ORIGINAL ARTICLE

Common inflammatory markers in the screening of knee arthroprosthesis infections

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ABSTRACT

Aim To evaluate the sensitivity and specificity of serum C-reactive protein (CRP) in early and late total knee arthroplasty (TKA) infections.

Methods Blood tests to determine CRP levels (cut-off 10 mg/L) were conducted before surgery, at 1st day, 7th day and 15th day after surgery and at 1, 3, 6,12, 24 and 36 months. Patients had routine follow-up visits and radiological evaluations at 14 days and at 1, 3, 6, 12, 24 and 36 months. Infections were recorded and classified according to Widmer classification. The $\chi 2$ test or Fisher (in subgroups smaller than 10 patients) exact test was used to compare categorical variables. The statistical significance was set at $p < 0.05$.

Results A total of 19 infections were diagnosed during the follow-up. According to Widmer, five were classified as early post-operative and 14 as late chronic. All patients with early infections had suspected symptoms such as fever, swelling and pain. During the first month, 59 patients who had high CRP level but negative microbiological culture were considered as false positive representing a CRP sensitivity of 80% and a specificity of 67.6%. Fourteen patients had late chronic infection.

Conclusion This study suggests that a synovial fluid aspiration should be performed in patients with persistent inflammation symptoms with or without radiographic signs of loosening. Moreover, it recommends the use of different serum and synovial tests for periprosthetic joint infection (PJI) diagnosis.

Key words: knee, periprosthetic joint infection, synovial fluid

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INTRODUCTION

Periprosthetic joint infection (PJI) is one of the most devastating and challenging complications after total knee arthroplasty. The rates of PJI vary depending on the joint involved: they range from 5% in total knee arthroplasty (TKA) to 2% in total hip arthroplasty (THA) or reverse shoulder arthroplasty (1,2).

A correct and early diagnosis is essential to provide the most appropriate therapy. The PJIs were classified, according to Widmer, as early post-operative with a typical onset between 2 and 4 weeks after surgery with fever, swelling, redness; late chronic (> 1 month) with an insidious onset characterized by persisting pain after surgery and hematogenous infections that typically arise after a long period from surgery (> 2 years) with signs and symptoms similar to early post-operative infections. (3). A timely diagnosis would make less invasive treatment possible: an early infection may be treated with debridement, exchange of modular parts and retention of the fixed components. Late infections involve the removal of components for the formation of biofilm, which makes bacteria more resistant to antibiotic therapies. (4,5).

The usefulness of C-reactive protein (CRP) in the diagnosis of PJI has been long discussed. Elevated values of CRP may be due to other conditions, and normal values may be present in chronic and low-grade PJI (6-8). Recently, the definition of PJI was revised in a multicentre study conducted by Parvizi et al. They found an evidence-based and validated updated version of the criteria with higher sensitivity and similar specificity compared to the Musculoskeletal Infection Society (MSIS) criteria (9).

Although CRP is a first-line screening test, several studies have shown a false negative rate between 11 and 35%, demonstrating that CRP could misdiagnose PJI. (1,8,10)

The aim of this study was to evaluate the sensitivity and specificity of serum CRP in early and late TKA infections. Our hypothesis was that serum CRP level is a sensitive and specific test as a screening tool for the diagnosis of TKA infections, especially in late chronic infections.

PATIENTS AND METHODS

Patients and study design

All TKAs operated in Vito Fazzi Hospital of Lecce (Italy) between February 2017 and December 2019 had been prospectively followed to observe the onset of the TKA infection. During the period, a total of 225 TKA were performed. Demographic characteristics including age, gender, pre-operative comorbidities and the American Society of Anesthesiologist's (ASA) physical status (11) were collected from medical records.

Exclusion criteria were: secondary osteoarthritis (such as post-traumatic arthritis), previous joint replacement, in addition to patients who were unwilling to participate in the study. In the end, 187 patients were ultimately selected. The patients were treated according to the ethical principles of the Helsinki Declaration and were asked to read, understand and sign an informed consent.

Methods

Blood tests to determine the CRP level (cut-off 10 mg/L) were conducted before surgery, at 1st day, 7th day and 15th day after surgery and at 1, 3, 6, 12, 24 and 36 months. The patients had a routine follow-up visit and radiological evaluations at 14 days and at 1, 3, 6, 12, 24 and 36 months. The patients who had a high CRP level with suspected symptoms for PJI (such as swelling, fever, redness and predisposing risk factors) underwent a joint aspiration to evaluate synovial white blood cell count (WBC), polymorphonuclear percentage (PMN%) and microbiological culture to confirm the infection. The infections were recorded and classified according to the Widmer classification: early postoperative infections between 2 and 4 weeks after surgery, late chronic between 1 month and 2 years and hematogenous after 2 years (3). Sensitivity was calculated as the proportion of infected TKA correctly identified by high CRP level and microbiological positive culture (the number of true positive divided by the sum of true positive and false-negative results). Specificity was calculated as the number of true negative divided by the sum of true negative and false positive.

Statistical analysis

Descriptive statistics were used to summarize the characteristics of the patients, including mean

and standard deviation (SD) of all continuous variables. The t-test was used to compare continuous outcomes. The $\chi 2$ test or Fisher (in subgroups smaller than 10 patients) exact test was used to compare categorical variables. Statistical significance was set at $p<0.05$.

RESULTS

During the period, a total of 225 TKA were performed, of which 187 patients were ultimately selected after exclusion criteria.

During the first month, 59 patients who had high CRP level and underwent joint aspiration but negative culture were founded. All these patients resolved spontaneously symptoms and were considered as false positive. This represents a CRP sensitivity of 80% and a specificity of 67.6%.

A total of 19 infections were diagnosed during the follow-up. According to Widmer (3), five were classified as early post-operative and 14 as late chronic (Figure 1).

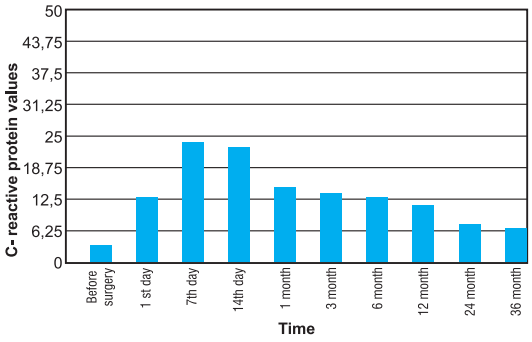

Figure 1. Trend of C-reactive protein (CRP) values during 36 months of follow-up

The mean age of patients with early infections was 71.6 (±SD) years; there were two males and three females. The mean delay from surgery to infection was 17.2 days (range 9-25 days). The mean CRP value was 14.71 mg/L. Four of five patients showed high CRP values and one had a normal value. All patients with early infection had suspected symptoms such as fever, swelling and pain (Table 1).

Fourteen patients had late chronic infection, seven males and seven females. The mean age was 70.4 (±SD) years. The mean delay from surgery to infections was 546 days (range 93-701 days). The mean CRP value was 18.33 mg/L. Although nine patients showed high CRP level, five had normal values. All patients with late chronic infection had a normal physical examination, they only presented with persistent pain and stiffness, and no clear loosening was observed in the radiographs. High CRP level was found in 41 patients, but no infection. Sensitivity was 64% and specificity 62% (Table 2).

Table 1. Demographic and clinical characteristics of five patients with early infection

Patient	Gender	Age (years)	Number of days from surgery to infection	CRP at the time of diagnosis (mg/L)	Micro-organism isolated
Patient 1	Male	67	16	14.25	*Staphilococcus aureus*
Patient 2	Female	75	9	21.55	*Staphilococcus aureus*
Patient 3	Male	78	21	13.42	*MRSA*
Patient 4	Female	70	25	8.63	*Corynebacterium pyogenes*
Patient 5	Female	68	15	15.71	*Escherichia coli*
Mean±SD		71.6±4.72	17.2±6.1	14.71±4.65	

CRP, C-reactive protein; MRSA, methicillin resistant *S. aureus*;

Table 2. Demographic and clinical characteristics of 14 patients with late chronic infection

Patient	Gender	Age	Range (days) surgery-infection	CRP (mg/l) at the time of diagnosis	Micro-organism isolated
Patient 1	Female	58	421	29.1	CNS
Patient 2	Female	63	370	18.33	CNS
Patient 3	Female	66	125	16.45	*Staphhylococcus aureus*
Patient 4	Female	73	258	18.67	*S taphylococcus aureus*
Patient 5	Male	77	637	9.78	CNS
Patient 6	Male	79	323	8.28	CNS
Patient 7	Male	75	368	25.43	*Peptostreptococcus anaerobius*
Patient 8	Male	72	399	9.6	CNS
Patient 9	Female	62	93	15.33	CNS
Patient 10	Male	77	187	13.25	*Corynebacterium pyogenes*
Patient 11	Male	68	415	8.75	*Staphylococcus aureus*
Patient 12	Male	66	701	7.79	*Propionbacterium acnes*
Patient 13	Female	72	685	9.3	CNS
Patient 14	Female	78	665	17.41	CNS
Mean±SD		70.42±6.65	546.2±131.2	18.33±8.41	

CRP, C-reactive protein; CNS, coagulase negative staphylococcus, SD, standard deviation

DISCUSSION

The most important finding of the present study is that serum CRP was associated with a false-negative result between 20% and 36% and could be misdiagnosed as TKA infections, especially in late chronic infections usually caused by low-virulence micro-organism. Mainly, the sensitivity

of serum CRP was 80% overall and 64% in chronic infections, while specificity was 67.5% and 62%, respectively.

On the basis of these results, the primary hypothesis of the study was rejected. Similar results have been found in several previous studies. Pérez-Prieto et al. noted that out of 73 patients with different PJI, 17 patients had normal CRP, erythrocyte sedimentation rate (ESR) and a normal physical examination demonstrating that CRP and ESR could be of little use in low-grade and chronic infections (2). Other studies have demonstrated an association between false-negatives and low-virulence microorganisms; McArthur et al. found a rate of around 4% of patients with PJI and normal CRP and ESR values on 414 THAs and 538 TKAs revisions (6). The role of CRP and ESR as markers for PJI diagnosis is different in various criteria: for the Musculoskeletal Infection Society (MSIS) they are included in one criterion for PJI. At the same time, for the American Association of Orthopaedics Surgeons (AAOS) patients with normal CRP and ESR were identified as aseptic cases and levels do not require further tests (12-13).

Sensitivity and specificity of CRP and ESR have been assessed by Barè et al. (14) who found that CRP had a sensitivity of 60% and a specificity of 63%, while ESR had 63% and 55%, respectively, while Austin et al. (15) assessed for CRP and ESR, respectively, a sensitivity of 94% and 91% and a specificity of 74% and 72%. (14-15). Their specificity results were inconsistent with those reported by Johnson et al. demonstrating the specificity of 33% and 20 % for ESR and CRP, respectively. They assumed that one reason for the difference was that ESR and CRP were not routinely performed when the clinical suspicion of infections was low, and therefore a negative test was more likely to be a false negative (16).

Recently, the search for synovial biomarkers of PJI has generated interest (1). While some authors assessed that synovial CRP is more accurate in diagnosing PJI than the serum CRP, others argue that synovial fluid test is equivalent to the serum test (17-19). A study conducted by Deirmengian et al. on the connection between synovial fluid CRP and infecting organism demonstrate that CRP is highly dependent on the infection organism and is more likely to give a false-negative result with fewer virulent-organisms (17). This finding was also demonstrated by Kheir et al., who found that serum and synovial markers were related to organism type (20).

Other studies documented the role of a new biomarker such as alpha-defensin test and serum D-dimer test in the diagnosis of PJI. In a study conducted on 106 patients, the alpha defensin test was shown to maintain high sensitivity when compared with the ESR, CRP even in the setting of antibiotics treatment (21).

Shahi et al. measured pre-operatively D-dimer level in a cohort of 245 patients undergoing primary and revision arthroplasty suggesting that adding serum D-dimer as a marker for PJI because high D-dimer level in patients undergoing reimplantation could be a sign of persistent infection (22).

In the last years, some studies have demonstrated that the infection could also be present in patients who do not meet diagnostic criteria. Koh et al., in a multicentre study, found that one-third of the patients with PJI did not meet MSIS criteria and concluded that in one-third of the patients, the diagnosis was based on clinical suspicion (23). Recently, based on these new diagnostic tests, Parvizi et al. (9) developed a validated updated version of the criteria in a multicentre study. The major criteria were two positive cultures of the same microorganism or the presence of a sinus tract. Minor preoperative criteria included serum (CRP, D-Dimer and ESR) and synovial markers (white blood cell count, polymorphonuclear percentage, leukocyte esterase, alpha-defensin, and synovial CRP).

Several limitations are present in this study. First of all, the small sample size. Another limitation is the non-exclusion of patients with a systemic inflammatory disease such as rheumatic diseases that could influence the serum CRP. The main limitation of this study is that no other markers have been measured and their usefulness has not been compared.

Although serum CRP level is the first-line screening test on PJI diagnosis, a normal value cannot rule out late PJI, that is frequent due to low-virulence microorganisms. This study suggests that a synovial fluid aspiration should be performed in patients with persistent symptoms with or without radiographic signs of loosening. Moreover, it recommends the use of different serum and synovial tests for PJI diagnosis.

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TRANSPARENCY DECLARATION

Competing interests: None to declare.

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