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C-reactive protein, procalcitonin and interleukin-6 kinetics in pediatric postoperative patients☆

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1. Introduction

Some postoperative pediatric patients require admission to Pediatric Intensive Care Unit (PICU) [1]. Systemic Inflammatory Response Syndrome (SIRS) occurs after surgery in >80% of patients [2] and makes infection diagnosis difficult by clinical criteria [3]. Biomarkers, such as C-reactive protein (CRP), procalcitonin (PCT) and interleukin-6 (IL-6) are employed in clinical practice to help in the diagnosis of infectious complications in the postoperative period.

CRP, PCT and IL-6 are inflammation markers, so their elevation is secondary to a SIRS due to an infectious or non-infectious cause such as a surgical intervention. The knowledge of the kinetic biomarkers after surgery is important for the postoperative patient management. It has been described that IL-6 reaches its peak value quicker than (2–3 h) than PCT (6–12 h) or CRP (36–48 h) after surgical intervention. Subsequent decline to baseline values is faster for IL-6, followed by PCT and then CRP [4,5]. Besides, kinetic biomarkers differ depending on the type of surgery [6,7].

Controversy exists over which biomarker has better diagnosis accuracy to characterize infection in postoperative period. There are studies that support PCT usefulness as prognostic marker and diagnostic tool for infection diagnosis during this period [8-19]. Nevertheless, there are other studies that conclude that CRP [20-23] or IL-6 [18,21,24,25] are valid or better for this purpose than PCT. However, the majority of those studies were conducted in children or adults after cardiac surgery and cardiopulmonary bypass [8-10,12,25].

We designed a prospective observational study to evaluate the kinetics of CRP, PCT and IL-6 after different types of surgery in children and compare them regarding the proportion of patients with biomarker increase above the cutoff level suggested for diagnosis of sepsis.

2. Materials and methods

2.1. Patient characteristics

We conducted a prospective observational study set in an eight-bed PICU of a University Hospital from October 2011 to April 2014. We included all consecutive postoperative patients with informed consent. A total of 123 children were included. Eight patients who suffered from infectious complications in postoperative period were excluded. CRP, PCT and IL-6 levels at 0, 24, 48 and 72 h of postoperative period were analyzed. Patient's epidemiological and clinical data were also collected. The study protocol was approved by the Hospital Ethics Committee of Hospital Universitario Central de Asturias. Written informed consent was obtained from the patient's parents or guardians.

2.2. Classification of surgical procedures

Children were classified in different subgroups according to the type of surgical procedure: abdominal surgery, thoracic surgery, Ear, Nose and Throat (ENT) surgery, neurosurgery and orthopedic surgery. Patients were also classified in the four classes of surgical wound types based on degree of bacterial contamination of surgical wounds and risk of infection established by American College of Surgeons [26,27]: class I: clean surgery (ClS), class II clean-contaminated surgery (ClCoS), class III: contaminated surgery (CoS) and class IV: dirty or infected surgery (DS).

2.3. Interpretation of biomarker values

Previous published CRP and PCT cutoff values for sepsis in a study performed at our PICU were considered as reference values (CRP: 5.65 mg/dl, PCT: 1.16 ng/ml) [28]. There is less clinical knowledge about the usefulness of IL-6 in sepsis or infection diagnosis and there is a disagreement between the cutoff values established by different authors (ranging from 50 pg/ml to >200 pg/ml) [4,29-32]. We have chosen 100 pg/ml as a reference cutoff value for sepsis. Proportion of

Abbreviations: PICU, Pediatric Intensive Care Unit; SIRS, Systemic Inflammatory Response Syndrome; CRP, C-reactive protein; PCT, procalcitonin; IL-6, interleukin-6; ENT surgery, Ear, Nose and Throat surgery; ClS, clean surgery; ClCoS, clean-contaminated surgery; CoS, contaminated surgery; DS, dirty or infected surgery.

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samples with biomarker levels above the suggested cutoff values for sepsis were compared between CRP, PCT and IL-6.

2.4. Measurement of PCT, CRP and IL-6

Blood samples were drawn into tubes containing lithium-heparin as anticoagulant, for determination of CRP, PCT and IL-6. Plasma CRP was measured on a Modular Analytics Cobas 6000 (Roche diagnostics, Indianapolis, IN, USA) by an immunoturbidimetric technique. Roche's electro-chemiluminescence immunoassay (ECLIA) was performed on a Cobas 6000 analyzer (e601 module) for measuring PCT and IL-6. Analytical detection limits were 0.07 mg/dl for CRP, 0.02 ng/dl for PCT and 1.5 pg/ml for IL-6.

2.5. Statistical analysis

Patient's clinical data and values of plasma biomarkers (CRP, PCT and IL-6) during postoperative period were described using frequencies, percentages, means and medians.

CRP, PCT and IL-6 maximal median peak values in postoperative period were analyzed by using Kruskal-Wallis test (non-parametric test), because they do not follow the normality and homoscedasticity hypothesis. The post hoc test of Nemeyi was used when significant differences were found. The percentage of samples that rose above cutoff values for sepsis for each biomarker was analyzed. These percentages were compared between the different surgical subgroups by using Fisher test, and between the different biomarkers by using McNemar test. The level of significance was set at $p < 0.05$.

3. Results

3.1. Patient characteristics

A total of 115 patients were included in the study. Patient characteristics, severity scores, respiratory and inotropic support, red cell transfusions and type of surgery are shown in Table 1.

In the abdominal group the most frequent surgical interventions were appendectomy (9 patients; 28.1%) and intestinal anastomosis/resection (8 patients; 25.0%); thoracoscopic drainage for empyema (12 patients; 36.3%) was the most frequent in thoracic surgery; scoliosis surgery (8 patients; 88.8%) in orthopedic surgery and brain tumor resection (10 patients; 47.6%) in neurosurgery subgroup. In the ENT surgery group there was many surgical procedures (e.g. tonsillectomy 3/16 patients, 18.8%; abscess drainage 3/16 patients, 18.8%; cochlear implant placement 2/16 patients, 12.5%; cholesteatoma surgery 1/16 patients, 6.3%) with no predominance between them. The most frequent surgical procedure in ClS was brain tumor neurosurgery (10 patients; 27.7%), while in the case of DS the most frequent surgical procedure was thoracoscopic drainage for empyema (12; 36.3%) followed by appendectomy (9; 27.3%). In the ClCoS group the most common surgical procedure was scoliosis surgery (8/31; 25.8%) and intestinal anastomosis/resection (7/15; 46.7%) in CoS subgroup.

The most common perioperative antibiotic prophylaxis in our patients consisted of three doses of cefazolin (33.9% of the patients, mainly from neurosurgery and ENT groups). DS patients received antibiotic treatment according to the type and localization of infection (e.g. empyema, appendectomy).

Table 1
Patient characteristics, severity scores, respiratory and inotropic support, red cell transfusions and type of surgery. Results are presented as mean (95% Confidence Interval) for age, weight, number of days in PICU and absolute frequencies and percentages for the rest. TISS-28 = Therapeutic Intervention Scoring System 28; PRISM III = Pediatric Risk of Mortality Score III.

Epidemiological data	
Age at admission (years)	7.10 (6.15–8.05)
Number of days in PICU	4.29 (2.73–5.85)
Weight (kg)	27.95 (24.32–31.58)
Male sex (%)	54.90
PRISM III (absolute value)	1.39 (0.83–1.95)
TISS-28 at 24 h (absolute value)	19.46 (17.67–21.25)
TISS-28 at 48 h (absolute value)	15.95 (14.37–17.53)
TISS-28 at 72 h (absolute value)	15.68 (13.64–17.72)
Mechanical ventilation	39 (33.9%)
Non-invasive ventilation	32 (27.8%)
Inotropic support	3 (2.6%)
Red cell transfusion	21 (18.2%)
Type of surgery	
Abdominal surgery	32 (27.8%)
Thoracic surgery	33 (28.7%)
ENT (Ear, Nose & Throat) surgery	16 (13.9%)
Neurosurgery	21 (18.3%)
Orthopedic surgery	9 (7.8%)
Other types of surgery	4 (3.5%)
Clean surgery	36 (31.3%)
Clean-contaminated surgery	31 (27.0%)
Contaminated surgery	15 (13.0%)
Dirty surgery	33 (28.7%)

3.2. CRP kinetics in non-complicated postoperative period after different types of surgery

CRP peak level was reached at 48 h after all types of surgery except for orthopedic and ENT surgery (peak value at 72 h) and ClS (peak value at 24 h). CRP median peak values are shown in Table 2. There were differences between the types of surgery ($p = 0.04$) with neurosurgery vs abdominal surgery close to the level of significance ($p = 0.06$).

In all cases except for ClS, CRP peak median values were elevated above cutoff value for sepsis in postoperative period (Fig. 1). Percentages of samples with CRP levels above cutoff values for sepsis diagnosis are shown in Table 3. There were differences between ClS compared to ClCoS and DS, $p < 0.001$.

3.3. PCT kinetics in non-complicated postoperative period after different types of surgery

PCT peak level was reached at 24 h after all types of surgery except for ENT surgery and orthopedic surgery (peak value at 48 h). PCT median peak values are shown in Table 2 and Fig. 2. There were differences between the types of surgery: $p < 0.001$, specifically between neurosurgery and abdominal surgery $p = 0.02$; abdominal and orthopedic

Table 2
CRP (mg/dl), PCT (ng/ml) and IL-6 (pg/ml) median of maximal peak values, standard deviation (in brackets) and percentiles 10/90 (below) depending on the type of surgery.

	CRP[a]	PCT[b]	IL-6[c]
Type of surgical procedure			
Abdominal surgery	13.10 (11.75)	1.12 (8.39)	173.0 (846.7)
	1.88/25.20	0.26/13.29	20.50/3696.00
Thoracic surgery	7.04 (9.81)	0.26 (0.67)	131.0 (111.2)
	2.02/34.51	0.14/10.24	14.00/309.00
ENT (Ear, Nose & Throat) surgery	1.40 (5.80)	0.08 (0.23)	20.0 (22.2)
	0.21/11.50	0.03/0.40	6.00/67.00
Neurosurgery	4.44 (4.41)	0.14 (0.12)	35.0 (338.5)
	0.05/10.61	0.06/0.21	5.00/51.00
Orthopedic surgery	6.60 (6.09)	0.11 (0.21)	81.0 (57.3)
	2.60/10.60	0.07/0.41	22.00/162.00

[a] Kruskal-Wallis for differences between the types of surgery: $p = 0.04$. Nemenyi post hoc: neurosurgery vs abdominal surgery $p = 0.06$.
[b] Kruskal-Wallis for differences between the types of surgery: $p < 0.001$. Nemenyi post hoc: neurosurgery vs abdominal surgery $p = 0.02$; abdominal vs orthopedic surgery $p = 0.03$; abdominal vs ENT surgery $p = 0.002$; abdominal vs thoracic surgery $p = 0.017$.
[c] Kruskal-Wallis for differences between the types of surgery: $p < 0.001$. Nemenyi post hoc: neurosurgery vs abdominal surgery $p = 0.036$; abdominal vs ENT surgery $p < 0.001$; ENT vs thoracic surgery $p = 0.003$.