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Interleukin-6 and leptin levels are associated with preoperative pain severity in patients with osteoarthritis but not with acute pain after total knee arthroplasty

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ABSTRACT

Background: Identifying drivers of pain that can serve as novel drug targets is important for improving perioperative analgesia. Total knee arthroplasty (TKA) is associated with significant postoperative pain. Cytokines contribute to the pathophysiology of osteoarthritis (OA) and associated pain. However, the influence of perioperative cytokine levels after TKA surgery upon postoperative pain remains unexplored.

Methods: We designed a prospective observational study to profile three proinflammatory cytokines, interleukin-6 (IL-6), tumor necrosis factor α (TNFα), and leptin in serum, synovial, and cerebrospinal fluid of TKA patients perioperatively to determine associations between cytokine levels and pain. We characterized time-trajectories in cytokines pre- and post-surgery and explored their relationships to pain across gender.

Results: Preoperative pain, measured by functional pain disability scores (PDQ), was predictive of postoperative pain. There were no gender differences in severity of preoperative pain or acute postoperative pain. Serum IL-6, serum leptin, and synovial fluid leptin were positively correlated with body mass index and preoperative pain severity. Stratification of patients by gender revealed strong correlations between serum IL-6, leptin, and PDQ only in females, suggesting that females may be more sensitive to the nociceptive actions of these cytokines. Although serum IL-6 increased dramatically (and TNFα increased modestly) four hours after surgery and remained elevated at 72 h; they were not associated with the severity of acute postoperative pain.

Conclusions: Our data suggest that while preoperative chronic pain is predictive of the severity of acute postoperative pain in TKA patients, the pre- and post-operative inflammatory status does not predict postoperative pain.

1. Introduction

Osteoarthritis (OA) is defined by progressive cartilage loss and is accompanied by significant pain and functional disability [1,2]. Cytokines released from inflammatory cells are involved in the progression of OA and contribute to peripheral and central

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pain [3]. For example, tumor necrosis factor α (TNF-α) released from activated macrophages in OA joints has been shown to directly evoke discharges in A- and C-fibers when applied to dorsal root ganglion neurons signifying its role in nociception [3]. Several clinical studies have characterized levels of cytokines in various tissue compartments of OA patients before and after joint surgery [4–9]. Remarkably, given their role in nociception, there is limited information on whether cytokine profiles correlate with and/or are predictive of pre- or postoperative pain.

Total knee arthroplasty (TKA) surgery is associated with significant acute postoperative pain and chronic preoperative pain and disability positively correlate with the severity of pain after TKA [10,11]. TKA patients are usually discharged two to three days after surgery while still experiencing significant acute postoperative pain [12]. Cytokines that are elevated in OA patients and are known instigators of preoperative pain may likewise be predictive of acute postoperative pain severity. To explore these associations, we characterized key inflammatory markers in serum, cerebrospinal fluid (CSF), and joint synovial fluid (JSF) in OA patients undergoing TKA in parallel with perioperative pain assessments. Our analysis focused on three pro-inflammatory cytokines; leptin, TNFα, and interleukin-6 (IL-6). Leptin was selected because obesity is a known risk factor for knee pain [13–15] and leptin (which is produced in adipose tissue) is also a pro-inflammatory cytokine [16]. There is evidence that TNFα and IL-6 contribute to the progression of OA [3] and serum and JSF levels of TNFα are elevated in patients with knee pain [9,17]. IL-6 has been proposed as a potential therapeutic target for OA because it is a procatabolic cytokine and expressed in OA cartilage [3]. Surprisingly, the contribution of IL-6 toward OA pain is poorly defined. However, serum IL-6 levels have been shown to correlate with reduced mobility while JSF IL-6 negatively correlates with knee range of motion [17,18]. Clearly, additional studies examining associations between cytokines and baseline OA pain are needed.

We designed our prospective observational study to test the hypothesis that leptin, TNFα, and/or IL-6 levels in serum, CSF, and JSF are elevated in OA patients with greater preoperative functional pain disability, reflective of a pro-inflammatory state. Furthermore, we also explored whether obesity, baseline cytokine levels, and perioperative changes in cytokines are predictive of acute postoperative pain during the first 72 h after TKA.

2. Patients and methods

2.1. Ethics statement

The experiments conducted herein were approved by the Stony Brook University institutional review board and written consent was obtained from each patient (CORIHS-B #295049). This study was performed in accordance with the Declaration of Helsinki (1964) [19].

2.2. Experimental setting, design & data collection

Eligible TKA patients enrolled for this prospective, observational study were recruited from Dr. Nicholson's clinic at the Joint Replacement Center, Department of Orthopaedics, Stony Brook University Hospital. Only patients from Dr. Nicholson's clinic who fit the enrollment criteria were included in the study and written consent was obtained from all enrolled subjects. All enrolled patients were scheduled for elective unilateral TKA under spinal anesthesia in combination with femoral nerve blockade. We excluded patients with 1) medical conditions which precluded use of regional anesthesia; 2) chronic pain with opioid usage over 100 mg morphine-equivalents orally daily; 3) history of abuse of opioids or other drugs of abuse; 4) patients scheduled for bilateral TKA; and 5) patients scheduled for a TKA revision. The period of recruitment extended from March 2011 to December 2013.

As a part of the prospective study design, information about demographics, social, medical and surgical history and medication usage was collected from all included subjects. On the day of surgery, the enrolled TKA patients underwent assessment of pain disability status using the Pain Disability Questionnaire (PDQ) [20], which is well validated in patient groups with chronic pain or musculoskeletal disorders compared to asymptomatic normal individuals. The PDQ contains two components, a functional status component and a psychosocial component. Functional items include ability to walk, run, bend, lift, reaching objects overhead, personal care, work and travel. The PDQ functional subscale consists of eight items, each of which is answered on a scale from 0 to 10 [21]. Pain at rest was also assessed using the verbal numerical rating scale (NRS, 0–10) prior to surgery at the time of obtaining the PDQ; as well as postoperatively. Postoperatively, NRS scores were obtained when the patients were at rest by the nursing staff on the floor every four hours for the first 24 h and again by the study team at 72 h at the time of the last blood collection. CSF was collected from the TKA patients at the time of the spinal anesthesia prior to surgery. Importantly, given the dependence of leptin on blood glucose and circadian rhythm [22], CSF samples were collected in the fasting patients in the period between 9 am and 12 pm. Blood was collected from the patients three times: at the time of the CSF sample, four to six hours and 72 h post-operatively. JSF was collected intra-operatively for analysis of the same three cytokines (only 20 JSF samples were obtained due to later Institutional Review Board (IRB) approval of this study procedure).

2.3. Analysis of cytokines

Serum samples prepared from freshly drawn blood and CSF collected in sterile uncoated tubes (BD Vacutainer) were flash frozen in liquid N_2 and stored at −80 °C until analysis. JSF samples were subjected to centrifugation at 1800 ×g for 15 min at four degrees Celsius and the supernatant fluids were flash frozen and stored at −80 °C. On the day of the assay, the samples were

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