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REVIEW

Procalcitonin and intestinal ischemia: A review of the literature

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Abstract

Intestinal ischemia is common after emergency gastrointestinal or cardiovascular surgery. At present, there are no diagnostic tools for the early diagnosis of intestinal ischemia. In the last decade, procalcitonin (PCT) has been suggested as a marker of this condition. Here, we review the use of PCT as a diagnostic tool for intestinal ischemia. Two reviewers independently searched the PubMed and EMBASE databases for articles on intestinal ischemia and PCT. They then considered (1) the criteria applicable to preclinical and clinical data; and (2) PCT's predictive value in the diagnosis of intestinal ischemia. Article quality was rated according to the STAndards for Reporting of Diagnostic accuracy. Between 1993 and 2014, seven studies (including two preclinical studies and five clinical studies) dealt with the use of PCT to diagnose intestinal ischemia. Procalcitonin's sensitivity, specificity, positive predictive value and negative predictive value ranged between 72% and 100%; 68% and 91%; 27% and 90% and 81% and 100%, respectively. The area under the receiver operating characteristic curve ranged from 0.77 to 0.92. In view of the preclinical and clinical data, we consider that PCT can be used in daily practice as a tool for diagnosing intestinal ischemia.

Key words: Procalcitonin; Intestinal; Ischemia; Diagnosis; Review

Core tip: The serum procalcitonin level is clinically relevant for the diagnosis of intestinal ischemia. In the diagnosis of intestinal ischemia, procalcitonin's sensitivity is greater than 70% and its negative predictive value is greater than 80%.

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INTRODUCTION

Intestinal ischemia is a common complication of intestinal diseases (*e.g.*, small bowel obstruction and ischemic colitis) that can occur during disease progression (either

spontaneously or after abdominal or cardiovascular surgery)[1,2]. The condition has been defined as impairment of the intestinal blood supply from the celiac axis, the superior mesenteric artery and the inferior mesenteric artery; this results in tissue injury and a low-flow state with poor intestinal arterial perfusion[3,4]. In the United States, intestinal ischemia accounts for 0.1% of all hospital admissions. The incidence of this condition has increased over the last few decades (from 1 in 1000 to 1 in 200 hospitalizations for abdominal pain). In most cases, intestinal ischemia requires emergency treatment to avoid tissue necrosis, infectious outcomes, septic shock or potentially lethal multiple organ failure. This is notably the case in ischemic colitis (the most frequent gastrointestinal vascular disease, the incidence of which ranges from 4.5 to 44 cases per 100000 persons per year)[5].

Management of intestinal ischemia is difficult because the clinical symptoms associated with this condition (mild but sudden pain, diarrhoea, low gastrointestinal bleeding, abdominal distension with vomiting, fever, tachycardia, and tachypnoea) are not specific enough to rule out a number of other differential diagnoses[6]. In addition to the clinical symptoms, tissue damage be assessed using computed tomography angiography, Doppler ultrasound and endoscopy[7]; however, the lack of sensitivity and specificity associated with these examinations may mean that the diagnosis is only confirmed during the surgical procedure (*i.e.*, too late)[8].

With a view to improving the preoperative diagnosis, some researchers have suggested measuring several biomarkers: L and D-lactate[9-11], leukocytes[11,12], α glutathione S-transferase (αGST)[12-14], diamine oxidase[15], trehalase[16], alcohol dehydrogenase[17]), intestinal fatty acid binding protein[18-20], and D-dimer[21]. Whilst most of these markers prove to be accurate in preclinical studies, their use in clinical practice has been limited by several shortcomings (lack of sensitivity and specificity; poor assay reproducibility and the presence of species-specific metabolites). Hence, a clinical consensus on the use of these substances has not been reached.

Over the last decade, procalcitonin (PCT) has been suggested as a novel biomarker of the tissue damages associated with intestinal ischemia[22,23]. Procalcitonin is a 12.6 kDa, 116-amino-acid (AA) precursor of calcitonin that was first described in 1993 by Assicot *et al*[24] as a marker of infection. It has three domains: a 57 AA N-terminal domain, the 32 AA calcitonin fragment (involved in the regulation of calcium and phosphorus metabolism) and the 21 AA katakalcin fragment (measured in PCT assays)[24]. Procalcitonin is a member of the calcitonin gene-related peptide family and is encoded by the *CALC-1* gene located on the chromosome 11 (11p)[24-26].

In healthy subjects, the "hormokine" PCT is released from the C cells of the thyroid[27]. In a disease context, PCT production can be stimulated by trauma[28], bacterial endotoxins, pro-inflammatory cytokines [tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6)] or cardiogenic shock[24]. It is thought that this PCT is released by the liver parenchyma[29]. In most laboratories, PCT levels are measured with the Kryptor® TRACE assay. The normal level (from the third postnatal day onwards) is below 0.05 ng/mL. After surgery, the PCT level can rise to as much as 1 ng/mL (in cases of minor or aseptic surgery) or even 2 ng/mL (in cardiac surgery)[30,31].

The half-life-time of PCT is between 18 and 24 h, in patients with kidney failure, between 24 and 30 h (with a peak at 24 h)[31]. As shown by Meisner *et al*[32], the kinetics of serum PCT are not influenced by age, gender or renal function (because only a proportion of PCT is excreted by the kidneys).

Here, we review the literature data on the use of PCT in the diagnosis of intestinal ischemia.

RESEARCH

Search strategy and selection criteria

Two reviewers independently searched the PubMed and EMBASE databases for articles related to intestinal ischemia and PCT and published between 1993 and 2014. The search terms were "intestinal ischemia", "gut ischemia", "mesenteric ischemia" and "procalcitonin". Only full, original articles written in English were selected. For each selected article, the list of references was checked for studies not listed in the PubMed and EMBASE databases or not found in the search.

Data extraction and analysis

The two reviewers extracted the following data from each selected study: first author, date, type of study (preclinical or clinical), the number of included patients and the diseases assessed. The data were separated into two categories: those related to PCT's characteristics (structure, pharmacokinetics and pharmacodynamics), and those related to the detection of intestinal ischemia by measuring PCT (thresholds and predictive values). All extracted data were recorded in a table.

Assessment of the quality of selected publications

The methodological quality of the diagnostic studies was independently evaluated by the two reviewers according to the STAndards for Reporting of Diagnostic accuracy (STARD) criteria[33]. The studies were graded based on items relevant for this review. Studies were divided into groups as a function of the calculated STARD score; a score of 8 or 9 indicates good quality; a score of 6 or 7 indicates fair quality and a score of 5 or less indicates poor quality.

Any disagreements between the two reviewers over data quality were resolved by consensus.

THE DIAGNOSTIC VALUE OF PROCALCITONIN

According to our search results, a total of 32 studies related to PCT and ischemia were published between 1993

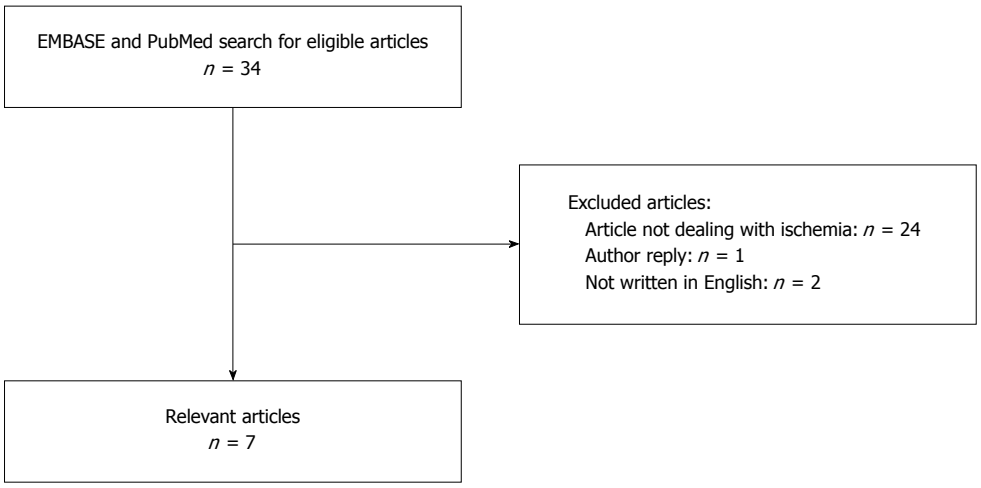

Figure 1 Review'S flow scheme.

Table 1 Preclinical data on procalcitonin for the diagnosis of intestinal ischemia

Ref.	Model	Number of animals	Model of ischemia	Range of procalcitonin values (ng/mL)	Assessment methods
Ayten *et al*[34]	New Zealand rabbits	30	Ligature of a 10-cm distal ileum segment and (in some cases) the mesenteric artery	0.225-0.514	Immunoluminometry
Karabulut *et al*[35]	New Zealand rabbits	21	Ligature of the superior mesenteric artery	0.11-0.98	ELISA (kit E0689)

Table 2 Clinical data on procalcitonin for the diagnosis of intestinal ischemia

Ref.	Condition	Number of patients	Range of procalcitonin values (ng/mL)	Assay method
Nagata *et al*[36]	Open aortic surgery	93	< 0.5 - > 10	Immunochromatographic test
Markogiannakis *et al*[22]	Small and large bowel obstruction	242	4.89-14.35	LUMItest
Cosse *et al*[23]	Small bowel obstruction	166	0.29-2.03	Kryptor TRACE
Cosse *et al*[37]	Small bowel obstruction	59	0.06-8.1	Kryptor TRACE
Cosse *et al*[38]	Ischemic disease (ischemic colitis and mesenteric infarction)	99	0.217-621.2	Kryptor TRACE

and 2014 (Figure 1). Only seven of these studies were relevant. All seven were of fair quality (*i.e.*, with a STARD score of between 6 and 7).

Preclinical data

Only two groups reported on the use of PCT as a diagnostic tool for bowel ischemia in an animal model (Table 1). In 2005, Ayten *et al*[34] studied 30 New Zealand rabbits in which intestinal ischemia was induced by ligature of a 10-cm distal ileum segment and (in some cases) ligature of the mesenteric artery. The researchers used an immunoluminometric method to measure serum PCT values during ischemia, which ranged from 0.22 to 0.51 ng per mL. In 2011, Karabulut *et al*[35] reported on a study in which intestinal ischemia was induced in 21 New Zealand rabbits by ligature of the superior mesenteric artery. The serum PCT level was measured with an ELISA (the E0689 kit) and ranged from 0.11 to 0.98 ng per mL.

Clinical data

The use of PCT in clinical practice has been investigated by three groups in a total of 659 patients (Table 2). In 2007, Nagata *et al*[36] evaluated the value of PCT for diagnosing colonic ischemia in a cohort of 93 patients undergoing open aortic surgery. The PCT levels were assayed using an immunochromatographic method and ranged from below 0.5 ng/mL in patients without ischemia to > 10 ng/mL in patients with ischemia. In 2011, Markogiannakis *et al*[22] suggested that PCT could be used as a diagnostic tool for ischemia and necrosis on the basis of their study of 242 patients treated for small or large bowel obstruction due to various aetiologies. According to the LUMItest, the PCT levels in patients with ischemia or necrosis ranged from 4.89 ng/mL to 14.35 ng/mL. In 2013, our group investigated the value of measuring PCT in the management of small bowel obstruction in a cohort of 166 patients from a randomized

Table 3 Diagnostic utility of procalcitonin for the diagnosis of intestinal ischemia

Ref.	Outcome	Threshold (ng/mL)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)	Area under the curve
Nagata *et al*[36]	Colonic ischemia	2	100	83.9	27	100	NR
Markogiannakis *et al*[22]	Bowel ischemia	0.25	72	73	60	83	0.77
Markogiannakis *et al*[22]	Bowel necrosis	0.25	83	78	52	95	0.87
Cosse *et al*[23]	Small bowel ischemia	0.57	83.3	91.3	83.3	91.3	0.91
Cosse *et al*[37]	Small bowel ischemia	0.53	80	84.8	40	90.7	0.86
Cosse *et al*[38]	Bowel necrosis	2.47	94.6	68	89.8	80.9	0.92

NR: Not been reached.

clinical trial[23]. We reported that when measured with the Kryptor TRACE method, the PCT values ranged from 0.29 ng/mL to 2.03 ng/mL in patients with ischemia. Moreover, we validated these data in a second, distinct cohort of 59 patients treated for small bowel obstruction by showing that PCT values (measured with the same assay) ranged from 0.06 ng/mL to 8.1 ng/mL in individuals with intraoperatively confirmed ischemia[37]. Our group also evaluated the value of PCT for characterizing tissue damage in cases of intestinal ischemic diseases (including ischemic colitis and mesenteric infarction)[38]. In a cohort of 99 patients, we found that PCT values ranged from 0.217 to 621.2 ng/mL when necrosis was described in the pathologist's report.

Diagnostic value

A variety of PCT upper threshold values have been reported for the diagnosis of ischemia and necrosis (Table 3). Even though the thresholds differed from one study to another, the predictive characteristics were similar. For example, the sensitivity ranged from 72% to 100%. The lowest values (72%-83%) were found for the lowest thresholds (0.25-0.57 ng/mL) in small bowel ischemia, whereas the highest values (95% and 100%) are found for high thresholds (> 2 ng/mL, *i.e.*, four times the normal upper limit) in colonic ischemia and necrosis. Furthermore, the clinical data were also associated with high negative predictive values (NPVs). With relatively low thresholds, the NPVs ranged from 81% to 100% for the diagnosis of ischemia and necrosis. The fact that the area under the curve (AUC), was greater than 0.75 emphasizes the clinical relevance of PCT as a diagnostic tool under these conditions.

NEED FOR NEW BIOMARKERS

Here, we reviewed the preclinical and clinical data on the use of PCT as a diagnostic tool for intestinal ischemia. All these data argue in favour of PCT as a new biomarker for this condition.

The diagnostic value of PCT in ischemia in general (and intestinal ischemia in particular) was suggested some time ago on the basis of two studies in rabbits. This concept has since matured in the scientific community. Indeed, acute intestinal ischemia is a life-threatening condition that requires emergency treatment and so must be diagnosed as soon as possible. To this end, clinicians can use biomarkers. The best-defined biomarkers are the D-lactate level and the leukocyte count. Murray *et al*[9] (1994) and Poeze *et al*[10] (1998) showed that D-lactate has a sensitivity of 80% for diagnosing ischemia, whereas Evenett *et al*[11] (2009) and Delaney *et al*[12] (1999) reported that the leukocyte count is more relevant. However, these "old" markers are used less and less because their accuracy is subject to debate. Although other molecules (such as αGST and D-dimer) have been suggested as alternatives to D-lactate and leukocytes, their value has yet to be established; this has prompted a search for other candidates[13-14,21].

As shown in clinical studies, PCT is a promising biomarker for the diagnosis of intestinal ischemia. Indeed, the groups working on PCT have reported that it has high diagnostic value. With low thresholds (0.25-0.5 ng/mL), the serum PCT value provides the clinician with information on the presence of reversible ischemic injuries and can identify patients requiring emergency treatment or those requiring close monitoring. The good agreement between the various groups' findings and the high reported AUC values (even though the assay technique varied from one study to another) underline the reproducibility of PCT assays and means that the clinician can envisage use of the latter in clinical practice.

ROLE OF PROCALCITONIN IN THE PHYSIOPATHOLOGY OF ISCHEMIA

Procalcitonin's value in the diagnosis of intestinal ischemia may perhaps be explained by the physiopathology of this condition. Ischemia is defined as a decrease in blood flow through the vessels. An inflammatory reaction then triggers the release of reactive oxygen species, which in turn promote the secretion of TNF-α and IL6. The resulting oxidative stress affects the intestinal mucosa and enterocytes, thus reducing the permeability of the intestinal wall. The indigenous bacteria in the gastrointestinal tract (*Escherichia coli*, *Lactobacillus* species, *Klebsiella, Bacteroides* species, *etc.*,) proliferate and generate bacterial endotoxins that ultimately promote the release of PCT

into the blood stream[39].

WEAKNESSES AND STRENGTHS OF PROCALCITONIN AS A BIOMARKER

Given that PCT was first studied as a marker of infection, its diagnostic value in intestinal ischemia might conceivably be limited by the presence of a bacterial infection. Indeed, several groups have reported that PCT is a diagnostic marker for (1) the sepsis[40-42] that can occur during ischemia; and (2) the necrosis related to multiple organ failure. When faced with suspected ischemic injuries and a high PCT value, the physician should request a microbiological analysis to rule out infection. Indeed, ischemic phenomena are closely related to infectious phenomena because PCT secretion depends respectively on inflammation and on bacterial translocation leading to infection. Chronic kidney disease might also conceivably influence PCT values, although Meisner *et al*[32] have reported that this is not the case. Moreover, PCT levels may be elevated by some non-ischemic phenomena (cardiac arrest, drug reaction with eosinophilia and systemic symptoms syndrome, heat wave, *etc.*) and decreased by others (previous effective antibiotic therapy, tuberculosis, *etc.*). To counterbalance these shortcomings of PCT, new biomarkers (such as copeptin and proadrenomedulin) should be investigated in ischemic conditions associated with PCT release. Moreover, the discordance between preclinical models and differences in the aetiologies of ischemia in clinical studies may be confounding factors in the assessment of PCT's diagnostic value.

Nevertheless, the findings of preclinical studies are generally in agreement (*i.e.* with the same trends in similar animal models). Furthermore, the clinical data support the use of PCT as a relevant tool for the diagnosis of ischemia (regardless of the aetiology) with thresholds of 1-2 ng/mL).

CONCLUSION

In view of the available preclinical and clinical data, we consider that PCT can be used in daily practice as a tool for diagnosing intestinal ischemia.

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