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Original Article

Characterizing the Acute Phase Response in Healthy Patients Following Total Joint Arthroplasty: Predictable and Consistent

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ABSTRACT

Background: During surgery, trauma to musculoskeletal tissue induces a systemic reaction known as the acute phase response (APR). When excessive or prolonged, the APR has been implicated as an underlying cause of surgical complications. The purpose of this study was to determine the typical APR following total joint arthroplasty in a healthy population defined by the Charlson Comorbidity Index (CCI).
Methods: This retrospective study identified 180 healthy patients (CCI < 2) who underwent total joint arthroplasty by a single surgeon for primary osteoarthritis from 2013 to 2015. Serial measurements of C-reactive protein (CRP) and fibrinogen were obtained preoperative, perioperative, and at 2 and 6 weeks postoperative.
Results: Postoperative CRP peaked during the inpatient period and returned to baseline by 2 weeks. Fibrinogen peaked after CRP and returned to baseline by 6 weeks. Elevated preoperative CRP correlated with a more robust postoperative APR for both total hip arthroplasty and total knee arthroplasty, suggesting that a patient's preoperative inflammatory state correlates with the magnitude of the postoperative APR.
Conclusion: Measurement of preoperative acute phase reactants may provide an objective means to predict a patient's risk of postoperative dysregulation of the APR and complications.

The acute phase response (APR) is a systemic reaction to tissue injury; it is mediated by the liver and characterized by the modulation of more than 1000 genes. This response results in the production of cytokines that prevent hemorrhage, combat infection, and stimulate wound healing. Although the APR is essential for normal coagulation and immunity, dysregulation leads to complications such as life-threatening hemorrhage, poor wound healing, and venous thromboembolism [1]. These thromboembolic complications stem from Virchow's triad of venous stasis, endothelial injury, and hypercoagulability. Prior studies have demonstrated that the magnitude and duration of this response directly correlates with the level of initial tissue injury and predicts poor outcomes in injured patients [2-4].

Surgical trauma during total joint arthroplasty (TJA) evokes a profound APR [5-7]. Prior studies have shown that C-reactive protein (CRP), an acute phase reactant, and erythrocyte sedimentation rate (ESR), an indirect marker of the APR, follow general trends post-TJA [5-7]. Yet, these early studies from the 1990s were conducted under different conditions than current standards of practice and have high variability for maximum inpatient values and time to resolution for CRP and ESR [6,8]. Moreover, this variability is also seen in a recent study by Yombi et al [9] following conventional and minimally invasive total knee arthroplasty (TKA). These studies did not address the APR in the context of an objectively defined healthy population and a large sample size [6,8,9]. Therefore, this study aims at measuring the APR following arthroplasty in a

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healthy population with current implants, techniques, and standards of practice. Furthermore, this investigation proposes to use fibrinogen to study the APR rather than ESR. ESR quantifies inflammation through an indirect measurement of fibrinogen [10,11], an acute phase reactant that is upregulated following injury [12]. Prior investigations showed that ESR does not return to normal within 1 year following TJA [6]. This imprecision has lead others to conclude that while ESR advanced medical science when introduced in the 1920s, it is often misleading because it is greatly influenced by immunoglobulins, plasma constituents, and changes to erythrocyte morphology and number [13]. Thus, ESR is a less-sensitive marker for the APR than fibrinogen, an acute phase reactant.

This study aims at describing the typical APR exhibited by healthy patients following uncomplicated TJA with current surgical techniques through serial measurement of CRP and fibrinogen. The authors hypothesize that the APR following uncomplicated primary TJA in healthy patients is both consistent and predictable.

Methods

Sample Population and Inclusion Criteria

This IRB-approved retrospective cohort study (level of evidence III) was conducted on patients undergoing primary total hip arthroplasty (THA) and primary TKA at Vanderbilt University Medical Center from 2013 to 2015; 207 patients were enrolled in the study; 180 patients met both the inclusion and exclusion criteria. Adult patients aged between 17 and 88 years with a Charlson Comorbidity Index (CCI) <2 were included in the study. The CCI is a widely accepted and tested method for predicting the influence of comorbidities on functional outcomes [14], implant survival [15], length of stay [16,17], and mortality [18]. The score ranges from 0 to 33 with an increasing score indicating the presence of multiple comorbidities [19]. The CCI was calculated for each patient through review of comorbidities in the electronic medical records.

Surgical Approach and Exclusion Criteria

All surgeries included in the study were performed by a single surgeon (G.G.P.). The surgeon used a posterior surgical approach for the THA and a medial parapatellar arthrotomy with tourniquet use for the TKA. All patients in the study were placed on Celebrex during the perioperative period unless contraindicated. Contraindications included known hypersensitivity to celecoxib, sulfonamides, aspirin, or other nonsteroidal anti-inflammatory drugs as well as patients with a history of gastrointestinal sensitivity or peptic ulcer disease. Atypical or complex primary arthroplasty procedures for postinfectious arthrosis, posttraumatic osteoarthritis, or arthroplasty were excluded from the study. Patients requiring THA or TKA revision were also excluded. The electronic medical record, containing both office and hospital records, was reviewed for complications in the 6-week postoperative period.

Laboratory Methods

CRP and fibrinogen laboratory values were collected at preoperative, perioperative, and postoperative 2-week and 6-week time points as part of regular standard of care for tracking acute inflammation. Laboratory tests were drawn on the floor and processed by our institution's clinical laboratory, which is Clinical Laboratory Improvement Amendments (CLIA) certified, accredited by the College of American Pathologists, and licensed by the state of Tennessee. Fibrinogen was tested in accordance with the Clauss clotting method using the STA-R Evolution Analyzer with reagents from Diagnostica Stago, Inc. Interassay coefficients of variation have been reported to range from 3.0% to 4.8% [20]. CRP levels were measured using an immunoturbidimetric assay with the Architect C1600 by Abbott Laboratories with reported interassay coefficients of variation of 0.44% to 1.25% [21].

Temporal Criteria for Laboratory Values

The preoperative period was defined as 40 days before surgery; perioperative period was defined as the end of surgery to discharge; week 2 was defined as postoperative day 10 to 20; and week 6 was defined as postoperative day 35 to day 50. The wide time intervals for postoperative laboratory values were secondary to variability in clinic scheduling. Laboratory values not taken during these time frames were excluded from analysis. Percent resolution of max for CRP and fibrinogen was defined as the change from maximum at 2 and 6 weeks divided by the maximum change from baseline.

Statistical Analysis

Mann-Whitney 2-tailed unpaired *t* tests were performed to compare the non-Gaussian THA and TKA cohorts. Unpaired *t* tests using the Holm-Sidak method were performed to compare the 25th and 75th percentile CRP and fibrinogen values of the patient cohorts and to compare the THA and TKA APR time courses.

Estimates of sample size were calculated based on the evaluation of peak CRP and fibrinogen following TKA and THA. For a study of alpha = 0.05 and 1-beta = 0.80, 13 patients were required for each group based on a difference in population means of 49.7 mg/L and standard deviation of difference of 59.25 mg/L for CRP. This was consistent with prior studies [8]. For fibrinogen with alpha = 0.05 and 1-beta = 0.80, 54 patients were required for each group based on a difference in population means of 42.5 mg/dL and standard deviation of difference of 109.8 mg/dL. This study was adequately powered with 118 TKA and 62 THA patients.

Determination of Consistency and Predictability

To test the hypothesis that the APR is consistent and predictable, these terms must first be established. Consistency is defined as the ability to significantly distinguish between the THA and TKA cohorts with respect to inpatient maximum value and time to inpatient maximum. Predictability is defined as the ability for preoperative acute phase reactants to predict the postoperative APR. This will be tested by a subset analysis of the THA and TKA cohorts in the 25th and 75th quartiles for preoperative CRP values. If there is a significant difference between the quartiles for

Table 1
Sample Demographics of Patients Undergoing Total Knee Arthroplasty and Total Hip Arthroplasty.

Demographics	Total Knee Arthroplasty	Total Hip Arthroplasty
Number (n)	118	62
Age	64 (55.8-86.0)	58 (46.5-65.0)
Gender	64 Female/54 male	30 Female/34 male
Mean Charlson Comorbidity Index	0 (0-1)	0 (0-1)
Postoperative complications at 6 wk	0	0

Values presented as median and 25th and 75th interquartile range or absolute number. Unpaired, nonparametric Mann-Whitney *t* tests were used to calculate *P* values.