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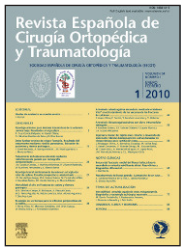

RESEARCH

Procalcitonin in the diagnosis of postoperative infection in knee arthroplasty

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KEYWORDS
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Abstract
Purpose of the study: Procalcitonin (PCT) is a 116 aminoacid polipeptyde synthesized in the thyroid C-cells. Its levels rise in the presence of bacterial infection. The aim of this work was to study the evolution of PCT levels in the postoperative period of knee arthroplasty and to assess its usefulness in the diagnosis of the infection process and its relationship to Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP).
Material and methods: Blood samples from 128 patients undergoing total knee arthroplasty surgery were taken one hour before surgery and 24, 48 and 72 hours after. PCT, ESR and CRP levels were measured and related to clinical complications. The number of leukocytes, blood transfusions, type of implant and minutes of ischaemia were studied and correlated to PCT concentrations above 0.5 ng / mL.
Results: PCT<0.5 ng / mL correlated with absence of clinical complications in 95% of the cases, and levels of PCT>0.5 ng / mL correlated to clinical complications in 75% of the cases. ESR and CRP increased in all of the patients in the postoperative period.
Conclusions: Difficulties in establishing an unquestionable diagnosis of infection do not allow us to firmly assert that PCT levels higher than 0.5 ng / mL are exclusive of bacterial infection, but it does seem to be more useful than ESR and CRP in the management of these patients.

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PALABRAS CLAVE
Procalcitonina;
Diagnóstico de infección;
Artroplastia;
Rodilla

La procalcitonina en el diagnóstico de infección postoperatoria en las artroplastias de rodilla

Resumen
Objetivo: La procalcitonina (PCT) es un polipéptido de 116 aminoácidos sintetizado en las células C del tiroides cuyas concentraciones se elevan en presencia de una infección bacteriana. El objetivo del trabajo es estudiar el comportamiento de las concentraciones de PCT en el postoperatorio de las artroplastias de rodilla y valorar su utilidad en el diagnóstico de procesos infecciosos y su relación con la velocidad de sedimentación globular (VSG) y la proteína C reactiva (PCR).
Material y métodos: Se estudiaron las concentraciones de PCT, PCR y valores de VSG en 128 pacientes intervenidos para una artroplastia primaria de rodilla desde el preoperatorio y los tres primeros días tras la intervención para relacionar los cambios en los niveles de estos marcadores con la aparición de complicaciones. Se estudió la variación en el número de leucocitos, el número de transfusiones, la utilización de diferentes implantes y el tiempo de isquemia buscando correlación con la aparición de concentraciones de PCT > 0,5 ng/mL.
Resultados: Concentraciones de PCT < 0,5 ng/mL se correspondieron con ausencia de complicaciones clínicas en el 95% de los casos mientras que concentraciones de PCT > 0,5 ng/mL se correspondieron con aparición de complicaciones clínicas en el 75%de los casos. La PCR y la VSG se incrementaron en todos los casos.
Conclusiones: La dificultad para hacer el diagnóstico incuestionable de infección no permite afirmar categóricamente que una concentración de PCT > 0,5 ng/mL sea marcador exclusivo de complicación infecciosa pero su determinación parece de mayor utilidad que la de VSG y PCR.

Introduction

The reported infection rate in knee arthroplasty is 1%2%in the different series published.[1,2] These studies refer to review surgery and chronic conditions. Infection is the leading cause of early failure of knee prostheses[3] and raises the question for the surgeon of carrying out a wide debridement followed by antibiotic therapy or removing the implant. In cases with less than 3-4 weeks development, it may be possible to salvage the prosthesis.[4,5]

A response mediated by the immune system is produced in the body during the postoperative period and in relation to surgical aggression. This is similar to that which occurs in the course of an infection. The clinical signs of infection are similar to those seen in the postoperative period as a result of the surgery itself, and also depend on the subjective criterion of the observer. The analytical parameters commonly used in infection diagnosis, C reactive protein (CRP) and erythrocyte sedimentation rate (ESR), increase in the postoperative period due to the surgical procedure itself.[6-9]

Procalcitonin (PCT) is a polypeptide with 116 amino acids, precursor of calcitonin, synthesised in thyroid C cells whose levels are elevated in the presence of a bacterial infection. Its determination has been used in the postoperative management of patients undergoing abdominal, cardiothoracic and vascular surgery and neurosurgical and transplant processes.[10-12]

The purpose of this study is to assess the behaviour of PCT concentrations in the immediate postoperative period of knee arthroplasty, attempting to relate their elevation with increases in laboratory parameters commonly used in the diagnosis of infection, such as CRP and ESR, and the onset of clinical complications.

Material and methods

A total of 128 patients were included in this study, 86 women and 42 men, who were intervened at our hospital in 2007 for total knee arthroplasty due to degenerative joint problems.

After obtaining the written consent of the patients, we took 4 blood samples: the first, one hour before the intervention, the second 24 hours later, the third 48 hours later and the fourth 72 hours after surgery. Coinciding with the extractions, we measured blood pressure, heart rate and body temperature.

In the blood samples, ESR, the number of leukocytes, CRP and PCT were measured. The determination of PCT was performed with a Kryptor autoanalyzer (Brahms, Hennigsdorf, Germany), using Time Resolved Amplified Cryptate Emission (TRACE) technology. The analytical range of the method was 0.02-50 ng/ml, with a functional sensitivity of 0.06 ng/ml.

We collected the medical records of patients and the following data from the surgical intervention: ischemia time

Table 1 Evolution of PCT concentrations in ng/mL and complications appearing in patients with PCT >0.5ng/mL in some determination

	PCT 24 h	PCT 48 h	PCT 72 h	Complications
1	< 0.5	2.4351	UCI	Pancreatitis. Renal failure. Not done at 72 h due to patient transfer
2	< 0.5	0.7362	< 0.5	Positive drainage. Positive culture
3	< 0.5	< 0.5	4.652	Positive drainage. Positive culture
4	< 0.5	1.359	0.7188	Heart failure. Necrosis edge of wound
5	< 0.5	1.057	0.6422	Necrosis edge of wound
6	1.663	2.292	1.456	Positive drainage. Positive culture
7	< 0.5	2.665	1.757	Necrosis edge of wound
8	0.7012	0.6778	0.5137	No complications
9	< 0.5	0.7248	< 0.5	No complications
10	18.15	28.92	16.98	Pneumonia. Reflex ileum. Renal failure. Fever
11	0.5903	0.5541	< 0.5	Wound drainage. Negative culture
12	0.5834	0.5197	< 0.5	No complications
13	0.6330	< 0.5	< 0.5	Necrosis edge of wound
14	0.6933	1.016	0.8239	Positive drainage. Positive culture
15	0.5576	0.8107	0.7632	Positive drainage. Positive culture
16	0.7643	1.461	0.9255	No complications
17	< 0.5	< 0.5	0.5337	No complications
18	0.6265	< 0.5	< 0.5	Necrosis edge of wound
19	1.021	1.812	1.9120	Positive drainage. Positive culture
20	< 0.5	0.7085	0.8079	Positive drainage. Negative culture
21	1.533	22.47	11.19	Necrosis edge of wound. Positive culture
22	< 0.5	0.5931	0.7695	No complications
23	0.7613	4.8790	5.0680	Paralyzed ileum. Sciatic lesion. Renal failure
24	0.7247	0.7937	< 0.5	Positive drainage. Positive culture
25	< 0.5	< 0.5	1.270	Positive drainage. Positive culture
26	< 0.5	0.9670	< 0.5	Necrosis edge of wound
27	0.5210	< 0.5	< 0.5	No complications

measured in minutes, surgeon in charge of the case, type of implant used, antibiotic prophylaxis and blood transfusions received measured in number of packed red blood cells. We reviewed medical records to assess the occurrence of postoperative complications, defined as necrosis of the edges of the surgical wound and/or exudate with bacterial culture within the first 30 days after the operation.

Two groups of patients were formed, taking the value PCT <0.5 ng/ml as the limit below which the presence of a bacterial infection was unlikely.[10] Patients who maintained PCT concentrations <0.5 ng/ml in the 4 determinations were placed in Group 0, and patients who had a PCT concentration >0.5 ng/mL in any of the determinations were placed in Group 1.

Subsequently, we established another 6 groups (A and B), (C and D) and (E and F). Group A were patients who had PCT <0.5 ng/ml at 24 hours and Group B those with PCT >0.5 ng/ml at 24 hours. The same was done for Group C, PCT <0.5 ng/ml and Group D, PCT >0.5ng/ml at 48 hours and Group E, PCT <0.5 ng/ml and Group F, PCT >0.5 ng/ml at 72 hours.

The ESR, CRP and WBC variables were compared between the two groups and the correlation of different intervention variables with the appearance of PCT concentrations >0.5 ng/ml was studied. For the statistical analysis, Stata 9.0 (College Station, Texas) software was used.

Results

All patients presented a PCT concentration <0.5 ng/ml in the preoperative determination. Out of the 128 patients, 27 presented a PCT concentration >0.5 ng/ml at some point during the postoperative period. Among those, 15 presented PCT >0.5 ng/ml in the determination after 24 hours, 20 after 48 hours and 18 of them 72 after the surgical procedure.

Of the 27 patients, 8 presented PCT concentrations >0.5 ng/ml in the 3 postoperative determinations. Out of these, 2 did not present any complications in their clinical history, as can be seen in table 1.

The PCT concentrations showed an elevation in the determinations after 24 hours and 48 hours, with a tendency to decrease 72 hours after surgery in patients who always maintained PCT <0,5 ng/ml, as can be observed in figure 1.

The mean age was 69.34 years in patients who always maintained PCT concentrations <0.5 ng/ml (Group 0) and 70.4 years in those who at some time presented PCT concentrations >0.5 ng/ml. The difference was not statistically significant.

Antibiotic prophylaxis (Cefazolin 2g) was administered to 123 patients half an hour before surgery, with the dosage

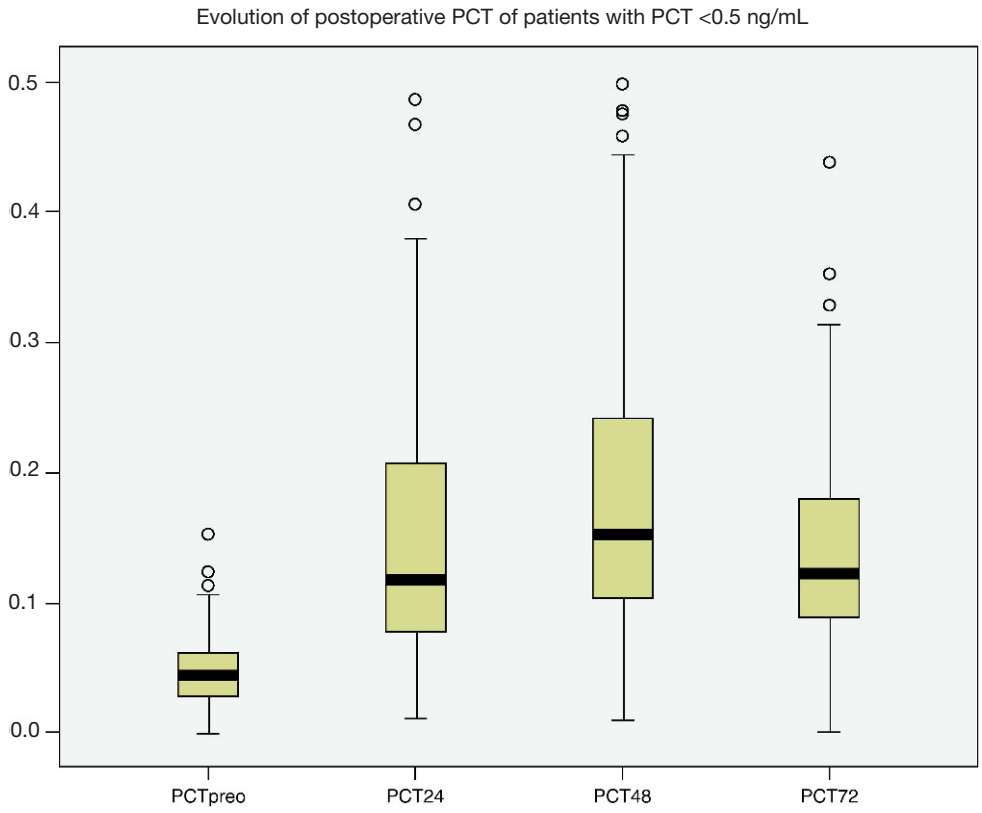

Figure 1 Evolution of PCT concentrations in the postoperative determinations of patients with PCT values <0.5ng/mL.

lowered after that to 1g every 8 hours for 2 days. Five patients received vancomycin 1g, 2 hours before surgery followed by 1g every 12 hours for 2 days. No correlation was found between using one or the other antibiotic and the appearance of PCT concentrations >0.5 ng/ml.

The mean values of systolic and diastolic blood pressure and heart rate were similar in Groups 0 and 1, with no statistically-significant differences being found.

No correlation was found between the use of different implants, the surgeon in charge of the case and PCT concentrations >0.5 ng/ml.

With respect to ischemia time measured in minutes, the mean was 64.1 minutes, with a standard deviation of 12.4 minutes and a range between 40 and 125 minutes. The mean time for patients in Group 1 was 64.5 minutes, with a standard deviation of 12.5 minutes and a range between 40 and 96 minutes. In Group 0, the mean was 64 minutes, with a standard deviation of 12.5 minutes. These differences were not statistically significant.

Of all patients studied, 41 did not receive a transfusion, 26 received a concentrate of red blood cells, 42 patients received 2 concentrates, 11 of them received 3 concentrates and 8 received 4 concentrates. The overall mean of red blood cell concentrates transfused was 1.3. Mean concentrates transfused to patients in Group 0 was 1.29703 and the mean red blood cell concentrates transfused to patients in Group 1 was 1.62963. The difference between both groups was not statistically significant.

Behaviour of ESR

A total of 61 patients presented values above what is considered normal (20mm) in the preoperative determination. Subsequently, there was a progressive increase at 24, 48 and 72 hours in all cases, as shown in figure 2.

The mean ESR values were higher in all determinations (24, 48 and 72 hours) in patients who at some point presented PCT >0.5 ng/ml (Group 1), although they were only statistically-significant at 72 hours (fig. 3). When comparing Groups A and B, C and D and E and F, mean ESR values were always higher in patients with PCT >0.5 ng/ml, although differences were not statistically significant in any case.

Behaviour of CRP

A total of 17 patients presented CRP levels above 1 mg/dl in the preoperative determination, which were considered above normal in the absence of clinical manifestations of infection. In the postoperative period, there was an increase in CRP concentrations at 24 and 48 hours, which tended to decrease after 72 hours, as shown in figure 4.

Mean CRP levels were always higher in Group 1, with the difference being statistically significant at 24 and 72 hours (fig. 5).

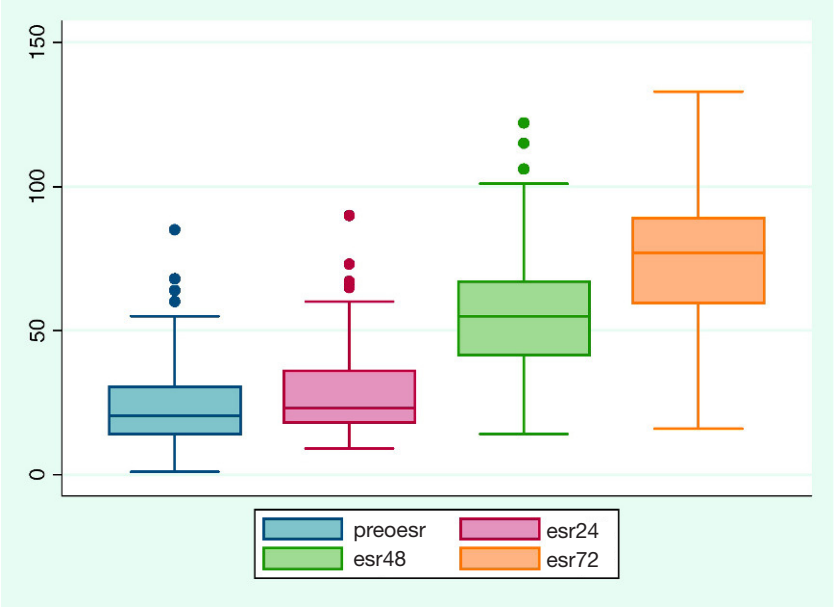

Figure 2 ESR values in the preoperative determination, and at 24, 48 and 72 hours.

Surgical complications

Complications of the surgical wound

In 14 patients, we observed sero-haematic drainage from the wound. Of these, 10 had PCT concentrations >0.5 ng/ml at some point and 4 maintained PCT concentrations <0.5 ng/ml.

In total, 8 patients presented some degree of necrosis at the edges of the wound. Of these, 7 presented PCT concentrations >0.5 ng/ml at some point and

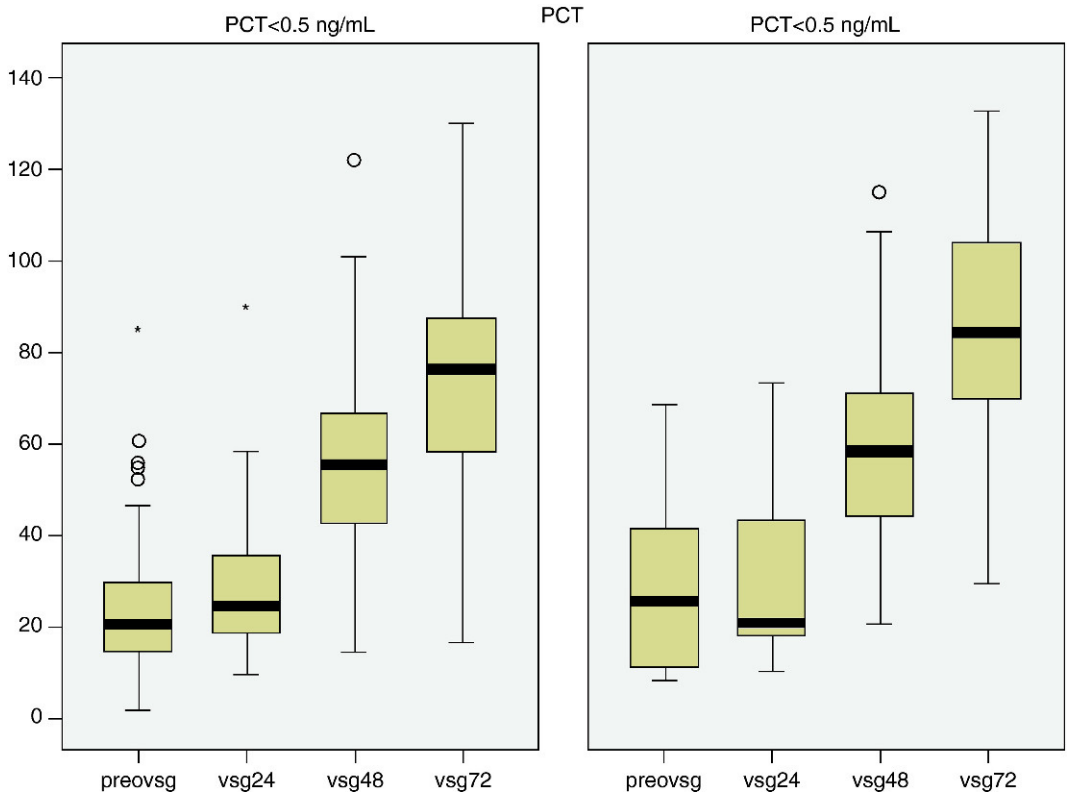

Figure 3 Evolution of mean ESR values in the groups of patients who always presented PCT concentrations <0.5ng/mL (Group 0) and those who presented PCT concentrations >0.5ng/mL in some determination (Group 1).

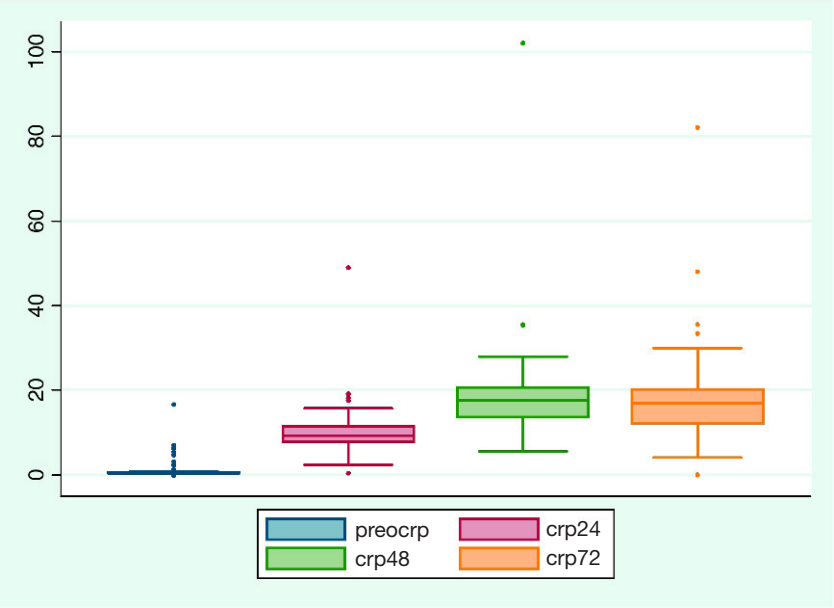

Figure 4 Concentrations of CRP in the preoperative determination, and after 24, 48 and 72 hours in all patients.

one of them always showed a PCT concentration <0.5 ng/ml.

Bacterial culture was performed in 15 patients, 14 of them with drainage and 1 patient with necrosis of the wound edges.

Of all the cultures, 11 were positive (in 6 cases by *Staphylococcus aureus* and 5 by *Staphylococcus epidermidis*) and 4 came back negative. Of the 15 cultures, 11 were from patients with PCT concentrations >0.5 ng/ml at some point and of those, 2 were negative and

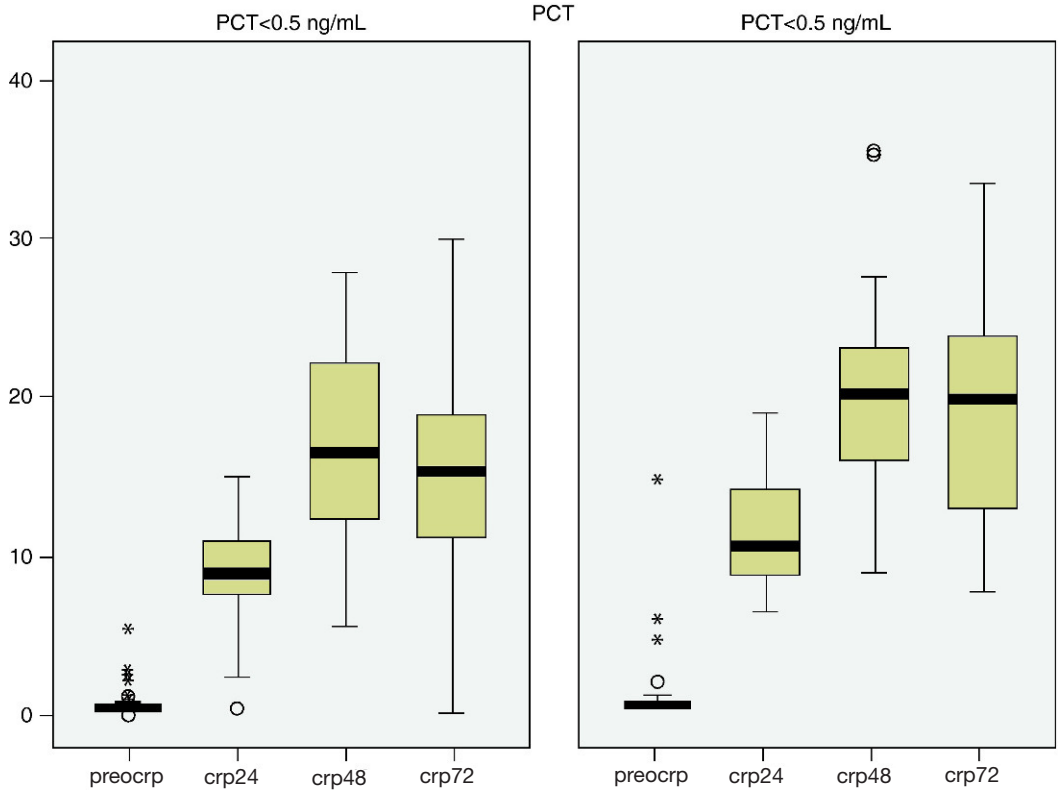

Figure 5 Evolution of mean CRP concentrations in the preoperative determination and at 24, 48 and 72 hours in patients with PCT <0.5ng/mL and in patients with PCT >0.5 ng/mL.

9 positive. The other 4 were taken from patients with PCT concentrations <0.5 ng/ml who had sero-haematic drainage, with 2 of them being positive and 2 negative.

Systemic

One case of pneumonia was resolved with antibiotic therapy and one case of heart failure was controlled through the use of medication. One patient had a temperature above 38ºC at 72 hours (the patient with pneumonia). Three patients developed renal failure, which reverted with fluids and medication. One patient suffered reflex ileus and a sciatic lesion, both of which resolved spontaneously. There was one case of pancreatitis, which required transfer to ICU.

All of the above patients had PCT concentrations >0.5 ng/ml at some point.

No complications

A total of 7 patients presented PCT concentrations >0.5 ng/ml in some determination and no complications were reflected in their medical records.

Discussion

Bacterial infections are a major cause of mortality and morbidity.[13] Diagnosing a bacterial infection is often a challenge because its clinical presentation does not differ much from that of a fungal or viral infection. In addition, many inflammatory conditions such as those due to trauma and surgery may also have a presentation similar to infection.

Different organisms may produce different responses in their hosts, resulting in a varied repertoire of markers and mediators. It is, therefore, too complex a process to simplify it into the measurement of a biomarker. In any case, elevated levels of biomarkers may increase the suspicion of the presence of infection. The "gold standard" is the main problem to be resolved. Any observational study to investigate the utility of a biomarker is skewed by the choice of the gold standard,[14] that test or situation to be used to compare this new test. Historically, clinical signs, symptoms and the use of imaging enabled the diagnosis of an infectious process. The measurement of clinical signs and the interpretation of imaging tests are not standardised and can produce great interobserver variability. Traditional laboratory tests such as ESR, CRP and leukocyte count determination lack sufficient specificity, while other inflammatory mediators such as TNF-α, IL-1 and IL-6 may show discrete elevations even in severe septic conditions.[15,16] In infections of the joints, joint fluid analyses combined with culture tests are considered more specific and sensitive, but still show a high number of false positives and false negatives.[17] Moreover, these invasive tests are not without risk.[18,19]

Clinical signs such as increased temperature or symptoms such as pain are very non-specific and may be influenced by the pain medication used systematically in the period after surgery.[20] Signs related to the surgical wound and oedema,[21] redness or heat can be perceived differently by different observers and can occur during the immediate postoperative period in the absence of infection, especially in patients with prior circulatory disorders. Allami et al[22] analysed the reliability of some of the diagnostic criteria proposed by the CDC[21] for surgical wound infection by measuring the differences between 4 observers. They concluded that heat, redness and swelling were perceived differently by different observers, so these indicators could not be recommended as diagnostic criteria.

The emergence of drainage along the edges of the wound may lead to suspicion of an infection when maintained over time.[23] However, in the immediate postoperative period, the appearance of exudate with resolution of the haematoma is quite common without there really being an infection. In this study, 14 patients presented sero-haematic drainage of the wound. Of these, 10 presented PCT concentrations >0.5 ng/ml at some point and 4 of the patients had levels that remained below 0.5 ng/ml (table 1). Cultures were collected in all cases, with 10 being positive for staphylococcus. Four cultures did not grow. Of the patients who maintained PCT <0.5 ng/ml, 2 presented a culture and 2 were negative. The presence of staphylococcus is not always indicative of infection because it can be a contaminant of skin flora and thus should not cause an elevation in PCT concentration. However, the tendency is to treat drainage positivity with antibiotics.[24]

The appearance of small areas of skin necrosis around the surgical wound is common in knee arthroplasties.[25] These are usually superficial and smaller than 3cms, so they can be cured with disinfection and their progression is usually favourable.[26] In the present study, we objectified 8 cases of wound edge necrosis listed as such in history. In 7 of them, the PCT concentration was >0.5 ng/ml at some point. One patient had a massive necrosis of the skin. This was a patient with rheumatoid arthritis who presented elevated PCT levels. Patients with smaller areas of necrosis presented concentrations close to 0.5 ng/ml and not in a sustained manner, which may indicate the presence of contamination in areas of necrosis that the body itself resolved quickly.

Analytical markers of infection

Erythrocyte sedimentation rate

In this study, 61 patients were above normal in the blood extraction performed one hour prior to surgery, with values up to 66mm but no clinical evidence of any infections. An increase after surgery took place in all cases. Therefore, it seems that the ESR goes through an elevation due to surgical aggression. The elevation was even higher in patients with PCT concentrations >0.5 ng/ml, in whom there may theoretically have been an infection, although scarcely significant. These data are consistent with that from other studies evaluating the behaviour of ESR in the postoperative period for knee replacement surgery and lower limb surgery.[8,9]

We conclude that ESR is not a good marker of postoperative infection because it can be elevated before surgery in the absence of infection and the surgical aggression itself produces its increase.

C reactive protein

In the present study, 17 patients had CRP levels above 1mg/dl in the preoperative extraction. However, none of the patients presented infection at that time. These concentrations slightly exceeded the normal range of 1-2mg / dl, except in 5 patients. One patient, who presented a preoperative concentration of 14mg/dl, subsequently had surgical wound complications with drainage and persistent oedema. The CRP concentrations increased in the samples taken at 24 and 48 hours, tending to decrease after 72 hours of surgical stimulation.

Patients with PCT concentrations >0.5 ng/ml had higher CRP levels, which could be independent from the increase due to the surgical aggression itself and could possibly be related to the presence of an infectious process.

These data are consistent with that from other studies evaluating the behaviour of CRP concentrations in the postoperative period in knee joint arthroplasties and lower limb surgery.[8,9]

Procalcitonin

In the normal population, PCT concentrations are below 0.1 ng/ml.[27] In this study, 11 patients were above this level in the preoperative assessment, although only 2 exceeded a concentration of 0.15ng/ml (0.27 ng/ml and 0.33 ng/ml respectively). Neither presented obvious infections nor showed a postoperative PCT concentration >0.5 ng/ml.

There was a slight increase in PCT concentration in the first 48 hours postoperative, generally without reaching the value of 0.5 ng/ml (fig. 1). Some authors[11] attribute this increase to transient bacteraemia from the area of incision, but the truth is that the reason is unknown.

Generally, 0.5ng/ml is considered the concentration above which it is possible to establish a diagnosis of bacterial infection.[27,28] This cut-off point is usually used in the different studies published that attempt to measure the usefulness of PCT in this area. However, in cases of multiple trauma,[29,30] burn victims[31] and postoperative follow-up,[32-35] using higher cut-off concentration levels is suggested. It is not currently known by what mechanism the concentration of PCT rises in these situations in the absence of infection, although it is known that these variations are small. In cases of localised infections, such increases are minor and the proposed cut-off point for PCT concentration is higher than 0.2ng/ml in the diagnosis of septic arthritis.[36] In this work, there were 27 patients who at some point presented PCT concentration >0.5 ng/ml. Of these, in 7 cases there was no clear evidence of complications collected in their respective clinical histories.

Only 8 patients presented a PCT concentration >0.5 ng/ml in the 3 tests and out of them only 2 showed no clinical and infectious complications. The highest concentrations were mostly between 1-2 ng/ml, except in 4 cases who presented obvious and serious clinical complications: pancreatitis, pneumonia and massive necrosis of the surgical wound edges and one patient with paralyzed ileum and renal failure. It is clear that patients with serious systemic complications showed patent elevations of PCT concentrations in all measurements and that patients with PCT levels <0.5 ng/ml had no clinical complications (or at least these were not reflected in their clinical histories), except for 4 patients who suffered surgical wound drainage that resolved without complications.

There are many published studies that asses the usefulness of PCT concentration determinations in the postoperative period of different types of surgery: abdominal, thoracic, and neurosurgery.[11,32,33,35,37-40] All of them find benefits in the determination, although more in the management of patient evolution than in the definitive diagnosis of infection. However, some published meta-analyses raise doubts with respect to the consistency of the studies from the methodological point of view.[42-45] On the one hand they are often small, heterogeneous samples, while on the other, the reference test or "gold standard" (which should be bacterial culture) does not always include the same number of samples or these are not taken in the same way, and there is no way to rule out the possibility of colonisation. In addition, the spectrum of patients is usually selected, thereby introducing bias. It consequently appears that a single determination cannot be enough to adopt a therapeutic approach with respect to certain presence of infection. There does seem to be agreement about how changes in PCT concentrations can help monitor patients with suspected infection.

Conclusions

All patients included in the study presented preoperative PCT concentrations <0.5 ng/ml, while many had elevated levels of CRP and ESR in the absence of clinical infection. The PCT concentrations <0.5 ng/ml corresponded to an absence of clinical complications in 95% of the cases, while the PCT concentrations >0.5 ng/ml corresponded with the appearance of clinical complications in 75% of the cases. The difficulty in establishing an unquestionable diagnosis of infection does not allow us to categorically state that a PCT concentration >0.5 ng/ml is an exclusive marker of infectious complications. However, the low specificity of measurements commonly used in the diagnosis of infection (such as ESR and CRP), which increase in the immediate postoperative period after the surgical procedure and may even be elevated in many patients before surgery in the absence of infection, makes the determination of PCT concentrations a useful tool in the management of patients after a knee arthroplasty when there is suspicion of an infectious process.

Level of evidence

Expert opinion. Level of evidence V.

Conflict of interest

The authors declare no conflict of interest.

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