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Original research article

Monitoring both procalcitonin and C-reactive protein in the early period after tetralogy of Fallot correction in children promotes rational antibiotic use

Radoslaw Jaworski[a,*], Ireneusz Haponiuk[a,b], Ninela Irga-Jaworska[c], Mariusz Steffens[a], Maciej Chojnicki[a], Konrad Paczkowski[a], Jacek Zielinski[d]

[a] Department of Pediatric Cardiac Surgery, Copernicus Hospital in Gdańsk, Gdańsk, Poland
[b] Department of Rehabilitation and Kinesiology, Gdansk University of Physical Education and Sport, Gdańsk, Poland
[c] Department of Pediatrics, Hematology and Oncology, Medical University of Gdansk, Gdańsk, Poland
[d] Department of Surgical Oncology, Medical University of Gdansk, Gdańsk, Poland

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ABSTRACT

Purpose: This retrospective cohort study aimed to identify the early postoperative kinetics of C-reactive protein (CRP) and procalcitonin (PCT) in children undergoing tetralogy of Fallot (ToF) correction. The ability of these inflammatory markers to guide rational antibiotic usage was also determined.
Materials and Methods: All consecutive children who underwent ToF correction in 2009–2016 in our referral pediatric cardiac surgery clinic in Gdansk, Poland and did not exhibit infection signs on early postoperative days (POD) were identified. All patients received 48 h antibiotic prophylaxis. Antibiotic treatment was extended or empirical antibiotic therapy was introduced if the clinician considered it necessary. CRP and PCT levels were measured on POD1–4 and 1–3, respectively.
Results: Of the 60 eligible children, 44 underwent CRP testing only. The remaining 16 patients underwent both CRP and PCT testing. All patients had abnormally high CRP values after surgery. All patients who also underwent PCT testing also displayed elevated PCT levels. The CRP and PCT levels peaked on POD2 (median = 99.8 mg/L) and POD1 (median = 4.08 ng/mL), respectively. In the CRP-alone patients, antibiotic prophylaxis was prolonged or empirical antibiotic therapy was started in 59%; in the CRP and PCT group, this was 25% ($p < 0.05$).
Conclusions: The children had elevated CRP and PCT levels after ToF correction, with peaks observed on POD2 and POD1, respectively. Monitoring both CRP and PCT in the early postoperative period may guide antibiotic therapy, thus reducing unnecessary treatment, additional toxicity, and adverse drug interactions without increasing treatment failure. Rational antibiotic treatment may also reduce antibiotic resistance.

1. Introduction

Starting in the early 1990s, PCT levels have been used in clinical settings as a marker of bacterial infection. It was also shown that this marker is more specific and sensitive for this purpose than other commonly used acute phase markers such as C-reactive protein (CRP) [1]. However, it was later found that PCT and CRP levels not only rise in response to microbial acute phase stimulants; they also increase after surgery, burns, blood transfusions, and many other clinical situations. Also, cardiac procedures involving extracorporeal circulation (ECC) induce a nonspecific acute immune reaction termed systemic inflammatory response syndrome (SIRS), which is associated with elevated PCT and CRP levels.

In 2006, the Society of Thoracic Surgeons (STS) released their guidelines regarding the use of prophylactic antibiotics after cardiac surgery: it was recommended to limit prophylactic antibiotics to 48 h postoperatively. However, while this practice has now been widely adopted in adult cardiac surgery, it is often not followed in pediatric cardiac surgery [2]. Indeed, it is not uncommon that, after 48 h of routine antibiotic prophylaxis, the treatment is prolonged or new antibiotic therapy is prescribed. The reasons given for this include the “personal experience” of the attending physicians in empirical antibiotic therapy and/or the

* Corresponding author at: Department of Pediatric Cardiac Surgery, Copernicus Hospital in Gdansk, Al. Jana Pawla II 50, 80-462 Gdansk, Poland.
E-mail address: radicis@go2.pl (R. Jaworski).

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deterioration of or uncertainty regarding the condition of the patient. However, this caution may not be warranted: in 2016, Bath et al. showed that restricting antibiotic prophylaxis to 48 h after pediatric cardiac surgery does not increase the incidence of surgical-site infections [3]. Moreover, it is becoming increasingly important to reduce antibiotic consumption to the absolute minimum because of increasing rates of antibiotic-resistant bacteria and superinfections in pediatric intensive care units.

Acute phase markers may be useful when deciding when it is safe to adhere to the 48-h limitation of perioperative antibiotic therapy after pediatric cardiac procedures. However, to exploit this possibility, it is important to know how acute phase marker kinetics change in the early postoperative period after pediatric cardiac procedures.

The aim of this retrospective cohort study was to determine how the PCT and CRP levels in children change early after surgical correction of tetralogy of Fallot (ToF) with ECC. Moreover, it aimed to determine whether measuring PCT as well as CRP associates with more rational antibiotic treatment in children lacking clinical signs of infection early after surgery.

2. Material and methods

This retrospective cohort study was approved by the local ethics committee (no. 178/2012) and adhered to the tenets of the Declaration of Helsinki and its revisions. The need for informed consent was waived due to the retrospective nature of the study.

2.1. Patient selection

All consecutive children with ToF who were referred in 2009–2016 to our pediatric cardiac surgery clinic for primary ToF surgical correction with ECC were assessed for study eligibility. The inclusion criteria were lack of clinical signs of infection and absence of organ dysfunction, as determined by laboratory values, preoperatively. Patients were excluded if they met one or more of the following criteria: they had a congenital heart disease that was not ToF; their body weight was less than 2.5 kg; they had uncompensated hypothyroidism; they had clinical signs of an acute infection (including fever, diarrhea, cough, and urinary tract infection); their preoperative serum CRP and/or PCT values exceeded 5 mg/L and 0.5 ng/mL, respectively; they exhibited leukocytosis; they underwent perioperative steroid treatment; the index surgery was reoperation after previous ToF correction; and/or they died less than 3 days after surgery due to reasons other than infection.

2.2. Preoperative and operative procedures

All patients underwent routine preoperative echocardiography, chest X-ray examination, electrocardiography, and complete blood count and biochemistry analysis. All patients were also routinely screened for infection at admission, as required by our individually designed institutional practice [4].

General anesthesia was induced and maintained according to routine standards. Surgery was performed *via* median sternotomy with standard aorta and direct bicaval venous cannulations. Heparin was then administered (300 IU/kg body weight). A nonpulsatile roller pump (Sorin S5^{TM}) equipped with custom-made oxygenation and veno-arterial drains was used. If present, systemic-to-pulmonary shunts (modified Blalock-Taussig) were closed just after initiating bypass. Mild hypothermia (28–32 °C) during ECC and cardiac arrest with standard antegrade cold crystalloid cardioplegia were used. Hematocrit values were maintained above 30% during the ECC rewarming period with continuous hemofilatration commenced in the circuit. The right ventricular outflow tract obstruction (RVOTO) was widened though the right atrium and tricuspid valve using muscular excessive trabeculation resection. Cases of conal, valvular, and supravalvular obstruction underwent direct RVOTO reconstruction augmented with Contegra® xenograft implantation following a 'mono-cusp' technique. Malaligned ventricular septal defects were closed using a Gore-Tex® cardiovascular patch and a running monofilament suture technique. If necessary, tricuspid valve repair was performed in the area of the ventricular septal defect patch. Weaning from ECC and closing of the chest were performed by routine methods.

2.3. Postoperative care

All patients were thoroughly monitored postoperatively for signs of infection by clinical examinations, chest radiography, and laboratory and microbiological tests. Patients who were suspected of having an infection underwent routine microbiological examinations such as bronchial secretion, blood, and urine samples for culture. All children received perioperative antibiotic prophylaxis according to our institutionally designed in-hospital standards. In the first 2 years of the study period (2009–2010), the antibiotic prophylaxis consisted of amoxicillin and clavulanic acid. Thereafter (2011–2016), cefazolin became the antibiotic of choice in our department. It was given intravenously at 30 mg/kg 15–60 min before intervention. This administration was repeated every 3–4 h during surgery. Cefazolin was also administered at 30 mg per 100 mL of heart-lung machine priming while ECC was being initiated. After surgery,30 mg/kg cefazolin was given every 6 h until postoperative day (POD) 2. In the case of allergy against beta-lactams, clindamycin and gentamycin were electively used. Normally, the perioperative antibiotic prophylaxis was stopped after 48 h after surgery. However, in some cases, antibiotic prophylaxis was prolonged or an empirical antimicrobial treatment was introduced at 48 h. The final decision to prolong or introduce new antibiotic prophylaxis was left to the clinician in charge because there are no precise guidelines for reliably diagnosing infections in children early after cardiac surgery. The clinicians based their decision on the child's clinical status, indirect signs of possible infection, inflammatory markers and personal clinical experience. The clinicians were informed that decrease in CRP and/or PCT values in consecutive postoperative days might deny infection. Children who had a critical clinical status and low cardiac output 48 h after surgery were also started on empirical antifungal prophylaxis therapy (fluconazole) [5]. Steroids were not given routinely.

Blood samples were collected on POD 1, 2, 3, and 4 as part of our routine laboratory testing after surgery. All were sent to the local laboratory. Serum CRP concentrations were measured on POD 1–4 using a turbidimetric immunoassay. Serum PCT concentrations were measured on POD 1–3 using an electrochemiluminescence immunoassay. Serum CRP and PCT concentrations were considered to be correct if they were below 5 mg/L and 0.5 ng/mL, respectively. It should be noted that only some of the patients underwent both CRP and PCT testing: the majority underwent CRP testing only.

2.4. Data analyses

We assessed the kinetics of CRP and PCT levels after surgery and the type of antibiotics used in empirical therapy. To determine whether measuring both CRP and PCT promoted rational antibiotic usage relative to only measuring CRP, the CRP+PCT group was compared with the CRP-alone group in terms of the frequency with which the patients underwent prolonged antibiotic prophylaxis or received empirical antibiotic therapy after 48 h. The overall