The Role of Pre-Operative Inflammatory Markers in Predicting Postoperative Infection in Patients Undergoing Total Knee Arthroplasty

Ebrahim Khamis, MD, CABS* Mohammed AlSaif, MD, CABS**
Asma AlQaseer, MB BCh BAO*** Mohamed Husain, MD, CABS****

Background: C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are frequently used to aid the diagnosis of postoperative peri-prosthetic infections (PPIs) following total knee arthroplasty (TKA). The role of using these inflammatory markers preoperatively to predict the risk of postoperative PPIs in patients undergoing TKAs has not been well documented to date.

Objective: To evaluate the role and cost-effectiveness of preoperative markers; ESR and CRP in predicting postoperative PPIs in patients undergoing elective primary TKA.

Design: A Prospective Study.

Setting: Department of Orthopedic Surgery, Salmaniya Medical Complex, Kingdom of Bahrain.

Method: All patients who underwent primary or simultaneous bilateral TKA from 1 September 2014 to 31 December 2016 were included in the study. Patients who had uncontrolled diabetes, previous surgery or septic arthritis on the same knee, or lost for follow-up were excluded. Inflammatory markers were documented 1-2 days preoperatively. Patients were followed up over a period of 12 months postoperatively. All necessary data were collected prospectively and documented. The data were analyzed using SPSS 20.

Result: One hundred thirty-nine patients were included in this study. One hundred and forty-two primary TKAs were performed during the study period, three patients underwent simultaneous bilateral TKA. Eighty-seven (62.59%) patients were females and 52 (37.41%) were males. The mean age was 64 years. Ninety-five (68.34%) patients had one or more preoperative comorbidities. High preoperative levels of CRP and/or ESR were found in thirty-seven (26.62%) patients. Two (1.44%) patients developed postoperative infection and were treated successfully. No other complications were recorded.

Conclusion: In our study, we found no significant link between elevated preoperative inflammatory markers and the presence of PPI. Therefore, we do not support the routine use of preoperative inflammatory markers.

Bahrain Med Bull 2019; 41(1): 29 - 32

Osteoarthritis (OA) is a chronic degenerative disorder of the joints commonly affecting the knees and is the most common form of arthririts[1,2]. It carries a high prevalence, affecting 27 million Americans and 33.6% of the population above 65 years of age[1,2]. OA is the fifth leading cause of disability worldwide and is associated with a very high socioeconomic burden[1,2].

Total knee arthroplasty (TKA) is an effective treatment for OA after the failure of conservative measures. TKA is a well-established commonly performed elective procedure nowadays[3,4]. Due to its success in improving the quality of life and patient's mobility, it is estimated that the number of patients undergoing TKR will continue to rise in the coming years[3,5]. Despite that it is a safe and effective procedure, it carries financial challenges for the health care system, as well as postoperative complications which can be overwhelming for both the patients and surgeons. Periprosthetic infection (PPI) is one of the most common complications, yet it is challenging in its early stages for diagnosis and effective treatment[4,5].

* Consultant Orthopedic Surgery
Orthopedics Department
Salmaniya Medical Complex
** Chief Resident Orthopedic Surgery
Orthopedics Department
Salmaniya Medical Complex
*** Junior Resident
General Surgery Department
Salmaniya Medical Complex
**** Chief Resident Orthopedic Surgery
Orthopedics Department
Salmaniya Medical Complex
Kingdom of Bahrain
E-mail: dr.m.alsaif83@gmail.com, drebrahim@live.com

C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) are frequently used to diagnose post-TKA infections[1,2]. CRP and ESR are highly sensitive serum markers, albeit non-specific to the inflammation and infection process in the body[4]. Given its benefit in diagnosing postoperative infections, several studies encourage its use in the routine preoperative workup for patients undergoing joint replacement surgery. However, there is still no consensus with regards to preoperative inflammatory markers in predicting postoperative PPI.

The aim of this study is to evaluate the role of preoperative levels of CRP and ESR in predicting the postoperative risk of infection in patients undergoing elective primary TKA.

METHOD

A prospective study was performed from 1 September 2014 to 31 December 2016. All patients who underwent primary unilateral or simultaneous bilateral TKA during this period were included in the study. All TKAs were performed by one surgeon, using a standard surgical technique.

Patients who had uncontrolled diabetes, previous surgery or septic arthritis of the same knee, or lost for follow-up were excluded.

Blood samples for CRP and ESR were collected 1-2 days preoperatively. All patients received a preoperative dose of 3rd generation cephalosporin intravenously, given one hour before the surgery and three doses for 24 hours postoperatively. Patients with elevated markers were taken for surgery.

All patients were electively admitted and discharged on analgesics. Patients were followed up for 12 months postoperatively in the outpatient clinics at intervals of 2 weeks, 1 month, 3 months, 6 months and 12 months respectively. Patients who reported signs of infection were further investigated.

All data were documented prospectively. Data analysis was done using SPSS version 20. Statistical significance was defined as P-value of less than 0.05.

RESULTS

One hundred thirty-nine patients were included in this study. One hundred and forty-two primary TKAs were performed during our study period; three (2.2%) patients underwent simultaneous bilateral TKA. Eighty-seven (62.59%) patients were females and 52 (37.41%) were males. The age of the patients ranged from 51 to 77 years with a mean of 64 years.

Ninety-five (68.34%) patients had one or more preoperative comorbidities. Forty-two (30.2%) had hypertension followed by diabetes mellitus in 32 (23.0%) patients, see table 1.

ESR was considered elevated if the level was more than 20 mm/hr and CRP more than 3.0 mg/dL. The range of preoperative CRP was 0-15 mg/dL and ESR was 0-68 mm/h. High preoperative levels of CRP and/or ESR were found in 37 (26.62%) patients, see table 2.

Table 1: Patients Preoperative Comorbidities with Elevated Inflammatory Markers

Comorbidities	Patients (%)	Number of patients with elevated CRP and/or ESR
Diabetes Mellitus (DM)	32 (23.02%)	4 (2.87%)
Hypertension	42 (30.21%)	5 (3.59%)
DM and Hypertension	9 (6.47%)	2 (1.43%)
Hyperlipidemia	4 (2.87%)	1 (0.7%)
Hypothyroidism	2 (1.43%)	0
Ischemic Heart Disease	6 (4.32%)	1 (0.7%)
No comorbidities	44 (31.65 %)	24 (17.27%)
Total	**139 (100%)**	**37 (26.62%)**

Table 2: Preoperative Inflammatory Markers Levels

No. of patients (%)	ESR level	CRP level
102 (73.38%)	Normal	Normal
4 (2.87%)	Normal	High
6 (4.32%)	High	Normal
27 (19.42%)	High	High
Total 139 (100%)		

Two (1.43%) patients developed a postoperative infection at two weeks postoperatively, diagnosed and confirmed by positive growth. Patients were treated with early debridement and change of polyethylene tibial insert, followed by 2 weeks of intravenous antibiotics. Both had an uneventful recovery. Both patients had normal preoperative values of ESR or CRP. No other complications were documented.

In our study, we found no relationship between preoperative inflammatory markers level and the presence of PPI, P-value 1.000 (>0.05), see table 3 and 4.

Table 3: Chi-Square Test Showing the Relationship between CRP Levels and PPI

CRP Levels PPI		PPI		Total
		PPI	Non-PPI	
Normal	Count	2	106	108
	Expected Count	1.6	106.4	108.0
High	Count	0	31	31
	Expected Count	0.4	30.6	31.0
Total	**Count**	**2**	**137**	**139**
	Expected Count	**2.0**	**137.0**	**139.0**
Chi Square (X2) = 0.582 Degree of Freedom (df) = 1		P-value = 1.000		

Table 4: Chi-Square Test Showing the Relationship between ESR Levels and PPI

ESR Levels PPI		PPI		Total
		PPI	Non-PPI	
Normal	Count	2	104	106
	Expected Count	1.5	104.5	106.0
High	Count	0	33	33
	Expected Count	.5	32.5	33.0
Total	**Count**	**2**	**137**	**139**
	Expected Count	**2.0**	**137.0**	**139.0**
Chi Square (X2) = 0.632 Degree of Freedom (df) = 1		P-value = 1.000		

DISCUSSION

CRP and ESR are acute phase inflammatory serum markers widely used in diagnosing inflammation and/or infection in the body. These inflammatory markers have had important roles in detecting and monitoring several systemic diseases since 1930[5-7].

CRP and ESR are widely available inexpensive blood tests that are usually performed in patients undergoing primary TKA[7,8]. These inflammatory markers have high sensitivity and reasonable specificity for infection[9]. CRP is an acute phase protein synthesized in the liver, which acts by activating the complement system via the classical pathway[5,10]. ESR measures the inflammatory activity in the body by measuring the rate at which red blood cells sediment in one hour[4]. Several studies had found the natural history of ESR and CRP postoperatively[5,7,11]. CRP levels rise rapidly compared to ESR following TKA and the time needed to return to normal level postoperatively[7,11]. It has been found that CRP levels peak on the third-day post-TKA and remain high in most patients up to the third week postoperatively[5,7]. This is thought to be due to the surgical trauma[5]. In a study by Barretto et al, it was found that only one-third of the patients had their CRP level return to preoperative level after the third week[5]. CRP level usually returns to normal level after 2 months of knee arthroplasty[7]. CRP level increase post-TKA compared to hip arthroplasty[7]. Similarly, the ESR level peak on the fifth day postoperatively and returns to normal or preoperative level at the end of nine months[7]. Elevated levels of CRP had been used as a prognostic factor for developing cardiovascular disease, peripheral vascular disease and storke[4,12].

PPI is a major concern to the surgeons and a challenge for early diagnosis and management. Approximately 1-2% patients can develop postoperative PPI, which in turn is associated with high morbidity and possible mortality[8]. A possible infective process following TKA is considered if the patient develops any of the following signs: fever, erythema, hotness, discharge surrounding the surgical incision, or significant pain and/or stiffness during the 12 months postoperatively. However, a definite diagnosis of PPI is made if one or more of the following conditions are present: a sinus tract (fistula) or purulence around the prosthesis, leukocytes more than 2000 per microliter or more than 70% PMN in synovial fluid, presence of minimum of 23 PMN per 10 high power fields in periprosthetic tissue histology, and/or microbial growth from synovial fluid or tissue samples[7-9,12,13].

Many studies continue to support the benefit of using CRP and ESR in diagnosing postoperative PPI in patients who underwent TKA. It is, however, of lesser benefit in other joint arthroplasties, such as the hip and shoulder[4,6,7,11]. The interpretations of inflammatory markers can be difficult in staged bilateral TKA as their elevated levels are influenced by the primary surgery. In addition, comorbidities and systemic conditions could elevate the inflammatory markers[4,11].

In our study, we found no statistically significant correlation between elevated preoperative CRP and ESR level and the presence of postoperative PPI. Our findings were similar to a recent study by Godoy et al, who concluded that they do not support the routine preoperative use[4]. Similarly, Aukland et al found no difference in postoperative complications in patients having high sensitivity CRP level pre-operatively[4].

On the contrary, Piftzner evaluated the link by comparing the infected group against a control group[14]. The infected group had a higher, yet not statistically significant, increase in preoperative CRP and ESR compared to the control group[4].

Several studies have reported a possible indication of inflammatory markers pre-operatively to predict postoperative complications. However, due to the studies limitations, a common interpretation is still far from consensus[11].

CONCLUSION

We found no significant association between elevated pre-operative inflammatory markers and the presence of PPI. Therefore, we do not recommend the routine use of these inflammatory markers pre-operatively.

Further studies are needed to evaluate the predictability and efficacy of the routine use of preoperative inflammatory markers in diagnosing PPI following joint replacement surgeries, taking into consideration patient associated comorbidities.

Author Contribution: All authors share equal effort contribution towards (1) substantial contributions to conception and design, acquisition, analysis and interpretation of data; (2) drafting the article and revising it critically for important intellectual content; and (3) final approval of the manuscript version to be published. Yes.

Potential Conflicts of Interest: None.

Competing Interest: None.

Sponsorship: None.

Acceptance Date: 12 January 2019.

Ethical Approval: Approved by the Department of Orthopedics, Salmaniya Medical Complex, Bahrain.

REFERENCES

1. Neogi T. The Epidemiology and Impact of Pain in Osteoarthritis Cartilage 2013; 21(9): 1145–1153.
2. Bitton R. The Economic Burden of Osteoarthritis. Am J Manag Care 2009; 15(8 Suppl):S230-5.
3. Maradit Kremers H, Larson DR, Crowson CS, et al. Prevalence of Total Hip and Knee Replacement in the United States. J Bone Joint Surg Am 2015; 97(17):1386-97.
4. Godoy G, Sumarriva G, Ochsner JL, et al. Preoperative Acute Inflammatory Markers as Predictors for Postoperative Complications in Primary Total Knee Arthroplasty. Ochsner Journal 2016; 16:481–485.
5. Barretto JM, Loures FB, Albuquerque RSP, et al. Evaluation of Serum Levels of C-Reactive Protein after Total Knee Arthroplasty. Rev Bras Ortop 2017; 52(2): 176–181.
6. Lindsay CP, Olcott CW, Del Gaizo DJ. ESR and CRP are Useful between Stages of 2-Stage Revision for Periprosthetic Joint Infection. Arthroplasty Today 3 2017; 3(3): 183–186.
7. Piper KE, Fernandez-Sampedro M, Steckelberg KE, et al. C-Reactive Protein, Erythrocyte Sedimentation Rate and Orthopedic Implant Infection. PLoS One 2010; 5(2): e9358.
8. Tande AJ, Patel R. Prosthetic Joint Infection. Clin Microbiol Rev 2014; 27(2): 302–345.
9. Ghanem E, Antoci Jr. V, Pulido L, et al. The Use of Receiver Operating Characteristics Analysis in Determining Erythrocyte Sedimentation Rate and C-Reactive Protein Levels in Diagnosing Periprosthetic Infection Prior to Revision Total Hip Arthroplasty. International Journal of Infectious Diseases 2009; 13, e444—e449.
10. Jain S, Gautam V, Naseem S. Acute-Phase Proteins: As Diagnostic Tool. J Pharm Bioallied Sci 2011; 3(1): 118–127.
11. Honsawek S, Deepaisarnsakul B, Tanavalee Aree, et al. Relationship of Serum IL-6, C-Reactive Protein, Erythrocyte Sedimentation Rate, and Knee Skin Temperature after Total Knee Arthroplasty: A Prospective Study. Int Orthop 2011; 35(1): 31–35.
12. Johnson AJ, Zywiel MG, Stroh A, et al. Serological Markers Can Lead to False Negative Diagnoses of Periprosthetic Infections following Total Knee Arthroplasty. International Orthopaedics (SICOT) 2011; 35:1621–1626.
13. Aggarwal VK, Rasouli MR, Parvizi J. Periprosthetic Joint Infection: Current Concept. Indian J Orthop 2013; 47(1):10-7.
14. Pfitzner T, Krocker D, Perka C, et al. C-Reactive Protein. An Independent Risk Factor for the Development of Infection after Primary Arthroplasty. Orthopade 2008; 37(11):1116-20.