Postoperative hyperlipasemia in perforated appendicitis in children

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ABSTRACT

Objective. The objective of this study was to assess the hyperlipasemia cases detected in the postoperative period of perforated appendicitis.

Materials and methods. A retrospective analysis of the perforated appendicitis cases occurred in our institution over a 7-year period (2013-2019) was carried out. Only cases where preoperative and postoperative serum lipase levels were available were included. The variables collected were statistically assessed by means of a descriptive, univariate analysis.

Results. A total of 88 patients were studied. They were divided into 3 groups according to postoperative lipase levels – 57 were allocated to Group 1 (lipase: 70-194.0 U/L, normal range), 20 were allocated to Group 2 (lipase: 195-582 U/L), and 11 were allocated to Group 3 (lipase: > 582 U/L, which triples normal levels). Statistically significant differences were found in the following variables: sex, postoperative abscess, postoperative subocclusion/intestinal occlusion, preoperative lipase levels, days of parenteral nutrition, days of ICU stay, and days of hospital stay. Postoperative lipase had a moderate correlation with preoperative lipase, and none of the cases met acute pancreatitis diagnostic criteria.

Conclusions. Hyperlipasemia in the postoperative period of perforated appendicitis is not associated with developing clinical pancreatitis, but it is associated with worse progression in terms of increased complications, such as subocclusion/intestinal occlusion and intra-abdominal abscess, and longer ICU stay, hospital stay, and parenteral nutrition. There is a moderate correlation between preoperative and postoperative lipase, which means they could both prove useful as prognostic markers.

KEY WORDS: Perforated appendicitis; Serum lipase; Hyperlipasemia.

HIPERLIPASEMIA POSOPERATORIA EN APENDICITIS PERFORADA EN NIÑOS

RESUMEN

Objetivo. El objetivo del estudio es evaluar los casos de hiperlipasemia detectados en el posoperatorio de la apendicitis perforada.

Material y método. Se evaluaron retrospectivamente los casos de apendicitis perforada en nuestro centro durante 7 años (2013-2019), seleccionando aquellos con mediciones preoperatorias y posoperatorias de lipasa sérica. Las diferentes variables recogidas se analizaron estadísticamente de manera descriptiva y univariante.

Resultados. Se estudiaron un total de 88 pacientes que se dividieron en tres grupos según el valor de la lipasa posoperatoria: 57 corresponden al grupo 1 (lipasa 70-194 U/L, rango normal), 20 al grupo 2 (lipasa 195-582 U/L) y 11 al grupo 3 (lipasa > 582 U/L, valor tres veces por encima del normal). Las variables que mostraron diferencias estadísticamente significativas fueron el sexo, el absceso posoperatorio, la suboclusión/oclusión intestinal posoperatoria, la lipasa preoperatoria, los días de nutrición parenteral, los días de ingreso en UCI y los días de estancia hospitalaria. La lipasa posoperatoria mostró una correlación moderada con la lipasa preoperatoria y ningún caso cumplió criterios diagnósticos de pancreatitis aguda.

Conclusiones. La hiperlipasemia en el posoperatorio de la apendicitis perforada no se asocia al desarrollo de pancreatitis clínica, pero sí se asocia a una peor evolución en relación con un aumento de complicaciones, como la suboclusión/oclusión intestinal y el absceso intraabdominal, y un mayor número de días de ingreso en UCI, de días de nutrición parenteral y de estancia hospitalaria. Existe una moderada correlación entre la lipasa preoperatoria y posoperatoria, de modo que ambas podrían ser útiles como marcadores pronósticos.

PALABRAS CLAVE: Apendicitis perforada; Lipasa sérica; Hiperlipasemia.

INTRODUCTION

Perforated appendicitis, which represents 12-38% of all pediatric appendicitis cases[1,2], is more frequently associated with postoperative complications, such as surgical wound infection (2-9%), intra-abdominal abscess (4-20%)[3], and subocclusion/intestinal occlusion (0.5-3%)[4]. Another poten-

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tial complication is acute pancreatitis, which is associated with increased serum lipase levels exceeding more than 3 times the normal levels. This is occasionally detected in the postoperative period of perforated appendicitis[5].

No studies analyzing the increase in serum lipase levels associated with pediatric appendicitis were found in the literature. Therefore, the objective of this study was to assess the hyperlipasemia cases detected in the postoperative period of perforated appendicitis in children.

MATERIALS AND METHODS

A retrospective analysis of all patients under 15 years of age diagnosed with perforated appendicitis in our Pediatric Surgery Department from 2013 to 2019 was carried out. Only cases where preoperative and postoperative serum lipase levels were available were included. Inclusion criteria were: diagnosis of perforated acute appendicitis, preoperative and postoperative serum lipase levels available, and parent or guardian consent to access patient data with research purposes. Exclusion criteria were: cases of phlegmonous and gangrenous appendicitis – postoperative analytical controls are rarely conducted, and when they are, significantly increased serum lipase levels are infrequent –, cases of non-surgically managed appendicitis, and lack of preoperative or postoperative serum lipase levels.

Variables collected included age, sex, progression from abdominal pain onset to hospital care, preoperative absolute leukocyte and neutrophil count, preoperative serum C-reactive protein levels, preoperative and postoperative serum lipase levels – in cases where various levels were available, the highest one was recorded –, type of surgery – laparotomy or laparoscopy –, postoperative imaging test, postoperative complications – wound infection, intra-abdominal abscess, subocclusion/intestinal occlusion –, days of Intensive Care Unit (ICU) stay, days of hospital stay, days of parenteral nutrition (PN), and need for hospital re-admission. Perforated appendicitis was diagnosed as a result of the presence of an orifice in the appendicular wall, or the presence of a free appendicolith within the peritoneal cavity[6]. Preoperative lipase levels were requested at the discretion of the physician assessing the patient with abdominal pain at the Emergency Department. Postoperative lipase levels were measured at the regular analytical controls (every 24-72 hours) requested by the pediatrician or the pediatric surgeon during hospital stay. Serum lipase levels were all measured in the clinical analysis laboratory of our hospital using the same technique, with normal levels ranging from 70 to 194 U/L.

Statistical analysis was carried out using the SPSS 19.0 (SPSS Inc., Chicago, IL, USA, 2010) software for Windows. A descriptive, univariate analysis of the variables was carried out, with postoperative lipase levels being allocated to three different groups: Group 1 for normal lipase levels (70-194 U/L), Group 2 for increased lipase levels under 3 times the normal levels (195-582 U/L), and Group 3 for increased lipase levels ≥3 times the normal levels (>582 U/L). In the univariate analysis of qualitative variables, the Chi-squared test was used. For quantitative variables, bivariate correlation analysis was employed – either using Spearman's correlation coefficient when analyzing postoperative lipase levels as a numerical variable, or Kruskal-Wallis non-parametric test when analyzing postoperative lipase levels recoded in various categories. Statistical signification was established at $p < 0.05$ in all analyses. The study was approved by the Galician Clinical Research Ethics Committee.

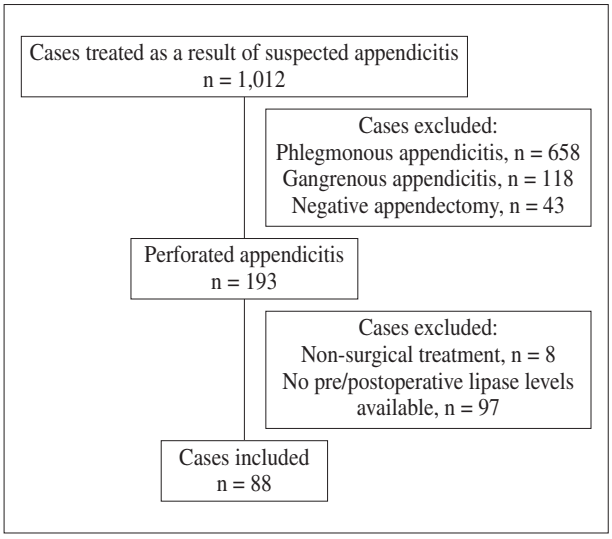

Figure 1. Patient selection flow diagram.

RESULTS

During the study period, 1,012 patients with suspected acute appendicitis were assessed (Fig. 1). Of the 193 perforated appendicitis cases, 88 patients met inclusion and exclusion criteria. Most patients excluded could not be part of the study as preoperative lipase levels were not available.

The descriptive analysis of the variables studied is featured in tables I and II. Only in 1 case, preoperative lipase levels exceeded 194 U/L (preoperative lipase – mean: 67.82 U/L; SD: 32.35; range: 13-267). The highest postoperative lipase level detected was 1,338 U/L (postoperative lipase – mean: 247.94 U/L; SD: 280.50; range: 13-1,338).

The univariate analysis found that the variables showing statistically significant differences among groups 1, 2, and 3 were sex ($p = 0.03$), postoperative abscess ($p = 0.02$), postoperative subocclusion/intestinal occlusion ($p < 0.01$), preoperative serum lipase levels ($p < 0.01$), days of PN

Table I. Descriptive, univariate analysis of non-parametric variables in the postoperative serum lipase groups.

	Postoperative serum lipase levels			
Variable	*70-194 U/L (n = 57)*	*195-582 U/L (n = 20)*	*≥583 U/L (n = 11)*	*p**
Sex, male/female (ratio)	41/16 (2.6:1)	8/12 (1:1.5)	8/3 (2.7:1)	0.03
Laparoscopy	12 (21.0%)	4 (20.0%)	3 (27.3%)	0.88
Wound infection	3 (5.3%)	2 (10.0%)	0 (0.0%)	0.50
Intra-abdominal abscess	5 (8.8%)	6 (30.0%)	4 (36.4%)	0.02
Subocclusion/intestinal occlusion	2 (3.5%)	4 (20.0%)	4 (36.4%)	<0.01
Re-admission	4 (7.0%)	2 (10.0%)	2 (18.9%)	0.49

**χ^2 test.*

Table II. Descriptive, univariate analysis of parametric variables in the postoperative serum lipase groups.

	Postoperative serum lipase levels					
Variable	*70-194 U/L (n = 57)*	*195-582 U/L (n = 20)*	*≥583 U/L (n = 11)*	*p**	*p***	*r_s****
Age (years), mean ± SD	8.4 ± 3.9	6.8 ± 4.1	7.1 ± 4.5	0.24	0.73	–
Progression time (hours), mean ± SD	45.2 ± 27.5	52.2 ± 28.1	55.6 ± 33.3	0.40	0.18	–
Preoperative lipase (U/L), mean ± SD	60.79 ± 25.53	73.70 ± 20.08	93.55 ± 60.07	0.02	<0.01	0.57
Leukocytes (× 10^9/L), mean ± SD	17.94 ± 6.07	17.25 ± 7.59	16.25 ± 6.79	0.63	0.93	–
Neutrophils (× 10^9/L), mean ± SD	15.18 ± 5.77	14.60 ± 7.14	13.84 ± 5.51	0.63	0.96	–
CRP (mg/l), mean ± SD	115.3 ± 78.1	161.1 ± 99.3	187.4 ± 152.5	0.10	0.14	–
PN days, mean ± SD	1.1 ± 2.5	2.3 ± 4.7	4.5 ± 4.0	<0.01	<0.01	0.33
ICU stay (days), mean ± SD	1.7 ± 2.6	3.8 ± 4.4	4.5 ± 2.7	<0.01	<0.01	0.45
Hospital stay (days), mean ± SD	8.1 ± 5.0	10.4 ± 5.6	10.6 ± 4.2	<0.01	<0.01	0.40

p: Kruskal-Wallis; p**: Spearman's correlation; r_s***: Spearman's correlation coefficient. SD: standard deviation; PN: parenteral nutrition; CRP: C-reactive protein; ICU: Intensive Care Unit.*

($p < 0.01$), days of ICU stay ($p < 0.01$), and days of hospital stay ($p < 0.01$) (Tables I and II). In the correlation analysis of postoperative lipase levels with the other quantitative variables, a moderate correlation with preoperative lipase levels (rs: 0.57) was found, and a weak correlation with days of PN (rs: 0.33), days of ICU stay (rs: 0.45), and days of hospital stay (rs: 0.40) was noted.

Abdominal pain compatible with acute pancreatitis was not present in any case, and in the postoperative imaging tests (ultrasonography and/or abdominal CT-scan; 8 cases in Group 3 and 11 cases in Group 2), no pancreatic involvement suggestive of pancreatitis was detected.

Of the 15 cases of intra-abdominal abscess, most of them (12 cases) required antibiotic treatment only; 2 cases (from Groups 1 and 2) required surgery; and 1 case (from Group 3) required interventional radiology and percutaneous drainage.

Of the 10 subocclusion/intestinal occlusion cases, 8 cases responded to conservative management, and 2 cases (from Groups 2 and 3) required surgery.

The increase in lipase levels always occurred in the first 48 hours following surgery, and they reached the highest point in the first week of admission, generally coinciding with the occurrence of complications. In all cases, lipase levels were back to normal in the second/third weeks of the postoperative period.

DISCUSSION

Acute pancreatitis in children has increased in recent decades, with an annual incidence of 1 in 10,000 children. The main etiologies include biliary obstruction, trauma, infections, toxins, systemic conditions, inherent metabolic error, and genetic predisposition[7]. Today, there are no evidence-based diagnostic guidelines available for the diagnosis of pancreatitis in children. According to the International Study Group of Pediatric Pancreatitis' criteria, which are based on adult ones, diagnosis requires at least two of the following criteria are met: a) abdominal

pain compatible with pancreatitis; b) serum amylase or lipase levels exceeding ≥3 times the normal higher limit; and c) imaging test findings compatible with pancreatitis[8]. To assess serum lipase levels, it is crucial to know the reference levels of each lab, which will help determine the diagnostic threshold. The sensitivity and the specificity of serum lipase to diagnose pancreatitis range from 87% to 100% and from 95% to 100%, respectively. Serum lipase levels start to increase in the first 6 hours following symptom onset, they reach their peak at 24-30 hours, and they remain high for more than 7 days[8,9]. Abdominal pain and/or irritability are the most common findings of pancreatitis, followed by pain at epigastric palpation, nausea, and vomit[8,10]. CT-scan is the best diagnostic imaging test, but it is not required for diagnosis and management purposes if clinical signs and serum markers are present. Ultrasonography, which is mainly used when biliary pancreatitis is suspected, has lower sensitivity when it comes to visualizing the pancreas. However, since it is a non-invasive, radiation-free test, it is recommended as a baseline test in children[8]. In our patients, no cases of abdominal pain compatible with pancreatitis or imaging test results suggestive of pancreatic involvement were observed. Therefore, diagnosis of pancreatitis was not established in any case.

Significant increases in serum lipase levels, which can exceed 3 times their normal level, are observed in pancreatitis cases and in other conditions that can be divided into four groups: a) Situations of impaired elimination or physiological condition (acute or chronic renal insufficiency, macrolipasemia potentially associated with celiac disease, Crohn's disease, hypergammaglobulinemia, liver cirrhosis, multiple myeloma, and systemic lupus erythematosus); b) Intra-abdominal processes including pancreatic causes without pancreatitis (hepatobiliary disorders such as biliary atresia, cholecystitis, cholangitis, post-endoscopic retrograde cholangiopancreatography, neoplasias such as hepatic metastasis of intestinal tumors and pancreatic or hepatocellular carcinoma, non-pathological pancreatic hyperenzymemia, and other conditions such as gastric ulcer, intestinal necrosis, intestinal perforation, intestinal obstruction, peritonitis, and intra-abdominal bleeding); c) Critically ill patients (head trauma, intracranial bleeding, multiorgan failure); and d) Other causes (diabetes, alcohol, medicines, and HCV/HIV infections)[5,9].

Apart from the pancreas, the lipase is found in the gastrointestinal tract (tongue, esophagus, stomach, duodenum, and colon) and in the liver. Although lipase content in these tissues is much lower than in the pancreas, it could explain hyperlipasemia in those conditions where the pancreas is not involved[5,11]. In our study, the increase in serum lipase levels above the normal range occurred following surgery and after a 12-hour minimum period of disease progression. Increased preoperative lipase levels were found in 1 case only. Therefore, inflammation, necrosis, or intestinal perforation do not seem to be directly accountable for this. Hyperlipasemia exceeding more than 3 times normal serum lipase levels is extremely rare in appendicitis cases before surgery, with only 1 case reported in the literature – subhepatic appendicitis probably with pancreatic involvement due to contiguity[12].

A potential explanation for hyperlipasemia associated with perforated appendicitis could be moderate pancreatic damage caused by low splanchnic perfusion as a result of reduced intravascular volume or reperfusion of previously ischemic tissues following surgery. This is similar to what occurs in children with diabetic ketoacidosis, where transient hyperlipasemia is often detected in the first 12-24 hours following treatment initiation, which is correlated with the degree of dehydration[13].

In this study carried out in children, increased postoperative lipase levels were associated with worse progression in terms of increased complications, such as subocclusion/intestinal occlusion and intra-abdominal abscess, and longer ICU stay, hospital stay, and parenteral nutrition.

According to the literature review carried out, this is the first study specifically assessing the increase in serum lipase levels in cases of perforated appendicitis in children. Nevertheless, the study has certain limitations – it is a retrospective one, and Groups 2 and 3 were quite small in size. This is due to the fact cases of increased postoperative lipase levels are rare, and many patients were excluded since preoperative lipase levels were not available.

CONCLUSION

Hyperlipasemia in the postoperative period of perforated appendicitis in children is not associated with developing clinical pancreatitis, but it is associated with worse progression in terms of increased complications, such as subocclusion/intestinal occlusion and intra-abdominal abscess, and longer ICU stay, hospital stay, and parenteral nutrition. There is a moderate correlation between preoperative and postoperative lipase levels, which means they could both prove useful as signs of poor disease progression. Prospective studies are required to confirm these findings and establish which preoperative and postoperative lipase levels are the most useful prognostic markers.

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