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Biomechanical Evaluation of the Accuracy of Radiographic Assessment of Femoral Component Migration Measurement after Total Hip Arthroplasty

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Received Sept. 10, 2019; Accepted for publication Dec. 13, 2019; Published online April 17, 2020

ABSTRACT

Introduction. Implant subsidence is one criteria utilized to monitor for prosthesis loosening after total hip arthroplasty (THA) with initial implant subsidence assessment often done utilizing plain radiographs. The specific aim of this study was to identify the most reliable references when using plain radiographs to establish an image magnification with the goals being easy to use, inexpensive, reliable, and accurate.

Methods. Two femoral stem implants (stem lengths: 127 mm, 207 mm) were utilized to simulate hemiarthroplasty of the hip with composite femurs. Different combinations of femoral stem distances from the radiographic film (ODD), source-detector differences (SDD), hip rotation, and hip flexion were elected. Standardized anterior-posterior pelvis for each parameter combination setup were taken. Radiographic measurements (head diameter, stem length, stem seating length) were undertaken five times by three examiners. Radiographic image magnification factors were generated from two references (head diameter and stem length). Radiograph measurement reproducibility and stem seating length errors using these magnification factors were evaluated.

Results. High level of repeated measurements reliability was found for head diameter (99 ± 0%) and stem length (90 ± 7%) measurements, whereas seating length measurements were less reliable (76 ± 6%). Stem length error using the femoral head magnification factor yielded 11% accuracy. Stem seating length error using both magnification factors were not reliable (< 7% accuracy). All parameters, except SDD, showed significant effect on calibrated measurement error.

Conclusion. Current methods of assessing the implant subsidence after THA are inaccurate and unreliable. Clinicians should recognize these limitations and be cautious when diagnosing implant stability using plain radiographs alone. Kans J Med 2020;13:65-70

INTRODUCTION

The stability of the prosthetic components after total hip arthroplasty (THA) is critical for long-term implant performance. Early migration of prosthetic stems and cups greater than 3 mm resulted in later aseptic failure of the prosthesis.1,5 The prognostic value of early recognition of prosthetic component migration for long-term implant performance also has been demonstrated.2,10,16 With small distances of implant migration being critical, the accuracy of measurement methods to evaluate component migration after THA is essential.

Femoral stem subsidence is one criteria utilized to monitor for prosthesis loosening after THA with initial implant subsidence assessment often utilizing plain radiographs. Several studies investigated the validity and reliability for measuring displacement on plain radiographs for different parts of the body.17-20 Their results indicated that caution should be taken when interpreting clinical results using plain radiographs to measure displacement. However, these studies did not suggest improving accuracy and reliability when using radiographs to calculate the radiographic image magnification factor and implant migration. Walker et al.12 pointed out that using landmarks close together on the femur and the stem of the implant were optimal for determining femoral stem migration. To our knowledge, there have been few studies to evaluate the effect of selecting different references for the radiographic image magnification factor that could lead to better accuracy or precision when determining femoral stem migration. The specific aim of this study was to identify the most reliable references when using plain radiographs to establish an image magnification with the goals being easy to use, inexpensive, reliable, and accurate.

METHODS

Two femoral stem implants were utilized, one with a stem length of 127 mm (SL-1) and the other with a stem length of 207 mm (SL-2; Figure 1). The stem length of these implants were measured from the tip of the proximal end to the distal tip of the stem. Both implants had a femoral head size of 32 mm. Two composite large femurs (Model 3406, Sawbones USA, Vashon Island, WA) were used to simulate hemiarthroplasty of the hip utilizing the two selected femoral stems (Figure 1). The femur was placed into a custom-designed holding jig to replicate patient positioning in a supine position while obtaining a radiographic image.

Testing all combinations of different femoral stem distances from radiographic film (ODD), source-detector differences (SDD), hip rotation, and hip flexion systematically created a large number of possible combinations prohibitively large (Figure 2). This study elected to test combinations of parameters that were clinically relevant and included ODD: 82 mm, 177 mm, 277 mm; SDD: 102 cm, 122 cm; hip rotation angle: -15° (internally rotated), 0°, 15° (externally rotated); and hip flexion angle: 0°, 5°, 10°. The ODD of 82 mm was selected presumptuous the radiographic film cassette was on the radiographic table top and right under a patient’s buttocks. When the radiographic film cassette was put under the radiographic table the ODD increased to 177 mm, as the distance between the radiographic table top to the radiographic film cassette; drawing for the cassette under the radio-
The ODD of 277 mm was assumed; the femoral stem was 100 mm above the radiographic table top.

Radiographic images were simulated as standardized anterior-posterior (AP) pelvis radiographs in a supine position for each parameter combination setup (Figures 3a and 3b). Three examiners evaluated the radiographic measurements for each image, which were provided in a randomized order. These radiographic measurements included measurement of femoral head diameter (FHD), femoral stem length (FSL), and femoral stem seating length (FSSL). The femoral stem seating length was measured between the most medial and inferior point of the resected portion of the femur and the distal tip of the stem (Figure 3c). Standardized magnification (zoom in) was utilized to “landmark” the most superior and most inferior aspects of the femoral stem, similar for the femoral seating length and the femoral head diameter. After all the measurements were recorded, the measurements on the radiographs were cleared and the images zoomed out to normal view. This process was repeated five times by each examiner with at least one day between repeated measurements. All radiographs were evaluated using the Sectra IDS7 PAC system (Sectra AB, Linköping, SWEDEN) with a measurement resolution of 0.1 mm.

Two references for the radiographic image magnification were selected: femoral head diameter (FHD) and femoral stem length (FSL). The magnification factor (Mag_FHD, Mag_FSL) was generated by comparing either the FHD to the known implant diameter or the FSL to the known implant stem length, respectively.

\[
\text{Mag}_{\text{FHD}} = \frac{\text{FHD}}{\text{actual head diameter}} \\
\text{Mag}_{\text{FSL}} = \frac{\text{FSL}}{\text{actual stem length}}
\]

With femoral head diameter as the magnification factor, the “calibrated femoral stem lengths” then were calculated using the generated Mag_FHD.

\[
\text{calibrated femoral stem length}_{\text{FHD}} = \frac{\text{FSSL}}{\text{Mag}_{\text{FHD}}}
\]

Stem length error was defined as the difference between the calibrated femoral stem length and the actual known stem length.

\[
\text{stem length error}_{\text{FHD}} = \text{calibrated femoral stem length}_{\text{FHD}} - \text{actual stem length}
\]

The femoral stem seating length measured on the radiographs was modified using both generated magnification factors (Mag_FHD, Mag_FSL) to arrive at a calibrated seating length for both.

\[
\text{calibrated stem seating length}_{\text{FHD}} = \frac{\text{FSSL}}{\text{Mag}_{\text{FHD}}}
\]

\[
\text{calibrated stem seating length}_{\text{FSL}} = \frac{\text{FSSL}}{\text{Mag}_{\text{FSL}}}
\]

The stem seating length error was defined as the difference between the calibrated FSSLs and the actual stem seating length. The actual stem seating length for the two selected implant stem lengths of 127 mm and 207 mm were physically measured and were 93 mm and 166 mm, respectively (Figure 1).

\[
\text{stem seating length error}_{\text{FHD}} = \text{calibrated FSSL}_{\text{FHD}} - \text{actual stem seating length}
\]

\[
\text{stem seating length error}_{\text{FSL}} = \text{calibrated FSSL}_{\text{FSL}} - \text{actual stem seating length}
\]

**Statistical Analysis.** Data retrieved from the radiographic measurements were analyzed using a histogram to evaluate the frequency distribution of the absolute differences between the five repeated measured values for each radiograph, and for each examiner, to represent the majority of the measurement error. This study also calculated the percent of absolute differences that were less than 0.5 mm between radiographic measurements to provide an estimate of intra-reliability. An absolute difference of less than 0.5 mm was defined as an “excellent” reliability. Descriptive statistics of the mean, standard deviation, 95% confidence interval, and range were determined for all radiographic measurement variables. Frequency distribution analyses were utilized to represent the distribution of the stem length errors and seating length errors using the two reference magnification factors.
RESULTS

A total of 92 radiographic images of simulated THAs were included and reviewed. On the same radiographs, all examiners displayed a high level of repeated measurements reliability for FHD and FSL measurements with $99 \pm 0.2\%$ and $90 \pm 7.1\%$ within 0.5 mm error difference in measurements, respectively. The mean absolute differences for these two measurements were $0.16 \pm 0.13$ mm (range: $0.0 - 1.0$ mm, 95% CI: $0.01$ mm) and $0.24 \pm 0.23$ mm (range: $0.0 - 2.2$ mm, 95% CI: $0.02$ mm), respectively (Table 1). The reliability for FSSL measurements was less consistent than the other two measurements above (reliability: $76.3 \pm 5.5\%$ within 0.5 mm error; mean absolute difference: $0.39 \pm 0.35$ mm; range: $0.0 - 4.6$ mm; 95% CI: $0.02$ mm; Table 1). A frequency of measurement errors is shown in Figure 4.

When investigating the stem length error using the generated magnification factor from the femoral head diameter, there were only 11% accurately measured with an error of 0 mm between the calibrated stem length and the actual stem length (Figure 5). There was 45% accuracy to within 1 mm between the calibrated stem length to the actual stem length. The accuracy of radiographic calibrated stem length was higher with the shorter stem length (127 mm) when compared to the longer stem length (207 mm; Figure 5).

When comparing the calibrated stem seating length measurement with the two reference magnification factors (Mag_FHD, Mag_FSL) it was found that the overall accuracy measurement with both reference magnification factors were not reliable with only 6% and 3% within 0 mm error, respectively (Figure 6). There was less than 50% (Mag_FHD: 47%, and Mag_FSL: 39%) accuracy to within 2 mm error when compared to the actual stem seating length. It was also noticed that the accuracy of calibrated stem seating length was higher with the longer stem length (207 mm) when compared to the shorter stem length (127 mm; Figure 6).

The results of this study observed significant differences in calibrated measurement error with combinations of different femoral stem distances from radiographic film (ODD), hip rotation angle, and hip flexion angle. However, there was no significant difference detected in calibrated measurement error with the effect of the SDD (Table 2, p > 0.05).

DISCUSSION

Several radiological measurement techniques using conventional plain radiographs have been developed and utilized for the detection of implant migration. Some studies utilized different reference lines or points on the implants and the bone, and/or used markers on the bone for these measurements.\textsuperscript{21-24} Some recognized that the accuracy and precision of each measuring method varies. Malchau et al.\textsuperscript{25} have shown that measurements of stem migration on conventional radiographs varied from 4 mm to 12 mm when compared to the results with radiostereometry (RSA), depending on the choice of landmarks. Several other studies\textsuperscript{26-29} also evaluated the validity and reliability for measuring displacement on plain radiographs of different parts of the body, and their results indicated that caution should be taken when interpreting clinical results using plain radiographs to measure displacement.

![Figure 4. Histogram analysis of radiographic measurement error between each repeated measurements for all three examiners of femoral head diameter, femoral stem length, and femoral stem seating length.](image-url)
Figure 5. Frequency distribution analysis of calibrated femoral stem length errors using magnification factor based on the femoral head diameter (mag_fhd).

Figure 6. Frequency distribution analysis of calibrated stem seating length errors using different reference magnification factors, mag_fhd and mag_fsl.

This study utilized two references for the radiographic image magnification with the hypothesis that using femoral stem length to generate the radiographic image magnification factor shall provide a more reliable and accurate reference for determining femoral stem migration after THA. The results agreed with previous studies that measuring displacement on plain radiographs is not reliable regardless of selecting different references for the radiographic image magnification. This may be because plain radiographs provide a two-dimensional projected representation of a three-dimensional object.

The selected reference for the correction of magnification and the choice of the reference lines on conventional radiographs have significant effect on the accuracy and precision of the implant migration measurement. Even with standardized radiographic positioning and procedures guidelines, the radiographic images of the same patient at different points in time produce difficulties with accuracy and reliably to measure implant migration. The present study showed that minor changes in hip rotation, hip flexion, and ODD of the patient resulted in significant changes in calibrated radiographic measurement error. A change in hip rotation of 15°, hip flexion of 5°, and ODD of 100 mm resulted in a maximum absolute change of 1.9 mm, 2.2 mm, and 0.6 mm in calibrated stem seating length error of chosen reference for the radiographic image magnification, respectively (Table 2).

| Parameter                  | Average ± SD | Min-Max   |
|----------------------------|--------------|-----------|
| **Stem Length Error**      |              |           |
| Rotation                   |              |           |
| -15°                       | -0.8 ± 2.1   | (-7.7 - 3.6) |
| 0°                         | -1.8 ± 1.9   | (-9.0 - 2.3) |
| 15°                        | -2.5 ± 1.9   | (-9.2 - 8.9) |
| Stem Seating Length FHD    | -0.7 ± 2.5   | (-5.4 - 6.3) |
| Stem Seating Length FSL    | -1.8 ± 2.6   | (-7.1 - 6.9) |
| Stem Seating Length FSL    | -3.0 ± 2.8   | (-9.6 - 5.1) |
| Flexion                   |              |           |
| Stem Length Error          |              |           |
| 0°                         | -2.1 ± 2.0   | (-9.2 - 1.3) |
| 5°                         | -0.6 ± 1.9   | (-6.2 - 8.9) |
| 10°                        | -1.4 ± 2.0   | (-8.4 - 3.2) |
| Stem Seating Length FHD    | -0.6 ± 2.6   | (-6.2 - 6.9) |
| Stem Seating Length FSL    | -2.8 ± 2.1   | (-7.4 - 4.0) |
| Stem Seating Length FSL    | -3.4 ± 2.2   | (-9.6 - 2.3) |
| ODD                        |              |           |
| Stem Length Error          |              |           |
| 177 mm                     | -1.5 ± 2.0   | (-9.0 - 8.9) |
| 277 mm                     | -1.3 ± 2.1   | (-9.2 - 3.6) |
| Stem Seating Length FHD    | -2.0 ± 2.5   | (-7.3 - 6.9) |
| Stem Seating Length FSL    | -2.6 ± 2.7   | (-9.6 - 6.2) |
| Stem Seating Length FSL    | -3.3 ± 2.1   | (-8.6 - 1.7) |
| SDD                        |              |           |
| Stem Length Error          |              |           |
| 102 cm                     | -1.6 ± 2.3   | (-9.2 - 8.8) |
| 122 cm                     | -1.6 ± 1.6   | (-8.4 - 2.6) |
| Stem Seating Length FHD    | -1.8 ± 3.0   | (-9.6 - 6.9) |
| Stem Seating Length FSL    | -1.8 ± 2.7   | (-8.6 - 4.7) |
| Stem Seating Length FSL    | -3.2 ± 2.2   | (-9.9 - 1.7) |
| Stem Length                | SL-1         | -0.8 ± 1.5 | (-8.4 - 8.9) |
| Stem Length                | SL-2         | -2.4 ± 2.1 | (-9.2 - 3.6) |
| Stem Seating Length FHD    | SL-1         | -3.4 ± 2.0 | (-8.6 - 12.0) |
| Stem Seating Length FSL    | SL-2         | -0.2 ± 2.7 | (-8.2 - 6.9) |
| Stem Seating Length FSL    | SL-1         | -4.0 ± 1.8 | (-9.9 - 1.7) |
| Stem Seating Length FSL    | SL-2         | -2.2 ± 2.1 | (-8.0 - 1.0) |
Most studies dealing with radiographic measurements consider even small differences in length as significant.\textsuperscript{1,15} This raises the question if radiographic parameters, as suggested in literature, truly provide reliable information on outcomes after THA in clinical routine. If displacement measurements from plain radiographs are inaccurate and reliable, then it is impossible to understand the effect of implant subsidence on outcome, and clinicians cannot communicate effectively about the stability of prosthetic components after THA based on radiographic evaluation. The stability of the prosthetic components after THA, therefore, shall not be diagnosed exclusively with a sequence of radiographic images, it shall be diagnosed with a combination with clinical situation and symptoms.

Roentgen stereophotogrammetric analysis (RSA) generally is accepted as the gold standard of implant migration measurement tools, especially regarding accuracy and three-dimensional (3-D) migration measurement. RSA use has been reported with an accuracy within 0.2 mm for implant subsidence.\textsuperscript{2,23–30} RSA has added a great deal to the assessment of implant subsidence in THA, and these 3-D reconstructions aid significantly in evaluating post-operative implant migration and the rate of migration. However, this is not being used for routine post-operative follow-up due to concerns of cost, feasibility only for prospective study designs as small radio-opaque markers are introduced into the bone and the prosthesis to serve as well-defined artificial landmarks, and impracticality for long-term studies with large patient populations.\textsuperscript{23–31}

This study has certain limitations. First, this biomechanical investigation was performed using radiographs of Sawbones models without soft tissues which potentially could differ from the radiographic quality of images than are obtained in the clinical setting. Second, this study contained only two selected implants (SL-1 and SL-2) that could limit the generalization to different types, sizes, or shapes of implants. Third, femoral stem seating length was measured from the most medial and inferior point of the resected portion of the femur, which is not a typical clinical assessment. The authors understood that the most common landmark on the femur used to measure the stem seating length is with the lesser trochanter, as the resected portion of the femur will change over time. It was performed this way for the present study due to the fact the lesser trochanter was sometimes difficult to visualize in radiographic images depending on the orientation of the femur, whereas the resected portion of the femur could be observed easily in all the evaluated radiographic images. The main goal was to determine the accuracy of displacement measurement between calibrated radiographic measurement to the actual implant measurement. Despite these limitations, the outcomes of this study were valuable because this study shed light on the limitations of utilizing serial digitized plain radiographs to perform radiological displacement measurements. Further evaluation is required to support our findings.

CONCLUSIONS
Current methods of assessing the implant subsidence after THA are inaccurate and unreliable. Literature citing acceptable implant migration displacement based on plain-film radiographic parameters should be interpreted with caution. Our results indicated that measurement errors are most likely to be expected. Clinicians should recognize these limitations and be cautious when diagnosing implant stability using plain radiographs alone.

ACKNOWLEDGEMENTS
The authors want to acknowledge Cheryl Hanson, RT (R), Kayla Klipping, RT (R), and Brent Colby, MS DABR of Sanford Health Department of Radiology for their technical support and assistance with the radiograph images obtained for this study. The authors especially thank Colin Bond, MS, Michelle McGearry, BS, and Sean-Tom Garry, BS of Sanford Sport Science Institute for their assistance on this study.

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Keywords: radiography, hip replacement arthroplasty, hip dislocation, bone-implant interface, biomechanical phenomena
Urine Screening for Opioid and Illicit Drugs in the Total Joint Arthroplasty Population
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Received Sept. 10, 2019; Accepted for publication Dec. 15, 2019; Published online April 17, 2020

ABSTRACT

Introduction. Recent studies have shown an increase in post-operative orthopaedic complications associated with pre-operative opioid use. It is, therefore, important to know if patients use opioids before scheduled surgery. The purpose of this study was to determine if urine drug screening (UDS) is an effective screening tool for detecting opioid and illicit drug use prior to joint arthroplasty (JA) procedures.

Methods. This retrospective chart review was performed with IRB approval on 166 out of 172 consecutive patients in a community-based practice. All the patients had a pre-operative UDS prior to primary or revision JA by a fellowship trained orthopaedic surgeon between March 2016 and April 2017. Patient demographics documented opioid and illicit drug use, co-morbid diagnosis, and UDS results were collected from clinical charts. Statistical analysis was conducted using Pearson Chi-square, Fisher’s exact, McNemar test, and t-tests with IBM SPSS Statistics, ver. 23. Significant differences were p < 0.05.

Results. Sixty-four of 166 patients (38.6%) tested positive for opioids. Among them, 55.0% (35/64) had no history of prescription opioid use. Significant differences were observed when comparing the test results of the UDS with the patient reported history of prescribed opioids (p = 0.001).

Conclusion. With a significant number of patients testing positive for opioids without evidence of a previous prescription, UDS may be beneficial for initial risk assessment for patients undergoing JA procedures. Kans J Med 2020;13:71-76

INTRODUCTION

Alarming increases have occurred in the rate of drug overdose deaths involving synthetic opioids, such as tramadol, fentanyl, and its analogs. Data from the National Vital Statistics System (NVSS) reported that the age-adjusted rate of drug overdose has increased 88% per year from 2013 to 2016, and rose another 9.6% in 2017.1 This report also showed that trends for natural and semisynthetic opioids, such as oxycodone and hydrocodone, have also increased steadily. Similarly, the 2016 National Survey on Drug Use and Health (NSDUH) estimated 28.6 million Americans aged 12 years or older were current illicit drug users.2 These drugs included marijuana, cocaine (including crack), heroin, hallucinogens, inhalants, methamphetamines, and the misuse of prescription pain relievers such as tranquilizers, stimulants, and sedatives that were prescribed to someone else.

Prescription Opioid Use. A driver of this misuse is an overwhelming increase in physicians prescribing a long-term course of pain relievers, such as opioids, for chronic pain.3-4 One such condition is degenerative joint disease, or osteoarthritis, which is the leading cause of chronic pain and physical disability in older populations.5 Opioids, which are powerful pain-relieving substances, often are prescribed to patients with joint disease. Evidence indeed supports the effectiveness of opioids, showing an average 3-point decrease in pain as measured by a 10-point pain rating scale.5

However, studies have suggested an increase in post-operative orthopaedic complications associated with pre-operative opioid use.6-11 Pre-operative drug users are at risk for longer hospital stays, have higher mortality rates, and more surgical complications, including postoperative infection, anemia, convulsions, osteomyelitis, and blood transfusion.12 More specifically, pre-operative opioid users have less favorable outcomes following total knee (TKA) and total hip arthroplasty (THA).13-17 Besides the fact that they require more opioid refills, remain on opioids longer after surgery, and have an increased risk of chronic opioid use postoperatively,18-20 Evidence of common characteristics of those who use opioids include patients aged 35 to 49 years, taking five or more other medications, insured by Medicare or Medicaid, established versus new patients, treated by primary care versus specialty physicians, and in prescribing regions of the south or west.21

In recognition of this misuse, state-level prescription drug monitoring programs have been implemented in most states. Research to evaluate the effectiveness of these programs has been difficult because they vary by design and requirements. One study analyzed physician-reported data on prescribing opioids and found that these programs appeared to be unsuccessful when trying to reduce physicians prescribing opioids.22 It has been estimated that opioids are prescribed in 1 of 5 patients with non-cancer pain or pain-related diagnoses in an office-based setting.23 This wide spread prescribing practice predisposes patients to chronic drug misuse and overdose related deaths.24-26

Illicit Drug Use. Seemingly, stricter enforcement of the prescription drug monitoring programs is merited and could lead to reduced drug misuse. However, this may lead to another issue in appropriate pain management: increased illicit drug use.27 Indeed, recent literature showed an increase in complications in the trauma population associated with illicit drug use.28 With ever increasing access to and use of illicit drugs in the United States,29 rates of drug misuse necessitates awareness and surveillance by all physicians. In elective orthopaedic procedures where the underlying goal is to improve the quality of the patient’s life, it is important for orthopaedic physicians to have a thorough risk assessment of the patient to determine the most appropriate treatment course for his/her diagnosis. An accurate and up-to-date history and physical examination may be the best

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way to evaluate the patient’s risks for surgery. However, due to negative perceptions of opioid and illicit drug use, patients may be reluctant to disclose this information to the physician.

**Study Objective.** To evaluate the extent to which patients disclose opioid and illicit drug use, we conducted urine drug screening (UDS) in our clinic for all patients who were scheduled for joint arthroplasty (JA). Our primary objective was to minimize complications and readmissions following JA in high-risk patients. The purpose of this study was to compare self-reported pre-operative drug use with UDS test results to determine if UDS would be an effective screening tool for detecting opioid and illicit drug use. We hypothesized that there would be a significantly high number of individuals in the JA population who do not reveal pre-operative drug use prior to surgery, thus putting themselves at undo risk of postoperative complications.

**METHODS**

**Participants.** A cross-sectional, retrospective chart review was performed on 172 consecutive patients in a community-based practice. Adult patients who had a pre-operative UDS prior to primary or revision JA were eligible to participate. Included in the subjects were patients scheduled for a JA between March 2016 and April 2017 by an adult reconstructive fellowship trained orthopaedic surgeon. JA was defined as primary or revision total hip arthroplasty (THA), total knee arthroplasty (TKA), patella femoral joint arthroplasty (PFJ), or uni-compartment knee arthroplasty (UKA).

This study was approved by the institutional review board (IRB). Each patient was told during the evaluation in the clinic to have a urine test for opioids and other associated illicit drugs prior to scheduling of the surgery. All patients used a private restroom with a member of the work staff outside the door in the senior author’s clinic to collect their sample for the UDS. The UDS company used in this study was “Tru-Fit”. All screens initially were examined by a strip in the clinic office, then confirmed off-site by the company using a gas chromatography. The UDS test cost the patient approximately sixty dollars, however, this varied with the type of insurance. At the time of presentation in clinic, the intake form that documented the patient’s current prescribed drugs was initiated by the patient, then reviewed by a medical assistant with the patient to confirm the accuracy.

**Measurements.** Patient information was extracted from the charts, which included age, gender, body mass index (BMI), primary diagnosis, co-morbid diagnoses (including psychiatric disorders), smoking status, surgical date, history of medication list, type of insurance (Medicare, private, or workers’ compensation), and JA procedure type. Data on comorbidities included diabetes, hypertension, hyperlipidemia, renal disease, major depression disorder, and general anxiety disorder. Pre-operative prescribed opioid use and UDS results also were collected.

**Outcomes.** The primary outcomes were the dichotomous UDS test result from four drug panels. The opiate/opioid drug panel included tests for 6-monoacetyl morphine, buprenorphine, codeine, EDDP, fentanyl, hydromorphone, meperidine, methadone, morphine, naloxone, naltrexone, norbuprenorphine, norfentanyl, O-Desmethyl tramadol, oxycodone, oxymorphone, tapentadol, and tramadol. The remaining drug panels were categorized as illicit drugs that included the amphetamine panel (amphetamine, MDA, MDEA, MDMA, methamphetamine, methylphenidate, and phentermine), the cannabinoid panel (THC, J-122_4-HYDROXYL and JWH-200), and the “other drug” panel (benzylecgonine, dextromethorphan, mitragynine, PCP, and propoxyphene). For secondary outcomes, patients’ pre-operative prescription medicine list was evaluated to determine if they were taking any pre-operative opioids. The number of patients taking pre-operative opioids was analyzed and compared to the patients that tested positive on UDS.

To eliminate false-positive results, the senior author offered a second drug screen to patients who tested positive for illicit drugs prior to cancelling their surgery.

**Statistical Analyses.** Data analysis was performed to determine the number of patients who had a positive urine toxicology for pre-operative opioid use or for illicit drugs, along with the number of patients who initially did not reveal the pre-operative drug use. Descriptive statistics included frequencies and percentages for categorical data. Continuous data were evaluated for normality and subsequent summarized with means and standard deviations. Groups were compared by positive or negative UDS results using the following two-tailed tests: Pearson Chi-square asymptotic and exact tests, McNemar test, and t-tests. Significant results were identified as those with p < 0.05. Analyses were conducted with IBM SPSS Statistics, ver. 23.

**RESULTS**

The analysis included 166 of the 172 patients; six patients were excluded because they underwent a procedure other than a JA. Data were missing on six participants for BMI, smoking, and insurance; two participants had missing data for comorbidities. The sample included 95 (57.2%) females and 71 (42.8%) males. The mean age was 64.5 years, with a standard deviation of 10.9 years. Many of the patients (61.9%; 99 /160) were obese. Of the 166 patients screened with UDS, 64 (38.6%) tested positive for opiate/opioids. Regarding the illicit drug panels, 7 (4.2%) tested positive for Amphetamines, 6 (3.6%) for Cannabinoids, and 2 (1.2%) for other drugs (one participant tested positive for multiple drug panels within this category).

Table 1 summarizes participant characteristics by positive UDS results. Two participant characteristics significantly differed by UDS: over 44% (41/92) of current/former smokers tested positive for opiate/opioids (p = 0.036), while almost 55% (18/33) diabetic patients tested positive (p = 0.033). No other patient factors differed significantly by UDS results including sex, age, BMI, insurance type, type of scheduled arthroplasty, or other comorbidities. However, almost 40% of patients (34/92) scheduled for total knee arthroplasty tested positive for opiate/opioids; similarly, almost 44% (21/48) scheduled for total hip arthroplasty tested positive. (Note: because few patients tested positive for the three illicit drug panels, no other statistical tests were conducted for these drugs with only frequencies reported for these drug classes.)
Table 1. Participant characteristics by urine drug screen results.

| Characteristics          | Positive Urine Drug Screen |          |          |          |          |          |
|--------------------------|----------------------------|----------|----------|----------|----------|----------|
|                          | N (%)                      | N (%)    | p        | N (%)    | p        |          |
| Female                   | 95 (57.2)                  | 37 (52.8)| 0.904    | 9 (64.3) | 0.577    |          |
| Male                     | 71 (42.8)                  | 27 (42.2)|          | 5 (35.7) |          |          |
| Mean age (SD)            | 166 (100.0)                | 63.5 (11.8)| 0.342    | 59.6 (10.9)| 0.081    |          |
| BMI                      |                            | 0.991    |          | 0.389    |          |          |
| Normal                   | 15 (9.4)                   | 6 (9.7)  |          | 1 (7.1)  |          |          |
| Overweight               | 46 (28.7)                  | 18 (29.0)|          | 2 (14.3) |          |          |
| Obese                    | 99 (61.9)                  | 38 (61.3)|          | 11 (78.6)|          |          |
| Smoking status           |                            | 0.036    |          | 0.213    |          |          |
| Current                  | 31 (19.4)                  | 18 (29.0)|          | 3 (21.4) |          |          |
| Former                   | 61 (38.1)                  | 23 (37.1)|          | 8 (57.1) |          |          |
| Never                    | 68 (42.5)                  | 21 (33.9)|          | 3 (21.4) |          |          |
| Insurance type           |                            | 0.982    |          | 0.314    |          |          |
| Medicare/Medicaid        | 89 (55.6)                  | 34 (55.7)|          | 6 (42.9) |          |          |
| Commercial               | 71 (44.4)                  | 27 (44.3)|          | 8 (57.1) |          |          |
| Type of arthroplasty     |                            | 0.536*   |          | 0.186*   |          |          |
| Total knee: primary      | 92 (55.4)                  | 34 (53.1)|          | 6 (42.9) |          |          |
| Total hip: primary       | 48 (28.9)                  | 21 (32.8)|          | 3 (21.4) |          |          |
| Patella femoral joint    | 11 (6.6)                   | 3 (4.7)  |          | 2 (14.3) |          |          |
| Total knee: revision     | 9 (5.4)                    | 4 (6.3)  |          | 2 (14.3) |          |          |
| Total hip: revision      | 3 (1.8)                    | 2 (3.1)  |          | 1 (7.1)  |          |          |
| Uni-compartment knee     | 3 (1.8)                    | 0 (0.0)  |          | 0 (0.0)  |          |          |
| Co-morbidities (choose all that apply)** | | | | | |
| Hypertension             | 98 (59.8)                  | 39 (61.9)| 0.658    | 7 (50.0) | 0.436    |          |
| Diabetes                 | 33 (20.1)                  | 18 (28.6)| 0.033    | 3 (21.4) | 0.899    |          |
| Thyroid Disease          | 28 (17.1)                  | 14 (22.2)| 0.166    | 1 (7.1)  | 0.302    |          |
| Heart Disease            | 27 (16.5)                  | 10 (15.9)| 0.872    | 1 (7.1)  | 0.325    |          |
| PMH of Cancer            | 29 (17.7)                  | 7 (11.1) | 0.081    | 0 (0.0)  | 0.070    |          |
| Rheumatoid Arthritis     | 19 (11.6)                  | 6 (9.5)  | 0.515    | 3 (21.4) | 0.229    |          |

*Pearson Chi-square exact 2-sided test
**Other co-morbidities reported, but not listed in the table due to spare data: Atrial fibrillation = 7, Chronic kidney disease = 8, COPD = 8, hypercholesterolemia = 13, psychiatric disorders = 10.
Positive UDS results were compared to self-reported history of prescribed opioids (Table 2). Results from the amphetamine panel showed seven patients tested positive, with four disclosing a history of prescribed opioids. For cannabinoids, six were positive, two of which disclosed a history of opioids. UDS results for the other drug panel showed two positive, with one self-reported opioid prescription. The opiate/opioid panel showed 38.6% (64/166) tested positive, but 35 of 64 patients were using opioids without a prescription ($p < 0.01$). Twenty-eight percent or 35 of 125 with no prescription for opioids test positive on UDS. Twenty-nine of 41 with a prescription of opioids tested positive on UDS. Thus, it appeared opioid use was significantly under-reported prior to surgery.

**DISCUSSION**

This study suggested that opioid use is relatively common in elderly patients who are evaluated for JA surgery in a community-based orthopaedic clinic. The results from this study also demonstrated that a significantly high portion of these patients have a positive UDS for opioids that failed to disclose this information on their initial pre-operative examination. The prevalence of positive UDS for illicit drugs was higher than expected, especially for this relatively elderly population.

This study had limitations. The first limitation was the small population size from a single senior author’s clinic with a limited number of cases in our study timeframe. The other limitation may come from the relatively narrow detection time of UDS. For instance, oxycodone may not be detected if administered more than three days prior to testing, according to the Mayo Clinic Laboratories Guidance (https://www.mayocliniclabs.com/test-info/drug-book/opiates.html). Also, this study did not consider the duration and dosage of opioid use, which Nguyen et. al.\(^\text{13}\) has shown to effect clinical outcomes.

However, recent studies such as Ben-Ari et al.\(^\text{3}\) found that 39.1% of patients that underwent a TKA in the U.S. Veterans Affairs (VA) system were prescribed long-term opioids pre-operatively; 2.2% of these patients required a revision within a year. They concluded that long-term opioid use prior to TKA was associated with an increase in knee revisions.\(^\text{3}\) Similarly, Zywiel et al.\(^\text{17}\) found pre-operative opioid use prior to TKA was associated with diminished functional scores, increase risk for complications, and prolonged painful recovery. Singh et al.\(^\text{15}\) found an increased correlation between patients on pre-operative opioids prior to TKA and risk of complications within the first 90 days post-operatively. They further concluded that pre-operative opioid use should be disclosed as a risk for complications to patients and should be taken into consideration by the physicians prior to opioid management. All these studies justified that pre-operative

| Table 2. Positive UDS test results for each drug and number of patients with history of prescribed opioids. |
|---------------------------------------------------------------|
| **Positive Urine Drug Screen**                                |
| **Self-Reported History of Prescribed Opioids**               |
| **Yes** | **No** | **Total** |
| **Amphetamines Panel**                                       |
| 4 | 9.8 | 3 | 2.4 | 7 | 4.2 |
| **Amphetamine**                                               |
| 2 | 4.9 | 2 | 1.6 | 4 | 2.4 |
| **Phentermine**                                               |
| 2 | 4.9 | 0 | 0.0 | 2 | 1.2 |
| **MDEA**                                                     |
| 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Methamphetamine**                                          |
| 0 | 0.0 | 2 | 1.6 | 2 | 1.2 |
| **Methylphenidate**                                          |
| 0 | 0.0 | 1 | 0.8 | 1 | 0.6 |
| **Cannabinoids Panel**                                       |
| 2 | 4.9 | 4 | 3.2 | 6 | 3.6 |
| **THC**                                                      |
| 2 | 4.9 | 4 | 3.2 | 6 | 3.6 |
| **Opiate/Opioid Panel**                                      |
| 29 | 70.7 | 35 | 28.0 | 64 | 38.6 |
| **Oxymorphone**                                              |
| 13 | 31.7 | 4 | 3.2 | 17 | 10.2 |
| **Oxycodone**                                                |
| 12 | 29.3 | 3 | 2.4 | 15 | 9.0 |
| **O-Desmethyltramadol**                                      |
| 10 | 24.4 | 14 | 11.2 | 24 | 14.5 |
| **Tramadol**                                                 |
| 10 | 24.4 | 14 | 11.2 | 24 | 14.5 |
| **Hydrocodone**                                              |
| 7 | 17.1 | 17 | 13.6 | 24 | 14.5 |
| **Hydromorphone**                                            |
| 4 | 9.8 | 11 | 8.8 | 15 | 9.0 |
| **Morphine**                                                 |
| 3 | 7.3 | 1 | 0.8 | 4 | 2.4 |
| **Codeine**                                                  |
| 0 | 0.0 | 3 | 2.4 | 3 | 1.8 |
| **EDDP**                                                     |
| 0 | 0.0 | 2 | 1.6 | 2 | 1.2 |
| **Fentanyl**                                                 |
| 0 | 0.0 | 0 | 0.0 | 0 | 0.0 |
| **Methadone**                                                |
| 0 | 0.0 | 2 | 1.6 | 2 | 1.2 |
| **Other Drug Panel**                                         |
| 1 | 2.4 | 1 | 0.8 | 2 | 1.2 |
| **Dextromethorphan**                                         |
| 1 | 2.4 | 0 | 0.0 | 1 | 0.6 |
| **Benzoylcegonine**                                          |
| 0 | 0.0 | 1 | 0.8 | 1 | 0.6 |
opioid use should be screened at the initial examination as part of a thorough risk analysis of the patient. Interestingly, these studies only looked at the reported prescriptions. The current study may illustrate that these patients need to be screened even further because patients have access to these medications beyond their current prescriptions.

Levy et al. evaluated the prevalence of illicit drug use in orthopaedic trauma patients. They found that patients tested positive for alcohol (25%), cocaine (22%), and marijuana (21%). They further found that patients with a positive screen had more severe orthopaedic injuries and longer hospital stays. Similarly, Lank et al. also utilized the UDS to evaluate trauma patients over 55 years of age and found that patients who tested positive for marijuana and cocaine resulted in longer lengths of stay in the ICU compared to patients with negative UDS. This is in contrast to the current study, which had a more elderly patient population and patients who were evaluated for elective cases like JA. Our study found only 3.6% of patients tested positive for marijuana. However, this study was not performed where marijuana is legal. Furthermore, one could suspect that this prevalence would be higher in a state where marijuana has been legalized. With this increase in the number of states legalizing the use of marijuana, future studies need to evaluate how this will affect outcomes in patients who undergo elective orthopaedic cases such as JA procedures.

In this study, all histories of medication intake were clarified with the patients when the results of the urine drug screen returned. When excluding the patients testing positive for marijuana, 6% of patients in this study tested positive for other illicit drugs. This is clinically significant especially in a community-based practice such as this study was performed. The literature on how illicit drugs affect the outcomes with orthopaedic procedures is limited, especially in elective cases. However, the ability to evaluate illicit drugs such as cocaine, amphetamines, or heroin in elective JA procedures likely is limited for future research. It is more realistic for future studies to determine how canceling these cases may affect the overall complication rate.

With recent literature reporting an increase in post-operative complications with pre-opioid use, combined with the significantly high prevalence of pre-opioid and illicit drug use found in this elderly general population and patients not disclosing this information on their exam, it may be necessary to utilize the UDS for initial risk assessment for patients undergoing JA procedures. However, further studies need to evaluate how a positive UDS for pre-operative opioids affects patient’s undergoing JA procedures complications post-operatively and function outcomes. This study found that access to these opioid drugs, other than what patients are prescribed, is prominent in the community-based orthopaedic clinic setting and further screening needs to be evaluated for pre-operative opioid use. Thus, UDS may be clinically helpful in assessing patient’s risks pre-operatively.

CONCLUSION

With a significant number of patients testing positive for opioids without evidence of a previous prescription, UDS may be beneficial for initial risk assessment for patients undergoing JA procedures.

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Keywords: opioid-related disorders, substance abuse detection, total joint replacement
INTRODUCTION

Stridor, a high-pitched monophasic sound indicative of airway obstruction, is a common presenting symptom in pediatric emergency department (ED). Although underlying cause of stridor is infectious in most cases, such as croup or bronchiolitis, clinicians should maintain a broad differential diagnoses when dealing with a child with stridor. We are presenting a unique case of cervico-mediastinal thymic cyst presenting as stridor and ultimately leading to acute hypoxic respiratory failure.

CASE REPORT

A previously healthy 18-month-old boy presented to an emergency department (ED) with fever, tachypnea, inspiratory stridor, and brief period of apnea with cyanosis. Oxygen saturation improved with adequate airway positioning and administration of oxygen via nasal cannula. He was given racemic epinephrine for continued stridor in addition to combination therapy with ipratropium bromide and albuterol. He then was transferred to a pediatric ED for a higher level of care.

In the pediatric ED, he was noted to have dyspnea and stridor with sudden desaturation, along with seizure-like activity, including clenching of his jaws. He was given lorazepam for seizure-like activity. He continued to receive supplemental oxygen via placement of oral airway for airway protection. He required intubation by direct laryngoscopy following an episode of emesis associated with desaturation. He was admitted to the pediatric intensive care unit (PICU), where septic workup was completed with chest x-ray (CXR) showing a right patchy opacity, negative blood cultures, and negative respiratory viral panel. He was started on intravenous (IV) dexamethasone and IV ceftriaxone. A diagnosis of febrile seizures was made after an electroencephalogram showed no evidence of focal or epileptiform abnormalities. A repeat CXR showed diminished lung volumes with a consolidative medial right upper lobe opacity. Heart size and central vascularity were within normal limits but a prominent thymic shadow was seen (Figure 1).

He was extubated after three days on mechanical ventilation. Immediately after extubation, he had severe desaturations which improved with jaw thrust and bag and mask ventilation. He was supported on continuous positive airway pressure (CPAP), and an otolaryngologist was consulted. A bedside flexible laryngoscopy showed no evidence of upper airway obstruction. Immediately following the procedure, he had another decompensation requiring re-application of CPAP. He received a high-dose methylprednisolone burst over seven days and was weaned off of CPAP. He eventually was discharged home with a one-week prescription of dexamethasone and antibiotics along with a referral for a primary care physician (PCP) follow-up.

Due to persistent dyspnea and stridor, the patient was continued on oral steroids at home by his PCP and again was seen by an otolaryngologist who recommended further evaluation. He underwent microlaryngoscopy and rigid bronchoscopy six weeks after admission to the PICU, where he was found to have severe distal tracheal obstruction. A computed tomography (CT) scan of chest with angiogram revealed a large thymic cyst compressing his innominate artery and distal airway (Figure 2). He underwent an excision of cervicmediastinal cyst and was extubated immediately after surgery without having desaturation episodes. He was weaned to room air and was discharged home on post-operative day two.

DISCUSSION

By the sixth week of gestation, the thymus can be recognized as a separate paired organ. Embryologically, it is derived from the third and fourth pharyngeal pouch. On the onset of the eighth week of gestation, thymic anlage develops into the thymopharyngeal duct. This duct runs from the mandibular angle to the anterior superior mediastinum, the ultimate position of the thymus. The upper end of the thymus regresses and gradually disappears. The remnant of endodermal epithelium undergoes regression and forms the Hassall’s corpuscles.
Figure 2. CT scan of chest with angiogram with a large thymic cyst compressing innominate artery and distal airway.

Two main theories for the origin of cervical thymic cyst have been suggested. First, a unilocular cyst is more common which is thought to originate from the persistence of thymopharyngeal duct. Second, a multilocular cyst is attributed to the degeneration of thymic Hassal's corpuscle.

Cervico-mediastinal thymic cysts (CTC) are increasingly rare with only 100 cases reported in the literature. Most of the time, it is asymptomatic, making diagnosis difficult; thus a large number of cases are discovered incidentally. CTCs have strong male preponderance, more predilection toward the left side and present themselves during the first decade of life as a painless slow growing mass in the areas located between the angles of the mandible to sternum. In nearly half of the cases, the CTC may reach up to and make contact with the mediastinum. If symptomatic, patients usually present to the outpatient department with complaints of stridor, dysphonia, or dysphagia, as was in our case.

The differential diagnosis of CTCs in the pediatric population is extensive, ranging from common congenital causes, such as thyroglossal duct cyst, branchial cyst to benign tumors (dermoid cysts, epidermoid cysts), malignant tumors (lymphoproliferative, soft tissue sarcoma and other metastatic lesions), and tumors arising from thyroid and parathyroid. Imaging studies, mainly CT scan and magnetic resonance imaging (MRI), along with surgical findings and histopathological correlation play an important role in diagnosing a thymic cyst.

The treatment of choice is surgical excision and no recurrences have been reported after complete resection. However, it is imperative that the existence of a mediastinal thymus be confirmed with MRI or fine needle aspiration cytology prior to surgery, because thymectomy during childhood can cause severe impairment of immune status later in life. Thymic carcinoma and myasthenia gravis are some of the rare complications of surgery which should be taken into account.

CTC, albeit a rare cause of pediatric neck mass, should not be overlooked as a diagnosis when a child presents with asymptomatic cervical neck mass or persistent stridor with hypoxic respiratory failure despite adequate ventilatory support. Ultrasound, MRI, and CT scan along with histopathological examination are the best modalities to create a definitive diagnosis. CTCs have excellent prognosis and can be treated with surgical excision with minimal chance of recurrence.

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Keywords: thymic cyst, mediastinal cyst, stridor, airway obstruction, tracheal stenosis
Chronic Anterior Knee Pain in a Wrestling Athlete from a Neuroma of the Infrapatellar Branch of the Saphenous Nerve

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Received Sept. 4, 2019; Accepted for publication Dec. 16, 2019; Published online April 17, 2020

INTRODUCTION

Anterior knee pain is the most common knee complaint presenting to primary care and orthopaedic offices. Many cases are chronic and are not related to a specific precipitating injury or trauma. Knee pain due to a neuroma is not a common cause of anterior knee pain, and as such is ill defined in medical literature.

There have been few case reports identifying painful neuromas from the infrapatellar branch of the saphenous nerve (IBSN) as a cause of chronic pain in patients. The saphenous nerve is a division of the femoral nerve. It divides into the main saphenous branch and the IBSN. Anatomic models show the IBSN crossing the anterior knee below the patella and dividing into three branches eventually combining to form the patellar plexus.

The IBSN is a pure sensory nerve. This nerve may be injured through direct trauma6-9 or surgical procedures such as knee arthroplasties and arthroscopic procedures. In some cases, patients may have pain without significant known trauma. Previous case reports have identified this in older patients post-surgically. This report presents a case of a neuroma causing chronic anterior knee pain in a high school athlete, which to our knowledge is the first reported case in the literature.

CASE REPORT

A 17-year-old male presented for evaluation of a six-month history of right knee pain. The patient, a high school wrestler, stated that the pain began after he landed directly onto his knee. The pain was located on the anterior medial aspect of the knee, occurring specifically with wrestling activities. He characterized it as a severe, burning pain only with kneeling, sometimes associated with a shocking and shooting sensation directly over the affected area without radiation of pain. He denied any mechanical symptoms of locking, catching, or giving way and there was no pain with walking, running, or at rest. The patient was unable to wrestle effectively due to pain.

Before presenting to our clinic, the patient had been evaluated by two outside orthopaedic surgeons and had already undergone the following imaging and procedures:

1. On initial evaluation in 2017, a small extra-articular mass at the medial border of the patella was palpated. A palpable painful fibroma within the prepatellar bursa was presumed to be the source of the pain per the outside physician. Plain film radiographs were unremarkable; no further imaging was obtained. The patient underwent prepatellar bursa resection and excision of the tender fibroma. The pathology report demonstrated dense fibrosis and fibroadipose tissue with focal reactive changes and reactive vascular proliferation with mild inflammation. Following the procedure, he completed a course of physical therapy.

2. Three months following the above procedure, there was no improvement and patient was evaluated by a second orthopaedic surgeon. An MRI demonstrated mild edema of the subcutaneous tissues anterior to the knee, thought to be postsurgical, as well as a tibial tubercle non-united ossicle that was deemed to be an incidental finding corresponding to his previous history of Osgood-Schlatter disease. The MRI was otherwise unremarkable. A diagnostic arthroscopy was performed, identifying a small chondral injury measuring 8 mm x 9 mm along the medial margin of the medial femoral condyle which roughly corresponded to the location of the pain. A chondroplasty was performed, but there was no improvement of the pain after 10 weeks.

The patient presented to our clinic seeking a third opinion for his knee pain. At the initial visit, a diagnostic supra-patellar, landmark-guided intra-articular injection with 4 ml lidocaine and 3 ml ropivacaine was performed. The patient did not obtain any relief from the injection, thus suggesting an extra-articular cause of his pain unrelated to the chondral lesion that was noted on previous arthroscopy. At that time, patient opted for a trial of conservative management with topical analgesics, including 1% topical diclofenac gel and lidocaine patch.

At one-month follow-up, the patient reported no change in his pain despite using the topical analgesic. Standard knee exam was benign without focal tenderness. His pain was reproduced by having him kneel in the exam room. Once the area of pain was localized, physical exam revealed point tenderness and a subtle mass that was located medial to the patella, only noted with the knee flexed past 90 degrees. The palpable, painful, fibrous-like band reproduced the pain. A landmark-guided soft tissue injection was performed at the site of palpable pain using 0.5 ml of 1% lidocaine and 20 mg of triamcinolone. However, this injection did not relieve pain significantly and he was referred to an orthopaedic surgeon for resection of the possible neuroma. An incision was made directly over the painful band over the medial femoral condyle and it was dissected to where the band could be palpated. There appeared to be an IBSN neuroma. This was dissected back and resected.

At two weeks post-operatively, the patient reported significant improvement in his pain. At the six-week follow-up, his wound was healed and he was able to progressively resume full activities. Since then, he has been able to continue his wrestling career at the collegiate level.
DISCUSSION

There is a wide differential for chronic anterior knee pain in the student athlete. Common causes of knee pain can be due to patellofemoral pain, ligamentous or meniscal injuries, osteochondral lesions, infrapatellar bursitis, Hoffa syndrome, Osgood-Schlatter disease, patellar or quadriceps tendonitis, or tendinosis. It is important to differentiate between intra-articular and extra-articular causes of pain. Knee pain as a result of a neuroma from the IBSN is an extra-articular manifestation. Post-surgical causes of neuromas of the IBSN have been described better than traumatic causes.

In a review of two cases from motor vehicle accidents after a dashboard injury, no neuromas were identified, but neurolysis of the IBSN provided immediate resolution of pain. Another review of five cases of neuralgia from direct trauma to the anteromedial aspect of the knee that failed conservative treatment, achieved complete resolution of pain from neurolysis of the IBSN.

In a review of surgical cases, there have been many identified cases related to arthroscopy, anterior cruciate ligament reconstruction with hamstring graft harvesting, and total knee arthroplasties. In respect to patients who had total knee replacements with persistent neuromatous pain who had failed conservative therapy, Dellon et al. reported significant pain relief in 60 out of 70 patients who proceeded with selective denervation. There are few reports describing neuromas of the IBSN secondary to knee trauma. To our knowledge, there are no reported cases in a student athlete.

Detailed history and careful physical examination may be able to identify a specific area of pain to elucidate pain coming from the IBSN. Trigger point injections may identify the pain as a report from Grabowski et al. demonstrated the use of lidnocaine, providing at least two weeks of pain relief. However, in our patient, the trigger point injection did not result in any subjective relief of the pain at the time of injection of local anesthetic nor in the weeks post-procedure in response to the corticosteroid. Failure of trigger point injection does not rule out pain from the IBSN and that neurolysis or surgical exploration and resection is an appropriate next step. Another consideration would be to order additional imaging such as MRI or musculoskeletal ultrasound if no recent images were available.

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Keywords: infrapatellar branch of saphenous nerve, anteromedial knee pain, infrapatellar neuralgia, infrapatellar pain syndrome
INTRODUCTION

In 2019, approximately 330,000 new cases of breast cancer are estimated to be diagnosed, with about 80% of those likely to be the invasive breast cancer type. On average, 75% of all newly diagnosed breast cancers are hormone receptor-positive (HR+). Although HR+ breast cancer expresses both estrogen and progesterone receptors (ER; PR), ER signaling pathways ultimately determine cellular growth and survival. As a result, drug therapies were developed that selectively target vital steps in this ER signaling pathway and historically have been the foundation of HR-positive breast cancer treatment. As a group, these agents are termed endocrine therapy and include aromatase inhibitors (e.g., letrozole, anastrozole, and exemestane), selective ER modulators (tamoxifen), and selective ER down-regulators (fulvestrant).

Endocrine therapy alone has its limitations. Not only do certain breast cancer patients have inherent estrogen hormone resistance, but also HR+ tumor cells have the capability to use alternate, non-estrogen dependent pathways for further growth and survival. One such known alternate route is the cyclin D-cyclin-dependent kinase 4/6-inhibitor of CDK4-retinoblastoma pathway. Recently, CDK4/6-inhibitors have been developed and investigated to be used alone or with traditional endocrine therapy for HR+ breast cancer.

Palbociclib is an oral selective inhibitor of CDK4/6. This novel agent was awarded accelerated approval by the US Food and Drug Administration (FDA) in 2015 following the PALOMA-1 trial data showing that the combination of palbociclib with letrozole results in improved progression-free survival rates in metastatic, ER+, human epidermal growth factor receptor 2 (HER2)-negative postmenopausal breast cancer patients who had not had prior treatment for advanced disease. Subsequently, based on PALOMA-3 trial results, palbociclib also was approved for advanced breast cancer refractory to endocrine therapy when used in combination with fulvestrant.

CASE REPORT

A 79-year-old female presented to the emergency department with acute encephalopathy and jaundice. Her past medical history was notable for stage IV invasive ductal carcinoma of the breast with bone metastasis, ER+, PR+, HER2- by fluorescence in situ hybridization (FISH), who failed initial standard of care chemotherapy, and was started on palbociclib and fulvestrant (1st cycle: oral palbociclib 125 mg oral daily for days 1-21 of a 28-day cycle plus 7-day rest; 2nd cycle: oral palbociclib 100 mg daily for days 1-21 of a 28-day cycle plus 7-day rest; intramuscular fulvestrant 500 mg on days 1, 15, and 29). In addition, her chronic medical conditions included type 2 diabetes mellitus, hyperlipidemia, and gastric esophageal reflux disease which were being managed with metformin 500 mg daily, atorvastatin 10 mg daily, and omeprazole 20 mg daily, respectively.

The patient had completed her second cycle approximately one week prior to presentation. On admission, liver injury was evident based on lab results showing a total bilirubin of 4.6 mg/dl (1.0 mg/dl one month prior), aspartate transaminase of 200 u/l (AST, 50 u/L one month prior), alanine transaminase of 50 u/l (ALT 20 one month prior), alkaline phosphatase of 150 u/l (90 u/L one month prior), INR of 3.8, and ammonia of 70 u/L. Serum analysis was negative for elevated acetaminophen. A thorough autoimmune serology and viral hepatitis workup for other possible causes of liver injury was non-revealing. Thrombocytopenia and macrocytic anemia with equivocal support for hemolysis was present based on platelets of 35 x109/L, hemoglobin of 8.5 g/dl, mean corpuscular volume of 124 fl, lactic acid dehydrogenase of 950U/L (1450 one month prior), fibrinogen of 170 mg/dl; D-dimer of 11,000 ng/mL, undetectable haptoglobin levels, and presence of schistocytes on peripheral smear analysis. Infectious workup revealed WBC of 7.5 x109/L 22% bands, 1 of 2 blood cultures positive for pansensitive Escherichia coli.

Roussel Uclaf Causality Assessment Method (RUCAM) and Drug-Induced Liver Injury Network (DILIN) severity scores for palbociclib were 8 (probable) and 5+ (fatal), respectively. Biochemically, the liver injury was cholestatic (R factor of 0.2) with a marked increase in total bilirubin suggestive of biliary cholestasis. Imaging studies showed a homogenously enlarged and lobulated liver surrounded by perihepatic free fluid. The right liver lobe tip extended inferiorly beyond the right kidney suggesting significant hepatomegaly (Figure 1). The gallbladder and biliary ducts were unremarkable. These findings were notable when compared to CT images of the abdomen performed two-years prior which was negative for hepatomegaly, cirrhosis, or a lobular appearance. Based on the patient’s clinical history, presentation, and sonography, acute liver injury was more probable.

Despite standard of care therapies and steroids she developed refractory hypotension, her labs and encephalopathy worsened, and her overall condition deteriorated. The patient’s liver enzymes and bilirubin continued to trend up: AST of 1268 u/l, ALT of 167 u/l, and total bilirubin of 9.8 u/l. The patient subsequently received supportive treatment and transitioned to comfort care.

DISCUSSION

HR+ breast cancer treatment guidelines support the combination of CDK-inhibitor plus endocrine therapy based on randomized control trial data showing that when used together these therapies are effective, delay tumor progression, and improve the rates of progression-free survival and overall survival. In the large clinical trials, adverse events
were common and led to dose reductions and discontinuation of medications. However, there have been few case reports of clinically severe liver injury attributable to palbociclib.

**Figure 1. Ultrasound, liver.** Left image: Homogenously enlarged liver with a grossly nodular and lobular appearance (arrows). Right image: Significant hepatomegaly represented by liver tip extending inferiorly beyond the level of the kidney, ascites (arrows).

Targeted therapies have revolutionized the landscape of oncologic treatments. Several studies have evaluated the safety and efficacy of palbociclib in combination with endocrine therapy. Elevated liver function tests were a rare but reported adverse event (AE) in 7.2% of the palbociclib-treated patients in the PALOMA-1 study. In the PALOMA-2 study, ALT and AST elevations were reported as AEs (all grades) in 99% and 97.6% of palbociclib-treated patients, respectively. In the PALOMA-3 study, there was one fatal serious AE of hepatic failure with grade 5 disease progression in the palbociclib group; however, the patient’s medical history included progressive liver metastasis and disease progression. Across all PALOMA studies, a pooled safety analysis demonstrated that grade 3/4 AST and ALT elevations occurred in 3.3% and 2.3% of palbociclib-treated patients, respectively, again highlighting a reported but rare occurrence.

Among all three PALOMA trials, neutropenia was the most frequently reported adverse reaction. Combination therapy of palbociclib with either letrozole or fulvestrant uncommonly resulted in grade 3 or 4 serious adverse events. The most frequently reported serious adverse reactions in patients who received palbociclib plus fulvestrant were infections, neutropenia, and pulmonary embolism. Among the 1,348 patients enrolled in the three PALOMA trials, none experienced fulminant hepatotoxicity that lead to stopping drug therapy. In the intention-to-treat populations, six cases of elevated AST (n = 1, 1%), ALT (n = 3, 1%), γ-glutamyl transferase (GGT, n = 2, 2%) were observed when palbociclib was administered in combination with letrozole. Ascites of any grade (n = 3, 1.7%) was noted for patients receiving dual therapy of palbociclib plus fulvestrant. Thus, overall few treatment-related acute liver injuries were observed. However, final trial analysis of palbociclib plus fulvestrant noted one liver-related death that was not attributed to palbociclib. Moreover, the diagnosis of drug-induced liver injury remains challenging.

DILIN causality assessment process, despite its shortcomings, remains an important method in the field and a reasonable diagnostic standard. The mechanism of palbociclib-induced liver enzyme elevation is not well understood. Palbociclib is metabolized predominately by the hepatic CYP3A4 pathway. Thus, liver injury could be caused by the production of a toxic or immunogenic intermediate. Equally plausible, is coadministration with a strong CYP3A inhibitor, which increases the plasma exposure of palbociclib.

Open source software and databases show there would be a low likelihood of clinically significant drug-drug interactions between any of the patient’s home medications and palbociclib. However, atorvastatin, metformin, and omeprazole are all CYP3A4 substrates and possible inhibitors. Thus, palbociclib metabolism theoretically could be inhibited causing increased serum concentrations of the substance. Currently, there is no official monitoring guidelines in terms of liver function testing when a patient is administered palbociclib therapy.

Likely based on PALOMA trial data, the palbociclib’s FDA-approved product monograph only recommends monitoring for neutropenia by complete blood counts prior to starting palbociclib therapy, at the beginning of each cycle, and on day 14 of the first two cycles, as well as clinically indicated. No dose adjustment is required for patients with mild or moderate hepatic impairment. However, the recommended dose of palbociclib for patients with severe hepatic impairment (Child-Pugh class C) is 75 mg once daily. The patient detailed in this case had no history of hepatic impairment prior to starting treatment. Also, her liver function testing was unremarkable during assessments between cycles one and two of drug therapy.

In conclusion, the patient described in this case report illustrated an uncommon but serious complication from palbociclib in the treatment of metastatic breast cancer. Palbociclib should be considered as a possible cause of drug-induced liver injury when targeted CDK 4/6-based regimens are used. Serum aminotransferase elevations above 3- to 5 times the upper limit of normal or any elevations accompanied by jaundice should alarm physicians and lead to temporary or permanent cessation of palbociclib therapy.

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Keywords: palbociclib, acute hepatic failure, hepatic encephalopathy
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