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KINETICS OF PROCALCITONIN, INTERLEUKIN-6 AND C-REACTIVE PROTEIN AFTER SURGERY FOR JAKOB III HUMERUS LATERAL CONDYLE FRACTURES IN CHILDREN

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Conflicts of Interest: Nil
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Abstract:
The objective of this study was to investigate the kinetics of procalcitonin (PCT) , interleukin-6 (IL-6) and C-reactive protein (CRP) after surgery for Jakob III humerus lateral condyle fractures in children and the relationship with postoperative wound infection. A total of 58 Chinese children who visited our hospital between May 2016 and September 2017 with Jakob III humerus lateral condyle fractures were enrolled in this study. Blood was collected before surgery and on the 1st, 3rd, and 5th day after surgery. PCT and IL-6 were quantified by an immunoluminometric assay, while CRP was measured by an automated nephelometry. Results: No postoperative wound infections occurred in any of the participants. Plasma levels of PCT, IL-6, and CRP reached their peak on day1 after surgery and gradually declined thereafter. Moreover, CRP levels strongly correlated with IL-6 ($p<0.001$) at all the time points tested.
Conclusion: None of the participants suffered from postoperative incision infection. Changes in the kinetics of circulating PCT, IL-6, and CRP in children following surgery for Jakob III humerus lateral condyle fractures may indicate infectious complications and require close attention.
Keywords: Procalcitonin, Interleukin-6 and C-reactive protein, humerus lateral condyle, fracture, children

INTRODUCTION

Humerus lateral condyle fractures, the second most common elbow fractures in children, account for 12% to 17% of all distal humerus fractures in children [1], after supracondylar fracture of the humerus. The Jakob classification [2] categorizes humerus lateral condyle fractures into three types, of which the third type is the most severe form due to the rotation and lateral shift of the fracture block to the proximal side which results in dislocation of the olecranon and the humeral head. Because of the intra-articular nature, humerus lateral condyle fracture requires surgical intervention for resetting and proper internal fixing of the joint. The results of a incorrectly treated lateral condyle fracture may hinder the healing as well as the function of the elbow joint, can be affected. At present, surgical methods for Jakob III humerus lateral condyle fractures in children mainly include open reduction, Kirschner wire placement for internal stabilization combined with gypsum external fixation [3,4]. Postoperative plaster fixation, however, limits the surveillance of the incision for sepsis, which can be done only a few weeks after the removal of plaster and can delay or complicate treatment in the event of incisional infection.

Materials and Methods:

In total 58 traumatized Chinese children treated for Jakob III humerus lateral condyle fractures between May 2015 and September 2017 at Trauma Department of Orthopedics, Affiliated Hospital of Chengde Medical College, and China were included in the study. The mean age was 6.8 ± 4.4 years, and 56.9% was male (n = 33), and the main cause of injury was a fall. Patients with any other condition which could confound the study results were excluded per the investigator's discretion. Inclusion criteria were: age less than 14 years and positive side X-ray of the elbow joint showing surgery for Jakob III humerus lateral condyle fractures. Exclusion criteria were: acquired or inherited immunodeficiency, history of inflammatory disorder, existing inflammation, hepatitis or radiotherapy, open fracture, emergency operation.

Written informed consent for participation in the study was taken from each patient or a close relative. This study protocol was reviewed and approved by the institutional ethics committee of the Affiliated Hospital of Chengde Medical College, China.

Blood sample from each subject was collected before surgery and on the 1st, 3rd, and 5th day after surgery. PCT and IL-6 were quantified by an immunoluminometric assay using the Modular Analytics E170 analyser (Roche Diagnostics, USA). This assay has a functional sensitivity of 0.06 ng/mL. CRP was measured by an automated nephelometry. CRP was measured by an automated nephelometry. Chest X-ray was routinely performed before surgery.

Surgical procedure: Under general anesthesia, the patient was placed in a supine position, disinfected in the field, and covered with a sterile towel. A tourniquet was used during the surgery. A 5 cm posterior lateral longitudinal incision of the elbow joint was used to cut the subcutaneous tissue of the skin and reveal the fracture. The bones and joints were cleaned and the external hemorrhoid fractures were assessed to be satisfactory. At a satisfactory reduction position, two or three 1.6-2.0mm Kirschner wires were cross-fixed from the outside to the inside of the humerus and sutured the incision. The long arm cast was fixed to the elbow at 90 degrees.

Preoperative prophylactic cefazolin was administered. No postoperative infections were clinically observed in any of the patients. Children were reviewed 1, 2, 4, and 6 weeks after the surgery for general health conditions and X-ray examination of the elbow joint to assess joint healing. If the fracture healing was good, the cast was removed and internal fixation was performed at 6 weeks after surgery.

Statistical analysis:

Statistical analysis was performed using SPSS 22.0 software. Normally distributed continuous variable data was expressed as mean +/- standard deviation. A paired Students t-test of was used for comparison between the groups; non-normally distributed continuous variables are represented as median and quartile, and comparison between groups was performed by nonparametric Wilcoxon related tests. Correlation of postoperative parameters was performed using spearman correlation. A value of $P<0.05$ was statistically significant.

Results:

None of the children exhibited postoperative wound infection. Preoperative PCT levels increased from 0.05(0.02~0.09)ng/mL before surgery to 0.11 (0.06~0.20)ng/ml on day 1(P＜0.001) and 0.07(0.05~0.11) mg/L on day 3 (P=0.018) and 0.05(0.03~0.09) mg/L on day 5(P=0.0817) after surgery. IL-6 levels increased from 11.10(7.02~15.13)pg/ml before surgery to 24.37(16.60~38.19)pg/ml on day 1(P＜0.001) and 10.89(5.85~16.37) pg/ml on day 3 (P=0.996) and 10.65(5.68~16.30) pg/ml on day 5(P=0.0817) after surgery. C-reactive protein levels increased slightly above normal from 0.5 mg/dL to 1.1 mg/dL. CRP levels increased from 1.78 (1.28~6.17)mg/L before surgery to 18.4(6.69~26.82) mg/L on day 1(P＜0.001) and 11.85(2.23~23.27) mg/L on day 3 (P＜0.001) and 4.40(1.28~9.85) mg/L on day 5 (P=0.008) after surgery CRP levels strongly correlated with IL-6 levels at all the time points tested (table 1-4/Fig 1-3).

Table 1: Results of preoperative and postoperative values

Variable	Pre-surgery	1	2	5
PCT (ng/ml) [M（Q1~Q3）]	0.05 [0.02~0.09]	0.11 [0.06~0.20]	0.07 [0.05~0.11]	0.05 [0.03~0.09]
IL-6(pg/ml) [M（Q1~Q3）]	11.10 [7.02~15.13]	24.37 [16.60~38.19]	11.85 [5.85~16.37]	10.65 [5.68~16.30]
CRP(mg/L) [M（Q1~Q3）]	1.78 [1.28~6.17]	18.4 [6.69~26.82]	10.89 [2.23~23.27]	4.40 [1.28~9.85]

Table 2: Correlation with preoperative values

Variable	Sampling point (d)		
	1	3	5
PCT	r=0.339 P=0.009	r=0.294 P=0.025	r=0.355 P=0.006
IL-6	r=-0.114 P=0.394	r=0.229 P=0.084	r=0.147 P=0.272
CRP	r=0.283 P=0.032	r=0.295 P=0.025	r=0.329 P=0.012

Table 3: Results compared with preoperative values

Variable	Sampling point (d)		
	1	**3**	**5**
PCT	Z=-4.316 P<0.001	Z=-2.374 P=0.018	Z=-0.232 P=0.817
IL-6	Z=-6.217 P<0.001	Z=-0.043 P=0.996	Z=-0.399 P=0.690
CRP	Z=-5.996 P<0.001	Z=-4.943 P<0.001	Z=-2.661 P=0.008

Table 4: Correlation with CRP

Variable	Sampling point (d)			
	Pre-surgery	**1**	**2**	**3**
PCT	r=0.196 P=0.140	r=-0.002 P=0.986	r=0.178 P=0.181	r=0.023 P=0.861
IL-6	r=0.240 P=0.069	r=0.468 P<0.001	r=0.567 P<0.001	r=0.458 P<0.001

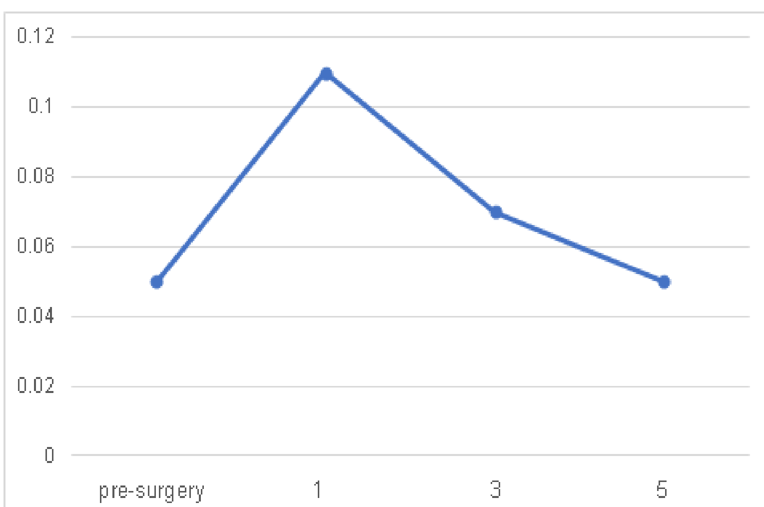

Figure 1: Preoperative and postoperative values of PCT (ng/ml)

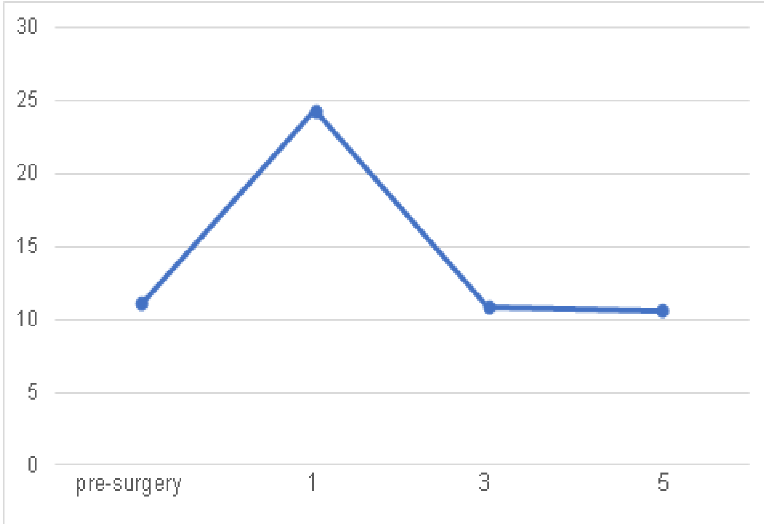

Figure 2: Preoperative and postoperative values of IL-6(pg/ml)

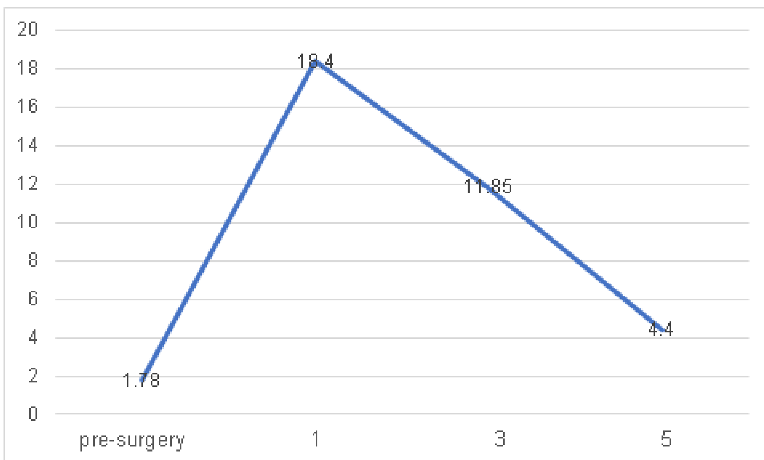

Figure 3: Preoperative and postoperative values of CRP(mg/L)

Discussion:

Lateral condyle fractures of the humerus, which account for 12% to 17% of all distal humerus fractures, are the second most common operative elbow injury in children after supracondylar fractures. They are most prevalent in children between the ages of 5 and 10 years [5]. The Jakob Classification, which is based on degree of displacement and rotation of the lateral condylar fragment, categorizes lateral condyle fractures of the humerus into three types: Type I is a non-displaced fracture with an intact articular surface ; type II is a minimally displaced fracture where the fracture line completely passes through the articular surface; type III is a displaced fracture with rotation of the fracture block, and dislocation of the olecranon and the humeral head.

The third type of displacement is the most serious kind because it is an intra-articular fracture, and requires appropriate reduction and internal fixation for proper healing. Incorrect fixation can affect the healing, and eventually function of the elbow joint. At present, surgical procedure for the type III fractures includes open reduction, and placement of Kirschner wire for internal stabilization, which are left exposed and removed later, and gypsum cast for external fixation. However, the postoperative casting of the limb makes it difficult to monitors the degree of healing of the incision. It is usually only a few weeks after the plaster has been removed before the incision can be observed, which can delay and complicate treatment in case of sepsis. Therefore, the aim of the present study was to describe postoperative kinetics of IL-6, PCT, and CRP levels in children following surgery for the humerus lateral condyle fractures with the intent to provide meaningful information for predicting possible postoperative infection. Although not widely used as routine screening tests, we selected PCT, and IL-6 because both of the markers can be evaluated simultaneously in the same sample and thereby mitigate the burden of multiple blood draw on the patients. Our study showed that PCT, IL-6, and CRP levels peaked at day1 post surgery followed by a gradual decline over the rest of the time points.

PCT is a protein of 116 amino acids, produced by neuroendocrine and parafollicular cells of the thyroid. Because PCT level in blood increases in response to bacterial infection, serum PCT test has a high diagnostic accuracy for the identification of systemic infection [6, 7]. Nevertheless, an increased serum PCT also has been reported in severe clinical insults and systemic inflammatory response syndrome (SIRS) without infection, such as severe trauma, burns, and head stroke after surgery. Plasma concentrations of PCT are, to some extent, related to the type and severity of surgical trauma [8].

Besides PCT, acute phase proteins such as IL-6, and CRP have been used diagnostically in sepsis. [9] IL-6 is a multifunctional cytokine, which is produced by a large number of cells mainly monocytes, macrophages, T-lymphocytes, fibroblasts and endothelial cells. It mediates transition from innate to acquired immunity via activation of acute phase protein production in the liver such as C-reactive protein (CRP).

IL-6 as part of the pro-inflammatory cascade was verified as the most reliable prognostic marker of inflammation[10]. Zant et al. [11] reported that the postoperative increase in IL-6, PCT, and CRP in children undergoing liver transplantation was an acute reaction to the surgery, and not due to infection. In the same study, the authors concluded that IL-6 was the best predictor of postoperative sepsis.

Moreover, PCT and IL-6 are promising markers of bacterial infection in children with cancer and febrile neutropenia [12]. IL-6 correlates with injury severity [13, 14]. Gebhard et al. in a study on 94 severely traumatized adult patients demonstrated that plasma IL-6 levels increased immediately after trauma when measure over several days following trauma [13].

Our results showed that CRP levels on days 1, 3, and 5 strongly correlated with IL-6. Elevation of CRP, an acute phase protein and predominantly produce by hepatocyte, was reported in response to interleukin-6 trigger [15], tissue injury, infection or inflammation. Yoon et al. [16] studied CRP levels before and over several days for three weeks post-surgery in 57 patients with long bone fractures and 11 patients undergoing joint replacement surgery and found that circulating CRP was the highest at 2-3 days after surgery, and returned to normal in the third week after surgery. Similarly, Neumaier et al. [17] found peak CRP on the second day after surgery in 349 patients with proximal femoral fractures treated with different surgical procedures. The authors further reported that CRP can be used to assess fracture and tissue damage after surgery. As seen in Yoon et al. [16], CRP was observed to return to normal levels within 2-3 weeks after surgery depending on the procedure and location of surgery. A second increase of ≥100mg/L in CRP after the initial decline, however, is indicative of the emergence of complications [18].

While most of the studies were conducted in adults, clinical data on the significance of cytokines in pediatric trauma still do not exist [19]. Havránek et al. [20] compared the change in CRP after surgery in children with fractures around the elbow, and conservative wrist fractures and found that CRP reached its highest value on the second day after surgery and returned to normal on the third day after surgery, regardless of antibiotics usage. They concluded that a continued increase in CRP over seven days after surgery is indicative of postoperative infection.

This study provides dynamic changes in PCT, IL-6, and CRP after open reduction surgery for Jakob type III humerus lateral condyle fractures. Abnormal postoperative kinetics of PCT, IL-6, and CRP indicated that close attention should be paid on the occurrence of surgery-related complications in children. In this study, due to the small number of patients, we did not observe any case of postoperative infection. Future long-term prospective studies in a larger cohort of patients are required to validate the present findings and further analyze the relationship between PCT, IL-6 and CRP and postoperative infection, and the impact of different surgical methods on these inflammatory indicators.

PCT, IL-6 and CRP measurements are affordable, easy and readily available. And using either or three of them could make the implementation of a risk model, if proven feasible, easier and more cost-effective.

Conclusion:

PCT, IL-6 and CRP levels peaked on day 1, and gradually decreased over time in children with Jakob III humerus lateral condyle fractures who underwent open reduction and internal fixation without incision infection. Any abnormal changes in these markers, therefore, may indicate the presence of infectious complications and require close attention.

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