

Prevention of infectious complications after heart surgery in children: procalcitonin-guided strategy

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Kardiologia i Torakochirurgia Polska 2014; 11 (2): 140-144



Abstract

Introduction: Infectious complications remain a significant problem of modern cardiac surgery. New prevention strategies, based on the pathogenesis of such complications occurring after cardiopulmonary bypass (CPB) procedures, should be evaluated.

Aim of the study: To evaluate the effectiveness of a procalcitonin (PCT)-guided strategy involving the use of IgM-enriched intravenous immunoglobulins (IVIgs) in children with congenital heart disease with systemic inflammation during the early postoperative period.

Material and methods: Sixty consecutive patients aged 25 (21-30) months who underwent cardiac surgery with CPB and had blood PCT levels > 2 ng/mL on the 1st postoperative day were enrolled in this single-center prospective randomized clinical trial. The patients were randomized into two groups, comparable in terms of the severity of their initial condition, age, and CPB time. IgM-enriched IVIGs (Pentaglobin, Biotest Pharma GmbH, Germany) were administered during the first 3 postoperative days (5 mL/kg each day) in the study group ($n = 30$) in addition to the standard treatment, which was also provided to the control group ($n = 30$). The data are presented as medians with 25-75th percentiles; they were compared by the Mann-Whitney *U*-test, and *p* values of < 0.05 were considered as statistically significant.

Results: Postoperatively, 1/30 (3.3%) patients in the study group and 8/30 (26.7%) in the control group suffered from infectious complications (study group: urinary tract infection [UTI] – 1; control group: pneumonia – 4, pneumonia and sepsis – 2, peritonitis with multiorgan failure – 1, UTI – 1), $p = 0.03$. The length of hospital stay in the study group was shorter than in the control group: 19 (16-23) days vs. 24 (19-29) days, $p = 0.002$, as was the length of intensive care unit (ICU) stay: 3 (2-4) days vs. 4 (2-8) days, $p = 0.03$.

Conclusions: High PCT levels on the 1st postoperative day are associated with an increased risk of infectious complications after cardiac surgery. Early administration of IgM-enriched IVIGs can prevent the development of infectious complications.

Streszczenie

Wstęp: Powikłania infekcyjne pozostają istotnym problemem współczesnej kardiologii. Należy poddać ocenie nowe strategie prewencyjne oparte na patogenezie tego typu komplikacji występujących po zastosowaniu płucoserca (*cardiopulmonary bypass* – CPB).

Cel pracy: Ocena efektywności stosowania terapii prokalcytoninowej (PCT) wykorzystującej dożylnie preparaty immunoglobulin (*intravenous immunoglobulins* – IVIG) wzbogacone w immunoglobuliny klasy M (IgM) u dzieci z wrodzonymi wadami serca, u których we wczesnym okresie pooperacyjnym występuje systemowy stan zapalny.

Materiał i metody: W jednośrodkowym, prospektywnym badaniu klinicznym z randomizacją udział wzięło 60 kolejnych pacjentów w wieku 25 (21–30) miesięcy, którzy zostali poddani operacjom kardiologicznym z zastosowaniem CPB i u których stężenie PCT we krwi przekraczało 2 ng/ml w pierwszej dobie pooperacyjnej. Pacjentów przydzielono losowo do dwóch grup, porównywalnych pod względem początkowego stanu pacjentów, ich wieku oraz czasu stosowania CPB. Preparaty immunoglobulinowe wzbogacone w IgM (Pentaglobin, Biotest Pharma GmbH, Niemcy) podawane były w badanej grupie ($n = 30$) komplementarnie do standardowego leczenia stosowanego również w grupie kontrolnej ($n = 30$). Dane przedstawiono jako mediany z percentylami 25–75 i porównano za pomocą testu Manna-Whitneya; za istotną statystycznie przyjęto wartość $p < 0,05$.

Wyniki: Pooperacyjne powikłania infekcyjne wystąpiły u 1/30 (3,3%) pacjentów z grupy badanej oraz u 8/30 (26,7%) pacjentów z grupy kontrolnej [grupa badana: zakażenie układu moczowego (ZUM) – 1; grupa kontrolna: zapalenie płuc – 4, zapalenie płuc i sepsa – 2, zapalenie otrzewnej z niewydolnością wielonarządową – 1, ZUM – 1], $p = 0,03$. Długość hospitalizacji w grupie badanej wyniosła 19 (16–23) dni w porównaniu z 24 (19–29) dniami w grupie kontrolnej, $p = 0,02$. Pacjenci w grupie badanej pozostawali na oddziale intensywnej terapii znacznie krócej niż pacjenci z grupy kontrolnej: 3 (2–4) dni vs 4 (2–8) dni, $p = 0,03$.

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Key words: cardiac surgery, infectious complications, immunoglobulins, procalcitonin.

Wnioski: Duże stężenie PCT w pierwszej dobie pooperacyjnej związane jest ze zwiększonym ryzykiem powikłań infekcyjnych po zabiegu kardiologicznym. Wczesne podanie dożylnych preparatów immunoglobulinowych wzbogaconych o IgM może zapobiegać rozwojowi powikłań infekcyjnych.

Słowa kluczowe: kardiologia, powikłania infekcyjne, immunoglobuliny, prokalcytonina.

Introduction

Infectious complications continue to represent a serious problem of cardiac procedures, regardless of the improving surgical techniques and antibacterial prophylaxis. Some researchers have commented on the higher occurrence of postoperative complications in children as compared to adults resulting from age-specific anatomical and physiological features, the prevalence of patients in a severe condition, and the much greater complexity of pediatric cardiac surgery. According to Seghaye *et al.* [1], various complications were observed after the surgical correction of congenital heart disease (CHD) in almost 50% of pediatric patients; they included congestive heart failure, respiratory failure, and infection. Another study reported that the occurrence of infectious complications reached 30.8% after pediatric cardiac surgery [2].

The development of postoperative complications depends on many factors such as the initial condition of patients, comorbidity, type and complexity of surgery, etc. Postoperative infectious complications are associated with significantly longer hospital stay, greater cost, as well as higher morbidity and mortality [3].

The development of infectious complications after open-heart surgery cannot be explained only by violations of aseptic and antiseptic principles during surgical manipulations. One probable explanation could be the involvement of an endogenous route of infection in cases in which cardiopulmonary bypass (CPB) is playing the key role. It is known that cardiac surgery with CPB is often associated with the development of systemic inflammatory response syndrome (SIRS) [4]. Various factors can explain the CPB-associated inflammatory reactions; the most important of them are: the exposure of blood to non-physiological surfaces of the extracorporeal circuit, surgical trauma, myocardial ischemia-reperfusion, hypothermia, and endotoxin release. Complement and leukocyte activation as well as the release of oxygen free radicals, arachidonic acid metabolites, cytokines, platelet-activating factor, nitric oxide, and other inflammatory mediators are frequent after cardiac surgery with CPB [4]. The multifactorial impact of all the mentioned components on the body's tissues determines the clinical manifestations of post-perfusion syndrome and may cause severe postoperative complications in some patients.

Changes in homeostasis and impaired microcirculation due to CPB can lead to tissue ischemia. Compromised splanchnic perfusion and the resulting intestinal mucosal injury lead to decreased function of the mucosal barrier in

the gut. The translocation of intestinal flora and endotoxemia maintain and aggravate the course of postperfusion syndrome and can promote infectious complications [5-7].

Morphological, functional, and immunological incompleteness of the gastrointestinal tract barrier predisposes newborns and children to bacterial translocation – the formation of the intestinal barrier is not accomplished by the time of birth and is protracted for several years after birth [8].

It is well known that the clinical signs and symptoms of SIRS are non-specific; therefore, the use of biomarkers such as PCT is required to differentiate the cause of this condition. It has been demonstrated that PCT is a specific marker of severe bacterial infections and sepsis [9, 10]. In contrast to many other markers, the blood plasma levels of PCT are only slightly influenced by CPB; as a result, PCT is useful for the diagnosis of bacterial infections in cardiac surgery patients. High levels of PCT are associated with mortality, infections, and severe complications early after cardiac surgery [11].

The participation of the bacterial factor in the pathogenesis of postoperative systemic inflammation and the transient cellular and humoral immunosuppression after operations with CPB are the reasons for the administration of intravenous immunoglobulin (IVIG) preparations in the early postoperative period [12, 13]. It is an established fact that antigen-antibody complexes are better activators of phagocytosis than non-opsonized antigens [14]. It is also known that endotoxin clearance depends on the serum level of immunoglobulin M (IgM). It was demonstrated on an experimental murine model of endotoxin shock that endotoxin clearance decreases sharply in IgM-deficient animals, and that it can be recovered after the infusion of an IgM preparation [15]. The effectiveness of the prophylactic use of IgM-enriched preparations, both pre- and postoperative, has been demonstrated in some studies [16, 17]. The use of IgM-enriched preparations during the early postoperative period in adult patients with anergy and a high risk of infection resulted in the reduction of the prevalence of infection in the postoperative period to 5% in the study group receiving IgM-enriched IVIGs versus 43% in the placebo group [17].

It has been established that IgM-enriched immunoglobulins are more effective in comparison with standard IVIG preparations in cases of severe bacterial infections [18]. We assumed that PCT as a specific marker of sepsis and bacterial SIRS can facilitate the selection of patients who suffered from CPB-associated microbial aggression for the treatment with IgM-enriched IVIG preparations.

Aim of the study

To evaluate the effectiveness of PCT-controlled use of IgM-enriched immunoglobulins in high-risk children with CHD after cardiac surgery with CPB.

Material and methods

The study protocol was approved by the local Ethics Committee. After informed consent was obtained from legal representatives, 60 pediatric patients with PCT blood plasma levels of 2 ng/mL or above on the 1st day after the surgery (which is a sign of a systemic reaction of the body to an endogenous bacterial load) were enrolled in the study. All these patients had a high potential risk of infectious complications, as determined by the presence of two or more of the following criteria: complex heart defect and expected prolonged CPB or aorta cross-clamping time, severe initial condition, previous cardiac surgery, concomitant pathology, previous hospitalizations.

The patients' age was 25 (21-30) months. None of them had exhibited any signs of infection before surgery. All the included patients had a high risk of postoperative complications due to the presence of complex heart defects (Table I), severe initial condition, significant concomitant pathology, and the complexity of surgery.

Among the underlying diseases, the most prevalent were central nervous system pathology ($n = 19$) and hypothyroidism ($n = 12$). Four patients were diagnosed with Down syndrome, another one had a previous cerebrovascular accident, and two patients had multiple congenital malformations. Polyvalent allergy was present in 5 cases. The medical history of 37/60 (61.7%) patients included previous cardiac and vascular surgery: systemic-pulmonary shunt – 29, banding of the pulmonary artery (Dammann-Muller procedure) – 5, balloon atrioseptostomy – 2, resection of the aortic coarctation – 1. Twenty-two (36.7%) patients had signs of chronic congestive heart failure on admission (enlarged liver, peripheral edema). Decreased exercise tolerance was observed in all studied patients. Initial cyanosis, arterial hypoxemia ($\text{PaO}_2 < 80$ mmHg), and reduced saturation of arterial blood with oxygen were revealed in 32 patients (53.3%).

The patients were randomized into two groups with the use of envelopes. The IgM-enriched IVIG preparation (Pentaglobin, Biotest Pharma GmbH, Germany) was administered i.v. to the patients in the study group ($n = 30$) in addition to standard treatment (first 3 days after surgery, 5 mL/kg each day). Patients in the control group ($n = 30$) received only standard treatment (artificial lung ventilation as well as infusion, inotropic, hemostatic, and antibacterial therapies, etc).

Patients in both groups were comparable in terms of the severity of their initial condition, age, as well as CPB and aorta cross-clamping time (Table II).

Procalcitonin blood plasma concentrations were measured by the immunoluminometric method (PCT LIA, Brahms AG, Germany) with normal values of ≤ 0.5 ng/mL. Statistical analysis was performed using the Statistica 7.0 software

Tab. I. Congenital heart disease in the studied patients, $n = 60$

Type of CHD	Study group, $n = 30$	Control group, $n = 30$
Tetralogy of Fallot	15	12
Ventricular septal defect	3	5
Ebstein's anomaly	3	3
Double-outlet right ventricle	4	1
Pulmonary atresia (type I)	2	3
Common atrioventricular canal	1	2
Transposition of the great arteries	1	1
Double-outlet left ventricle	2	–
Mitral valve insufficiency	1	1

Tab. II. Comparison of the randomized groups

Parameters	Study group, $n = 30$	Control group, $n = 30$	p
Age, months	25 (21-30)	26 (19-29)	0.75
CPB time, min	128 (105-151)	126 (110-141)	0.6
Aorta cross-clamping time, min	79 (64-90)	75 (69-79)	0.52

(StatSoft, Inc., USA). The data are presented as medians with 25% to 75% interquartile range. They were compared by the Mann-Whitney U -test, and p values of less than 0.05 were considered as statistically significant.

About the procalcitonin test

Procalcitonin (PCT) is a precursor of the hormone calcitonin with molecular weight of approximately 14.5 kDa. Under physiological conditions, all the PCT synthesized by thyroid C-cells is converted into calcitonin and is practically non-detectable in the bloodstream [19]. PCT half-life time is approximately 24 hours and does not depend on renal excretion [20]. The use of different classes of medications (antibiotics, heparin, diuretics, vasoactive drugs, and others) does not influence PCT concentration. PCT concentrations increase in cases of severe bacterial infection and sepsis, i.e. SIRS of bacterial origin. Under these conditions, the level of PCT usually exceeds 2 ng/mL (often more than 10 ng/mL). Viral and fungal infections as well as allergic and autoimmune diseases are not associated with a marked increase of PCT levels [21]. Procalcitonin is not a marker of infection per se, but rather a marker of its generalization [22].

Results

Procalcitonin levels were significantly higher in the control group in comparison with the study group from the 2nd postoperative day (Table III).

After the surgery, patients in both groups demonstrated a gradual decrease of serum PCT concentrations, with

Tab. III. Postoperative PCT monitoring data

Group	PCT levels, ng/mL			
	Day 1	Day 2	Day 3	Day 6
Study	4.57 (3.16-7.38)	2.69 (1.32-4.12)	1.13 (0.87-1.51)	0.42 (0.32-0.47)
Control	5.24 (4.13-7.91)	3.6 (2.83-4.4)	1.19 (1.34-2.87)	0.79 (0.56-1.18)
<i>p</i>	0.27	0.1	0.01	< 0.001

Tab. IV. Postoperative infectious complications

Infectious complications	Study group, <i>n</i> = 30	Control group, <i>n</i> = 30
Pneumonia	–	4 (13.3%)
Pneumonia and sepsis	–	2 (6.7%)
Peritonitis, multiorgan failure	–	1 (3.3%)
Urinary tract infection	1 (3.3%)	1 (3.3%)
Total	1 (3.3%)	8 (26.7%)*

**p* = 0.03

faster decrease rates in the study group, where, by the 6th postoperative day, PCT levels were returning to normal values (< 0.5 ng/mL) in the majority of patients (83%). At the same time, in the control group, 80% of patients continued to exhibit elevated PCT levels, which indicated the presence of bacterial inflammation (*p* < 0.001).

Postoperatively, 1/30 (3.3%) patients in the study group and 8/30 (26.7%) patients in the control group suffered from infectious complications, *p* = 0.03 (Table IV).

The presented data indicate that an infectious complication developed only in one patient in the study group, and this complication (urethritis) was assessed as non-serious. The prevalence of infectious complications was markedly higher in the control group, including such serious conditions as ventilator-associated pneumonia, peritonitis, and sepsis. The mortality rate in this group (*n* = 3) was directly associated with infectious complications: sepsis (*n* = 2) and peritonitis with multiorgan failure (*n* = 1). Two lethal cases in the study group were caused by arrhythmia and severe heart failure. The length of hospital stay in the study group was shorter than in the control group: 19 (16-23) days vs. 24 (19-29) days, *p* = 0.02, as was the length of intensive care unit (ICU) stay: 3 (2-4) days vs. 4 (2-8) days, *p* = 0.03.

The administration of pentaglobin was not associated with any adverse events.

Discussion

Postoperative infectious complications significantly worsen the results of surgical treatment of CHD. In children with complex CHD, the risk of postoperative complications, including infectious complications, is elevated due to their often grave initial condition, the presence of arterial hypoxemia, tissue hypoxia, congestive heart failure, and concomitant somatic pathology, as well as the considerable complexity of cardiac surgery.

All the above-mentioned factors significantly impair host defense, as reflected by the high prevalence of postoperative infectious complications in patients in our study, reaching 8/60 (13.3%), which also corresponds to the data of some other researchers [1, 2]. Cardiac surgery with CPB appears to exert a multifactorial influence on all body systems, impairing microcirculation, which results in tissue hypoxia and impairment of the mucous barriers of the gastrointestinal tract. The translocation of intestinal flora into systemic circulation and its further involvement in systemic inflammation has been proved experimentally [23]. The use of the PCT test as a specific marker of systemic inflammation of bacterial origin enables one to prove or reject the bacterial etiology of systemic inflammation in real time. The processes underlying the postoperative increases of PCT levels are under continuous discussion. The majority of researchers tend to explain this by the activation of the immune system in response to the translocation of endogenous intestinal flora following intraoperative gastrointestinal tract ischemia [24, 25]. It should be mentioned that PCT levels in uncomplicated cardiac surgery patients were reported to be either normal or slightly elevated [11]. Similar results were obtained in pediatric patients after cardiac operations [26].

The analysis of our results demonstrated that the incidence of infectious complications in the study group was 8 times lower than among the patients who did not receive immunotherapy (3.3% and 26.7%, respectively; *p* = 0.03). Moreover, life-threatening complications were noted in the control group, including pneumonia and sepsis.

Conclusions

Early treatment with IgM-enriched IVIG preparations starting on the first postoperative day provides a reduction in the prevalence and seriousness of infectious complications in high-risk pediatric patients, resulting in a significant shortening of the length of ICU and hospital stay. The PCT test can verify the bacterial load and infection at the earliest stage, which facilitates the selection of the target group of patients requiring treatment with IVIGs.

Disclosure

The authors report no conflicts of interest.

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