

Evaluation of procalcitonin as a biomarker of diagnosis, severity and postoperative complications in adult patients with acute appendicitis

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Abstract

Background: Delay in diagnosis and treatment of acute appendicitis (AA) results in an increased rate of perforation, postoperative morbidity, mortality and hospital length of stay. Several biochemical parameters including white blood cell (WBC) count, C-reactive protein (CRP), interleukin-6 (IL6) and Procalcitonin (PCT) have been used to further improve the clinical diagnosis of AA. The aim of this study was to assess the value of procalcitonin as a predictor of diagnosis and severity of appendicitis in order to improve the clinical decision making, since other studies have been unable to demonstrate a diagnostic value for PCT elevation in acute appendicitis.

Methods: One-hundred patients who underwent open appendectomy, including 75 men and 25 women with a mean age of 28 years were included in this study. Procalcitonin values were measured by an immunofluorescent method. Serum PCT > 0.5 ng/ml was considered positive. The PCT serum values were measured in four different categories, including < 0.5 ng/ml, 0.5-2 ng/ml, 2-10 ng/ml and more than 10 ng/ml.

Results: The sensitivity and specificity of PCT level measurement for acute appendicitis diagnosis were 44% and 100% respectively. The value of PCT increased with the severity of appendicitis and also with the presence of peritonitis and infection, at the site of surgery.

Conclusions: Procalcitonin measurement cannot be used as a diagnostic test for adult patients with acute appendicitis and its routine use in such patients is not cost effective and conclusive. Procalcitonin values can be used as a prognostic marker and predictor of infectious complications following surgery and it can help to carry out timely surgical intervention which is highly recommended in patients with PCT values more than 0.5 ng/ml.

Keywords: Appendicitis, Procalcitonin, Diagnosis, Prognosis.

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Introduction

Appendectomy for acute appendicitis (AA) is the most commonly performed emergency operation in the world. Appen-

ditis is a disease of the young with 40% of cases occurring in patients between the ages of 10 and 29 years (1). Delay in diagnosis and treatment results in an increased

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rate of perforation, postoperative morbidity, mortality and hospital length of stay. Despite the advent of sophisticated laboratory and imaging diagnostic modalities, in-hospital observation and repeated clinical examination remains the most common way of diagnosis of acute appendicitis but this may lead to an increase in the number of patients operated with false positive diagnosis of AA. Several biochemical parameters including white blood cell (WBC) count, C-reactive protein (CRP), interleukin-6 (IL6) and Procalcitonin have been used to further improve the clinical diagnosis of AA (2). The aim of this study was to assess the value of procalcitonin as a predictor of diagnosis and severity of appendicitis in order to improve the clinical decision making.

Methods

This cross sectional study included one hundred patients who underwent open appendectomy, based on the clinical diagnosis of acute appendicitis during a two-year period from March 2007 to March 2009 in the surgical department of Hazrat-e-Rasool Hospital, an academic teaching hospital in Tehran- Iran. This study was approved by Iran University of Medical Science Ethics Committee and was a post-graduate thesis. Exclusion criteria were patients, in whom another diagnosis other than acute appendicitis was confirmed during the operation, being under antibiotic use two weeks before admission and presence of another infectious lesion or disease in any other part of the body. No antibiotics had been prescribed for patients by the primary physician prior to referring to a surgeon and taking a careful history to confirm the condition. All other patients without exclusion criteria, who underwent appendectomy, whether or not the appendix was normal or inflamed, included in this study.

Clinical and laboratory information of patients including age, sex, duration of symptoms, Alvarado score, WBC count and differential, pre-operative procalciton-

in level, final histopathological diagnosis/status of appendix (normal-inflamed-gangrenous-perforated), presence of localized or generalized peritonitis and post-operative complications (wound infection-intra-abdominal abscess) were recorded.

All patients were informed about the aim of the study and an informed consent was obtained. Since the study was supported by a financial grant from the Tehran University of Medical Sciences, no extra cost regarding the procalcitonin level determination was imposed on the patients.

Procalcitonin values were measured by an immunofluorescent method using the B.R.A.H.M.S PCT kit (B.R.A.H.M.S Diagnostica, Berlin, Germany). Pre-operative separate clotted and citrated blood samples were used for measuring procalcitonin level and WBCs, respectively. Serum PCT >0.5 ng/ml was considered positive. PCT serum values were measured in four different categories, including <0.5ng/ml, 0.5-2 ng/ml, 2-10ng/ml and greater than 10ng/ml.

Statistical analysis was performed by SPSS 13 software for Windows. Analysis of distribution of data was assessed by the Kolmogorove-Smirnov test. For normally distributed data (Alvarado Score), the null hypothesis was based on the assumption that no difference in values existed between the two groups. In order to show whether the variance of data in two groups are equal or not, the Leven test was used. Since the variances were not equal in both groups, Mann Whitey U test (nonparametric independent-paired comparison) used to compare different groups. The PCT values were analyzed by means of Chi square test analysis.

Mean values and standard deviations (SD) was calculated for WBC and polymorphonuclear (PMN). Additional calculations of sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of PCT were included in the data analysis. Statistical significance was set at the <5% level.

This research was based on the post-

graduate thesis of Dr. Roohollah Taghavi with the supervision of Dr. Mohammad Vaziri entitled "Evaluation of Procalcitonin as a biomarker of diagnosis, severity and postoperative complications in adult patients with acute appendicitis", which was performed in Minimally Invasive Surgery Research Center, Iran University of Medical Sciences, Tehran, Iran.

Results

One-hundred patients who underwent open appendectomy consisted 75 men (75%) and 25 women (25%) with a mean age of 28 years (age range 15-60 years) were included in this study. Duration of symptoms from the onset of clinical discomfort and at the time of the first visit by a surgeon was recorded which included a mean of 33 hours (range:15 hours to 96 hours). The mean for Alvarado score was 8 (range: 5-10) and the mean WBC value was 12338/mm³ (range:6500-19500/mm³). The patients had no underlying disease.

Of 100 patients operated, 94 had appendicitis confirmed by the final pathologist report (negative appendectomy rate of 6%). The severity of the appendix inflammation determined for each patient at the time of operation included the following: early suppurative (42 patients), late suppurative (26 patients) and gangrenous/perforated appendix (17 patients). Peritonitis due to perforated appendicitis was confirmed in 9 patients intra-operatively. Post-operative complications including surgical site infec-

tion (SSI) was detected in 6 patients.

Procalcitonin value in 59 patients was less than 0.5ng/ml and hence considered negative. In the remaining 41 patients, 27 had a serum PCT value between 0.5 – 2ng/ml, 9 between 2 -10ng/ml and 5 more than 10ng/ml. Among nine patients with peritonitis, five patients had a PCT value more than 10ng/ml and this value was between 2-10ng/ml in four patients. In six cases of surgical site infection, one patient had a PCT value more than 10 ng/ml, four between 2–10 ng/ml and one patient had a negative PCT value.

Based on the final pathologic report, we classified the patients into two groups: Group I with no evidence of appendicitis and Group II with a confirmed appendicitis report and the aforementioned values were calculated and allocated accordingly (Table 1).

The sensitivity and specificity of PCT level measurement for acute appendicitis diagnosis was 44% and 100% respectively. The corresponding sensitivity for detecting peritonitis and surgical site infection were 100% and 65% and their specificity were 83% and 62% respectively. The NPV and PPV of PCT in appendicitis were 0.1(10%) and 1(100%) respectively (Table 2).

Statistical analysis showed that there was a significant difference in PCT value between the two groups of patients based on pathologic report (Chi-square test: $p=0.023$). The value of PCT increased with the severity of appendicitis and presence of peri-

Table 1. Values of PCT, WBC and PMN in two groups of patients with and without appendicitis, group 1 and 2 respectively.

	Group 1 Normal appendix	Group 2 Appendicitis	Total
Number of patients	6	94	100
Age (Years)	19.16(±2)	28.57(±10.57)	28(±10.46,9-60)
Sex	0 Male/6 Female	75 Male/19 Female	27 male/25 female
WBC	16.67(±16.67)	12.06(±2.86)	12.33(±3.14,6.5-19.5)
PCT	6[<0.5 ng/ml],0 [0.5-2 ng/ml], 0 [2-10 ng/ml],0[>10 ng/ml]	53 [<0.5 ng/ml], 27 [0.5-2 ng/ml], 9 [2-10 ng/ml],5 [>10 ng/ml]	59 [<0.5 ng/ml], 27 [0.5-2 ng/ml], 9 [2-10 ng/ml],5[>10 ng/ml]
PMN	71.67(±8.08)	79.35(±9.04)	78.89(±9.53-95)
Duration of operation	19(±2.55)	33.98(±19.37)	33(±19.12,15-96)

WBC= white blood cell, PCT= Procalcitonin, PMN= Polymorphonuclear

Table 2. Sensitivity, Specificity, Negative predictive value (NPV), and positive predictive value (PPV) of PCT in Appendicitis, Peritonitis and Surgical site infection.

	acute appendicitis	detecting peritonitis (due to appendicitis)	surgical site infection (after appendectomy)
Sensitivity of PCT	44%	100%	83%
Specificity of PCT	100%	65%	62%
NPN	10%	100%	98%
PPV	100%	100%	100%

PCT= Procalcitonin, NPV = Negative predictive value, PPV= positive predictive value

tonitis and surgical site infection. There was a significant difference in the PCT between two groups of patients with peritonitis due to perforated appendicitis and patients who had no peritonitis. (Chi-square test: $p < 0.05$). There was also a significant difference in the PCT values based on the severity of the appendix inflammation determined at the time of operation (Chi-square test: $p = 0.036$).

The PCT levels were also increased in cases with higher Alvarado score and WBC elevation. There was a significant difference in Alvarado Score data in two groups of patients based on pathological findings. (Mann Whitney U Test: $p = 0.041$)

Discussion

The lifetime rates for appendectomy were 12% for men and 25% women with 7% of all people undergoing appendectomy for acute appendicitis during their lifetime. Despite the increased use of sophisticated imaging and non-invasive diagnostic modalities such as graded compression sonography, high-resolution helical computed tomography (CT) and laparoscopy, the rate of misdiagnosis of appendicitis has remained constant (15%) and so has the rate of appendiceal rupture (1). In addition, these procedures have a number of significant limitations including cost, radiation exposure, operator dependency, availability, contrast agent allergy, false positive and false negative diagnoses, exposure to anesthetics and special considerations in children and pregnant patients.

An accurate and cost-effective diagnostic test is highly desirable to further improve the clinical assessment of patients and to be life-saving and reassuring patients and physicians respectively.

The purpose of this study was to determine whether or not the PCT levels have any diagnostic value in the serum of patients with acute appendicitis.

Procalcitonin is a calcitonin precursor which degrades to catacalcin-calcitonin and residual protein with a half-life of about 25-30 hours which allows timely repeated measurements that may reflect changes of the underlying clinical condition. It is elevated in a number of localized and systemic infections including lower respiratory tract infections (3), meningitis (4), infectious endocarditis (5), pancreatitis (6) and acute pyelonephritis (7). The PCT has also become increasingly popular as a marker of infection after surgical procedures (8). Bacterial lipopolysaccharides and the pro-inflammatory cytokines are the most potent inducers of PCT release. It has been demonstrated that the injection of bacterial endotoxin into healthy subjects causes an increase in PCT by 0.5ng/ml per hour after a latency of about 2-3 hours and reaching a plateau after 6-12 hours (9).

The available data evaluating the diagnostic value of PCT for patients with acute appendicitis are sparse and predominantly related to children. An available study that investigated adult patients is by Kisacik et al (10) who studied 34 adult patients with acute appendicitis and 28 with familial Mediterranean fever attacks. They reported PCT levels that are higher than 0.5ng/ml in 62% of their patients with acute appendicitis and in 11% of their patients with familial Mediterranean fever. The large fraction of patients with acute appendicitis who demonstrate a PCT increase in this study (62%) was contradictory to study by Sand et al (11) in which only 14.3% of patients had PCT levels > 0.5 ng/ml. The latter study

concluded that PCT elevation with a remarkably poor sensitivity of 0.14 prohibits its use as a standard laboratory test for the diagnosis of acute appendicitis.

A few other studies, mainly performed in children and adolescents, have also been unable to demonstrate a diagnostic value for PCT elevation in acute appendicitis. Kouame et al (12) found PCT level higher than 0.5ng/ml in 12% of their pediatric patients with acute appendicitis (PCT sensitivity 28%), reflecting no role for PCT as a predictive or diagnostic marker. This finding was also confirmed in other study by Blab et al (2) who examined various diagnostic parameters in 233 cases of pediatric appendicitis (mean age of 10.47 years). On the other hand a number of studies have demonstrated that PCT measurement can be used as a prognostic marker of acute appendicitis complications and a good indicator of the severity of this disease, leading to surgical exploration in patients with PCT values > 0.5ng/ml (10,11,13).

In a prospective study conducted by Chandal et al (14) in India in forty pediatric patients up to 15 years of age, the serum PCT was found to be a better indicator for diagnosing the acute appendicitis than the serum CRP and other tests. The authors concluded that the serum PCT when combined with reliable clinical signs and symptoms is an excellent diagnostic marker of the disease and should be done in pediatric appendicitis patients to prevent unnecessary appendectomies.

In a prospective study conducted by Kaya B (15) et al the diagnostic utility of D-dimer, PCT and CRP measurements in the acute appendicitis were evaluated. They concluded that due to their low sensitivity and diagnostic value, PCT and D-dimer are not better markers than CRP for the diagnosis of acute appendicitis.

Yu CW et al (16) evaluated the diagnostic value of PCT, CRP and WBC in uncomplicated or complicated appendicitis by means of a systematic review and meta-analysis. Interestingly, their conclusion is quite similar to our study: PCT has little

value in diagnosing acute appendicitis, however, it has greater diagnostic value in identifying complicated appendicitis.

The results of yet another recent study confirm our final finding. Wu JY et al (17) assessed the diagnostic value of PCT in 214 emergency department (ED) patients with suspected appendicitis. Their study did not support the hypothesis that the PCT test could be used for screening ED patients for appendicitis. However, determination of the PCT level may be useful for risk assessment of ED patients with suspected complicated appendicitis.

In our group of 94 patients with confirmed diagnosis of appendicitis, 41 had PCT levels of > 0.5ng/ml. The sensitivity of PCT for the diagnosis of appendicitis was calculated to be 0.44 which considered low and cannot be recommended as a diagnostic marker.

However, PCT measurement in our patients showed that the likelihood of observing an elevation in values increases with the severity of appendicitis and the presence of peritonitis. In all patients with gangrenous appendicitis (17 cases) and peritonitis (9 cases) PCT values was more than 0.5ng/ml. It is to be noted that in five patients with peritonitis the value was more than 10ng/ml and five out of six patients with post-operative surgical site infection showed elevated values pre-operatively.

Conclusion

The PCT measurement cannot be recommended as a diagnostic test for patients with acute appendicitis and its routine use in such patients is not conclusive. The PCT values can be used as a prognostic marker and predictor of infectious complications following surgery for acute appendicitis and it can help to carry out timely surgical intervention which highly is recommended in patients with values more than 0.5ng/ml.

References

1. Jaffe BM, Berger DH. The Appendix. In: Brunicaardi FC (ed) Schwartz's principles of surgery.

9th edn. McGrawHill, 2010; pp 1073-1089.

2. B lab E, Kohlhuber U, Tillawi S, et al. Advancements in the diagnosis of acute appendicitis in children and adolescents. *Eur J Pediatr Surg*. 2004; 14(6): 404-9.

3. Christ-Crain M, Jaccard-Stolz D, Bingisser R, et al. Effect of procalcitonin-guided treatment on antibiotic use and outcome in lower respiratory tract infections: cluster-randomised, single-blinded intervention trial. *Lancet*. 2004; 363:600-607.

4. Marc E, Ménager C, Moulin F, Stos B, Chalmers M, Guérin S, et al. Procalcitonin and viral meningitis: reduction of unnecessary antibiotics by measurement during an outbreak. *Arch Pediatr*. 2002; 9:358-364.

5. Mueller C, Huber P, Laifer G, Mueller B, Peruchoud AP, et al. Procalcitonin and the early diagnosis of infective endocarditis. *Circulation*. 2004; 109:1707-1710.

6. Oláh A, Belágyi T, Issekutz A, Makay R, Zaborczyk A. Value of procalcitonin quick test in the differentiation between sterile and infected forms of acute pancreatitis. *Hepatogastroenterology*. 2005; 52(61): 243-245.

7. Pecile P, Miorin E, Romanello C, Falletti E, Valent F, Giacomuzzi F. Procalcitonin: a marker of severity of acute pyelonephritis among children. *Pediatrics*. 2004; 114(2):249-254

8. Carboni GL, Fahrner R, Gazdhar A, Printzen G, Schmid RA, Hokschi B. Comparison of procalcitonin and CRP in the postoperative course after lung decortications. *EJCTS* 2008; 33:777-780.

9. Brunkhorst FM, Heinz U, Forycki ZF. Kinetics of procalcitonin in iatrogenic sepsis. *Intensive Care Med*. 1998; 24:888-892.

10. Kısacık B, Kalyoncu U, Erol MF, Karadağ O, Yıldız M, Akdoğan A, et al. Accurate diagnosis of acute abdomen in FMF and acute appendicitis patients: how can we use procalcitonin? *Clin Rheumatol*. 2007; 6(26): 2059-2062.

11. Sand M, Trullen XV, Bechara FG, et al. A prospective bicenter study investigating the diagnostic value of procalcitonin in patients with acute appendicitis. *Eur Surg Res*. 2009; 43(3): 291-297.

12. Kouame D.B, Garrigue MA, Lardy H, et al. Is procalcitonin able to help in pediatric appendicitis diagnosis? *Ann Chir*. 2005; 130(3):169-74.

13. Kafetzis DA, Velissariou IM, Nikolaidis P, et al. Procalcitonin as a predictor of severe appendicitis in children. *Eur J Clin Microbiol Infect Dis*. 2007; 24(7):484-7.

14. Chandal V, Batt SH, Bhat MY, et al. Procalcitonin as the biomarker of inflammation in diagnosis of appendicitis in pediatric patients and prevention of unnecessary appendectomies. *Indian J Surg* 2011;73(2):136-141

15. Kaya B, Sana B, Eris C, Karabulut K, Bat O, Kutanis R. The diagnostic value of D-dimer, procalcitonin and CRP in acute appendicitis. *Int J Med Sci*. 2012; 9(10):909-15.

16. Yu CW, Juan LI, Wu MH, Shen CJ, Wu JY, Lee CC. Systematic review and meta-analysis of the diagnostic accuracy of procalcitonin, C-reactive protein and white blood cell count for suspected acute appendicitis. *Br J Surg*. 2013 Feb; 100(3):322-9.

17. Wu JY, Chen HC, Lee SH, Chan RC, Lee CC, Chang SS. Diagnostic role of procalcitonin in patients with suspected appendicitis. *World J Surg*. 2012? Aug; 36(8):1744-9.