart surgery on CPB. We assessed patients who were selected for elective cardiac surgery at the 200-bed academic tertiary care hospital. The criterion for inclusion in the study was the type of the operation: coronary artery bypass grafting (CABG) surgery, valve reconstruction, combined CABG and valve procedures. Entry criteria included stable and unstable angina pectoris; valve insufficiency, left ventricle ejection fraction (LVEF) above 30%, and epidemiological status with saprophyte bacteria. We excluded patients selected for redo cardiac operations, thoracic aortic surgery, as well as patients having active endocarditis and patients with LVEF <30%. Patients with preoperative signs of infection (leukocyte count >12000/L; body temperature >38°C) were excluded.

The predicted surgical risk was calculated as the European system for cardiac operative risk evaluation (EuroSCORE) by an independent resident in internal medicine [11]. We randomly assigned suitable patients either for standard antimicrobial therapy (standard group) or procalcitonin-guided antimicrobial treatment (procalcitonin group) according to a computer-generated randomization scheme [12]. Thereafter, we monitored patients from admission to ICU, and the entire hospital stay.

Procedure

Blood samples were collected 24 hours before induction of anaesthesia (T0), 6 hours after the end of surgery (T1), and on the 1st (T2) and 2nd (T3) day postoperatively at 5:00 AM. Blood samples were collected from the peripheral vein and immediately centrifuged for 20 minutes. Serum was divided in two aliquots for biochemical analysis and the measurement of inflammatory parameters.

The procalcitonin concentrations in serum were measured by the immunoluminometric assay with the commercially available LUMI-test PCT (B.R.A.H.M.S Diagnostica GmbH, Berlin, Germany). The interassay precision of the kit was 6% to 10%; the lower limit detection was 0.08 ng/mL. Normal plasma and serum concentrations of procalcitonin were below 0.5 ng/mL [2].

The serum CRP concentration was measured using quantitative immuno-turbidimetric determination of CRP (BIOKIT, Barcelona, Spain). The leukocyte and the platelet count were determined using a Coulter counter (ACT diff, Coulter Electronics).

Antibiotic prophylaxis was performed in all patients. Preferred regimen of antimicrobial prophylaxis was recommended by the American Society of Health-System Pharmacists [13]. Antimicrobial prophylaxis was performed with intravenous cefazolin 1.0 g after induction and 1.0 g at the end of the CPB during valve surgery. We used cefalozolin if the patient had β-lactam allergy: vancomycin with or without gentamycin or gentamycin alone.

The patients were divided at the time of surgery into the standard group and the procalcitonin group. In the standard group the antibiotic use was applied according to the criteria based on the laboratory and clinical signs; no antibiotic therapy was administrated routinely in the absence of clinical signs of infection or a bacteriologic positive sample. In the procalcitonin group, on the basis of serum procalcitonin concentrations, the use of antibiotics was encouraged or discouraged. As it was proposed by Christ-Crain et al. [12], we judged that a serum procalcitonin concentration of 0.5 ng/mL or less indicated the absence of bacterial infection, at which point the use of antibiotics was discouraged. However, the final decision to initiate antimicrobial treatment was left to the doctor in charge [12, 14].

The clinical investigation, including body temperature, microbiologic examinations and chest radiography, was performed daily until ICU discharge. The Sequential Organ Failure Assessment (SOFA) score was routinely obtained at the first postoperative day [15], and was repeated once daily at 5:00 AM as SOFA1, SOFA2 and SOFA3. Microbiologic examinations such as sputum, blood, and urine samples for culture were performed routinely on the patients when infection, bacteriemia, or sepsis was suspected.

Primary endpoints were proportion of patients treated by antibiotics, overall cost of antibiotics per one patient, and total cost of antibiotics per one hospital day after operation. The antibiotic prices were calculated after completed treatment using an electronic database for each patient. We calculated the costs of all antimicrobial agents used during the hospital stay by adding the prices of LUMI-test PCT in the procalcitonin group. All prices were expressed in the Euro (€) per patient and per hospital-day [12].

Secondary endpoints were ICU stays, hospital stay, rehospitalization, incidence of infections, severe non-infection complications, and mortality rate. The database, which

included all hospital discharges and subsequent hospital admissions for patients enrolled in this study served for one year follow-up. Complications and infections were defined as proposed by Dorge et al. [16]. The mortality ratio was calculated as: a) in-hospital mortality, defined as death within 30 days of operation; and b) death within the same hospital admission.

Statistical analysis

Sample size calculation was based on the presumption that reduction from every second to every fourth patient's antibiotic use was clinically relevant, precisely a decrease from 45% of antibiotic use in the standard group to 22% in the procalcitonin group [17]. Data were expressed as mean values with standard deviations or as counts with percentages where appropriate. Baseline characteristics were compared by the Student's t test or Mann-Whitney U-test for continuous variables and Chi-square test for categorical variables. Changes in continuous variables over time were compared between patients in the procalcitonin group using general linear models for repeated measures. Outcomes independently associated with procalcitonin group were identified by univariate logistic regression models and represented by its significance, relative risk and 95% confidence interval [18].

All analyses were two-sided and based on an intention-to-treat principle. A value of $p<0.05$ was considered statistically significant.

RESULTS

Study population

Prospective consecutive data were collected on 205 patients undergoing CABG (112), valve replacement or repair (52), and combined procedures: CABG and valve operations (41). Demographic data, risk assessment and laboratory data taken preoperatively are reported in Table 1. In our cohort no statistical significant differences were found regarding the patient's age, gender, or laboratory data before surgery.

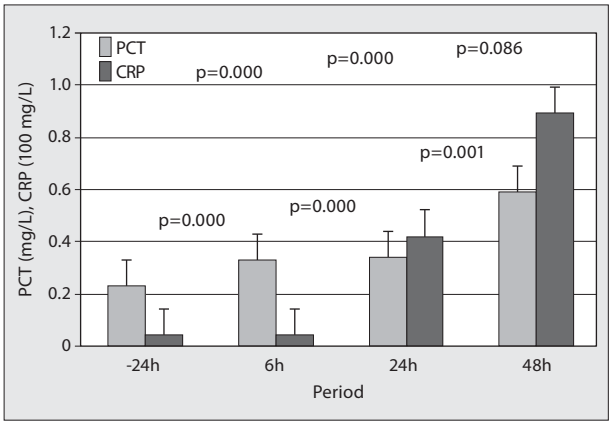
The operations performed and perioperative data are summarized in Table 2. The type of operation, cross clamping time, and CPB time were not statistically different between the two groups. Mean SOFA score showed a steady decline over the time in both groups. No difference was found concerning the leukocyte count on any postoperative day during the observation period.

Graph 1 shows procalcitonin and CRP concentrations in 102 patients of procalcitonin group. Mean procalcitonin levels prior surgery were (T0) 0.23±0.15 (0.08-0.71) ng/mL with median of 0.18 (0.12-0.30) ng/mL, indicating that nearly all patients were free from immunoreactivation at this point of time. Procalcitonin levels slightly increased 6 hours after the operation (T1) 0.33±0.59 (0.08-5.95) ng/

Table 2. Operative and postoperative variables

Variable		Groups of patients		p
		Procalcitonin (n=102)	Standard (n=103)	
CABG ratio (CABG/other)		57/45	54/49	0.620
Valve procedures ratio (Valve/other)		26/76	26/77	0.968
CABG+Valve ratio (CABG+Valve/other)		18/84	23/80	0.402
Duration of operation (minutes)		220.1±58.7	236.6±63.2	0.069
Duration of CPB (minutes)		105.9±43.8	112.7±54.9	0.337
Aortic cross-clamping (minutes)		65.4±29.6	69.5±34.7	0.364
SOFA	1st POD	1.31±1.67	1.62±1.65	0.112
	2nd POD	0.97±1.56	1.34±1.67	0.051
	3rd POD	0.63±1.11	1.13±1.68	0.098
	AUC	46.57±65.58	65.18±76.59	0.084
Leukocytes	1st POD	10.95±4.47	10.61±4.15	0.548
	2nd POD	12.36±3.94	12.17±4.01	0.466
	3rd POD	11.99±4.14	11.73±4.27	0.408
	AUC	570.79±170.31	562.04±174.69	0.477

CABG – coronary artery bypass grafting; CPB – cardiopulmonary bypass; SOFA – Sequential Organ Failure Assessment score; POD – postoperative day; AUC – area under the curve



Graph 1. Serum levels of procalcitonin (PCT) and C-reactive protein (CRP) in patients before and after cardiac surgery

Table 1. Demographic and preoperative characteristics of patients

Variable	Groups of patients		p	RR	95% CI	
	Procalcitonin (n=102)	Standard (n=103)			Lower	Upper
Age (years)	59.46±9.12	60.37±9.85	0.4925	0.99	0.96	1.02
Sex ratio (male/female)	71/31	69/34	0.6872	0.89	0.49	1.59
EuroSCORE	2.71±1.77	3.19±1.88	0.0611	0.86	0.74	1.01
Leukocytes	7.33±2.10	7.30±2.12	0.9074	1.01	0.88	1.15
Platelets	219.7±64.8	227.7±60.6	0.3623	0.99	0.99	1.00

n – number of patients; RR – risk ratio; 95% CI – 95% cofidence interval

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mL with median of 0.22 (0.14-0.39) ng/mL, and at day 1 postoperatively rose to (T2) 0.34±0.23 (0.08-1.28) ng/mL with median of 0.28 (0.17-0.49) ng/mL. The peak level was reached on the 2nd postoperative day (T3) 0.59±2.11 (0.08-21.39) ng/mL with median of 0.29 (0.21-0.50) ng/mL. Fisher's ANOVA detected a significant increase of procalcitonin levels in comparison to the levels prior surgery on the second postoperative day (F=15.09; p=0.000).

Initial CRP level prior to surgery was within the normal range in 78% of patients with mean value (T0) 4.86±10.00 (0.10-75.50) mg/L, and with median of 2.2 (1.1-5.00) mg/L. The time course of CRP induction was slower. CRP levels declined 6 hours after the operation (T1) 4.13±4.69 (0.01-28.60) mg/L with median of 2.2 (1.1-5.5) mg/L, and then increased on the 1st day postoperatively to (T2) 42.58±21.64 (7.60-96.10) mg/L with median of 40.95 (24.88-57.83) mg/L. Peak concentrations occurred on the 2nd day postoperatively (T3) 89.77±17.67 (7.80-125.80) mg/L with median of 89.40 (81.55-100.28) mg/L. Fisher's one way analysis of variance with repeated measurements was F=768.233 (p=0.000).

Patient-level antibiotic use and costs

Regarding the antibiotic therapy there were significant differences, concerning the number of patients treated by antibiotics and the antibiotic cost calculated per hospital-day (Table 3). Almost 19% of patients in the procalcitonin group were treated by antibiotics, while in the standard group 47% patients received antibiotics. The relative risk of antibiotic exposure in the procalcitonin group compared with the standard group was 0.22 (95% CI 0.10-0.46; p<0.0001), i.e. 3.81 (95% CI 2.03-7.17; p<0.0001) in the standard group compared with the procalcitonin group. The mean cost per patient in procalcitonin group was € 193.3±636.6 vs. € 372.1±841.1 (p=0.09) in the standard group. Considering the mean costs per hospital-day it was € 8.0±18.4 vs. € 17.8±36.3 (p=0.02), respectively. The total follow-up antibiotic cost for patients in the standard group was almost double compared to the procalcitonin group.

In-hospital outcomes

Evaluation of clinical outcomes is depicted in Tables 3-4. The study was conducted in a thirty-two bed ICU. Minority of patients needed prolonged treatment. There were no significant differences between the groups with respect to the time spent in the ICU and the length of the hospital stay (Table 3). After surgery, patients from the procalcitonin group remained on average 5.7 days in the ICU and 6.9 days in the standard group (p=0.45). Twenty-three (23%) patients remained for more than 96 hours in the ICU in the procalcitonin group (range 0-66 days) and 33 patients (34%) in the standard group (range 0-79 days). The hospital stay

Table 3. Clinical outcomes and antibiotics costs

Variable	Groups of patients		p	RR	95% CI	
	Procalcitonin (n=102)	Standard (n=103)			Lower	Upper
Intensive Care Unit stay (days)	5.74±11.49	6.97±11.61	0.4509	1.01	0.99	1.03
Length of hospital stay after operation (days)	12.08±11.28	12.93±10.73	0.5787	1.01	0.98	1.03
Antibiotics treatment (Yes/No)	19/83**	48/55	0.0000	3.81	2.03	7.17
Antibiotics + PCT costs per patient in Euro	193.3±636.6	372.1±841.1	0.0976	1.00	0.99	1.01
Antibiotics + PCT costs per hospital-day in Euro	8.0±18.4**	17.8±36.3	0.0204	1.00	1.00	1.03

**p<0.05; PCT – procalcitonin

Table 4. Complications, infections and overall outcomes

Variable		Groups of patients		p	RR	95% CI	
		Procalcitonin (n=102)	Standard (n=103)			Lower	Upper
Complications (Yes/No)	Patients with complications	40/62	41/62	0.4837	0.89	0.65	1.23
	Rethoracotomy	14/88	9/94	0.2615	0.60	0.25	1.47
	Cardiovascular	18/84	26/77	0.1873	1.57	0.80	3.10
	Pulmonary	18/84	9/94	0.0640	0.45	0.19	1.05
	Renal	0/102	0/103	-	-	-	-
	Gastrointestinal	13/89	7/96	0.1574	0.49	0.19	1.05
	Neurologic	1/101	5/98	0.1377	5.15	0.59	44.89
Infections (Yes/No)	Patients with infections	5/97**	22/81	0.0082	3.18	1.35	7.49
	Wound infection	2/100	3/100	0.6607	1.50	0.24	9.17
	Pneumonia	2/100	3/100	0.6607	1.50	0.24	9.17
	Sepsis, MODS	2/100	8/95	0.0736	4.21	0.87	20.33
	Urinary infections	1/101**	9/94	0.0330	9.62	1.20	77.13
Mortality (Dead/Alive)	Total	7/102	8/103	0.8038	1.14	0.39	3.28
	In-hospital 30-day	3/99	3/100	-	-	-	-
	Mortality during hospital stay after 30 days	4/95	5/95	-	-	-	-
Rehospitalization (Yes/No)		1/101	2/101	0.5740	1.99	0.18	22.40

** p<0.05

in various wards was similar comparing the procalcitonin and the standard group (p=0.57). Return to hospital after discharge within one year follow-up was similar (p=0.57).

The major postoperative complications are summarized in Table 4. Thirty-nine percent of patients (40/102) had 64 different kinds of complications in the procalcitonin group, whereas 40% of patients (41/103) had 56 complications observed in the standard group (p=0.48). Between the procalcitonin and the standard group a statistically significant difference was found regarding infections (p=0.008), precisely urinary infections (p=0.033). Five percent (5/102) of patients had infections in the procalcitonin group compared to 21% of patients (22/103) in the standard group. Some of the patients having infections had more than one infected site. The similar situation was observed concerning the non-infectious complications. Complications on the gastrointestinal and respiratory system were significantly frequent in the procalcitonin group, but procalcitonin-guidance had no influence on this outcome (e.g. bleeding from ulcus sanguinans, emphysema, etc). On the contrary, in the standard group the antibiotic overuse was not protective from total infections, especially urinary. Mortality rates were equal (p=0.80). During the first admission, six patients died; in hospital 30-day mortality was 3.0% in both groups. Mortality after 30 days was 3.9% in the procalcitonin group and 4.8% in the standard group.

DISCUSSION

The aim of this study was to explore a unique subgroup of our practice, to assess the cost and benefit of innovative laboratory diagnostics after surgical intervention, and to look into the difficulties of its routine application. We have shown that procalcitonin guidance substantially and safely reduces antibiotic overuse in patients undergoing open heart surgery. Diminishing the excessive antibiotic use did not compromise the clinical and laboratory outcomes.

Rapid developments in technology and pharmacology have led to a continued expansion of procedures available to patients suffering from cardiac diseases. In spite of being able to offer a wider spectrum of procedures, the morbidity and mortality after cardiac surgery continue to remain at a stable level or fall [19]. Factors such as blood exposure to nonphysiologic surfaces, surgical trauma, myocardial ischemia-reperfusion injuries, changes in body temperature, and endotoxin release have been shown to induce inflammatory mediators [8, 20]. CPB is known to produce transient immunosuppressive disturbance immediately postoperatively due to its effect on circulating lymphocytes and monocytes. The total lymphocyte count on bypass has been dropping dramatically. T-cell numbers are significantly decreased, particularly CD4 cells, while the ratio of CD3 and CD8 cells is retained. This event results in a transient immunosuppression that peaks at postoperative day 1 and gradually returns to normal by day 3 [20]. This time interval, between operation and ICU discharge, was the emphasis of the present study.

In order to determine which preoperative factors might affect the development of complications after cardiac operations, routine preoperative optimalization was carefully performed. Assessing and stratifying risk factors prior to surgery is essential for determining perioperative and postoperative mortality risk [11]. Although random plan selected several patients with higher EuroSCORE in the standard group, perioperative variables were evenly balanced among the two groups in our study.

Procalcitonin test has a significant role in the cardiac surgery. Preliminary results have shown that prognostic and diagnostic value of PCT-test differs according to the type of the surgery, the length of CPB, the degree of hypothermia, the need for an intraaortic balloon pump and for vasopressor support [21]. Kerbaul et al [10] reported that leukocyte count and CRP were not related to severe SIRS after elective CABG surgery. Conclusion from their study was that procalcitonin concentrations below 5.0 ng/mL were not associated with any postoperative complications. Brunkhorst et al [22] emphasized that patients with procalcitonin above 5.0 ng/mL were in life threatening condition. Nevertheless, there is no consensus regarding the diagnostic cut off value of procalcitonin in particular type of the surgical intervention [8]. The controversies also exist regarding the diagnostic cut-off value of procalcitonin for valve procedures, for combined CABG and valve surgery, for thoracic aortic surgery and in patients with congestive heart failure [23]. Hence, we investigated the clinical course of patients with good LVEF in uncomplicated cardiac surgery. Concerning the kind of operation, duration of CPB, aortic cross-clamping time, operative theatre time, our results were consistent with commonly referred results in scientific reports [8, 10, 21].

The decreased host immune defence is frequent in ICU patients, largely due to ongoing, concurrent disease processes. Hospital-acquired infections are common and associated with considerable morbidity and mortality, as well as with increased costs. In patients undergoing cardiac operations the site most commonly implicated in nosocomial infections is the lung, urinary tract, catheter-related bloodstream infections, and wound infections. The management of nosocomial infections relies largely on adequate, early, and appropriate antibiotic therapy [24]. Therefore, in a minority of patients in our study, invasive procedures facilitated the secondary bacterial infection of local mucosa or blood stream. Based on our data, low serum procalcitonin concentrations of less than 0.5 ng/mL can identify patients without relevant bacterial infections. In these individuals antimicrobial therapy could be withheld. In the standard group we found a significantly more patients treated by antibiotics due to urinary infections than in the procalcitonin group. Most patients with this diagnosis in our study had negative urine culture results, but in patients from the procalcitonin group to whom antibiotics were given for a limited period of time, the benefit was apparent. The doctors not knowing procalcitonin levels in the standard group give the impression that it is necessary to cure every single sign of inflammation (such as a high number of leukocytes, high body temperature,

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etc.) by antibiotics. This leads to an overuse of antibiotics and prolonged duration of antimicrobial treatment [25].

Open heart surgery is associated with a significant risk of SIRS and a subsequent unbalanced induction of proinflammatory cytokines. Clinically, this general immune dysfunction may lead to organ failure and increased postoperative morbidity. The occurrence and severity of SIRS following CPB is variable; only a minority of patients developed severe haemodynamic changes and multiorgan dysfunctions. In some patients this inflammatory cascade may cause postoperative complications, including fever of non-infectious origin, bleeding tendency, cardiovascular complications, pulmonary or renal dysfunction, neurological disorders, multiorgan failure or sepsis. Especially after cardiovascular surgery, nearly half of postoperative deaths are due to sepsis or complications of infectious origin [26].

Optimal severe sepsis/septic shock management requires continuum of early recognition, early intervention, rational selection of therapies, adequate monitoring and continuous medication of such patients [27]. Since it is of great importance to distinguish between SIRS and the infection caused by microbes especially early after open heart surgery, we repeated measurements of the procalcitonin level at that point of time. In our study, the doctor in charge was aware of the patients' treatment group assignment, which resulted in the introduction of adequate antibiotics in the case of procalcitonin concentrations above 0.5 ng/mL. In these patients the duration of antibiotics therapy and the replacement of inadequate antibiotics were adjusted by monitoring procalcitonin concentrations. Although two patients developed sepsis in the procalcitonin group, whereas eight patients were septic in the standard group, the difference did not reach statistical significance. However, the time of appearance was shorter and the length of hospital stay necessary for antimicrobial treatment was longer in the standard group (data not shown).

There are large differences in the prescription pattern of antibiotics, in documented and clinically suspected infections. In the present study antibiotics were given to 19 patients in the procalcitonin group, whereas 48 patients from the standard group received antibiotics ($p<0.05$). Additionally, although we did not find any differences in hospital stay between the two groups, antibiotic costs per hospital-day were twice lower in the procalcitonin than in the standard group.

CONCLUSION

Besides infectious complications, many non-infectious factors could explain the development of a post-CPB inflammatory reaction. We have found that procalcitonin-guided antibiotic treatment is safe and can significantly reduce the cost of postoperative care. Even more, the antibiotic usage during immediate postoperative course should be timely controlled and limited on documented bacterial infections.

REFERENCES

1. Le Moullec JM, Jullienne A, Chenais J, Lasmoles F, Guliana JM, Milhaud G, et al. The complete sequence of human preprocalcitonin. FEBS Lett. 1984; 167:93-7.
2. Meisner M. Procalcitonin. In: Meisner M, editor. A New, Innovative Infection Parameter. Stuttgart, New York: Georg Thieme Verlag; 2000. p.15-27.
3. Oberhoffer M, Stonans I, Russwurm S, Stonane E, Vogelsang H, Junker U, et al. Procalcitonin expression in human peripheral blood mononuclear cells and its modulation by lipopolysaccharides and sepsis related cytokines in vitro. J Lab Clin Med. 1999; 134:49-55.
4. Linscheid P, Seboek D, Schaer DJ, Zulewski H, Keller U, Muller B. Expression and secretion of procalcitonin and calcitonin gene-related peptide by adherent monocytes and by macrophage-activated adipocytes. Crit Care Med. 2004; 32:1715-21.
5. Bensousan TA, Vincent F, Assicot M, Morin JF, Leclerq B, Escudier B, et al. Monokines, procalcitonin (ProCT) and opioid peptides course during a model of SIRS. Shock. 1997; 8:S47-8.
6. Assicot M, Gendrel D, Carsin H, Raymond J, Gulibaud J, Bohuon C. High serum concentration in patients with sepsis and infection. Lancet. 1993; 341:514-8.
7. Simon L, Gauvin F, Anre K, Saint-Louis P, Lacroix J. Serum procalcitonin and C-reactive protein levels as markers of bacterial infection: a systematic review and meta-analysis. Clin Infect Dis. 2004; 39:206-17.
8. Sponholz C, Sakr Y, Reinhart K, Brunkhorst F. Diagnostic value and prognostic implications of serum procalcitonin after cardiac surgery: a systematic review of the literature. Critical Care. 2006; 10(5):R145.
9. Meisner M, Tschaikowsky K, Hutzler A, Schick C, Schüttler J. Postoperative plasma concentrations of procalcitonin after different types of surgery. Intensive Care Med. 1998; 24:680-4.
10. Kerbaul F, Guidon C, Lejeune PJ, Mollo M, Gouin F. Hyperprocalcitonemia is related to noninfectious postoperative severe systemic inflammatory response syndrome associated with cardiovascular dysfunction after coronary artery bypass graft surgery. J Cardiothor Vascul Anesthesia. 2002; 16:47-53.
11. De Maria R, Mazzoni M, Parolini M, Gregori D, Bortone F, Arena V, et al. Predictive value of EuroSCORE on long-term outcome in cardiac surgery patients: a single institution study. Heart. 2005; 91:779-84.
12. Christ-Crain M, Jaccard-Stolz D, Bingisser R, Gencay MM, Huber PR, Tamm M, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomized, single-blinded intervention trial. Lancet. 2004; 363:600-7.
13. Bratzler DW, Houck PM. Antimicrobial prophylaxis for surgery: an advisory statement from the National Surgical Infection Prevention Project. Clin Infect Dis. 2004; 38:1706-15.
14. Meisner M, Adina H, Schmidt J. Correlation of procalcitonin and C-reactive protein to the complications, and outcome during the intensive care of multiple-trauma patients. Crit Care. 2006; 10:R1.
15. Vincent JL, Moreno R, Takala J, Willats S, De Medonca A, Bruining H, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med. 1996; 22:707-10.
16. Dörge H, Schöndube FA, Dörge P, Seipelt R, Voss M, Messmer BJ. Procalcitonin is a valuable prognostic marker in cardiac surgery but not specific for infection. Thorac Cardiovasc Surg. 2003; 51:322-6.
17. Julious SA. Sample sizes for clinical trials with normal data. Statist Med. 2004; 23:1921-86.
18. Barber JA, Thompson SG. Analysis and interpretation of cost data in randomised controlled trials: review of published studies. BMJ. 1998, 317(7167):1195-200.
19. Vijay V, Gold JP. Late complications of cardiac surgery. In: Cohn LH, Edmunds LH Jr, editors. Cardiac Surgery in the Adult. New York: McGraw-Hill; 2003. p.521-37.
20. Rinder CS, Mathew JP, Rinder HM, Tracey JB, Davis E, Smith BR. Lymphocyte and monocyte subset changes during cardiopulmonary bypass: effects of aging and gender. J Lab Clin Med. 1997; 129(6):592-602.

21. Loebe M, Loczewski S, Brunkhorst FM, Harke C, Hetzer R. Procalcitonin (PCT) in patients undergoing cardiopulmonary bypass in open heart surgery – first results of the procalcitonin in heart surgery study (Prohearts). Intensive Care Med. 2000; 26:S193-8.
22. Brunkhorst FM, Wegscheider K, Forycki ZF, Brunkhorst R. Procalcitonin for early diagnosis and differentiation of SIRS, sepsis, severe sepsis, and septic shock. Intensive Care Med. 2000; 26 Suppl 2:S148-52.
23. Sandek A, Springer J, Habedank D, Brunkhorst F, Anker SD. Procalcitonin-guided antibiotic treatment in heart failure. Lancet. 2004; 363(9420):1555-6.
24. Vincent J-L. Microbial resistance: lessons from the EPIC study. European Prevalence of Infection. Intensive Care Med. 2000; 26 Suppl 1:S3-8.
25. Nobre V, Harbarth S, Graf J-D, Rohner P, Pugin J. Use of procalcitonin to shorten antibiotic treatment duration in septic patients. Am J Resp Crit Care Med. 2008; 177:498-505.
26. Sablotzki A, Muhling J, Dehne MG, Zickmann B, Silber RE, Friedrich I. Treatment of sepsis in cardiac surgery: role of immunoglobulins. Perfusion. 2001; 16(2):113-20.
27. Lyon C, Mou JA, Nguyen HB. The nuts and bolts of sepsis program implementation in the emergency department. Crit Care. 2006; 42-4.

Терапијска стратегија заснована на мерењу концентрације прокалцитонина ради смањења примене антибиотика код болесника подвргнутих кардиохируршком лечењу: рандомизирано контролисано истраживање

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КРАТАК САДРЖАЈ

Увод Прокалцитонин је прохормон штитасте жлезде, чија се концентрација у серуму повећава с развојем системске бактеријске инфекције. Његова дијагностичка гранична вредност није тачно установљена код болесника након операције на отвореном срцу.

Циљ рада Циљ истраживања био је да се испита да ли се узастопним мерењем прокалцитонина може смањити примена антибиотика без опасности по здравље болесника.

Методе рада Проспективна студија је обухватила 205 болесника подвргнутих кардиохируршком лечењу, који су сврстани у две групе методом случајног избора. Прву групу чинила су 102 болесника лечена антибиотицима, чија је доза одређивана на основу концентрације прокалцитонина (*PCT*-група), док су другу чинила 103 испитаника код којих је примењивана стандардна нега (стандардна група). На основу концентрације прокалцитонина употреба антибиотика је била препоручена (*PCT*≥0,50 *ng/ml*) или није саветована.

Резултати Релативан ризик од изложености антибиотицима у стандардној групи био је 3,81 (*95% CI*=2,03-7,17; *p*<0,0001). Средња вредност цене антибиотика по испитанику била је 193,3±636,6 евра у *PCT*-групи, а 372,1±841,1 евро у стандардној групи (*p*=0,206), док је средња вредност цене по болничком дану била 8,0±18,4 евра у *PCT*-групи, а 17,8±36,3 евра у стандардној групи (*p*=0,028). Код 40 болесника *PCT*-групе и 41 испитаника стандардне групе забележене су компликације неинфективне природе (*p*=0,592), док су инфективне компликације дијагностиковане код пет болесника *PCT*-групе и 22 испитаника стандардне групе (*p*=0,001). Од уринарних инфекција лечени су један болесник *PCT*-групе и девет испитаника стандардне групе; разлика је била статистички значајна (*p*=0,016). Испитаници *PCT*-групе боравили су у јединици за интензивну терапију 5,74±11,49 дана, а испитаници стандардне групе 6,97±11,61 дан (*p*=0,812), док су на укупном болничком лечењу провели 12,08±11,28 дана, односно 12,93±10,73 дана (*p*>0,05). Стопа морталитета била је слична у обе групе болесника (*p*=0,537).

Закључак Лечење антибиотицима засновано на мерењу концентрације прокалцитонина поуздано је и омогућава значајно смањење трошкова лечења након операције. Употребу антибиотика у раном периоду треба временски ограничити и применити само код потврђених бактеријских инфекција.

Кључне речи: прокалцитонин; антибиотици; узрочници запаљења; кардиохирургија

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