

Akut Apendisitli Hastalarda Kalsiyum ve Serum Fosfat Düzeyinin Klinik Önemi

The Clinical Significance of Calcium and Serum Phosphate in Patients with Acute Appendicitis

Hakan Buluş¹, Ömer Akyürek², Erdem Akbal³, Mustafa Doğan¹, Ahmet Koyuncu¹

¹Kecioren Training and Research Hospital, Department of General Surgery, Ankara
²Mevlana (RUMI) University Faculty of Medicine, Department of Internal Medicine, Konya
³Çanakkale Onsekiz Mart University, Department of Gastroenterology, Çanakkale, Turkey

Özet

Bu çalışmanın amacı, laboratuvar test sonuçlarında öncelikli değişiklikleri değerlendirmek ve bunların akut apandisit hastalarında rüptür riskini nasıl değiştirdiğini değerlendirmektir. Buna ek olarak, olası bir erken teşhis sağlamak için, bu sürecin gelişimini analiz etmek amaçlanmıştır. Bu çalışmaya genel cerrahi kliniğinde acil apendektomi uygulanan 110 (58 bayan ve 52 erkek) hasta alınmıştır. Hastaların serum Ca, P ve CRP düzeyleri WBC ile birlikte ölçüldü. Çalışmaya alınan hastalar perfore (n=30) ve perfore olmamış (n=80) olarak iki gruba ayrıldı. Preoperatif P düzeyi perfore olmamış grupta (2.66±0.58 mg/dl) perfore gruba (2.95±0.46 mg/dl) göre daha düşük saptandı ve istatistiksel olarak her iki grup arasında fark vardı (p=0.024). Ameliyat öncesi ve sonrası dönemlerde perfore olmayan gruptaki lökosit sayımı ve CRP düzeylerinde anlamlı düşüşler vardı. Ayrıca, operasyon öncesi ve sonrası dönemlerde perfore grubunda lökosit sayımı ile birlikte P ve CRP düzeylerinde istatistiksel olarak anlamlı değişiklikler vardı. Operasyon öncesi ve sonrası dönemlerde oluşan P düzey değişikliği perfore gruba istatistiksel olarak daha belirgin olarak saptandı (p=0.045). P seviyelerindeki artış tek başına akut apandisit tanısı koymak için yeterli değildir. Ancak, serum P düzeyleri perfore apandisit için erken tanısı için öngörü sağlar.

Anahtar kelimeler: Akut apandisit, kalsiyum, fosfat, tanı

Abstract

The aim of this study was to evaluate the primary changes in laboratory test results and assess how this alters the risk of rupture for patients with acute appendicitis. In addition, we sought to analyze the evolution of this process in order to provide a possible early diagnosis. This study was comprised of 110 patients (58 females and 52 males) who underwent emergency appendectomies at the general surgery clinic. Serum calcium (Ca), phosphate (P) and C-reactive protein (CRP) levels of the patients were measured along with the white blood cell (WBC) count. The prospective study participants were placed into the perforated (n=30) or non-perforated (n=80) group. The preoperative P value in the non-perforated group was lower (2.66 ± 0.58 mg/dl) than the perforated group (2.95 ± 0.46 mg/dl), and this was statistically significant (p=0.024). While there were no significant changes in the Ca and P levels in the non-perforated group in the pre- and postoperative periods, there were significant decreases in the WBC count and CRP levels. Furthermore, there were statistically significant changes in the P and CRP levels along with the WBC count in the perforated group, but the changes in the Ca levels did not reach significant levels in either the pre- or postoperative periods. With regard to the changes in laboratory values versus those during surgery, the P levels in the perforated group were significantly higher (p=0.045). An increase in P levels alone is not sufficient to make the diagnosis of acute appendicitis. Nevertheless, serum P levels are valuable for the early diagnosis of perforated appendicitis.

Key words: Acute appendicitis, calcium, phosphate, diagnosis

INTRODUCTION

Acute appendicitis is one of the most common causes of acute abdomen. Clinical examinations are still of primary importance in order to obtain an accurate diagnosis, and surgery remains the treatment of choice. The decision to operate on patients suspected of having acute appendicitis is based mainly on the patient's medical history and the physical examination findings, even though there seldom is a typical clinical presentation of this disease. Therefore, diagnostic errors are commonplace. In addition, one of the risk factors for a ruptured appendix is the prolonged period of time between symptom onset and treatment, but there is not much definitive knowledge regarding this subject (1). In

cases with an uncertain diagnosis, delaying the surgery and performing repeated assessments are commonly practiced to achieve a more precise diagnosis. In reality, all of these factors may contribute to the diagnostic or therapeutic delays in the management of acute appendicitis. In fact, a delay in treatment is regarded as the main cause of perforation and other complications, but there is controversy regarding whether pre- or post-admission delays are more responsible. Fortunately, death due to acute appendicitis is now rare, with the mortality rate ranging from 0-2.4% (2). Nevertheless, the failure to diagnose this condition in the early stages is still a leading cause of increased perforation and associated complications (complication rate 3.4-33%) (3). When

preoperative diagnostic difficulties occur, the percentage of incorrect diagnoses can reach 20% in the general population (4). In laboratory investigations involving the white blood cell (WBC) count, differential counts (the percentage of neutrophil granulocytes and band neutrophil granulocytes), and C-reactive protein (CRP) levels, It is believed that the accuracy of the clinical diagnosis of acute appendicitis between 76 and 92% (5). However, this computed tomography (CT) and ultrasound scans, negative appendectomy rate has declined, but remained higher perforation rate (22-62%) (6). Thus far, many inflammatory markers have been used in the diagnosis of acute surgical conditions, including acute appendicitis, but the most frequently performed laboratory tests involve the leukocytes and CRP (7). However, the effects that pre- and postoperative changes have on serum calcium (Ca) and phosphorus (P) levels are not known.

The primary objective of this study was to evaluate the primary changes in laboratory test results and assess how this alters the risk of rupture for patients with acute appendicitis. In addition, we sought to analyze the evolution of this process in order to provide a possible early diagnosis.

MATERIAL and METHODS

The prospective study was approved by the ethics and research committee of the hospital, and the patients' written consent was obtained. This study was made up of 110 patients (58 females and 52 males) between the ages of 16 and 65 who underwent emergency appendectomies at the general surgery clinic. The patients were divided into either a perforated group (n:30) or a non-perforated group (n:80). During this period of time, 137 patients had emergency appendectomies, but 27 did not meet our inclusion criteria because they had either undergone an interval appendectomy, were under the age of 16 or over the age of 65, had diabetes or a malignant disease, or had a suppressed immune system and antibiotic usage. The patients were first evaluated by an emergency resident. In cases in which appendicitis was suspected, they were then evaluated by a general surgeon in the emergency ward. The patients' clinical data and physical examination results along with their laboratory and imaging findings were the mainstays of the evaluation process. The patients who were diagnosed with acute appendicitis and those who underwent clinical observation were included in this study, and their symptoms at onset and their CRP, Ca, and P levels along with their WBC counts were recorded as well as the beginning and end times of the operation. In addition, all of the diagnosis and perforations were histopathologically compared blood samples that had been taken for diagnostic purposes during routine tests upon admission. Thus, no further blood samples were needed.

Statistical Analysis

The collected data was evaluated using the SPSS version 15 for Windows software program (SPSS Inc, Chicago, IL, USA). Continuous data was shown as mean \pm SD, and categorical data was shown as

a percentage. Furthermore, the Kolmogorov-Smirnov test was used to determine normal distribution, and the results were compared using Student's t-test. The Mann-Whitney U test was used to compare data which was not normally distributed, and Fisher's exact test and a chi square test were used to compare the differences between the rates. In addition, the degree of association between the continuous variables was calculated utilizing Pearson's correlation coefficient, and one-way analysis of variance (ANOVA) was used for group comparisons. A p value of <0.05 was considered to be statistically significant.

RESULTS

The number and average age of the patients in perforated and non-perforated group groups were 30 patients and 32.76 ± 12.50 years, and 80 cases and 29.36 ± 9.26 years, respectively. When we compared the two groups with regard to age ($p= 0.123$), height ($p= 0.556$), weight ($p= 0.865$), and BMI ($p= 0.652$), we found no statistically significant differences. In addition, when we compared the pre- and postoperative Ca and CRP levels and WBC counts in the laboratory findings, we also did not identify any statistically significant differences. However, the preoperative P values in the non-perforated group (2.66 ± 0.58 mg/dl) were lower than those in the perforated group (2.95 ± 0.46 mg/dl), and this difference was statistically significant ($p=0.024$) (Table 1). Moreover, while the pre- and postoperative differences in the Ca and P levels were not statistically significant in the non-perforated group, there was a noticeable decrease in the CRP levels and WBC count (Table 2). Statistically significant decreases were seen in the P and CRP levels as well as the WBC count in the perforated group (Table 3). ($p=0.001$, $p<0.001$, and $p<0.001$, respectively). Finally, when we compared the laboratory values with the operational values in both groups, the changes in the P values in the perforated group were statistically higher ($p=0.045$) (Table 4).

DISCUSSION

Acute appendicitis is the most common cause of community-acquired intra-abdominal infection and emergency surgery (8), which are slightly more common in men than women (1.4:1.0)(9). Our study had a higher ratio of males to females (1.24:1.0). Diagnosing acute appendicitis in a reliable manner is difficult; hence, various predictive indicators have been researched to try and make this process easier. Information is now gathered via clinical examinations, laboratory studies, radiological imaging, and sometimes even exploratory surgery. In the laboratory studies, the classic parameters that are most often used are the WBC count and CRP levels (10). A study, Asfar et al. show that the sensitivity and specificity of CRP was 86.6% and 93.6%, respectively, and they concluded that a normal CRP value probably indicates a normal, non-inflamed appendix (11). In a retrospective study, Wu et al. (12) determined that the WBC and neutrophil counts in conjunction with CRP monitoring increased the positive predictive value.

Table 1. Pre- and postoperative laboratory findings

	Non-perforated	Perforated	p value
Preop Ca	8.94 \pm 0.70	9.07 \pm 0.57	0.125
Preop P	2.66 \pm 0.58	2.95 \pm 0.46	0.024
Postop Ca	8.64 \pm 0.67	8.85 \pm 0.53	0.123
Postop P	2.55 \pm 0.81	2.46 \pm 0.76	0.592
Preop WBC	14.44 \pm 3.80	13.92 \pm 3.04	0.497
Postop WBC	10.23 \pm 1.43	10.10 \pm 1.58	0.686
Preop CRP	23.01 \pm 9.84	20.63 \pm 9.49	0.257
Postop CRP	15.55 \pm 6.89	13.93 \pm 6.18	0.263

Table 2. Pre- and postoperative Ca, P, and CRP levels along with the WBC count for the non-perforated group

	Preoperative	Postoperative	p value
Ca	8.94 \pm 0.70	8.64 \pm 0.67	0.348
P	2.66 \pm 0.58	2.55 \pm 0.81	0.178
WBC	14.44 \pm 3.80	10.23 \pm 1.43	<0.001
CRP	23.01 \pm 9.84	15.55 \pm 6.89	<0.001

Table 3. Pre- and postoperative Ca, P, and CRP levels along with the WBC count for the perforated group

	Preoperative	Postoperative	p value
Ca	9.07 ± 0.57	8.85 ± 0.53	0.121
P	2.95 ± 0.46	2.46 ± 0.76	0.001
WBC	13.92 ± 3.04	10.10 ± 1.58	<0.001
CRP	20.63 ± 9.49	13.93 ± 6.18	<0.001

Furthermore, Gronroos et al. (13) found that when both the WBC count and CRP levels were normal, acute appendicitis was highly unlikely (13). In our study involving perforated and non-perforated groups, the WBC count (non-perforated group 14.44±3.80; perforated group 13.92±3.04) and CRP (non-perforated group 23.01±9.84; perforated group 20.63±9.49) levels were higher preoperatively, but there was no statistically significant difference between the two groups. In addition, they decreased postoperatively but not a significant level (p=0.263).

Whenever a tissue is subjected to ischemia, a chain reaction begins that can eventually lead to cellular dysfunction and necrosis. Although no particular process has been identified that has a relationship to the ischemia-induced damage of the tissue, most studies have shown that the consumption of energy reserves and the accumulation of toxic metabolites contribute to cell death (14). Ischemia is defined as a significant reduction in blood flow that leads to an insufficient amount of oxygen and lack of nutrients in various tissues and organs. Differential diagnosis is very difficult, but early diagnosis and appropriate surgical intervention can serve to reduce the high morbidity and mortality rates associated with this condition (15). Serum phosphate levels are believed to be an early mediator of acute ischemia. In damaged tissue, these levels increase due to the reduction of P excretion in the kidneys, impaired clearance of P in the liver, and release of intracellular P into the circulation (16, 17). The ensuing hyperphosphatemia can then induce potentially symptomatic hypocalcemia due to Ca-P precipitation in the tissues (18). In previous studies, bowel necrosis, metabolic acidosis, and leukocytosis occurred, and the P and leukocyte levels increased but not at specific rates (19-24). Sawyer et al. (23) reported that elevated serum phosphate levels may be useful in the early diagnosis of bowel necrosis. In addition, elevated serum P levels have been found to be a poor prognostic indicator for ischemic bowel disease (24). Furthermore, Lores et al. (16) reported that they might be an early marker for necrosis rather than ischemia. In our study, the preoperative serum P levels were significantly higher in the perforated group, whereas in the non-perforated group there were no significant changes in the serum Ca and P levels in the non-perforated group.

An increase in P levels alone is not sufficient to make the diagnosis of acute appendicitis. Nevertheless, serum P levels are valuable for the early diagnosis of perforated appendicitis. To our knowledge, this is the first time that serum phosphate levels have been evaluated in patients with perforated and non-perforated appendicitis, and our data suggests that they might be useful in the early diagnosis of this emergency condition.

REFERENCES

1. Tzanakis NE, Efsthathiou SP, Danulidis K, et al. A new approach to accurate diagnosis of acute appendicitis. *World J Surg* 2005; 29(9):1151-56.
2. Gürleyik G, Gürleyik E. Age-related clinical features in older patients with acute appendicitis. *Eur J Emerg Med* 2003;10(3):200-3.
3. Aggenbach L, Zeeman GG, Cantineau AE, Gordijn SJ, Hofker HS. Impact of appendicitis during pregnancy: No delay in accurate diagnosis and

Table 4. Comparison of changes in laboratory values

	Non-perforated	Perforated	p value
Ca	0.30 ± 0.63	0.22 ± 0.75	0.619
P	0.11 ± 0.72	0.49 ± 0.59	0.045
WBC	4.21 ± 4.06	3.31 ± 3.54	0.656
CRP	7.46 ± 3.29	6.70 ± 3.57	0.294

4. Weyant MJ, Eachempati SR, Maluccio MA, et al. Interpretation of computed tomography does not correlate with laboratory or pathologic findings in surgically confirmed acute appendicitis. *Surgery* 2000;128(2):145-52.
5. Gurleyik E, Gurleyik G, Unalmiser S. Accuracy of serum C-reactive protein measurements in diagnosis of acute appendicitis compared with surgeon's clinical impression. *Dis Colon Rectum* 1995;38(12):1270-74.
6. Khan MN, Davie E, Irshad K. The role of white cell count and C-reactive protein in the diagnosis of acute appendicitis. *J Ayub Med Coll Abbottabad* 2004;16(3):17-19.
7. Ivancević N, Radenković D, Bumbasirević V, et al. Procalcitonin in preoperative diagnosis of abdominal sepsis. *Langenbecks Arch Surg* 2008;393:397-403.
8. Kozar RA, Roslyn JJ. The Appendix. In: Schwartz SI, Shires GT, Spencer FC, eds. *Principles of Surgery*. 7th ed. New York-London: The McGraw-Hill Companies Inc; 1999:1383-93.
9. Humes DJ, Simpson J. Acute appendicitis—clinical Review. *BMJ* 2006;333:530-4.
10. Eriksson S, Josephson T, Styru J. A high degree of accuracy is feasible in appendicitis diagnosis; laboratory testing, ultrasonography and computerized tomography of great value. *Lakartidningen* 1999;96(25):3058-61.
11. Asfar S, Safar H, Khourshed M, Dashti H, al-Bader A. Would measurement of C-reactive protein reduce the rate of negative exploration for acute appendicitis? *J R Coll Surg Edinb* 2000; 45:21-24.
12. Wu HP, Lin CY, Chang CF, Chang YJ, Huang CY. Predictive value of C reactive protein at different cutoff levels in acute appendicitis. *Am J Emerg Med* 2005;23(4):449-53.
13. Gronroos JM, Gronroos P. Leukocyte count and C reactive protein in the diagnosis of acute appendicitis. *Br J Surg* 1999;86(4):501-4.
14. Abraham SC, Taggart MW, Loftus EV Jr, Wu TT. Dysplasia-like epithelial atypia in ischemic bowel disease. *Hum Pathol* 2014;45(7):1348-57.
15. Ocak T, Duran A, Özyalvaçlı G, et al. Protective effects of montelukast and Hypericum perforatum against intestinal ischemia-reperfusion injury in hamsters. *Turk J Med Sci* 2014;44(3):381-6.
16. Kintu-Luwaga R, Galukande M, Owori FN. Serum lactate and phosphate as biomarkers of intestinal ischemia in a Ugandan tertiary hospital: a cross-sectional study. *Int J Emerg Med* 2013;6(1):44.
17. May LD, Berenson MM. Value of serum inorganic phosphate in the diagnosis of ischemic bowel disease. *Am J Surg* 1983;146:266-8.
18. Abbasian N, Burton JO, Herbert KE, et al. Hyperphosphatemia, Phosphoprotein Phosphatases, and Microparticle Release in Vascular Endothelial Cells. *J Am Soc Nephrol* 2015;5. pii: ASN.2014070642.
19. Deitch, EA, Berg R. Bacterial translocation from the gut: A mechanism of infection. *J Burn Care Rehab* 1987;8:475-2.
20. Akaydin M, Ipek T. Superior mezenenterik arter ligasyonuna bağlı mezenter iskemisinin biyokimyasal tanısı. *Klinik Deneyel Cerr Derg* 1994;2:195-209.
21. May MD. Value of serum inorganic phosphate in the diagnosis of ischemic bowel disease. *Am Jour Surg* 1983;146:266-8.
22. Berg RD, Garlington AW. Translocation of certain indigenous bacteria from the gastrointestinal tract to the mesenteric lymph nodes and other organs in a gnotobiotic mouse model. *Infect Immun* 1979;23(2):403-11.
23. Sawyer BA, Jamieson WG, Durand D. The significance of elevated peritoneal fluid phosphate level in intestinal infarction. *Surg Gynecol Obstet* 1978;146(1):43-5.
24. Guzman-Stein G. Intestinal handling facilitates enteric bacterial translocation. *Surg Forum* 1987;38:75-6.