Procalcitonin as a marker of intra-abdominal infection

ABSTRACT

Background: Procalcitonin is a specific biomarker of infection. In recent years it has shown its superiority to others markers of inflammation such as C-reactive protein for diagnosis and monitoring of a variety of infections. We undertook this work to elucidate the potential role of procalcitonin for diagnosis and management of these infections.

Discussion: Intra-abdominal infections are a heterogeneous group of infections that sometimes pose difficult challenges to physicians. Published studies have produced mixed results, leading to controversy on the utility of this marker in intra-abdominal infections.

Conclusions: This review summarizes these data and discusses the utility of procalcitonin in several intraabdominal infections including postoperative infections.

Key words: Procalcitonin, appendicitis, pancreatitis, peritonitis, bowel ischemia, postoperative infection.
BACKGROUND

Intraabdominal infections are a group of common diseases that together cause significant morbidity and mortality. The two main factors that are determinants of the treatment success of these infections are the control of the source of the infection and the speed with which the effective empiric antibiotic is given, circumstances that decrease the risk of complications and mortality. The majority of the times the history, physical examination, basic elemental imaging and laboratory studies allow establishing a diagnosis rapidly and, therefore, early appropriate treatment can be started. However, in some cases the diagnosis is not easy, even with oral and IV computed tomography (CT) with contrast, which is the method of choice to evaluate patients with suspected intra-abdominal infection and who do not require immediate laparotomy. Postoperative intra-abdominal infections can be particularly difficult to diagnose especially during the early phases when treatment would really be more effective. For this reason an attempt has been made to find a biomarker that would facilitate a rapid and early diagnosis of the infection. Procalcitonin is one of the most explored markers up to now, especially in Europe. In the U.S. interest has been shown in recent years for this marker and, in fact, in the guidelines sponsored by the American College of Critical Care Medicine and Infectious Diseases Society of America, it is established that procalcitonin can be used as a useful tool to identify infection as a cause of fever or sepsis in critically ill patients. In this study the current evidence regarding the usefulness of procalcitonin as a marker of intra-abdominal infection is reviewed.

Physiology of Procalcitonin

Procalcitonin was discovered in 1975 by a group of Spanish researchers directed by Moya. It is a protein constituted by 116 amino acids with a molecular weight of 13 kDa and constitutes the prohormone of the calcitonin produced by the C cells of the thyroid. Almost all procalcitonin produced by these cells is converted into calcitonin by the action of determined endopeptidases. Because of this its serum concentrations are very low in healthy patients (< 0.05 ng/mL). Procalcitonin production is regulated by the CALC-1 gene located on the short arm of chromosome 11. This gene expresses a protein of 141 amino acids. Preprocalcitonin from procalcitonin is produced by the action of an endopeptidase. Assicot et al. were the first group to describe in 1993 that, in a patient with a bacterial infection, plasma concentrations of procalcitonin are elevated. The structure of procalcitonin detected in the plasma of these patients is identical to that of the C cells of the thyroid as precursors of calcitonin. However, regulation of procalcitonin production is substantially different in the C cells of the thyroid and in the inflammatory processes. C cells of the thyroid produce this prohormone in response to the elevation in Ca concentrations in the plasma and to specific hormone stimuli (glucocorticoids, glucagon, gastrin, somatostatin and others). In the inflammatory processes, procalcitonin is not produced by C cells of the thyroid, and its production does not depend on the calcium concentrations but is linked directly to the stimuli generated by microbial antigens, especially endotoxins and indirectly to specific cytokines such as IL-1, IL-6 and TNF-α. It has been seen in some studies that infections caused by gram-negative bacteria induce greater procalcitonin production than that caused by gram-positive bacteria. In the absence of infection, the extrathyroid transcription of the CALC-1 gene is suppressed. However, when there is a bacterial infection, this gene is expressed by neuroendocrine cells spread throughout the body, localized especially in the liver, bowel, lung, kidney and pancreas. Procalcitonin concentrations increase at 2 or 3 h of their induction and increase gradually until they reach a plateau at 6-12 h. If the stimulus is stopped, its concentrations progressively decrease and return to baseline concentration at 5 or 7 days. Increase in procal-
citonin concentration in these situations is not followed by a parallel increase of calcitonin. It is believed that this is due to a double mechanism. On one hand, proinflammatory cytokines and endotoxins inhibit proteolysis of the procalcitonin chain and, on the other hand, outside the C cells of the thyroid the granules and enzymes necessary for its processing do not exist. Procalcitonin has a half-life of 24-30 h and can be detected equally in serum and in plasma. In patients with severe renal insufficiency its half-life is 35-40 h. In healthy persons the serum concentrations of procalcitonin are very low, almost always < 0.05 ng/mL. It is a very stable in vitro molecule so special measures during its storage and pre-test handling are not required, making its determination easier in routine clinical practice.

**Usefulness of Procalcitonin for Diagnosis of Intra-abdominal Infection**

It has been demonstrated that serum concentrations of procalcitonin increase in bacterial infections and numerous studies have been carried out to investigate its potential role in the diagnosis and treatment of various types of systemic and local infections. There is evidence that procalcitonin is a more specific marker of infection than other markers such as C-reactive protein (CRP) and there are some clinical contexts, such as respiratory infections or patients with sepsis, where it could be really useful. Some of these studies have demonstrated that procalcitonin may be valid for the diagnosis of certain intra-abdominal infections including postoperative infections. The usefulness of this marker on more common intra-abdominal infections and with greater clinical importance is analyzed below.

**Acute Appendicitis**

Acute appendicitis is the most common surgical emergency. Its diagnosis is usually easy and costly imaging studies are unnecessary. However, there is a 10% rate of unnecessary appendectomies. Even worse is that in some patients the diagnosis could be delayed, which at times leads to systemic septic complications. For this reason, some authors have investigated the role that certain markers could have, such as CPR and procalcitonin, in these patients. In a recent meta-analysis that included 1011 patients, it was concluded that procalcitonin has little value for the diagnosis of acute appendicitis, with less diagnostic reliability than CRP and leukocyte count. In addition to low sensitivity, CRP and procalcitonin also have a low ratio of negative probabilities, so they are also not useful for excluding the diagnosis of acute appendicitis. However, procalcitonin appears more certain for the diagnosis of complicated acute appendicitis with a sensitivity of 62% and a specificity of 94%, although perhaps this does not have great clinical use. In summary, procalcitonin has no usefulness in the diagnosis of acute appendicitis.

**Biliary and Pancreatic Infections**

There is a lack of studies that analyze the value of procalcitonin in patients with acute cholecystitis and cholangitis. There are two fundamental aspects in the treatment of patients with acute pancreatitis: 1) early detection of patients with a severe form of the disease and 2) early diagnosis of necrotic infection of the pancreas, which is the main indication for surgery. Different studies have found that the determination of procalcitonin in the first 24-72 h is useful for predicting the severity of acute pancreatitis with a sensitivity of 67-94% and a specificity of 73-89%. In a multicentric study published in 2007 by Rau et al., it was reported that a procalcitonin value of $\geq 3.5$ ng/mL the third day after the beginning of symptoms identified those patients who would not survive, with a sensitivity of 100%, specificity of 82%, positive predictive value (PPV) of 32% and negative predictive value (NPV) of 100%. In 2007 a meta-analysis with 1001 patients was published and, of these, 826 were valid for ana-
lyzing the usefulness of procalcitonin to evaluate the severity of the pancreatitis and 326 were used to analyze the prediction of pancreatic necrosis infection. In that study it was concluded that the determination of procalcitonin in the first 24 h is reasonably useful for identifying patients with severe pancreatitis, with a sensitivity of 72%, specificity of 86% and odds ratio (OR) of 14.9 (95% CI: 5.6-39.8).

There was no consensus in the studies included in this meta-analysis about which is the optimal cut-off point and if it is heterogeneous; however, a sensitivity analysis suggests that a value of > 0.5 ng/mL appears to be a safe predictor of severity, without significant heterogeneity among the studies that used this cut-off point. The determination of procalcitonin concentrations also allows detection of the appearance of necrotic infection in the pancreas with similar certainty as that of fine needle aspiration, but in the initial phases of the disease when the infection is still not well established. In the previous meta-analysis it was concluded that procalcitonin is useful as a predictor of pancreatic necrosis infection with a sensitivity of 80%, specificity of 91% and OR of 28.3 (95% CI: 13.8-58.3) with less heterogeneity than for the prediction of severity. Most studies reporting on procalcitonin as a predictor of pancreatic necrosis infection take into account its higher value in the first 2 weeks of evolution of acute pancreatitis. In the studies in which procalcitonin was analyzed on a daily basis, it was observed that in patients with pancreatic necrosis infection the procalcitonin concentrations progressively increased.

**Acute Diverticulitis**

There is a lack of studies that analyze the usefulness of procalcitonin in patients with acute diverticulitis.

**Intestinal Occlusion**

Intestinal occlusion is one of the most common surgical emergencies. The majority are secondary to postoperative adhesions, abdominal wall hernias or cancer of the colon. Those due to postoperative adhesions comprise the most common group and the ones that present the most difficulties at the time of deciding whether or not surgery is necessary and when the patient should be operated. Most of the time, the clinical picture resolves itself without need for surgery, but if the wait time is prolonged the number of patients who...
need intestinal resection could increase and, with it, morbidity and mortality. There are two studies in which the role that procalcitonin could have in this group of patients is analyzed. In the first one published in 2008, it was observed that procalcitonin was significantly elevated in patients with obstructive ileus with respect to patient who had paralytic ileus, with a mean of 0.75 ng/mL ± 0.26 vs. 0.17 ± 0.07 ng/mL. It was also seen that patients with ischemia had a higher procalcitonin value, with a mean of 2.09 ± 1.15 ng/mL. In the second study published in 2011 with 242 patients with intestinal occlusion of different etiologies, it was observed that procalcitonin concentrations at the time of diagnosis were significantly higher in patients with ischemia with respect to those who did not have ischemia (9.62 vs. 0.30 ng/mL). The elevation was more significant in patients who already had intestinal necrosis (14.53 ng/mL). Procalcitonin proved to be an independent predictive factor of ischemia and necrosis. The authors concluded that for the detection of intestinal ischemia a procalcitonin value of < 0.25 ng/mL had an NPV of 83% and a value > 1 ng/mL had a PPV of 95%. This indicates that procalcitonin allows for the identification, at the beginning of the clinical picture, of patients who would perhaps progress well without need for surgery and the patients who probably already had intestinal ischemia. Further studies are needed to be able to recommend the routine use of procalcitonin in this clinical context.

**Secondary Peritonitis**

In 2000, Reith et al., published a study that included 246 patients with peritonitis secondary to different etiologies in which it was observed that procalcitonin was a sensitive marker for the prediction of severe septic complications and that it had good prognostic value because it discriminated survivors from nonsurvivors with a sensitivity of 84% and a specificity of 91%. Nonsurvivors had a mean initial procalcitonin value of 4.2 ng/mL, with increase to a mean value of 13 ng/mL until the time of success Survivors, on the contrary, had an initial mean procalcitonin concentration of 2.1 ng/mL, with a peak of 4.9 ng/mL on the first postoperative day and with progressive decrease to normalization. In another study published by Rau et al., in 2007, the authors observed that a procalcitonin concentration > 1 ng/mL after the third week from the beginning of the symptoms correlated with mortality, with a sensitivity of 97%, specificity of 80%, PPV of 48% and NPV of 99%. Some researchers found a correlation between procalcitonin and already validated prognostic indices such as the Mannheim index. With an index > 29, all patients had a preoperative procalcitonin > 10 ng/mL, whereas with an index < 21, procalcitonin concentration was < 0.5 in 82% of the patients. In another study it was seen that the combined use of procalcitonin and APACHE II values in the first day allows for obtaining a score that identifies patients who will not survive with a sensitivity of 71% and survivors with a specificity of 77%. Finally, procalcitonin is also useful to evaluate the effectiveness of the surgical procedure in the elimination of the infectious focus in the abdomen when there is evidence, in this case, of progressive decline in its concentrations. In summary, in patients with peritonitis, procalcitonin is especially useful to evaluate the prognosis and response to surgical treatment.

**Postoperative Infections**

Surgery induces elevation of procalcitonin concentrations in the immediate postoperative period, although this increase is not the same for all types of surgery. It increases in 21-32% of the patients with minor or aseptic surgery, 47% of patients with thoracic surgery, 27% with major vascular surgery and 95% with gastrointestinal surgery. However, among the patients with gastrointestinal surgery there were no differences with respect to the type of pathology. In almost all the studies done to date...
it was observed that the maximum procalcitonin value is reached at 24 h from the time of surgery, with progressive normalization that tends to be reached in 5-7 days.29-31

The relationship between postoperative values of procalcitonin and the appearance of postoperative infection has been investigated in several studies, including intra-abdominal infection, which is the most frequent after gastrointestinal surgery. The results obtained in these studies are variable with regard to procalcitonin values obtained, but in almost all of them it is seen that patients with postoperative infection have significantly higher procalcitonin values than those without infection and this difference can be appreciated in the first postoperative days before the infection is clinically evident.27,30,32-38 Therefore, there appears to be a clear relationship between postoperative infection and procalcitonin concentration in the first postoperative days. However, in the studies where the reliability of procalcitonin was investigated for diagnosing postoperative infections it was observed that the sensitivity and specificity are on the order of 70% and 90%. Unfortunately, the PPV of procalcitonin is low, does not go > 60% and, therefore, procalcitonin does not appear to be useful for the diagnosis of these infections. However, the NPV is high, > 95% in almost all the studies published for a value \(-1 ng/mL\), which confers to this marker the ability to identify early those patients who will not have infectious complications. Undoubtedly, this could be useful clinically, for example, to facilitate the decision for early discharge.

**Usefulness of Procalcitonin as a Guideline for Antibiotic Treatment**

In recent years various studies have been published with random allocation, which investigated the usefulness of procalcitonin as a treatment guide with antibiotics in bacterial infections of various etiologies. Most of these studies refer to patients with lower respiratory infections and sepsis admitted to intensive care units. The results seem to support the idea that the development of protocols based on serial determinations of procalcitonin would allow reducing the overuse of antibiotics in both groups of patients, selecting those who should be treated with antibiotics and limiting the duration of treatment13,39-42 without it indicating an increase in mortality or recurrence of the infection.13,39-42 In surgical patients, few studies have been done with random allocation with a limited number of patients. Two of these studies include patients with sepsis or severe sepsis and the same group was used. The first included 110 patients13 and the second 27 patients.44 In both studies a group was treated conventionally and in the other the antibiotic treatment was interrupted when there were no signs of infection and procalcitonin was < 1 ng/mL or decreased to < 35% of its initial value. The authors concluded that in the group with antibiotic treatment guided by procalcitonin the cost of antibiotics was reduced 17.8% and the duration of treatment by a mean of 2 days. In another randomly allocated study published in 200533 with 20 patients with colorectal surgery, procalcitonin value was > 1.5 ng/ml during at least two of the first three postoperative days. Ten patients were treated with 2 g ceftriaxone every 24 h and the other ten patients received the same antibiotic treatment only when there were symptoms of infection. The first group had an incidence and severity of postoperative infections significantly less than the second group. The number of patients included in these studies is small and for this reason no definitive conclusions can be made; however, it seems that procalcitonin could facilitate the more rational use of antibiotics in surgical patients.

In conclusion, procalcitonin is useful for identifying patients with severe acute pancreatitis and may allow early diagnosis of infection of pancreatic necrosis. Procalcitonin seems to be useful in patients with intestinal obstruction and identi-
ifies those who perhaps will evolve well without surgery and patients with intestinal ischemia. In patients with peritonitis, procalcitonin is useful to assess the effectiveness of surgical treatment and prognosis. In the postoperative period, this protein helps to identify patients with a very low risk of serious infectious complications. Procalcitonin is useful to guide the duration of antibiotic treatment in surgical patients with infection.

**REFERENCES**


