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Preoperative Acute Inflammatory Markers as Predictors for Postoperative Complications in Primary Total Knee Arthroplasty

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Background: C-reactive protein (CRP) has been suggested as an independent risk factor for cardiovascular pathology in the nonsurgical setting. While postoperative CRP and erythrocyte sedimentation rate (ESR) have an established role in aiding the diagnosis of periprosthetic joint infections, some authors suggest a link between preoperative CRP and postoperative complications in patients undergoing total joint arthroplasty.

Methods: We conducted a retrospective cohort study of 351 patients who underwent unilateral primary total knee arthroplasty by a single surgeon during a 28-month period (January 2013 through April 2015). Patient medical records were reviewed for the following complications occurring within 90 days postoperatively: myocardial infarction, arrhythmia, pulmonary embolism, wound infection, acute renal failure, and reoperation.

Results: We found no statistically significant link between postoperative complications and preoperative CRP levels (P=0.5005) or ESR levels (P=0.1610).

Conclusion: The results of this study do not support the routine inclusion of CRP and ESR analysis as part of the preoperative evaluation for elective total knee arthroplasty.

Keywords: *Arthroplasty–replacement–knee, blood sedimentation, C-reactive protein, postoperative complications*

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INTRODUCTION

After conservative options have failed, total knee arthroplasty is an effective treatment for an osteoarthritic and painful joint. Total knee arthroplasty has become a common procedure associated with low to moderate risk, but complications still occur postoperatively, some of which may be life-threatening or require reoperation. Early possible complications associated with total knee arthroplasty include infection, deep vein thrombosis (DVT), pulmonary embolism (PE), neurovascular injury, periprosthetic fracture, pain, and stiffness.[1] Risk factors that have been identified to increase complications in joint arthroplasty include age >65 years, obesity, comorbidities (eg, diabetes and hypertension), and surgery performed in a low-volume hospital.[1] Postoperatively, studies have proven the benefit of using C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) in the diagnosis of periprosthetic joint infections.[2,3]

CRP and ESR are serum markers that show high sensitivity for inflammation in the body. ESR measures the rate at which red blood cells sediment during 1 hour, serving as a measure of acute phase response. Elevations in ESR can be the result of inflammation, infection, neoplasms, tissue ischemia/injury, or trauma. CRP, a protein produced by the liver and adipose tissues, is a sensitive and specific marker for inflammation and increases in direct relation to the degree of inflammation.[4] In a retrospective study of patients who underwent arthroscopic anterior cruciate ligament reconstruction, CRP and ESR levels were measured at various times in both the infection and noninfection groups.[5] The study determined that CRP peaked earlier than ESR in the infection group, and CRP was more useful than ESR in evaluating the response to treatment of infection.

In the nonoperative setting, elevated CRP values have been shown to be associated with increased cardiovascular risk.[6-8] Some authors believe CRP can be used as a prognostic factor for cardiovascular disease, in addition to the traditional risk factors.[8,9] CRP correlates inversely with cardiovascular fitness, an important determinant for out-

comes.[9] In a metaanalysis published in 2004, Danesh et al found that patients were 1.45 times more likely to have coronary disease when they were in the top third of baseline CRP compared to the bottom third (odds ratio=1.45, 95% confidence ratio 1.25, 1.68).[7] Studies since then have shown similar results.[6] Prospective studies suggest CRP may independently predict a patient's risk for cardiac death, stroke, and peripheral arterial disease.[8] These links suggest that CRP may be used when considering global vascular risk.[6]

Because elevated CRP appears to be associated with increased cardiovascular risks in the nonoperative setting, it seems plausible that an elevated CRP could also be associated with the risk of postoperative complications. The aim of this study was to explore if elevated preoperative levels of CRP and ESR correlated with postoperative complications among patients receiving primary total knee arthroplasty.

METHODS

Orthopedic surgeons frequently order a complete blood count (CBC) preoperatively to establish baseline hemoglobin and hematocrit levels. In addition to the CBC, one surgeon (J.L.O.) at our institution has been collecting CRP and ESR values as part of his routine preoperative evaluation for several years. This retrospective cohort study involved the review of medical records of patients who received primary total knee replacements during a 28-month period (January 2013 to April 2015) by a single surgeon (J.L.O.). The goal of this study was to evaluate if preoperative inflammatory markers (CRP and ESR) predisposed patients to postoperative complications.

Approval was obtained from the Ochsner Institutional Review Board. All data were obtained from the electronic medical records. The electronic medical database was queried for the Current Procedural Terminology (CPT) code 27447 (primary total knee replacement). The records of patients who received total knee replacements were then queried for International Classification of Diseases, 9th Revision (ICD-9) codes for the following complications: wound infection, acute renal failure, myocardial infarction, arrhythmia, pulmonary embolism, and reoperation. Early prosthetic joint infections are defined within the first 3 months after surgery;[10] therefore, the time range for postoperative complications for this study was chosen as 90 days postoperatively. Chart abstraction for all patients was performed to verify complications and primary surgery status. Laboratory values of ESR and CRP within 30 days before the surgery were recorded. All imaging, laboratory work, electrocardiograms (ECGs), postoperative notes, and clinic notes were reviewed from the date of surgery to 90 days postoperatively. All ECGs are reviewed and read by cardiologists at the time of their request, increasing the likelihood of correctly identifying cardiac complications. The following comorbidities were also recorded during the electronic chart review: diabetes, Crohn disease, hepatitis C, rheumatoid arthritis, and urinary tract infections (UTIs). Although UTIs are an acute infection and not a chronic comorbidity, UTIs may elevate inflammatory markers and were therefore classified as a comorbidity.

Table 1. Preoperative Comorbidities (n=351)

Patient Group	Number of Patients
Any comorbidity (1 or more)	123 (35.04%)
Diabetes	98 (79.67%)
Rheumatoid arthritis	20 (16.26%)
Urinary tract infection	19 (15.45%)
Crohn disease	3 (2.44%)
Hepatitis C	2 (1.63%)
No comorbidities	228 (64.96%)

Note: Some patients had multiple comorbidities.

Inclusion criteria for this study included primary unilateral total knee replacement. Patients who received surgery for one knee replacement and then received a subsequent surgery for the contralateral side (staged bilateral surgeries) within the time frame (January 2013 to April 2015) were counted as 2 patients in the analysis. Patients who received a revision total knee replacement or simultaneous bilateral total knee replacement, had prior knee hardware, or had incomplete laboratory values preoperatively were excluded from this study.

Patients were divided into 3 groups for both CRP and ESR: low normal, intermediate normal, and high. The normal range for CRP at our institution is 0-8.2 mg/L, so the categorization was 0-4.1 mg/L for low normal, 4.2-8.2 mg/L for intermediate normal, and $\geq$8.3 mg/L for high. The normal range for ESR is 0-20 mm/h, so the categorization was 0-10 mm/h for low normal, 11-20 mm/h for intermediate normal, and $\geq$21 mm/h for high. These cutoff values were selected to divide the population across consistent increases in laboratory values. The analysis was a comparison of the 3 groups for CRP and ESR rather than a comparison of complications within each group.

Statistical analysis was performed using SAS v.9.4 (SAS Institute). All data were categorical. The likelihood ratio test was performed for sample sizes $>$5. Fisher exact test was used when groups contained 5 subjects or less. Alpha was set at 0.05, and any *P* value less than alpha was considered to be statistically significant. No statistical tests were performed for combinations that had too small a sample size to calculate. CRP and ESR were evaluated independently against each complication.

RESULTS

A total of 351 total knee arthroplasties were performed on 317 patients. Thirty-four patients received bilateral surgeries on different dates more than 90 days apart. As previously stated, each staged bilateral surgery is considered to be 2 patients. Therefore, the total cohort size is 351 patients. Total knee replacement was performed on 147 males (41.88%) and 204 females (58.12%). The patients' mean age at time of surgery was 68.87 years (SD 9.57; range, 40-91 years). Of the 351 total knee replacements, 193 (54.99%) were performed on the left knee, and 158 were performed on the right (45.01%).

One hundred twenty-three patients had at least 1 preoperative comorbidity (Table 1). The comorbidity with the highest incidence was diabetes, reported for 98 patients.

Table 2. Postoperative Complications

Complication	Number of Patients	C-Reactive Protein			Erythrocyte Sedimentation Rate		
		Low Normal (0-4.1 mg/L)	Intermediate Normal (4.2-8.2 mg/L)	High ($\geq$8.3 mg/L)	Low Normal (0-10 mm/h)	Intermediate Normal (11-20 mm/h)	High ($\geq$21 mm/h)
Any complication (1 or more)	28	16	4	8	5	11	12
Myocardial infarction	1	1	0	0	1	0	0
Arrhythmia	8	4	1	3	0	3	5
Pulmonary embolism or deep vein thrombosis	5	2	1	2	0	2	3
Wound infection	8	5	3	0	2	3	3
Acute renal failure	12	7	2	3	3	4	5
Formal revision surgery	0	0	0	0	0	0	0
No complications	323	157	87	79	108	64	151
Total	351	173	91	87	113	75	163

Twenty-eight patients had 1 or more complications (Table 2): 1 patient had myocardial infarction, 8 had new arrhythmia, 5 had PE or DVT, 12 had acute renal failure, and 8 had infections. Six of the 8 infections were suspected to be superficial and described as "cellulitis." Of the 6 patients with superficial infections, 4 were readmitted and treated with intravenous (IV) antibiotics, 1 received oral antibiotics at a skilled nursing facility, and 1 received outpatient IV and oral antibiotics. The other 2 infections were deep and required incision and drainage and tibial polyethylene insert exchange. Additionally, 2 patients received incision and drainage for persistent drainage with negative intraoperative cultures. Operative findings revealed 1 case of subcutaneous dehiscence without fascial defect and 1 case of small superficial hematoma. No patients in this study required formal revision surgery within 90 days of the total knee arthroplasty.

When CRP levels were stratified, 173 patients had low-normal values, 91 patients had intermediate-normal levels, and 87 patients had high CRP levels. For ESR, 113 patients had low-normal levels, 75 had intermediate-normal values, and 163 had high ESR levels. No statistical significance was found between CRP or ESR and any complication, with P values of 0.5005 and 0.1610, respectively (Table 3). Any comorbidity was not a significant predictor for any complication (P=0.6347). Any comorbidity was significantly associated with elevated CRP and ESR, with P values of 0.0239 and 0.0002, respectively.

DISCUSSION

Although there is currently no consensus on the use of CRP and ESR for preoperative evaluation of orthopedic patients, 3 studies exploring this possibility have recently been published. All 3 studies suggest a link between preoperative CRP and postoperative complications. A limitation of all 3 studies is the relatively small sample sizes.

A 2008 study by Pfitzner et al retrospectively evaluated 50 patients in Germany who received primary total hip and knee arthroplasties.[2] The study compared 25 patients with postoperative infections against a control group of 25 patients without infectious complications matched for demographic data. The infected group had a higher, although not statistically significant, average preoperative CRP (13 $\pm$ 25 mg/L) compared to the control group (4 $\pm$ 7 mg/L). The authors recommended using a CRP threshold of 5 mg/L to determine if a cause for infection should be explored.

The other 2 studies evaluated high-sensitivity CRP (hsCRP) using cutoff values based on the Centers for Disease Control CRP stratification, classifying patients into low (<3 mg/L) and high (>3 mg/L) groups. In 2007, Ackland et al reported that hsCRP correlated to length of stay and delayed postoperative complications in a cohort of 129 prospectively followed patients who underwent total hip or knee arthroplasty.[9] Laboratory workups were performed at a mean of 13 days preoperatively (SD 8 days). Ackland et al found a statistically significant difference in length of stay and incidence of complications at postoperative day (POD) 8 between high CRP and low CRP groups, but they found no significant difference in complications on POD 5. In a prospective, cross-sectional study performed in India and published in 2009, Ghosh et al studied 121 patients who received total hip arthroplasty, total knee arthroplasty, and

Table 3. Statistical Results

Predictor Variable	Outcome Variable	Test	*P* Value	LR (L^2)
Laboratory value as a predictor for complication				
CRP	Any complication	LR	0.5005	1.3842
	Acute renal failure	FE	0.7496	NA
ESR	Any complication	FE	0.1610	NA
	Myocardial infarction	FE	0.2239	NA
	Acute renal failure	FE	0.9299	NA
Comorbidity as a predictor for complication				
Any comorbidity	Any complication	LR	0.6347	0.2258
Diabetes	Any complication	LR	0.6153	0.2526
Laboratory value as a predictor for comorbidity				
CRP	Any comorbidity	LR	0.0239	7.4705
ESR		LR	0.0002	17.0029
CRP	Diabetes	LR	0.1703	3.5409
ESR		LR	0.0018	12.6831
CRP	Urinary tract infection	LR	0.0924	4.7631
ESR		FE	0.1142	NA
CRP	Rheumatoid arthritis	LR	0.2612	2.6848

CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; FE, Fisher exact test; LR, likelihood ratio; NA, not applicable.
Note: Complications and comorbidities with sample sizes too small for analysis are not included.

hemiarthroplasty.[11] They collected preoperative, perioperative, and postoperative CRP values and found a statistically significant increase in both operative time and complications at POD 14; however, the authors found no significant difference in complications between the groups at POD 7.

In our study, CRP and ESR were not found to be significantly related to complications. Only 9 of the 87 patients with elevated CRP had any complications, and the largest groups only included 3 patients (acute renal failure and arrhythmia). With such small sample sizes, subgroup analysis would not have enough power to produce meaningful results.

A potential limitation of our study is that it was underpowered to show a statistically significant difference. Also, the comorbidities reported for some of the patients can independently affect levels of the inflammatory markers, potentially confounding the findings. Additionally, the retrospective nature of the study may have led to missing or omitted information. Attempts to minimize missed information included selecting complications that would likely be documented based on severity, using electronic medical records, and using both ICD-9 code queries and a review of the clinical notes.

CONCLUSION

This study did not show a statistically significant correlation between postoperative complications and preoperative ESR or CRP. The small number of patients with complications may not have been enough to power a statistically significant study. Further investigation is necessary to determine if preoperative CRP and ESR relate to postoperative complications among patients undergoing total knee arthroplasty.

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