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REVIEW

Impact of dental clearance on total joint arthroplasty: A systematic review

Christopher Frey, Sergio M Navarro, Terri Blackwell, Carla Lidner, H Del Schutte Jr

ORCID number: Christopher Frey (0000-0001-7009-7977); Sergio M Navarro (0000-0003-3455-1567); Terri Blackwell (0000-0003-0012-7020); Carla Lidner (0000-0003-2668-4386); H Del Schutte Jr (0000-0003-0921-5852).

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Christopher Frey, Department of Orthopedic Surgery, Stanford Medicine, Redwood City, CA 94063, United States

Sergio M Navarro, Department of Surgery, Baylor College of Medicine, Houston, TX 77030, United States

Sergio M Navarro, Said School of Business University of Oxford, Oxford OX1 1HP, United Kingdom

Terri Blackwell, H Del Schutte Jr, Comprehensive Joint Program, Charleston Institute for Advanced Orthopedics, Charleston, SC 29464, United States

Carla Lidner, Dentistry, Orange County Dental Society, Orange, CA 92868, United States

Corresponding author: Christopher Frey, MD, Doctor, Department of Orthopedic Surgery, Stanford Medicine, 50 Broadway Street Pavilion C, 4th Floor, Redwood City, CA 94063, United States. chris1fr@stanford.edu
Telephone: +1-571-2253999
Fax: +1-650-7213470

Abstract

Many orthopedic surgeons require that their patients obtain dental clearance before elective total joint arthroplasty (TJA). However, there is no consensus substantiating the practice. To this end, a systematic review on the prevalence of dental pathology in TJA patients, risk factors for failing dental screening, and impact of dental evaluations was performed. Literature was sourced from PubMed and Scopus databases. Six papers were sourced from the initial search, one study was extracted from the references of the original six manuscripts, and one new publication was retrieved from a second search conducted after the first. The prevalence of dental pathology ranged from 8.8% to 29.4% across studies. Two of four papers reported lower than average or improvements in post-operative infection with pre-operative dental evaluations while two found no such association. There is insufficient evidence to support universal dental clearance before TJA.

Key words: Total knee arthroplasty; Total hip arthroplasty; Total joint arthroplasty; Periprosthetic joint infection; Dental screening

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Core tip: There is insufficient evidence to support universal dental clearance before total knee arthroplasty or total hip arthroplasty procedures for reducing periprosthetic joint infection, even for higher risk patients.

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INTRODUCTION

While there have been improvements in total joint arthroplasty (TJA) throughout the years, it is compromised by the risk of periprosthetic joint infection (PJI), the most common cause of total knee arthroplasty (TKA) and total hip arthroplasty (THA) failure[1,2]. It is a devastating complication which results in significant patient morbidity. Infected revisions can easily exceed the cost of performing the primary arthroplasty and are projected to total $ 1.62 billion by 2020[3]. Key risk factors have been determined, and include poor nutritional status, smoking, inadequate blood sugar control, and poor dental health[4,5,6]. Ideally, knowledge of these factors can be used to develop risk mitigation strategies. One potential application is discerning the impact of dental procedures and pathologies on adverse outcomes in TJA.

There exists no absolute criteria or single test to diagnose PJI. Instead, diagnosis is based upon a mixture of lab results, cultures, and clinical findings[7]. The implication of a dental source is often based upon both the identification of a pathogen considered to be a constituent of the patient's oral flora at the infection site and the timing of the infection with a seeding procedure[8]. This premise is based upon the finding that many events such as dental scaling and brushing one's teeth can cause transient bacteremia when dental pathology is present[9,10]. Such reports have been cited when implementing dental prophylaxis in arthroplasty patients prior to dental procedures. Conversely, some orthopedic surgeons recommend that patients receive preoperative prophylactic antibiotics and/or dental clearance before TJA.

Given the lack of overarching guidelines on the role of dental clearance and its association with TJA outcomes, a systematic review was performed using data from primary studies to summarize the prevalence of dental pathology in patients scheduled for TKA and THA and the impact of dental evaluation and necessary interventions on outcomes.

METHODS

The literature search consisted of PubMed and Scopus database inquiries in February 2019 for the impact of dental clearance and the epidemiology of significant dental pathology in potential TJA patients (Figure 1). This was conducted by one author. Search terms consisted of "Arthroplasty AND Dental AND Clearance" and "Arthroplasty AND Dental AND Hygiene" for both databases. This yielded 6 papers that m*et al*l of the criteria (Table 1). One additional paper was selected from a review article that resulted from the initial search. Another paper was individually retrieved after the initial screen as it was accepted and published in May.

Literature assessing the association between dental clearance and TJA outcomes were included. Manuscripts examining prevalence of and risk factors for failing dental clearance were included as well. Considering the scarcity of evidence, various summary measures were accepted, with a preference for risk ratios. Only human studies within the last 25 years were included to ensure that the results are applicable. Interventional, case-control, and cross-sectional studies were included. In total, eight studies met criteria. All studies were evaluated for quality and bias using a modified 27 item Downs and Black checklist[11]. For the power analysis (item 27), we substituted a simple score of 0 or 1 score. Papers received one point if they included power calculations. We decided to utilize this instrument to evaluate methodological quality because it is validated for both randomized and non-randomized studies. We did not use a formal metric to estimate risk of bias across studies.

After the studies were included, data concerning impact of dental clearance, model

Table 1 PubMed and Scopus search results

Search	Hits
PubMed search results	
Arthroplasty and dental and clearance	5
Arthroplasty and dental and hygiene	21
Sourced from citations	0
Scopus search results	
Arthroplasty and dental and clearance	5
Arthroplasty and dental and hygiene	18
Sourced from citations	1

used, sample size, methods, results with statistical analysis, and conclusions were extracted by one author and transcribed in a table. This was reviewed by another author for verification. Next, inputs for the methodological quality analysis with the Downs and Black checklist were extracted.

RESULTS

Quality assessment

Eight studies were included[12-19]. Of the 8, 7 (86%) included a dental evaluation performed by a dental professional[12-14,16-19] and five utilized questionnaires or interviews (71%)[13-17]. One paper used a questionnaire alone[15]. Although papers were selected from peer reviewed publications, 2 were not listed on PubMed[15,19]. The articles scored between 15 and 23 using our modified DandB checklist (Table 2). The papers were limited by several factors. For instance, none of the selected manuscripts were randomized or blinded, increasing risk of bias. Additionally, many of the papers had small sample sizes, and none demonstrated calculation of power. Lastly, it should be noted that the paper by Barrington and Barrington was designed to capture the primary outcome of dental pathology incidence, not for detecting PJI[16].

Prevalence of periodontal pathology

Four studies focused on the prevalence of dental pathology and/or dental hygiene practices in patients to undergo TJA (Table 3)[12-15]. Adamkiewicz *et al*[12] had dental evaluations performed on patients admitted for TJA preoperative workup in Poland. They found that 28.5% had clinically significant periodontal disease. This compares with 23% in previously published national data[20]. There were no significant differences in inflammatory markers or cell counts between the periodontal disease and healthy groups.

Tokarski *et al*[13] employed a dental hygiene questionnaire along with a dental evaluation. They found that 12% failed dental clearance, which, in this case, was defined as requiring a tooth extraction or root canal. The number increases to 19% when patients requiring fillings are included. Additionally, they identified that patients with one of three key risk factors (narcotic use, tobacco use, and last dentist visit over one year ago) had a 22% chance of failing the dental evaluation, compared with 6% if they did not have any.

Vuorinen *et al*[14] also used both questionnaires and dental evaluation in an attempt to determine which patients ought to receive dental clearance based on risk factors. Twenty-nine point four percent of patients failed clearance, 34% were found to have moderate gingivitis, and 5.1% of patients had severe periodontitis. This compares with national reports that 27% of Finnish patients had periodontal disease[21]. It was found that the only significant risk factors for failing dental clearance were history of root canal, dental visit for symptoms within the last 3 mo, infrequent dental checkups, and tobacco use. Patients with regular examination and no history of root canal were 50% less likely to fail clearance.

Lastly Wood *et al*[15] used a post-operative dental hygiene survey without professional dental evaluation. They found that patients in general report adequate oral hygiene and 76% having had a dental cleaning within the last year. Only 5% admitted to not having a dentist.

Impact of dental clearance and/or scaling on infection

Four studies measured the impact of preoperative dental clearance on TJA outcomes

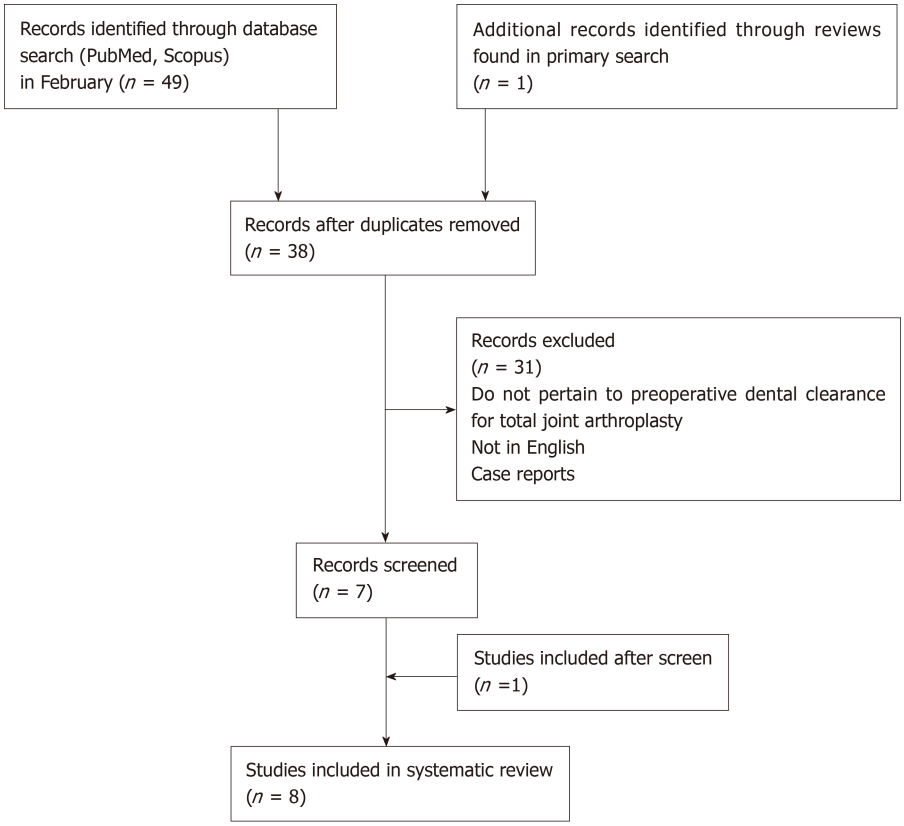

Figure 1 Workflow of PubMed and Scopus database query.

(Table 4)[16-19]. Barrington and Barrington required patients to receive dental evaluation and the appropriate interventions before elective TJA[16]. Twenty-three percent were found to have active tooth decay requiring treatment. There were no significant differences between primary and revision groups. Although it was not the primary outcome, there were no infections related to the operation detected within the first 90 d post-operatively in any of the 100 patients.

Lampley and colleagues compared postoperative infections between elective TJA patients who had received dental clearance and hip fracture patients who received THA or hemiarthroplasties who did not receive pre-operative dental clearance[17]. Out of the patients who received dental clearance, 8.8% required treatment for periodontal disease. There was no significant difference in postoperative infection (less than 6 mo post-op) requiring reoperation. Of the 6 (1.7%) patients with infections in the elective group, only one failed the dental screen. A pathogen was detected in 5 out of the 6 cases. Four (2.5%) patients in the hip fracture group required reoperation for infection concern. Only one patient had an identifiable pathogen. None of the pathogens except, possibly, Peptostreptococcus magnus in the dental clearance group were of likely dental origin.

Tai *et al*[18] utilized a retrospective data from the National Health Insurance Research Database (NHIRD) to compare TKA patients who required "removal of hardware" plus 7 d of antibiotics within five years of the operation to those who did not. They found that dental checkups and scaling were associated with significantly lower post-operative infection rates. Only 7.1% of the infection group had regular checkup and scaling (5-6 times over last three years) compared to 9.9% in the healthy group. Moreover, 73.1% had no visits in the infection group compared to 67.8% in the healthy group. The adjusted OR of PJI when receiving regular checkup and scaling was 0.69 (0.54-0.89) and 0.84 (0.71-0.99) when less frequent.

Sonn *et al*[19] performed a retrospective review of 2457 patients who underwent primary TJA. Seventy-nine point one percent of these patients received dental evaluation before the operation, however, it appears this was decided on an individualized basis and not based on a predetermined, randomized approach. Complication-free rates at 36 mo were similar between those who did and did not receive dental evaluation. Although not significant, both the dental evaluation and extraction groups appeared more hazardous than the groups that did not have a dental workup [Hazard ratio (HR) = 1.95, P = 0.07 and HR = 1.24, P = 0.57]. The rate of PJI was measured to be 1.51%, however this was not compared between groups.

Table 2 Quality assessment based on downs and black questionnaire

	Adamkiewicz *et al*[12]	Tokarski *et al*[13]	Vuorinen *et al*[14]	Wood *et al*[15]	Barrington *et al*[16]	Lampley *et al*[17]	Tai *et al*[18]	Sonn *et al*[19]
Q1	1	1	1	1	1	1	1	1
Q2	1	1	1	1	0	1	1	1
Q3	1	1	1	1	0	1	1	1
Q4	1	1	1	1	1	1	1	1
Q5	1	2	2	2	1	1	2	1
Q6	1	1	1	1	1	1	1	1
Q7	1	1	1	0	0	1	1	1
Q8	1	1	1	1	0	1	1	1
Q9	1	1	1	1	1	1	1	1
Q10	1	1	1	0	0	1	1	1
Q11	1	1	1	1	1	1	1	1
Q12	1	0	0	0	1	0	1	1
Q13	1	1	1	1	1	1	1	1
Q14	0	0	0	0	0	0	0	0
Q15	0	0	0	0	0	0	0	0
Q16	1	1	1	1	1	1	1	1
Q17	1	1	1	1	1	1	1	1
Q18	1	1	1	0	0	1	1	1
Q19	1	1	1	1	1	1	1	1
Q20	1	1	1	1	1	1	1	1
Q21	1	1	1	1	1	1	1	1
Q22	1	1	1	1	1	1	1	1
Q23	0	0	0	0	0	0	0	0
Q24	0	0	0	0	0	0	0	0
Q25	0	1	1	1	0	0	1	1
Q26	1	1	1	1	1	1	1	1
Q27	0	0	0	0	0	0	0	0
Total	21	22	22	19	15	20	23	22

DISCUSSION

In this systematic review, we attempted to capture the prevalence of dental pathology and risk factors in populations in consideration for TJA as well as the impact of dental clearance and interventions on the outcomes of TJA procedures. In order to advocate for the institution of these rules, the benefits of pre-operative dental evaluation must outweigh the not-insignificant costs imposed on patients and the healthcare system at a whole. Overall, there is not enough concrete evidence to support dental evaluation for all patients.

We included four studies that paint a picture of dental health of TJA patients. Failure of dental clearance ranged from 8.8%[17] to 29.4%[14]. However, the standards for evaluation varied. The criteria used by Tokarski *et al*[13] measured failure as requiring tooth extraction or root canal. In fact, when carious lesions are included, failure rates increased from 12% to 19%[13]. Similarly, Lampley *et al*[17] measured failure as dental pathology necessitating intervention prior to surgery and only found a failure rate of 8.8%. Wood and colleagues detected good overall dental hygiene at a tertiary care center in Canada with 76% having had a dental checkup within the previous 12 mo and only 5% admitting to not seeing a dentist[15]. When compared by region, TJA patients in American tertiary care centers had failure rates from 8.8% to 23%[13,16]. This is moderately higher than failure rates in Poland (28.5%)[12] and Finland (29.4%)[14]. However, it is difficult to pool data do to differences in baseline patient population oral health status and variation in dental evaluation practice.

Two of the studies evaluated risk factors for failing dental clearance. Tokarski *et al*[13] found that of several risk factors, patients who had one or more of: Narcotic use, tobacco use, and no dental visit within the last 12 mo had a 22% risk of failure compared to 6% for patients with no risk factors. The authors concluded that it is

Table 3 Risk factors and epidemiology of total joint arthroplasty patients

Author	Model	*n*	Methods	Results	Conclusion
Adamkiewicz *et al*[12]	Patients at a tertiary University Hospital in Poland	228	Patients admitted for elective TJA received dental evaluation along with standard preoperative workup	Clinically significant periodontal disease was detected in 28.5% of patients	Periodontal disease is prevalent in patients undergoing TJA
Tokarski *et al*[13]	Patients at a tertiary care center in the United States	300	Patients answered a dental hygiene questionnaire then received dental evaluations and necessary interventions	12% failed dental clearance. Patients with one or more of: Narcotic use, tobacco use, or last dentist visit over one year ago, had a 22% risk of failure compared to 6% for patients with no risk factors	It may be reasonable to only screen high risk patients for dental pathology
Vuorinen *et al*[14]	Patients at a public, tertiary care hospital in Finland	731	Patients filled out a prospective dental health questionnaire and underwent a dental examination and necessary interventions	29.4% of patients failed dental clearance. 5.1% of patients had severe periodontitis. Tobacco use and root canal were risk factors. Regular dental examination was a preventive factor	The inspection and treatment of dental pathology is important prior to elective TJA
Wood *et al*[15]	Patients at a large academic center in Canada	453	Patients answered a dental hygiene survey at their 6 wk post-operative appointment	76% of patients had a cleaning within 12 mo. 5% did not visit a dentist. 49% were informed of the impact of dental hygiene in reducing PJI	Patients generally have good oral hygiene, but patient education is inconsistent

PJI: Periprosthetic joint infection; TJA: Total joint arthroplasty.

feasible to exclusively screen those with high risk profiles. However, Vuorinen *et al*[14] found that tobacco use, history of root canal, dental visit for symptoms, and infrequent dental visits were significant risk factors. Patients with no root canal and regular checkups were less likely to fail, but grouping, as performed in the previous study, did not yield a significantly different risk profile. The authors concluded that they were unable to identify a group of patients who could avoid dental clearance.

We identified four papers that detail the impact of dental clearance and/or necessary interventions on the outcomes of TJA, with one of the four finding a significant positive impact of dental clearance and/or evaluation[16,18]. Firstly, Barrington and Barrington detected pathology requiring treatment in 23% of patients[16]. No periprosthetic joint infections were detected within 90 d of surgery. However, the study was small (n = 100) and not designed to capture the effect of dental evaluations so the results are difficult to interpret. Tai *et al*[18] found that patients with frequent dental scaling in the previous three years had 31% lower risk of PJI after TKA than those who did not receive scaling. Although these results reflect well upon frequent dental examination and scaling, it does not directly assess the impact of pre-operative dental clearance. In contrast, neither Lampley *et al*[17] nor Sonn *et al*[19] found evidence to support dental evaluations. Although the hip fracture group in the former study had an insignificantly higher reoperation rate (2.5% *vs* 1.7%), hardware was not removed in any of the four cases as no bacterial infection was identified. It should be noted that there were no true controls, follow up was poor in the hip fracture group (18% were deceased), and the threshold for failing clearance was high. Sonn *et al*[19] actually found higher complication rates in the dental evaluation and extraction groups, although this was not significant. This may be attributed to other confounding health risks not captured by the study.

The results of our systematic analysis are somewhat in line with current recommendations. In the proceedings of international consensus on orthopedic infections, 92% of voters agreed that patients with oral disease should receive appropriate interventions before elective TJA to reduce risk of infection despite limited evidence[8]. It was proposed that dental screening may be required for high risk patients. 76% of voters agreed that dental clearance should not be required for all patients to undergo TJA. Much like how prophylactic antibiotics for common dental procedures in all patients with joint prostheses is falling out of favor, we expect dental clearance protocol to change as new data emerges[22-25]. At the moment, we would not

Table 4 Impact of dental clearance on infection

Author	Model	*n*	Methods	Results	Impact of clearance
Barrington *et al*[16]	Patients at a metropolitan, tertiary arthroplasty practice in the United States	100	Patients obtained dental clearance, cleaning, and dental interventions. On POD 1 or POD 2, patients were interviewed	23% were not cleared due to dental decay and were treated. There were no periprosthetic infections within 90 d. One in four patients had dental pathology	It is difficult to draw a definitive conclusion
Lampley *et al*[17]	Elective TJA and hip fracture patients in a tertiary arthroplasty practice in the United States	519	Patients obtained dental clearance, cleaning, and interventions. On POD 1 or POD 2, patients were interviewed	Early postoperative infection rate was significantly lower in the clearance group. Only one infection had a possible dental source	Dental clearance and interventions did not reduce early postoperative infection
Tai *et al*[18]	Patients s/p resection arthroplasty and uninfected TKA controls from the Taiwanese NHIRD	6295	Patients with removal of infected TKA were matched with TKA patients without infections from the NHIRD and retrospectively analyzed	Compared to patients who did not receive scaling, those who received scaling once and 5-6 times in the previous three years had 20% and 31% less risk of TKA infection, respectively	Dental scaling was associated with lower risk of infection
Sonn *et al*[19]	Elective TJA patients at an unspecified location	2457	The data for a consecutive TJA patients was retrospectively analyzed	There were no significant associations between complication and dental evaluation or extraction	Dental evaluation +/- extraction did not improve complication rates

POD: Post op day; NHIRD: National health insurance research database; TKA: Total knee arthroplasty; TJA: Total joint arthroplasty.

recommend for universal dental screening before TJA.

We performed this study to preferred reporting items for systematic reviews and meta-analyses guideline standards, however, there were still several limitations. First and foremost, literature regarding dental clearance for TJA is scarce. Our methods only disinterred four papers capturing the impact of dental evaluation and/or treatment on infections after TJA. Considering the relatively low incidence of periprosthetic infection, few of the studies were adequately powered to detect significance and none were designed as randomized controlled trials. Additionally, there is no common standard for preoperative dental evaluation. Criteria for failing dental clearance ranged from diagnosing dental caries to requiring tooth extraction or root canals. Amongst studies assessing prevalence of dental pathology, differences in location and clinical setting hinder synthesis of data. Lastly, some studies relied on self-reporting of questionnaires and surveys, which incur several inherent biases[26].

CONCLUSION

With an aging population, the number of total joint arthroplasties is likely to continue growing. Periprosthetic infection remains a great concern and quality improvement problem despite improvements in sterile and prophylactic techniques. There is little evidence to support universal dental clearance before TJA, even for higher risk patients. There remains a need for future research to elucidate the mechanism of periprosthetic infections and more robust analysis of patients with high risk dental pathologies to help guide interventions.

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ORIGINAL ARTICLE

Basic Study

Pilot study of a novel serum mRNA gene panel for diagnosis of acute septic arthritis

Blake J Schultz, Timothy Sweeney, Malcolm R DeBaun, Melissa Remmel, Uros Midic, Purvesh Khatri, Michael J Gardner

ORCID number: Blake J Schultz (0000-0001-7739-9740); Timothy Sweeney (0000-0002-3596-1093); Malcolm R DeBaun (0000-0002-4391-5708); Melissa Remmel Remmel (0000-0002-9047-6891); Uros Midic (0000-0002-6635-1546); Purvesh Khatri (0000-0002-4143-4708); Michael J Gardner (0000-0003-0284-3397).

Author contributions: Sweeney T, Remmel M, Midic U, Khatri P ran the laboratory tests and performed data analysis and interpretation. Schultz BJ, DeBaun MR and Gardner MJ organized and ran the clinical trial. All authors provided critical feedback and helped shape the research, analysis and manuscript. All authors have read and approve of the final submitted manuscript.

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Blake J Schultz, Malcolm R DeBaun, Michael J Gardner, Department of Orthopedic Surgery, Stanford University, Redwood City, CA 94063, United States

Timothy Sweeney, Melissa Remmel, Uros Midic, Inflammatix, Inc, 863 Mitten Road, Suite 104, Burlingame, CA 94010, United States

Purvesh Khatri, Institute for Immunity, Transplantation and Infections, Center for Biomedical Research, Department of Medicine, Stanford University, Stanford, Redwood City, CA 94305, United States

Corresponding author: Blake J Schultz, MD, Surgeon, Department of Orthopedic Surgery, Stanford University, 450 Broadway Street Pavilion C, 4th Floor, Redwood City, CA 94063, United States. blakeschultzmd@gmail.com
Telephone: +1-650-4975281

Abstract

BACKGROUND

Septic arthritis is an orthopedic emergency requiring immediate surgical intervention. Current diagnostic standard of care is an invasive joint aspiration. Aspirations provide information about the inflammatory cells in the sample within a few hours, but there is often ambiguity about whether the source is infectious (*e.g.* bacterial) or non-infectious (*e.g.* gout). Cultures can take days to result, so decisions about surgery are often made with incomplete data. Novel diagnostics are thus needed. The "Sepsis MetaScore" (SMS) is an 11-mRNA host immune blood signature that can distinguish between infectious and non-infectious acute inflammation. It has been validated in multiple cohorts across heterogeneous clinical settings.

AIM

To study whether the SMS holds diagnostic validity in determining the etiology of acute arthritis.

METHODS

We conducted a blinded, prospective, non-interventional clinical study of the SMS. All patients undergoing work-up for a septic primary joint were enrolled. Patients proceeded through the normal standard-of-care pathway, including joint aspiration and inflammatory labs [white blood cell (WBC), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)]. Venous blood was also drawn into PAX gene RNA-stabilizing tubes and mRNAs were measured using

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Nano String nCounter™. SMS was calculated blinded to clinical results.

RESULTS
A total of 20 samples were included, of which 11 were infected based on aspiration or intra-operative cultures. The SMS had an area under the ROC curve (AUROC) of 0.87 for separating infectious from non-infectious conditions. For comparison, the AUROCs for ESR = 0.58, CRP = 0.6, and WBC = 0.59. At 100% sensitivity for infection, the specificity of the SMS was 40%, meaning nearly half of non-septic patients could have been ruled out for further intervention.

CONCLUSION
In this pilot study, SMS showed a high level of diagnostic accuracy in predicting septic joints compared to other diagnostic biomarkers. This quick blood test could be an important tool for early, accurate identification of acute septic joints and need for emergent surgery, improving clinical care and healthcare spending.

Key words: Biomarkers; Bioinformatics; Infection; Septic arthritis; Medical technology; Diagnostics

Core tip: Acute septic arthritis is an orthopedic emergency. The current gold standard diagnostic tool is synovial fluid culture, but this can take days to results, so decisions about surgery are made with imperfect information. A novel diagnostic "Sepsis MetaScore" (SMS) based on an mRNA signature has been identified that uses a blood sample to rapidly identify differentiate septic *vs* aseptic inflammation. Our pilot study showed the SMS had higher diagnostic accuracy than current standard of care inflammatory labs, showing potential for use as a rule-out test for septic arthritis, helping to minimize misdiagnosis and avoid unnecessary surgeries.

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INTRODUCTION

Acute arthritis is a common complaint in emergency rooms and orthopedic clinics, with over 13000 hospitalizations per year and over $750 million dollars in healthcare spending in the United States alone[1,2]. The etiology can be septic, commonly from a bacterial infection, or aseptic, such as gout, transient synovitis or other inflammatory, non-infectious etiologies. Acute septic arthritis of native joints is an orthopedic emergency requiring urgent surgical irrigation and debridement (I and D) to prevent irreparable damage to the joint, inpatient hospitalization and an extended course of IV antibiotics. Inflammatory arthritis is typically managed medically on an outpatient basis. The presentation of septic versus aseptic acute arthritis is difficult to distinguish clinically[3]. but making a quick and accurate diagnosis is critical given the drastically different treatments. Currently, clinicians rely heavily on imperfect serum and synovial fluid laboratory values to make acute decisions about emergency surgery[4-7], potentially exposing non-infected patients to unnecessary surgery.

The annual incidence of septic arthritis in native joints is 4-10 patients/100000 patient years, and is continuing to rise with increasing antimicrobial resistance, aging, immunosuppression and the increasing number of invasive or orthopaedic procedures[8-11]. The current diagnostic work-up includes serum inflammatory labs [white blood cell (WBC) counts, erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP)], and an invasive synovial fluid aspiration from the joint. These diagnostics are limited by their turn-around time and specificity. The definitive diagnosis of septic arthritis requires a positive culture from the synovial fluid, which can take multiple days to result. Serum labs result quickly and provide information about general systemic inflammation, but are not specific for infection[4]. Synovial

fluid evaluation reveals the inflammatory milieu within the joint, specifically WBC count, percentage of polymorphonuclear cells (PMNs), presence of crystals and a gram stain for bacteria, within a few hours, but again, these are not diagnostic, often leaving ambiguity about whether the source is infectious (*e.g*. bacterial) or non-infectious (*e.g*. gout)[4,5]. In addition, the presence of inflammatory cells can be artificially low in patients who are immunocompromised[6,12]. Furthermore, the presence of gouty crystals alone does not rule out a concomitant superimposed bacterial infection, making accurate diagnosis in this setting even more difficult[3]. Procalcitonin has recently been investigated as an inflammatory serum biomarker[13,14]. While it has shown promise in distinguishing septic from aseptic arthritis, it also does not accurately distinguish non-infective inflammation like gout from septic arthritis, and therefore is still a limited diagnostic biomarker[15].

The Sepsis MetaScore (SMS) is a novel diagnostic serum blood test that can efficiently distinguish between infectious and non-infectious acute systemic inflammation[16]. SMS works by interpreting the expression levels of 11 specific mRNAs in peripheral blood (the so-called "host response" to infection). Previous studies have validated its ability to distinguish infection from non-infectious inflammation in a variety of independent clinical settings including medical and surgical patients from ambulatory clinics to the ICU[17-19]. In this study, we hypothesized that the SMS could identify patients presenting acutely with septic arthritis based on positive cultures from those with aseptic arthropathies.

MATERIALS AND METHODS

Level II blinded, prospective, observational study

Following Institutional Review Board approval, we enrolled a convenience sample of adult patients presenting to the emergency department at a quaternary referral center with acute, atraumatic onset of a painful, swollen native joint. Non-native joints were excluded due to the different clinical and laboratory diagnostic cut-offs and treatment options for periprosthetic joint infections. Patients were enrolled in the trial at the time of presentation by an orthopaedic surgery resident.

All enrolled patients proceeded through the normal standard-of-care pathway, including inflammatory labs (WBC, ESR, CRP) and a joint aspiration performed by an orthopedic surgery resident. Aspirations were analyzed by the hospital lab for WBC count, percentage of PMNs, culture, gram stain and crystals. If the patient was taken for surgery, an additional intra-operative tissue sample was sent for culture. At the time of the initial lab draw, 2.5 cc of venous blood was also drawn into a PAX gene RNA-stabilizing tube. Blinded, deidentified samples were sent to Inflammatix, where the 11 mRNAs that comprise the SMS were measured using Nano String nCounter™. The SMS was calculated as previously described (difference of geometric means) blinded to clinical results[16]. The SMS score was calculated at the end of study enrollment, so no treating physician was aware of the results during patient care and it was not a factor in any clinical decisions. An independent observer (BS) retrospectively reviewed the charts and patients were diagnosed with septic arthritis if they had a positive culture resulted from the synovial fluid or tissue sample at time of surgery. All other patients were diagnosed with aseptic arthritis.

Statistical analysis

The primary endpoint of the study was the ROC curve (AUROC) of the SMS to determine clinically adjudicated septic joint status. Secondary endpoints were (1) The specificity of the SMS at the sensitivity > 95%, and (2) The AUROCs of comparator inflammatory biomarkers (serum WBC, CRP, ESR, and synovial WBCs and %PMNs). Student's *t*-tests were used to compare continuous variables. Multivariate least-squares logistic regression included only those patients with no missing variables. Significance was set a $P < 0.05$. Calculations were conducted in R, version 3.5.1.

RESULTS

Our cohort included 20 patients (14 males and 6 females), with an average age of 54.7 years (Table 1). With respect to anatomic location there were fourteen knees, three ankles, two elbows, and one wrist. Ten samples were septic and ten were aseptic based on final culture results. Types of bacterial infections included *Staphylococcus aureus*, *Streptococcus*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, and *Candida*[1,6]. There were two cases of a concomitant gout flare with articular bacterial infection and one case of concomitant pseudogout with articular bacterial infection; these three

cases were considered septic. There were four cases of gout that were aseptic, one had a surgical I and D due to acute concern for infection, however no aspirate or intra-operative cultures ever grew. In one septic patient the lab was unable to calculate the synovial cell counts because there was not enough fluid. One patient with concomitant gout and articular bacterial infection could not have the synovial PMNs calculated because of the high level of cellular degeneration. One aseptic patient did not have serum inflammatory labs drawn. All other patients had a full set of serum and synovial labs. All patients had an SMS calculated.

In the aseptic group (10 patients), average serum WBC = 11.7 cells/mm^3, ESR = 58.4 mm/h and CRP = 16.1 mg/dL, and the average synovial WBC = 39881 cells/mm^3, PMNs = 84.8% (Table 1). In the septic group (10 patients), the average serum WBC = 13.4 ESR = 80.4 and CRP = 19.6, and the average synovial WBC = 42800, PMNs = 80.6%. No significant statistical difference was found in any inflammatory labs between the septic and aseptic groups. However, there was a significant difference in the Sepsis MetaScore between groups; aseptic = -0.33, septic = 1.1 (P = 0.008).

The SMS had an area under the AUROC of 0.87 (95%CI: 0.71-1) for separating infectious from non-infectious conditions (Figure 1A). Notably, this is very similar to its diagnostic accuracy in multiple other cohorts, lending credence to the stability of the metric[16-18]. For comparison, the AUROCs for serum ESR = 0.58 (95%CI: 0.87-0.29), CRP = 0.6 (95%CI: 0.87-0.34), and WBC = 0.59 (95%CI: 0.85-0.33), and synovial WBC = 0.54 (95%CI: 0.81-0.28) and PMN = 0.51(95%CI: 0.79-0.24) (Figure 1B-F). At 100% sensitivity for infection, the specificity of the SMS was 40%. This suggests that a substantial fraction of non-septic patients could potentially be safely ruled out for further surgical intervention.

In practice, the decision for surgery is not based on one specific inflammatory marker, but rather on the constellation of the clinical and laboratory presentation. To account for this we performed a multivariate logistic regression on all patients with complete laboratory data to measure whether the SMS remained an independent predictor of infection status when accounting for blood and synovial markers of inflammation (Table 2). Note six observations removed due to missingness. SMS was the only significant predictor of infection status when combined with "standard" inflammatory labs, further indicating that it may continue to hold diagnostic utility compared to several standard-of-care labs at once.

Patients with septic arthritis can also have systemic infections, which can complicate the diagnosis. One patient who was admitted for a bacterial pleural effusion with positive blood cultures also had an acute onset of knee pain (Figure 2). The patient's knee was aseptic based on a negative aspirate culture and 15111 WBC, but the SMS was elevated. Note, because of the small sample size, a distinct cut-off has not yet been established for the SMS, but as Figure 2 indicates, SMS in the aseptic group tended to be lower (< 0) and SMS is septic group tended to be higher (> 1). This was ruled as a "false positive" since the joint was aseptic, though the SMS did accurately indicate that the patient had a systemic bacterial infection. Notably, if this patient is excluded from the data, the AUROC improves to 0.90 (95%CI: 0.76–1). Additionally, two patients in the septic group received antibiotics prior to SMS draw. Both had at least 12 h of antibiotics, and not surprisingly, their SMS scores were the two lowest of the septic group (Figure 2).

DISCUSSION

Septic arthritis can be difficult to distinguish from non-infectious arthropathies at the time of presentation. In this pilot study we determined the early diagnostic validity of a novel blood test, the Sepsis Metascore, for septic arthritis. Notably, the SMS had substantially higher AUROCs than standard-of-care inflammatory markers, though this did not reach significance in our small pilot study.

The current laboratory work-up for acute septic arthritis lacks diagnostic accuracy[4,5]. In our cohort, there was a trend towards lower serum WBC, ESR and CRP in the aseptic group compared to the septic group, however, this was not significantly different. The synovial PMN percentages were actually slightly lower in the septic group than the aseptic group, and both groups had synovial WBC averages lower than 50000 cells/mm^3 which is the generally accepted cut-off for septic arthritis[5,6,20]. This finding could be from the abnormalities in a few of the septic patients, including immunosuppression and gouty superinfections where the lab noted high levels of cellular degeneration that compromised an accurate cell count. While a larger sample size may decrease the effect of these abnormalities on the lab averages, these cases highlight the overall limited diagnostic potential of the current laboratory work-up. With a reasonable specificity (40%) at 100% sensitivity for infection seen in this study,

Table 1 Patient demographics and laboratory results

	Aseptic	Septic	*P* value	Number missing date
Number of patients	10	10		
Age (yr) +/- SD	54.8 +/- 20.0	54.6 +/- 12.1	0.98	0
Sex (male)	7	7	0.99	0
Serum WBC (k cells/mm^3)	11.7 +/- 4.0	13.4 +/- 8.2	0.57	1
Serum ESR (mm/hr)	58.4 +/- 35.2	80.4 +/- 50.7	0.33	4
Serum CRP (mg/dL)	16.1 +/- 10.1	19.6 +/- 12.8	0.53	2
Synovial WBC (k cells/mm^3)	39.8 +/- 62.8	42.8 +/- 46.5	0.91	1
Synovial % PMNs	84.8 +/- 13.7	80.6 +/- 30.2	0.73	2
Sepsis MetaScore	-0.33 +/- 0.63	1.1 +/- 1.3	$P = 0.008$	0

WBC: White blood cell; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; PMNs: Polymorphonuclear cells.

the SMS offers diagnostic potential as a rule-out test for acute septic arthritis in native joints. Its high sensitivity is ideal for the clinical urgency associated with acute septic arthritis, where a missed diagnosis could lead to devastating, irreversible articular destruction. In such scenarios, the test would have to be available in a rapid timeframe. The SMS has been licensed to Inflammatix for commercial development as part of a point-of-care test with a 30 min turnaround time, which would make it a valuable additional data point for early diagnosis.

The SMS has the potential to be particularly helpful in patients with inflammatory arthropathies and immunocompromise that further complicate septic arthritis diagnosis. Patients with gout can have elevated inflammatory labs and cellular degeneration in the synovial aspirate that make diagnosing a superimposed bacterial infection difficult[3]. In our sample, there was one patient with a history of gout who presented with acute knee pain and a synovial aspirate of 96000 WBC and 86% PMNs with few monosodium urate crystals. Despite no synovial culture results, the high inflammatory markers were concerning for a concomitant bacterial infection and the patient was taken emergently to the OR for a surgical I and D and admitted to the hospital for IV antibiotics. Neither aspirate nor multiple intra-operative cultures grew any bacteria, implying the joint was aseptic. The SMS was -1.05 here. This case was a prime example of a patient who underwent a surgical procedure in the setting of an ambiguous diagnosis that could have been best treated with only medical management.

SMS could be similarly helpful in patients with other inflammatory arthropathies such as rheumatoid arthritis. These patients have an increased risk of developing septic arthritis, especially if they are on immunomodulators, but often experience delay in clinical diagnosis because their inflammatory labs are often elevated at baseline, making it difficult to diagnose acute infection[21,22]. We had an example of this in our study with a patient with seropositive rheumatoid arthritis who presented with acute elbow pain and a synovial aspirate with 189000 WBC and 94% PMNs. Surgical I and D was performed, but neither the aspirate nor intra-operative cultures were positive. The SMS was low at -0.52. They re-presented eight months later with a similar clinical presentation with 176000 WBC with 85% PMNs on aspiration. The patient was taken for a second I and D, again with negative aspirate and intra-operative cultures. Acid fast bacilli, fungal cultures and 16S PCR were also negative. Ultimately our Infectious Disease colleagues diagnosed the patient with recurrent aseptic inflammatory arthritis.

Finally, the SMS could also be useful in patients with immunosuppression who have "falsely" low inflammatory markers[6,12]. There was one patient in the septic group on chemotherapy for leukemia who had suppressed inflammatory markers (WBC = 0.8, ESR = 58, CRP = 27.5, synovial WBC = 139, PMN = 9%) despite a positive aspirate culture that grew *Klebsiella*. Despite the low inflammatory labs, the SMS was correctly elevated at 1.28, showing its potential as a valuable tool in these special circumstances to prevent missed septic arthritis in patients with a compromised inflammatory response.

Although our pilot study focused on adult patients, the SMS also has potential utility in pediatric and adolescent septic arthritis. The common clinical presentation of transient synovitis of the hip, which is thought to be triggered by a systemic viral infection[23,24], presents similarly to septic arthritis. Additionally, pediatric patients have a high incidence of "culture negative" septic arthritis which makes diagnosis

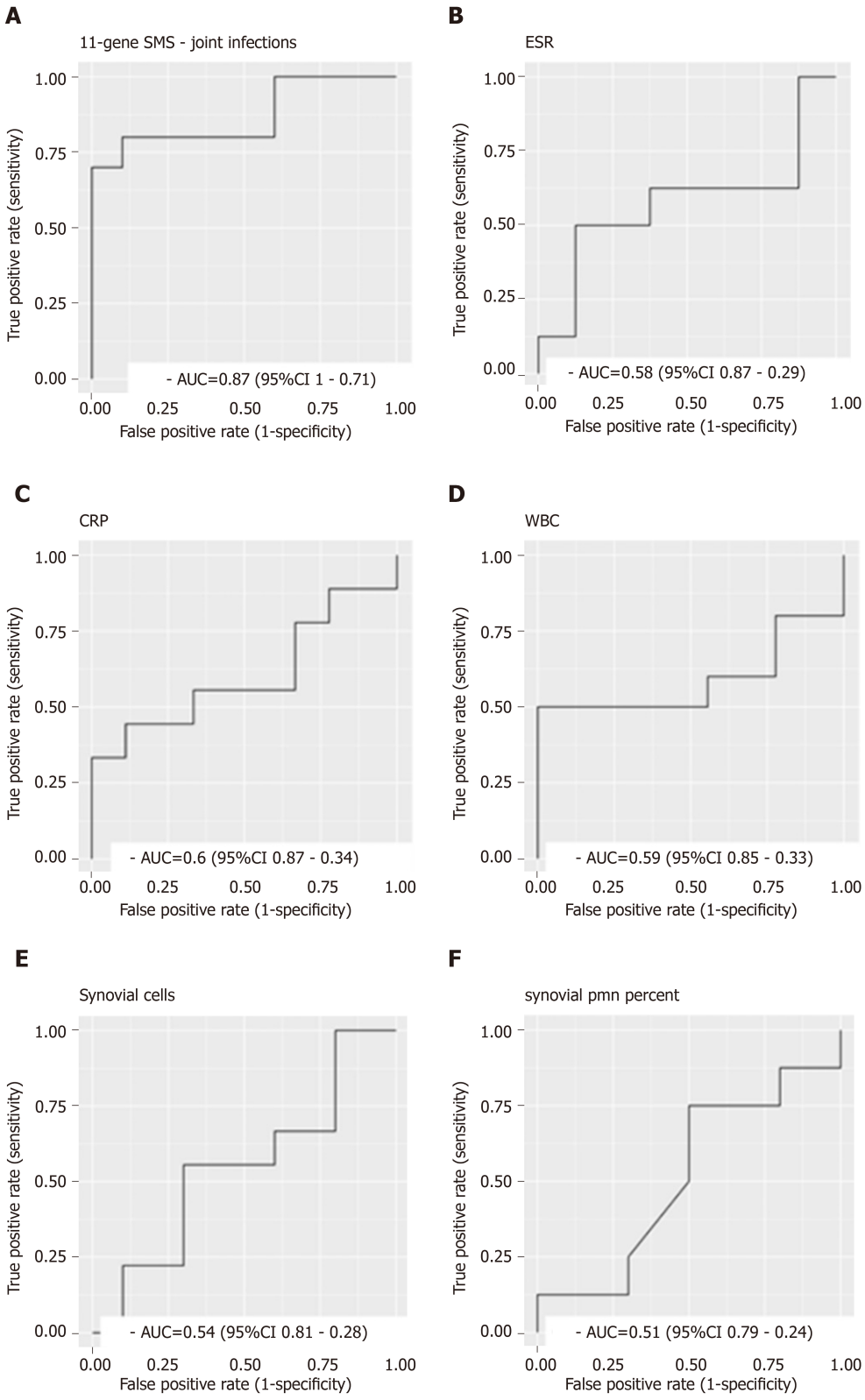

Figure 1 ROC curves for separating infectious from non-infectious joint infections. A: Sepsis Metascore area under the ROC = 0.87; B: Erythrocyte sedimentation rate area under the ROC = 0.58; C: C-reactive protein area under the ROC = 0.6; D: White blood cell area under the ROC = 0.59; E. Synovial cell area under the ROC = 0.54; F: Synovial polymorphonuclear cells % area under the ROC = 0.51. WBC: White blood cell; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; SMS: Sepsis MetaScore.

difficult[25]. Given the technical skill and advanced imaging needed to obtain a diagnostic hip aspiration, there would be tremendous benefit if the SMS proved to be an effective rule-out test in this population. Periprosthetic joint infection diagnosis is another area of potential application[26,27]. Although this case does not always require the same urgency that septic native joints require the SMS could potentially add

Table 2 Multivariate logistic regression analysis for the prediction of infection

	Effect estimate	Std. Error	*t* value	*P* value
Intercept	0.833	0.577	1.443	0.199
CRP	-0.022	0.015	-1.488	0.187
ESR	-0.001	0.004	-0.213	0.839
WBC	-0.001	0.024	-0.043	0.967
synovial WBC	0.000	0.000	0.438	0.677
synovial % PMN	-0.001	0.007	-0.149	0.887
Sepsis metascore	0.595	0.210	2.831	0.030
Residual standard error: 0.4478 on 6 degrees of freedom				
Multiple R-squared: 0.6275			Adjusted R-squared: 0.2551	
F-statistic: 1.685				

WBC: White blood cell; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; PMN: Polymorphonuclear cells.

another data point to suggest infection in equivocal cases prior to surgical intervention.

One limitation of this pilot study is its small sample size. A larger sample size, in a rigorously validated, properly statistically powered cohort of patients is necessary to confirm the diagnostic accuracy of the SMS. Another limitation of the study was the timing of SMS lab draw. While our protocol indicated lab draw at the same time as the initial inflammatory lab sample, this was not always possible, and sometimes occurred hours later. Still, we expect the SMS score to decrease with the administration of antibiotics and/or surgical debridement, so the fact that it was still accurate in predicting infection in these patients supports the validity of the test. More generally, a limitation of the SMS is the inability to distinguish systemic *vs* isolated articular infections. One patient with a bacterial pleural effusion had an aseptic aspirate of their knee. The SMS was elevated, correctly identifying the systemic bacterial infection, but in our data was ruled as a "false positive" since the joint was aseptic (Figure 2). With this in mind, the use of SMS to diagnose septic arthritis in patients with concomitant acute infections may be limited. Finally, a limitation in our data analysis is the reliance on synovial and intra-operative cultures to definitively diagnosing septic arthritis. While this is the current gold-standard diagnostic, it is not 100% sensitive, and can be influenced by administration of antibiotics prior to aspiration[28-30]. Additionally, clinical diagnosis of septic arthritis is not based on one or two lab values, but rather a clinical gestalt factoring in clinical exam, weight bearing status, prior antibiotic use, past medical history and presentation. While the regression model does allow us to compare a combination of lab values to the SMS, further study into the entire patient picture is warranted. Additionally, comparison to newer infection diagnostics such as pro-calcitonin and PCR analysis is warranted[14,31].

The literature is scarce regarding the incidence of patients who undergo emergent I and D for presumed septic arthritis that is ultimately deemed to be non-infected, but anecdotally at our institution this could be as high as 15%-20% of patients who undergo urgent I and D. This highlights the importance of a fast, reliable and less invasive rule-out diagnostic test to give clinicians confidence to choose not to intervene, sparing substantial costs, unnecessary surgery and patient morbidity.

Novel diagnostic tests are needed to quickly and accurately diagnose acute septic arthritis in native joints. In this pilot study, the SMS showed a high level of diagnostic accuracy in predicting septic joints compared to other diagnostic biomarkers. A large, prospective validation study is warranted to better establish the diagnostic accuracy and predictive values of the SMS. When confirmed in larger cohorts and available as a rapid blood test, the SMS could be an important tool for early, accurate diagnosis of acute septic joints and evaluation of need for urgent surgery. Future research should also expand to in investigate infection in non-unions, periprosthetic joints, infected hardware or grafts, transient synovitis, and others.

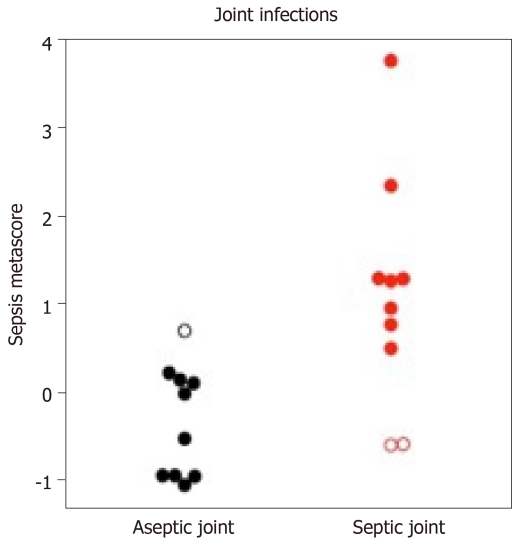

Figure 2 Scatter plot with Sepsis MetaScore on the Y-axis grouped by aseptic (black dots) and septic joints (red dots). Note the open circle in the aseptic group is the patient who had a concurrent systemic bacterial infection with a negative joint aspiration. The two open circles in the septic group, were given antibiotics at least 12 h prior to Sepsis MetaScore blood draw.

ARTICLE HIGHLIGHTS

Research background

Septic arthritis in native joints is an orthopedic emergency, requiting urgent surgical intervention. It can present similarly to non-septic arthritis such as grout, transient synovitis or inflammatory arthritis. Non-septic arthritis can be managed medically, so accurate diagnosis is important. Currently, diagnosis is based on a combination of clinic exam and serum and synovial biomarkers which do not reliability differentiate infection from non-infective inflammation. The gold standard of diagnosis is intra-articular aspiration cultures, which can take days to result, so decisions about urgent surgery are often made with incomplete information. Novel diagnostics are needed to improve the speed and accuracy of diagnosis.

Research motivation

Novel diagnostics are needed to improve the speed and accuracy of diagnosis of septic arthritis to prevent the irreversible damage to cartilage seen in septic arthritis of native joints and to avoid unnecessary surgery in patients with aseptic arthritis. The ability to quickly and accurately identify and monitor infection through serum biomarkers, instead of invasive aspirations, has many potential applications across orthopedics, including peri-prosthetic infection, pediatric transient synovitis, hardware infection and in the work-up of fracture non-union.

Research objectives

The main objective was to compare the ability of the Sepsis MetaScore (SMS) to diagnosis acute septic arthritis in native joints compared to current diagnostic serum and synovial biomarkers. The SMS proved more accurate than serum white blood cell (WBC), erythrocyte sedimentation rate, C-reactive protein and synovial WBC and polymorphonuclear cells %. With the ability to result in 30 min without an invasive intra-articular aspiration, there is potential for future research across orthopedics for diagnosis and monitoring of infection.

Research methods

We conducted a prospective, observational study of adult patients being worked up for acute septic arthritis of native joints in the emergency department. They proceeded through the standard of care work-up including inflammatory labs and aspiration, with an additional venous lab draw into a PAX gene RNA-stabilizing tube that was used to calculate the SMS. Decisions for surgery were made without consideration of SMS which was calculated at the end of the enrollment period, blinded to clinical results. Patients were retrospectively deemed infected or not based on synovial culture results. The SMS and other inflammatory labs were compared to this diagnosis

Research results

There was no significant difference in any of the standard serum or synovial labs between the septic and aseptic groups, except for the SMS which was significantly higher in septic patient compared to aseptic patient (P = 0.008). This pilot study data is encouraging, but still needs to be validated in a larger study.

Research conclusions

The SMS shows potential as a quicker and more accurate diagnostic tool for acute septic arthritis

than current serum and synovial biomarkers. It shows unique potential in complicated patients with histories of gout, inflammatory arthritis or immunocompromise where the current serum biomarkers are known to be less accurate. With development of the 30 min point of care testing, this is a potentially valuable diagnostic aid for decisions about emergency surgery and has potential applications across orthopedics subspecialties for infection diagnosis and monitoring.

Research perspectives

Novel serum biomarkers show potential to increase the accuracy and decrease the time to diagnosis of septic arthritis. Future research in a larger study population is needed to validate these findings, which could then be replicated to investigate other topics in orthopedics such as periprosthetic joint infection, septic arthritis in pediatric patients, fracture non-unions and hardware infection.

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ORIGINAL ARTICLE

Basic Study

Effect of clopidogrel in bone healing-experimental study in rabbits

Theodoros Lillis, Alexander Veis, Nikolaos Sakellaridis, Anastasios Tsirlis, Zoe Dailiana

ORCID number: Theodoros Lillis (0000-0002-9029-8714); Alexander Veis (0000-0001-7034-1220); Nikolaos Sakellaridis (0000-0001-9193-7787); Anastasios Tsirlis (0000-0002-1244-9919); Zoe H Dailiana (0000-0003-3890-0832).

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Theodoros Lillis, Zoe Dailiana, Department of Orthopaedic Surgery, Faculty of Medicine, University of Thessaly, Biopolis, Larissa 41500, Greece

Theodoros Lillis, Alexander Veis, Anastasios Tsirlis, Department of Dentoalveolar Surgery, Implantology and Oral Radiology, Faculty of Dentistry, Aristotle University of Thessaloniki, Panepistimioupoli, Thessaloniki 54124, Greece

Nikolaos Sakellaridis, Department of Clinical Pharmacology, Faculty of Medicine, University of Thessaly, Biopolis, Larissa 41500, Greece

Corresponding author: Zoe Dailiana, MD, PhD, Professor, Department of Orthopaedic Surgery, Faculty of Medicine, University of Thessaly, 3 Panepistimiou St, Biopolis, Larissa 41500, Greece. dailiana@med.uth.gr
Telephone: +30-2413-502723
Fax: +30-2413-501011

Abstract

BACKGROUND

Clopidogrel is a widely prescribed drug for prevention of myocardial infarction and stroke in patients at risk. It inhibits thrombus formation *via* inhibition of the $P2Y_{12}$ purinergic receptor on platelets, which is important in their activation by ADP. However, the $P2Y_{12}$ receptor has also been found to be expressed in both osteoblasts and osteoclasts. Accumulated evidence suggests that purinergic receptors regulate important functions of bone turnover. Previous studies on the effect of clopidogrel on bone metabolism indicated potential harmful effects, but their results remain conflicting. Thus, clopidogrel treatment may affect bone healing, but it has not yet been studied.

AIM

To evaluate if continuous perioperative clopidogrel treatment has any negative effect on bone healing in the rabbit calvarial defect model.

METHODS

Sixteen male white New Zealand rabbits were randomly assigned in two groups: One group received daily 3 mg/kg of clopidogrel per os and the other group received the vehicle alone for a week prior to the surgical procedures; the treatments were continued for another 6 wk postoperatively. The surgical procedures included generation of two circular calvarial defects 11 mm in diameter in every animal. After the 6-wk period of healing, postmortem radiographic and histomorphometric evaluation of the defects was performed.

RESULTS

Both the surgical procedures and the postoperative period were uneventful and

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well tolerated by all the animals, without any surgical wound dehiscence, signs of infection or other complication. New bone was formed either inwards from the defect margins or in the central portion of the defect as separated bony islets. While defect healing was still incomplete in both groups, the clopidogrel group had significantly improved radiographic healing scores. Moreover, the histomorphometric analysis showed that bone regeneration (%) was 28.07 ± 7.7 for the clopidogrel group and 19.47 ± 4.9 for the control group, showing a statistically significant difference between them (P = 0.018). Statistically significant difference was also found in the defect bridging (%), *i.e.* 72.17 ± 21.2 for the clopidogrel group and 41.17 ± 8.5 for the control group, respectively (P = 0.004), whereas there was no statistical difference in bone tissue density between the groups.

CONCLUSION
Our results indicate that maintenance of perioperative clopidogrel treatment does not negatively affect bone healing but rather promotes it. Further research is needed in order to find useful applications of this finding.

Key words: Clopidogrel; Bone healing; Purinergic signaling; Calvarial defect; Rabbit

Core tip: To our knowledge, the present study is the first to evaluate the effect of clopidogrel treatment on bone healing. Clopidogrel is an antithrombotic drug that inhibits platelet aggregation through inhibition of the $P2Y_{12}$ purinergic receptor on their surface. The $P2Y_{12}$ is also expressed in osteoblasts and osteoclasts, and previous studies have raised concerns about clopidogrel's possible effect on bone metabolism. We report our results on the effect of clopidogrel on bone healing using the rabbit calvarial defect model. Our results indicate that clopidogrel treatment does not negatively affect bone healing but rather promotes it.

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INTRODUCTION

Clopidogrel is a thienopyridine antiplatelet drug widely prescribed for the prevention of thrombotic events such as myocardial infarction and stroke[1]. Following metabolic transformation in liver, clopidogrel active metabolite (CAM) inhibits the platelet purinergic receptor $P2Y_{12}$ and, therefore, blocks ADP-induced platelet aggregation[2].

The purinergic signaling system is found in almost all tissues and is involved in several important cellular functions such as migration, proliferation, apoptosis and cytokine secretion[3]. The purinergic system is an autocrine and paracrine signaling system, where extracellular purines and pyrimidines act as extracellular signaling molecules, affecting several receptors subtypes[4]. Purinergic receptors are classified into two groups: P1 (further subdivided into A_1, A_{2A}, A_{2B} and A_3) and P2 (further subdivided into P2X ligand-gated ion channel receptors and P2YG-protein-coupled receptors). P1 receptors are activated by adenosine and P2 receptors by ATP, UDP and their breakdown products[5]. Research on purinergic signaling in bone has gained a lot of attention in recent years, but its role in bone healing and turnover has not been fully elucidated[6]. In particular, the expression of the $P2Y_{12}$ receptor on osteoblasts and osteoclasts has been demonstrated as well[7-9]. The few existing *in vivo* studies on the effect of clopidogrel on bone remodeling or osteoporosis show contrasting results, with some of them indicating positive[9,10] and others indicating negative[8,11] impact. For example, Su *et al*[9] report that clopidogrel treatment increased trabecular bone volume in adult ovariectomized mice, while Syberg *et al*[8] reported that it decreased the same parameter. Moreover, the effect of the $P2Y_{12}$ inhibitor clopidogrel on bone healing, when administered systematically, has not been studied yet.

Over the past years, a large body of medical literature in various specialties dealing

with bone surgery suggests perioperative maintenance of antiplatelet therapy, whenever possible, in order to avert any thrombotic risk caused by temporary antiplatelet discontinuation[12-15]. On the other hand, when dealing with skeletal surgery, clopidogrel may affect bone healing either directly, by acting on osteoblasts and/or osteoclasts[7,9], or indirectly, by acting on platelets that are known to have an important role in early stages of bone healing[16]. With this background, we undertook this study to evaluate if perioperative systemic administration of clopidogrel produces any negative effect on spontaneous healing of rabbit calvarial defects, which model clinical scenarios of bone defect healing in patients receiving clopidogrel for cardiovascular indications.

MATERIALS AND METHODS

Animals and study design

The present study was performed on 16 male New Zealand white rabbits that were housed at the institutional animal center. The animals were 6 mo old (mean body weight of 4.8 kg) and were acclimated for at least 1 wk before the experimental procedures, housed in individual cages, and fed with a standard laboratory *ad libitum* diet. The animal protocol was designed to minimize pain or discomfort to the animals, and it was approved by the Institutional Project Evaluation Committee and authorized by the local Prefectural Veterinary Service according to Directive 2010/63/EU and national law. The animals were randomly assigned in two groups of eight rabbits: An experimental (clopidogrel) group and a control group. Two calvarial defects were created in each animal, and, therefore, each group included 16 defects. The rabbits of clopidogrel group received a daily dose of 3 mg/kg, which has been shown to cause similar level of platelet aggregation inhibition with that of 75 mg in humans[17]. Clopidogrel was added to fruit juice and was administered orally to the rabbits *via* syringe daily, for 1 preoperative week and 6 postoperative weeks, while the rabbits of the control group received fruit juice without clopidogrel.

Surgical protocol

The surgical procedures were performed 1 wk after the beginning of fruit juice and drug administration. Every animal received antibiotic prophylaxis (enrofloxacin 10 mg/kg subcutaneously) 1 hour before general anesthesia (ketamine 20-30 mg/kg intramuscularly and xylazine2-5 mg/kg intramuscularly) and surgery. The surgical procedures were performed under proper aseptic technique, and the skull of every rabbit was shaved, while the skin was disinfected with povidone iodine solution. The parietal bones were exposed through an incision along the sagittal midline of the cranium. Two circular cranial defects were created using a trephine burr, 11 mm in diameter, on both sides of the sagittal suture (Figure 1). Special care was taken in order to avoid damage of their dura matter. This size of defect is considered to be critical in the 6-wk healing period[18,19]. The flaps were then sutured back in place layer by layer with resorbable suture to cover the defects with intact periosteum, in order to heal spontaneously without placing any barrier membrane or bone substitute. After 6 wk, the animals were euthanized by anesthesia overdose followed by whole body perfusion fixation with 10% neutral buffered formalin. Following euthanasia, the portions of cranial bones containing the defects were block-sectioned, and radiographic and histologic evaluation followed.

Radiographic evaluation

Digital radiographs of all specimens were taken using a dental x-ray unit (X-Mind AC, Satelec Acteon Group, Merignac, France) and a dental CCD sensor (Sopix2, Sopro Acteon Imaging, La Ciota, France), under the same operating parameters (70 kV, 8 mA, 0.125 s exposure time). Bridging and union within the defects were assessed blindly by two examiners (one of the authors and an independent evaluator, both dentists) using the scoring guide described by Patel *et al*[20]. This scoring system consists of the following five-grade scale: (0) No bone formation within defect; (1) Few bony spicules dispersed through defect; (2) Bony bridging only at defect borders; (3) Bony bridging over partial length of defect; and (4) Bony bridging entire span of defect at longest point (11 mm in the present study) (Figure 2).

Histological preparation

Dissected fragments containing the defects were dehydrated by sequential immersion of ascending concentrations of alcohol (50%, 70%, 90%, 100%), every 2 d. Then, the specimens were immersed in alcoholic solutions of increasing concentrations (50%, 70%, 90%) of methyl-methacrylate, also every 2 d (Techonit 7200, Heraeus Kulzer GmbH, Wehrheim, Germany). Next, the specimens were kept in 100% methyl-

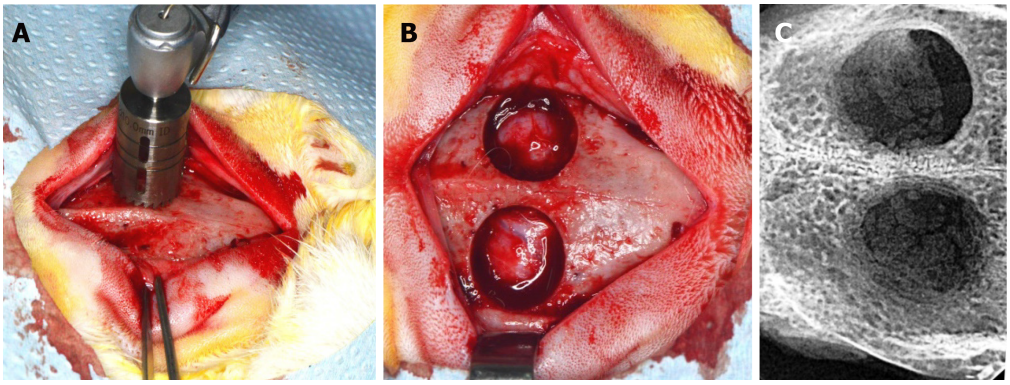

Figure 1 Surgical procedures. A: Generation of calvarial defects with trephine bur of 11 mm in diameter; B: Circular defects with intact dura matter; C: Postmortem radiograph of the defects.

methacrylate for 10 d, in order to achieve optimum resin infiltration, before they were incubated in fresh 100% methyl-methacrylate and were polymerized for 12 hours, using an appropriate light-curing device. Finally, the polymerized specimens were cut with a diamond band-saw microtome, bonded on glass slides, grinded, and polished as appropriate to create approximately 80 μm thin histological sections. All the above procedures were carried out by using the EXAKT system (Advanced Technologies GmbH, Norderstedt, Germany). The specimens were cut vertically and histological sections were duly oriented to coincide with the direction of maximum defect bridging, as indicated from the corresponding radiographs. The sections were then stained with Toluidine blue/Basic Fuchsin.

Histomorphometry

The slides were viewed under light microscope (Axiostar Plus®, Zeiss, Gottingen, Germany) and digital images were captured (AxioCam ICc3, Carl Zeiss), so as to perform histomorphometric measurements (Figure 3) with the appropriate software, Image Pro Plus (Media Cybernetics Inc., Rockville, MD, United States). The following primary histomorphometric parameters were measured: (1) Defect area: Defined by connecting the margins of the defect through appropriate extrapolated curvatures that represent the inner and outer contour of the pre-existing cranial bone, which was removed with the trephine burr; (2) Bone tissue area: Defined as the new bone tissue that was formed within the borders of the determined defect area, including new mineralized bone and associated non-mineralized tissue (osteoid, content of osteonal canals and bone marrow); (3) Bone area: Defined as the new bone matrix (mineralized bone and osteoid) that was formed within the borders of the determined defect area; (4) Defect horizontal dimension: Defined as the length of the line connecting the original margins of the defect; and (5) Total bone tissue horizontal dimension: Defined as the linear extent of the new bone tissue that was regenerated from the defect margins and the new bone tissue islands across the defect horizontal dimension. The following secondary parameters were calculated: (1) Defect regeneration (%): (Bone tissue area)/(Defect area) x 100%; (2) Defect bridging (%): (Total bone tissue horizontal dimension)/(Defect horizontal dimension) x 100%; and (3) Bone tissue density (%): (Bone area)/(Bone tissue area) x 100%. Both the nomenclature and the definitions of primary and secondary parameters are based on the 2012 updated report of the American Society for Bone and Mineral Research Histomorphometry Nomenclature Committee[21].

Sample size

Based on our pilot study and previous studies[18,19,22,23], we assumed that the primary outcome (defect regeneration %, as defined above) in the control group would be approximately 20% ± 5%. Thus, in order to detect a difference of ± 10% between the groups, we calculated that at least eight animals would be needed per group, when $\alpha = 0.05$ and $(1-\beta) = 0.95$. The sample size was calculated with G*Power v.3.1.9.2 (Frantz Faul, Univerisität Kiel, Germany).

Statistical analysis

Statistical analyses were performed using SPSS v.18.0 (SPSS, Inc., Chicago, IL, United States). The average radiographic score and the average histomorphometric parameters were initially calculated from the two defects for each animal. The radiographic scoring and histomorphometric parameters are presented as mean ±

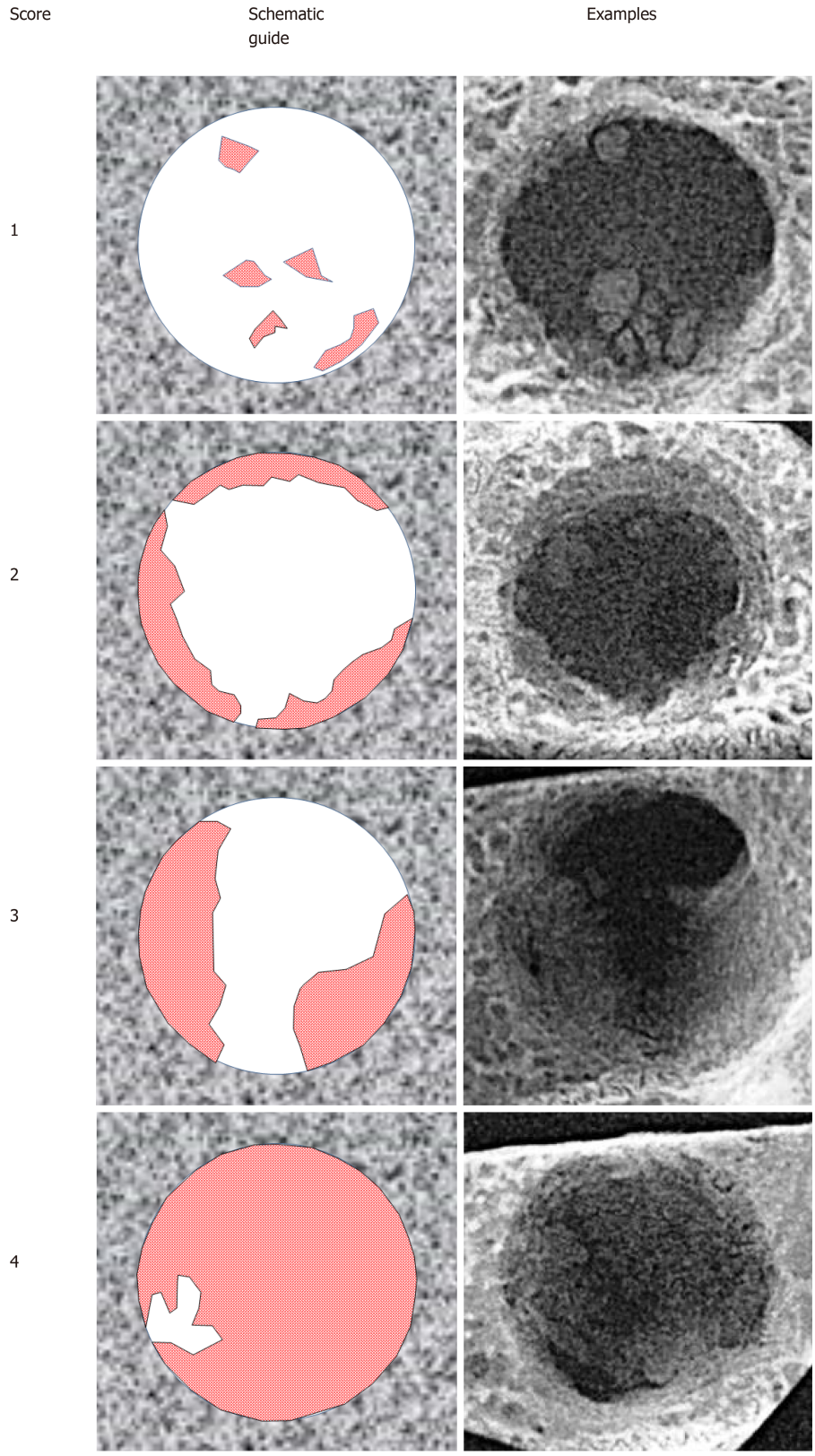

Figure 2 Radiographic scoring guide and example radiographs from material of the present study.

standard deviation within the groups. Inter-examiner agreement in radiographic scoring was evaluated by Cohen's kappa statistic. The significance of differences between the groups, in relation to radiographic scoring, was determined by the Mann-Whiney *U* test, since the data did not meet the criteria for normal distribution, as indicated by the Shapiro-Wilk test. The significance of differences between the groups, in relation to secondary histomorphometric parameters, was determined by the *t*-test, since the data were distributed normally, as indicated by the Shapiro-Wilk

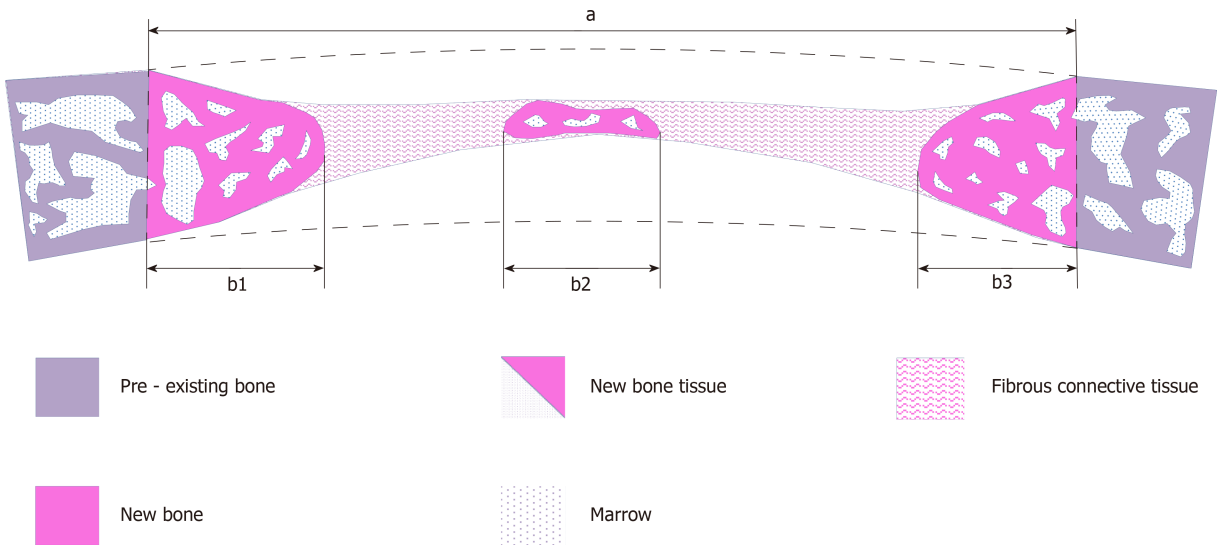

Figure 3 Schematic diagram of histological section through the calvarial defect showing primary histomorphometric measurements. Area within the dotted line represents the total defect area. Double arrows distances represent the defect horizontal dimension (a) and total bone tissue horizontal dimension (b1 + b2 + b3).

test. Statistical significance was determined at $P < 0.05$ level. The statistical methods of this study were reviewed by Ms Eirini Pagkalidou, Mathematician, Biomedical Statistician, MSc of Public Health in Comparative Effectiveness Research.

RESULTS

Both the surgical procedures and the post-operative period were uneventful and well tolerated by all the animals, without any surgical wound dehiscence, signs of infection or other complication.

Radiographic evaluation

The radiographic imaging showed radiopaque areas within the defects, indicating new bone formation in various extents (Figure 4). New bone was either formed inwards from the defect margins or located in the central portion of the defect as separated bony islets. The mean radiographic score was significantly higher in the clopidogrel group than in the control group, for both examiners [3.31 ± 0.2 *vs* 1.43 ± 0.2 for examiner A ($P < 0.001$) and 3.12 ± 0.3 *vs* 1.88 ± 0.2 for examiner B ($P = 0.007$); inter-examiner agreement: $k = 0.441$, $P < 0.001$].

Histologic and histomorphometric evaluation

In both groups, the defect area was partially filled with thin new bone tissue in various extents, and none of the defects was completely regenerated. New bone tissue was evident either as wedge-shaped protrusions from the defect margins or as separated bone tissue islets within the defect area (Figure 4). The area within the new bone tissue was filled with fibrous connective tissue. New bone was mainly woven, but lamellar bone was also evident in various extents (Figures 5 and 6). The lamellar bone was more pronounced in the new bone extending from the defect margins rather than in the islets. Complete bony bridging between the margins of the defect was indicated in one defect of the control group and in three defects of the clopidogrel group. Defect regeneration (%) and defect bridging (%), as assessed by histomorphometry, were significantly greater in the clopidogrel group as compared to the control group, whereas bone tissue density had no statistical difference (Table 1).

DISCUSSION

Identification of pharmacological agents that may affect bone healing is a challenging issue. Clopidogrel is a widely prescribed antiplatelet drug, and several *in vivo* studies have indicated that it may affect bone metabolism. To our knowledge, the present study is the first to assess the effect of systemic clopidogrel administration on bone healing. Our study was initially conducted in order to evaluate if clopidogrel received perioperatively for cardiovascular reasons had any negative effect on bone healing

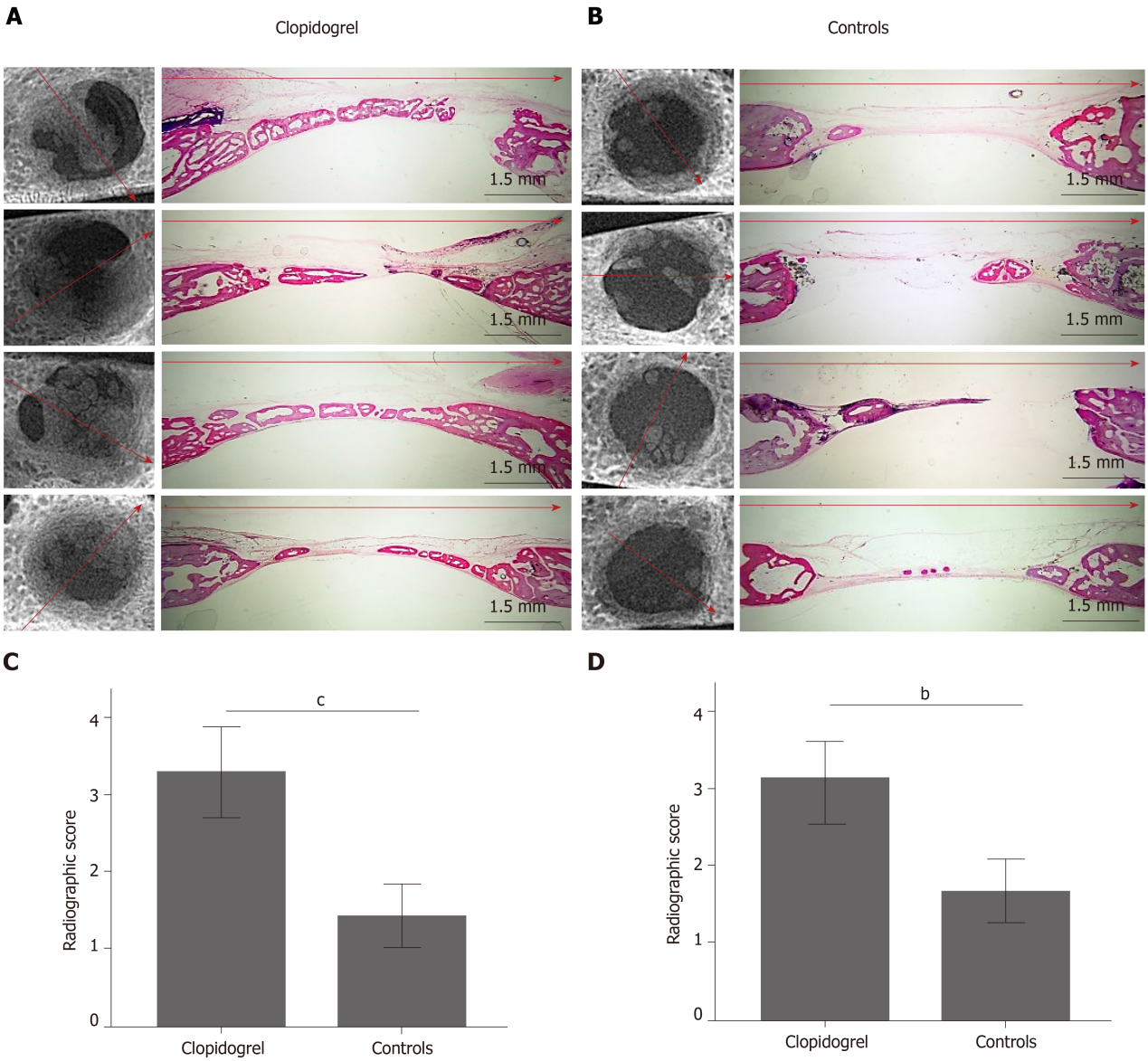

Figure 4 Representative radiographs and histological sections of the defects at 6 wk postoperatively. A: Clopidogrel group (red arrows showing the direction of histological section in each defect); B: Control group (red arrows showing the direction of histological section in each defect); C: Radiographic scoring from examiner A ($^{c}P < 0.001$); D: Radiographic scoring from examiner B ($^{b}P < 0.01$); scale bar of all histological figures is 1.5 mm.

following skeletal surgical procedures. Interestingly, our results showed that clopidogrel enhanced new bone formation and bridging in the rabbit calvarial defect model. Our results agree with one previous *in vivo* study[24] on the subject, where the effect of local application of the active metabolite of clopidogrel (CAM) and ticagrelor in rat calvarial defect healing was evaluated. After implanting collagen sponge or 3D printed resorbable calcium-triphosphate/hydroxyapatite scaffolds saturated with CAM in rat calvarial defects, they study showed that CAM promoted significantly bone regeneration compared to BMP-2 application.

Previous results on the effect of clopidogrel on bone metabolism and turnover, however, are contrasting, as it seems that both dosage and duration of treatment with clopidogrel are important factors for its effects on bone. Syberg *et al*[8] found in adult ovariectomized mice that treatment with clopidogrel (1 mg/kg/d) for 4 wk resulted in significant reduction of trabecular bone volume, as well as to the reduction in trabecular number in tibia and femur compared with controls. In contrast, Su *et al*[9] reported that adult ovariectomized mice, treated with high clopidogrel dose (30 mg/kg/d) for 2 or 5 wk, showed significant increase in trabecular bone volume in tibia and significantly decreased serum levels of osteoclast activity marker (CTX), as compared to vehicle-treated mice. Interestingly, the same investigator[9] found that a 30 mg/kg/d clopidogrel treatment for 9 d in young mice, in which bone turnover is high due to skeletal growth, resulted in significant increase in the trabecular bone

Table 1 Secondary histomorphomemtric parameters shown in mean ± standard deviation

	Clopidogrel group, *n* = 8	Control group, *n* = 8	*P* value
Defect regeneration, %	28.07 ± 7.7	19.47 ± 4.9	0.018
Defect bridging, %	72.17 ± 21.2	41.17 ± 8.5	0.004
Bone tissue density, %	72.13 ± 8.5	64.82 ± 11.9	0.179

volume and trabecular bone mineral density of tibia, whereas there was no effect in adult normal mice. Moreover, Su *et al*[9] demonstrated that a 30 mg/kg/d clopidogrel treatment for 9 d protected mice from tumor-associated bone loss in a mouse model of tumor metastasis in the tibia. Also, in support of a "trophic" role, Yamaguchi *et al*[10] found that 5 mg/kg/d clopidogrel for 4 wk significantly reduced the incidence of steroid-associated osteonecrosis in a rabbit model. Yet, in a large scale clinical retrospective cohort study, Jørgensen *et al*[11] showed that clopidogrel therapy is associated with increased risk of osteoporotic fractures. They studied 77503 Danish patients who were prescribed clopidogrel for any indication, dosing and duration of treatment, during the years 1996-2008 and 232510 matched nonusers, and they found that patients on clopidogrel therapy had up to 50% increase in risk of osteoporotic fractures (hip, forearm and spine), especially those in treatment of more than 1 year. However, patients receiving less than 0.01 of the defined daily dose of clopidogrel apparently had a lower risk of fracture than nonusers[11]. Interestingly, in 2017[25], the same group of researchers studied patients taking clopidogrel for stroke alone from the same cohort and found that while these patients run an increased risk of osteoporotic fractures, clopidogrel was not responsible for this. In contrast, they indicated that patients less adherent to the treatment run a lower risk than nonusers and patients with high adherence.

At the cellular level, the available studies indicate that clopidogrel should result in suppression of both bone formation and resorption *in vivo* and, thus, impairment of bone healing. For instance, CAM inhibited both osteoblast and osteoclast differentiation from bone marrow cells in culture[24]. Moreover, the application of clopidogrel in osteoblast cultures slowed osteoblast proliferation, decreased cell viability of mature osteoblasts and inhibited mineralized bone nodule formation, while the application in osteoclast cultures decreased their number, viability and resorptive activity[8]. Therefore, it appears that inhibition of the $P2Y_{12}$ receptor on bone cells alone may not explain our results showing bone regeneration at least at 6 wk postoperatively.

Taking into account the foregoing, it is tempting to speculate that clopidogrel may have indirectly enhanced bone regeneration in our study by interfering with various levels of the complex cascades that take place during tissue repair. Firstly, the $P2Y_{12}$ receptor is also expressed in other cellular players involved in bone healing such as platelets, leukocytes and endothelial cells[26]. Clopidogrel is known to affect various processes occurring in the early stages of tissue healing such as improving endothelial nitric oxide bioavailability and reducing platelet degranulation, platelet-leukocyte aggregate formation, expression of inflammatory cytokines and C-reactive protein[27]. Coimbra *et al*[28] found that high clopidogrel dose (75 mg/kg/d) increased the number of osteoblasts and mesenchymal stem cell proliferation in the areas of bone remodeling during the initial phase of inflammation resolution, following periodontitis. Moreover, the purinergic signaling system is known to regulate long-term (trophic) effects in tissue regeneration, and its components are highly interdependent and, occasionally, have opposite effects on cellular functions[29-32]. Thus, it is not unreasonable to assume that continuous inhibition of the $P2Y_{12}$ receptor in the perioperative period by clopidogrel may affect the functions of other purinoreceptor subtypes, resulting in a cumulative effect that favors bone healing, which cannot be fully explained yet.

Admittedly, our study bears some limitations. For example, due to enforced limitations on the number of experimental animals by the local Veterinary Service, the evaluation of bone healing at different time intervals was not possible nor was the administration of different doses of clopidogrel for different perioperative periods, which would have provided better metrics on the positive influence of clopidogrel on bone healing. In the future, comparison with other antiplatelet drugs, such as aspirin or ticagrelor, would provide valuable data for extensively used drugs. Moreover, our study would have benefited from the use of micro-computed tomography in order to obtain 3-D quantitative data of the defect regeneration, although our method (combination of radiographic and histologic interpretation) is also acceptable in the literature[33]. Finally, it should be considered that the present study is experimental, on

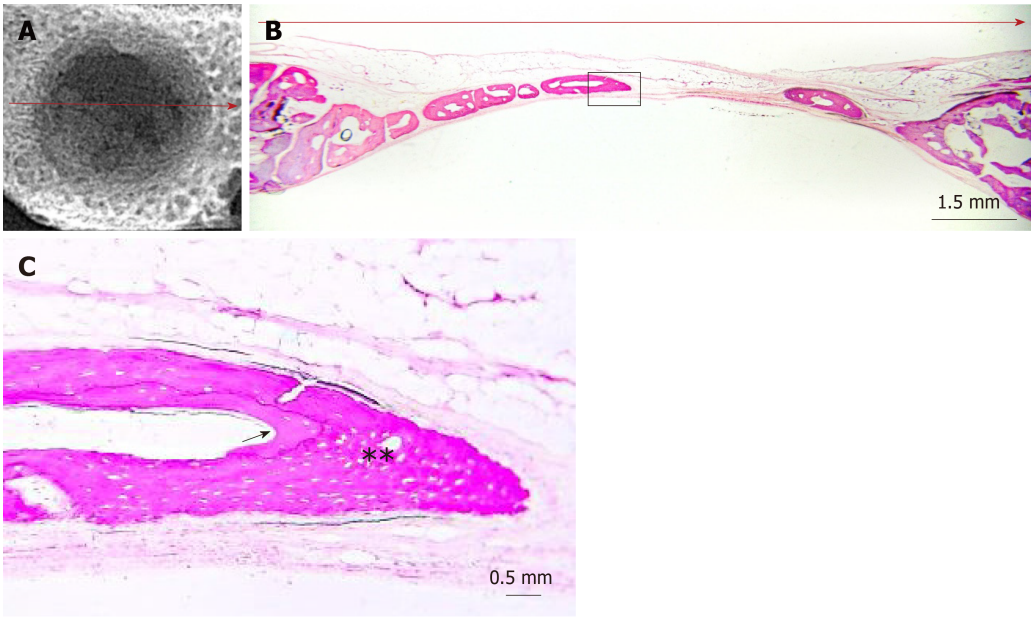

Figure 5 Representative specimen from the clopidogrel group. A: Planar radiographic image of the defect (red arrow showing the direction of histological section; scale bar is 1.5 mm); B: Histological section (red arrow showing the direction of histological section; scale bar is 1.5 mm); C: Higher magnification in the central part of the defect showing new formed bony islet consisting of woven (asterisks) and lamellar bone (black arrow, scale bar is 0.05 mm).

an animal model, and its results cannot fully be translated to humans.

Despite such limitations, our results indicate that perioperative administration of clopidogrel does not negatively affect bone healing but rather enhances it. Clopidogrel treatment may promote bone healing *in vivo* by influencing complex mechanisms that involve purinergic signaling on a number of cell types participating in the process. Considering the high clinical impact of the subject due to the wide use of clopidogrel, its role in bone healing and remodeling remains to be further elucidated. In addition, expansion of the present research may provide useful information for future clinical applications on the acceleration of bone healing and the prevention/management of bone loss.

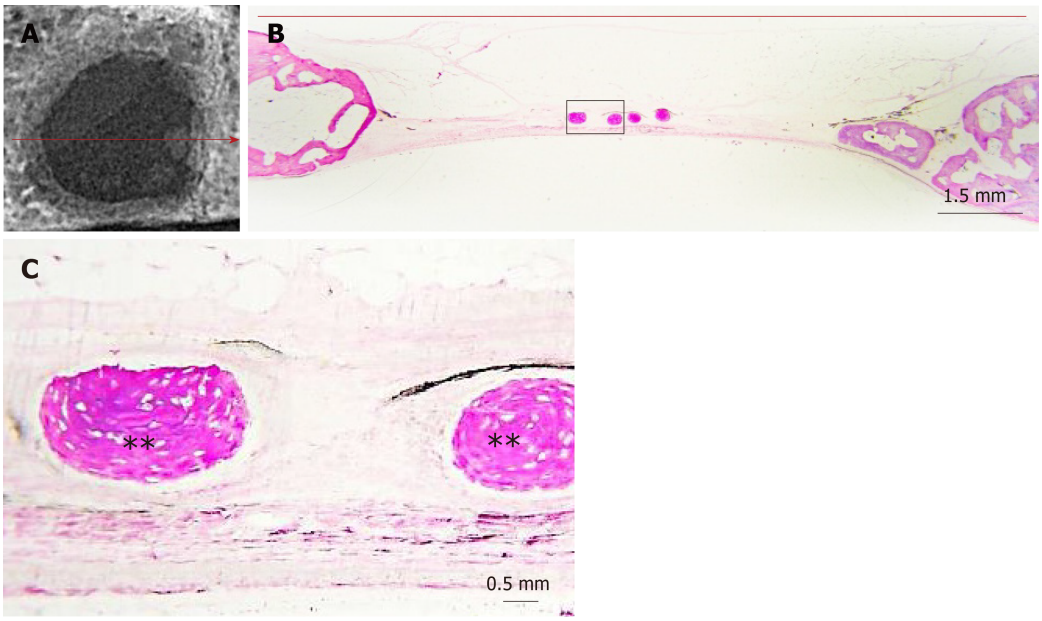

Figure 6 Representative specimen from the control group. A: Planar radiographic image of the defect (red arrow showing the direction of histological section; scale bar is 1.5 mm); B: Histological section (red arrow showing the direction of histological section; scale bar is 1.5 mm); C: Higher magnification in the central part of the defect showing new formed bony islet consisting of woven bone (asterisks, scale bar is 0.05 mm).

ARTICLE HIGHLIGHTS

Research background

Clopidogrel is a widely prescribed drug that inhibits platelet aggregation and, therefore, prevents thromboembolic events such as myocardial infarction and stroke. Clopidogrel acts by binding on the $P2Y_{12}$ purinergic receptor on the platelet surface. Purinergic receptors also play an important role in bone homeostasis, and $P2Y_{12}$, in particular, is expressed in osteoblasts and osteoclasts as well. The exact role of the $P2Y_{12}$ receptor and the effect of clopidogrel treatment in bone metabolism have not been elucidated. The few existing studies demonstrate contrasting results, with some of them indicating a negative impact on bone turnover. The effect of clopidogrel treatment in bone healing has not yet been studied.

Research motivation

The presence of a drug that may negatively affect bone healing during the perioperative period when dealing with skeletal surgery raised our concerns and motivated us to conduct this study.

Research objectives

The main objective of the present study was to evaluate bone healing during continuous perioperative clopidogrel treatment.

Research methods

Our study used the well-described critical sized calvarial defect model. Sixteen male New Zealand rabbits were used and randomly divided into two groups; an experimental group taking clopidogrel 3 mg/kg/d per os and a control group taking the vehicle alone. The treatment began 1 wk before the surgical procedures and continued for 6 wk postoperatively. Surgical procedures were conducted to create two circular bony defects on the cranium of every animal. After a 6-wk postoperative period, the animals were euthanized, and postmortem radiographical and histological evaluation was conducted. Radiological evaluation was conducted using a five grade qualitative scale. Histological evaluation included measurements of the percentages of the defect regeneration, bridging and bone density.

Research results

The postoperative period was uneventful and without any complication for all animals. The radiological examination showed that the clopidogrel group had a statistically significant improved radiographic score in bone bridging and union. The histomorphometric analyses also revealed significantly greater percentage of bone regeneration and bridging in the clopidogrel group than in the control group. However, bone density was not statistically different between the groups.

Research conclusions

The present study results indicate that continuous perioperative clopidogrel treatment does not impair bone healing; instead, it promotes new bone formation. This finding is important when dealing with skeletal surgery in patients who use this drug chronically for cardiovascular

indications.

Research perspectives

Future research may involve evaluation of the effect of other antiplatelet drugs of the same category, such as ticagrelor or prasugrel, and at different dosing and treatment duration. Moreover, further research is needed in order to evaluate if our findings have useful implications in bone healing improvement such as topically drug releasing vehicles or drug eluting orthopedic implants.

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ORIGINAL ARTICLE

Case Control Study

Anterior cruciate ligament reconstruction using a double bundle hamstring autograft configuration in patients under 30 years

Christopher Reece Lim, Tamalee Henson, Jay Ebert, Peter Annear

ORCID number: Christopher Reece Lim (0000-0002-2762-4468); Tamalee Henson (0000-0003-0664-2218); Jay Ebert (0000-0001-5843-6243); Peter Annear (0000-0001-5355-6115).

Author contributions: Lim CR is primary author, responsible for data collection and interpretation of results, writing of the manuscript and editing of the manuscript. Ebert J was responsible for interpretation of results and editing of the manuscript. Henson T contributed to data collection. Annear P was responsible for development of the original idea, interpretation of the results and editing of the manuscript.

Institutional review board statement: Attached is a copy of the ethics approval granted for the purpose of this study in 2015 which was originally written in the English language.

Informed consent statement: Attached is a copy of the patient consent forms used for the study which was originally written in the English language.

Conflict-of-interest statement: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data sharing statement: Technical appendix, statistical code, and datasets are available from the corresponding author at christopherlim22@gmail.com. Consent was not obtained but the presented data are anonymized and risk of identification is low.

Christopher Reece Lim, Department of Orthopaedics, Sir Charles Gairdner Hospital, Western Australia, Nedlands 6009, Australia

Tamalee Henson, Fiona Stanley Hospital, Western Australia, Murdoch 6150, Australia

Jay Ebert, School of Human Sciences (Exercise and Sport Science), University of Western Australia, Western Australia, Crawley 6009, Australia

Peter Annear, Perth Orthopaedic and Sports Medicine Centre, Western Australia, West Perth 6005, Australia

Corresponding author: Christopher Reece Lim, BSc, MBBS, Doctor, Medical Doctor, Department of Orthopaedics, Sir Charles Gairdner Hospital, Hospital Ave, Western Australia, Nedlands 6009, Australia. christopherlim22@gmail.com
Telephone: +61-43-2835277

Abstract

BACKGROUND

Anterior cruciate ligament reconstruction (ACLR) has a high incidence of re-tear in younger patients. Despite comparable functional outcomes, the incidence of re-tear using single and double bundle ACLR methods has not been well reported.

AIM

To hypothesize that double bundle hamstring ACLR has a lower graft rupture rate compared with single bundle hamstring ACLR grafts in young patients.

METHODS

One hundred and twelve patients < 30 years of age at the time of primary double bundle ACLR were eligible for study participation. 91 (81.3%) could be contacted, with a mean age of 20.4 years (range 13-29) and mean post-operative follow-up time of 59 mo (range 25-107). Telephone questionnaires evaluated the incidence (and timing) of subsequent re-tear and contralateral ACL tear, further surgeries, incidence and time to return to sport, and patient satisfaction.

RESULTS

Of the 91 patients, there were 6 (6.6%, 95%CI: 1.4-11.7) ACL graft re-ruptures, with a mean time to re-rupture of 28 mo (range 12-84). Fourteen patients (15.4%) experienced a contralateral ACL rupture and 14 patients (15.4%) required further surgery to their ipsilateral knee. fifty patients (54.9%) returned to pre-injury level of sport. Of those < 20 years (n = 45), 4 patients (8.9%, 95%CI: 0.4-17.3) experienced a re-rupture, with mean time to re-injury 15 mo (range 12-24).

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Comparative analysis with existing literature and revealed a non-significant Chi-squared statistic of 2.348 (P = 0.125).

CONCLUSION
A trend existed toward lower graft rupture rates in young patients undergoing double bundle ACLR utilizing a hamstring autograft, compared with rates reported after single bundle ACLR.

Key words: Anterior cruciate ligament reconstruction; Re-rupture; Double bundle; Young; Knee function; Clinical outcomes

Core tip: Double bundle anterior cruciate ligament (ACL) reconstruction has a low re-rupture rate (6.6%) in the young, active population. In addition, re-rupture rates are shown to be at least comparable with Single Bundle ACL reconstructions techniques.

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INTRODUCTION

Anterior cruciate ligament (ACL) tears are prevalent, and surgical ACL reconstruction (ACLR) is considered the current standard of clinical treatment[1]. Unfortunately, a high incidence of re-rupture (20%-30%) has been reported, particularly in younger patients[2,3]. While the gold standard in ACLR has traditionally been bone-patellar tendon-bone graft, hamstrings autografts have become more popular with a recent systematic review and meta-analysis suggesting comparable outcomes between the two and less post-operative complications using hamstrings[4,5].

The two distinct bundles of the ACL (anterior-medial bundle and posterior-lateral) are responsible for anterior-posterior stability and rotational stability retrospectively[6,7]. Despite this, traditional single bundle hamstring ACLR has become more favorable in recent years, which requires the harvest of hamstring tendon to create a single graft that is passed through a single tibial and femoral tunnel[5]. Double bundle hamstring ACLR involves the creation of two grafts and two additional tunnels. Studies have compared single and double bundle ACLR graft constructs[8-14]. A Cochrane review in 2012 by Tiamklang *et al*[8] concluded that a double bundle configuration may provide better knee stability and return to sport capacity; however, double bundle ACLR provided similar rates of re-rupture in adults and there was a higher incidence of subsequent notchplasty required due to notch impingement.

To the best of our knowledge, previous research has not sought to compare the outcomes of single and double bundle ACLR configurations using a hamstring autograft in the younger population, where the incidence of re-tear is considerably higher. This study aimed to investigate the rate of ACL re-rupture in young patients undergoing double bundle ACLR, and compared this to the available literature largely focused around single bundle ACLR graft constructs.

MATERIALS AND METHODS

Double bundle ACLR surgical technique

The arthroscopically-assisted double bundle ACLR operative technique involved autologous harvesting of semitendinosus and gracilis tendons to form two distinct grafts. Tibial tunnels were drilled based on the tibial ACL footprint with anterior-lateral and posterior-medial tunnels. Femoral tunnels were drilled in a similar fashion based on the anatomical footprint of the native ACL. Each graft was then passed through their respective tunnel and tensioned at maximal manual tension after ten cycles of the knee (0-90°). Post-operatively, patients were braced in an extension splint

for 2-3 wk to reduce knee swelling and protect the construct, with crutch ambulation as required. Early range of motion exercises were encouraged, with a focus on regaining full active knee extension. Stationary cycling, swimming, and closed chain conditioning were allowed at 6-8 wk. Jogging and open chain strength exercises were commenced at 16 wk with a return to sport between 9 and 12 mo.

Patients

All patients who underwent primary double bundle ACLR utilizing a hamstrings autograft under a single orthopedic surgeon (PA), between January 2008 and December 2015, were reviewed for eligibility for the study (n = 193) (Figure 1). Initially, the medical records (clinical notes, operation records, radiology reports) of all patients that underwent surgery through the nominated period were manually reviewed to determine eligibility. Patients were included in the current study if they were skeletally mature at the time of ACLR surgery and required a primary ACLR, consenting to the double bundle ACLR technique which was the preferred method of the principal investigator at the time, with or without concomitant meniscal surgery. Patients were excluded upon initial chart review if they were ≥ 30 years of age at the time of surgery, had bilateral injuries, had undergone prior ACLR on the ipsilateral or contralateral knee, and/or those that had < 24 mo of clinical follow-up. Of the 113 eligible patients, 1 had a femoral condyle impaction fracture with their ACL injury and was excluded from the study leaving 112 for data collection. Ethics was granted from the relevant hospital ethics committee.

Outcomes

Basic demographical and injury characteristics, together with details of pre- and post-operative clinical management were collected from chart review. All patients included as per the inclusion/exclusion criteria for this study were then contacted *via* phone, to ascertain the following outcomes: (1) The incidence (and timing) of subsequent ACL re-tear and/or contralateral ACL tear; (2) The incidence (and timing) of other ipsilateral and/or contralateral knee injuries/surgeries (whether they be related to the graft such as ACL re-tear, or not); and (3) Whether the patient had undergone any other second orthopedic opinions and/or surgeries relating to their operated (or contralateral) knee. Patient satisfaction with their surgical outcome was also evaluated, *via* a 5-point categorical scale: (1) Completely unsatisfied; (2) Mostly unsatisfied; (3) Uncertain; (4) Mostly satisfied; and (5) Completely satisfied. Finally, the timing and ability of the patient to return to their pre-injury level of sport were evaluated.

Statistical analysis

All information collected from the chart review and standardized phone interview was logged in an excel spreadsheet to ensure consistent collection and documentation. This study sought to determine the incidence of ACL re-injury, contralateral injury, and combined ACL (ipsilateral re-tear and contralateral rupture) injury in patients < 30 years, though also more specifically in younger patients < 20 years of age as previously undertaken and reported by Webster *et al*[2] χ^2 test were used to compare categorical outcomes between the current study (double bundle ACLR employing a hamstrings autograft) and that of Webster *et al*[2] (single bundle ACLR employing a hamstrings autograft). Statistical analysis was conducted using SPSS software (SPSS, Version 23.0, SPSS Inc., United States), while statistical significance was determined at $P < 0.05$.

RESULTS

Of the 112 patients eligible for the study based on inclusion criteria, 91 (81.3%) responded and consented to participation (Table 1). Of the non-responders (n = 21), 20 patients could not be contacted, and one patient did not consent.

Of the 91 patients < 30 years of age at the time of surgery, the mean age was 20.4 years (range 13-29) (Table 1). Six patients (6.6%, 95%CI: 1.4-11.7) patients had a re-rupture of their primary double bundle hamstring ACLR, with a mean time to re-injury of 28 mo (range 12-84) (Table 1). Of those < 20 years of age (n = 45), 4 patients (8.9%, 95%CI: 0.4-17.3) experienced a re-rupture, with a mean time to re-injury of 15 mo (range 12-24) (Table 1). Of the 6 patients that had experienced re-injury at the time of analysis, 5 patients (83.3%) had undergone revision ACLR and the remaining patient was on the wait list for revision.

A total of 14 patients (15.4%) experienced a contralateral ACL rupture at the time of study review (Table 1), with all of these having undergone contralateral ACLR without further injury at the time of review. There was a total of 20 (22.0%) ACL

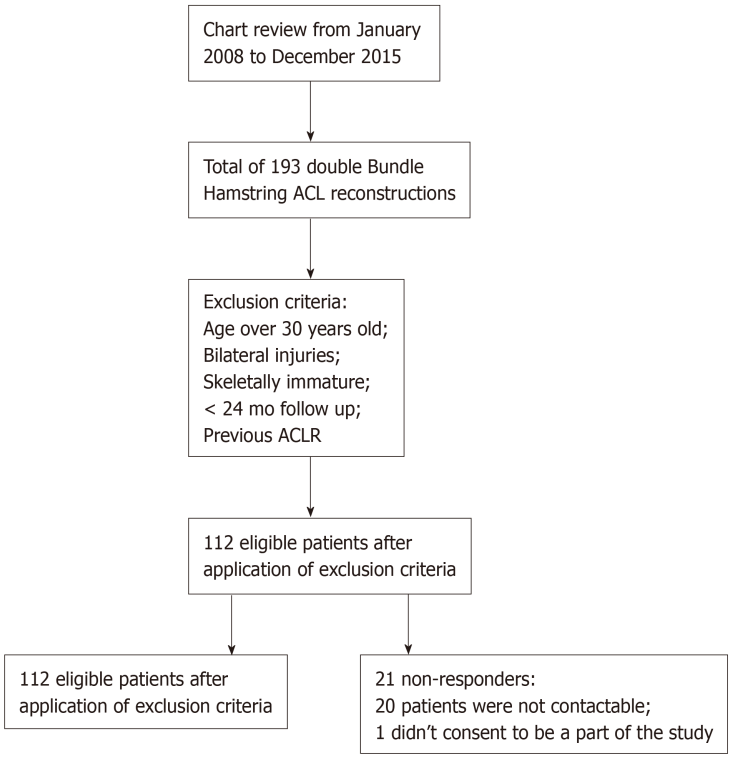

Figure 1 Methodology flow diagram. ACL: Anterior cruciate ligament; ACLR: Anterior cruciate ligament reconstruction.

injuries to either the ipsilateral or contralateral knee (Table 1). Of all the patients who suffered an ACL graft re-rupture, none had a contralateral ACL rupture. In those < 20 years of age, 5 patients (11.1%) had experienced a contralateral ACL tear.

A total of 14 patients (15.4%) required further surgery (including revision ACLR) to their ipsilateral knee, with 7 patients (15.6%) < 20 years of age requiring subsequent surgery (Table 1). The most common reason for re-operation was revision ACLR (5 patients), notchplasty (4 patients) or removal of the tibial screw (2 patients).

Overall, 50 patients (54.9%) returned to their pre-injury level of sport, with the mean time to return to sport at 13.4 mo (range 6-36). A total of 13 patients (14.3%) did not return to any level of sport. A total of 20 (22%) professional athletes were included in the study, of which 6 (30%) managed to return to a professional level of sport. Australian Rules Football (AFL) was the most common sporting reason for injury, occurring in 31 (34.1%) patients. This was followed by netball (n = 18, 19.8%), soccer (n = 7, 7.7%) and basketball (n = 6, 6.6%), with motor vehicle accidents accounting for 2.2% (n = 2). All 6 re-ruptures occurred in the 78 (6.4%) patients that returned to sport post-operatively. However, at the time of contact 1 of these re-ruptures had given up playing all sports. Mean satisfaction levels were 4.27 with 81 (89.1%) of patients being either mostly satisfied or completely satisfied with their knee outcome. Only 1 patient was completely unsatisfied, and he was awaiting revision ACLR for re-rupture of his graft.

The data from this population was then compared to a paper written by Webster *et al*[2] in 2016. As per Webster *et al*[2]'s classification of "young" ACLR patients (< 20 years of age), sub-group comparative analysis in ACL re-tears revealed a non-significant χ^2 statistic of 2.3 (P = 0.125), when comparing those < 20 years of age in the current study (Table 1).

DISCUSSION

ACL re-tears are common, particularly in the young active cohort, and a more robust graft construct may be required in these patients to reduce the incidence of a subsequent re-injury. The primary findings from this study are that double bundle ACLR construct in younger patients (< 30 years) resulted in: (1) A low rate of graft re-rupture (6.6%) and (2) A low rate of contralateral ACL insult (15.4%). A Cochrane review by Tiamklang *et al*[8] in 2012 comparing double bundle and single bundle

Table 1 Demographics and re-injury characteristics of the patient sample included in the study that underwent double bundle anterior cruciate ligament reconstruction, together with sub-group analysis based on age in comparison to that reported by Webster *et al*[2]

Variable	Measure	Total Cohort (< 30 yr)	Patients (20-29 yr)	Patients (< 20 yr)	
		Dataset (2018)	Dataset (2018)	Dataset (2018)	Webster *et al*[2], 2016
Patients	*n*	91	46	45	316
Age (yr)	mean (SD), range	20.4 (4.7), 13-29	24.0 (2.5), 20-29	16.2 (1.8), 13-19	17.2 (NR), 11-19
Clinical follow-up (mo)	mean (SD), range	59 (26), 25-107	63 (27), 29-107	55 (25), 25-102	60 (NR), 36-120
Males	*n* (%)	51 (56.0)	29 (63.0)	22 (48.9)	200 (63.6)
Right knee	*n* (%)	40 (44.0)	25 (54.3)	22 (48.9)	NR
Concurrent meniscal surgery	*n* (%)	44 (48.4)	18 (39.1.9)	26 (57.8)	NR
ACL re-ruptures	*n* (%)	6 (6.6)	2 (4.3)	4 (8.9)	57 (18)
ACL re-ruptures	95%CI	95%CI: 1.4%-11.7%	95%CI: 1.6%-10.3%	95%CI: 0.4%-17.3%	95%CI: 17%-29%
Mean time to re-rupture (mo)	mean (SD), range	28 (28), 12-84	55.0 (41.7), 25-84	15 (6), 12-24	21.6 (NR), NR
Repair of re-rupture	*n* (%)	5 (83.3)	1 (50)	3 (75)	NR
Subsequent surgery to ipsilateral knee	*n* (%)	14 (15.4)	7 (15.2)	7 (15.6)	NR
Contralateral ACL injury	*n* (%)	14 (15.4)	9 (19.6)	5 (11.1)	56 (17.7)
Combined ACL injuries	*n* (%)	20 (22.0)	11 (23.9)	9 (20.0)	113 (35.8)

ACL: Anterior cruciate ligament; SD: Standard deviation; NR: Not recorded; CI: Confidence interval.

ACLR combined six studies reporting a re-rupture rate of 1/169 (0.5%) *vs* 4/185 (2.2%), respectively. Since then, Suomalainen *et al*[9] conducted a randomized controlled trial and reported 11 graft failures in 90 (12.2%) patients undergoing primary ACLR at the time of five years follow up (mean age 33 years). Of the 30 patients undergoing a double bundle ACLR, only 1 (3.3%) graft rupture was reported, which was significantly lower when compared to single bundle ACLR[10]. More recently, Mohtadi *et al*[11], in 2014, conducted a randomized controlled trial of 109 double bundle and 111 single bundle ACLRs, with a mean age of 29 years, and compared graft failure rates. Results showed high failure rates, 19 graft failures (17.4%) in the double bundle population *vs* 29 (26.1%) in those undergoing single bundle ACLR (P = 0.043), with a mean time to failure of 16 mo[11]. The study also reported 6 (5%) contralateral ACL tears in their double bundle ACLR cohort[11]. These studies suggest that re-rupture rates in double bundle ACLR could indeed be lower.

This study reported an ACL re-tear incidence of 8.9% in patients < 20 years, with a further 11.1% experiencing a contralateral tear, at a minimum of 2 years post-surgery (mean 59 mo). It should also be noted that while there were only 4 re-ruptures in this young cohort, one of these patients returned to sport prior to complete their rehab at their own discretion. This potentially presents a higher re-tear rate than could have been observed should the minimum time to return to sport have been followed. Webster *et al*[2] presented outcomes on re-rupture incidence, time to re-rupture, re-operations and contralateral ACL tear in 316 patients < 20 years undergoing primary single bundle ACLR. They followed patients to a similar post-operative timeline (mean 60 mo, range 36-120) as the current study, and reported an 18% re-rupture rate, with almost 18% of patients further experiencing a contralateral ACL injury, with a mean time to re-rupture of 21.6 mo. Unfortunately, sample sizes within the two cohorts were not large enough to permit an adequately powered statistical comparison. There are known limitations with comparing samples across different studies, such as differences in post-operative rehabilitation regimes and differences in activity/sport status. However, these were both Australian patient cohorts and at the very least the encouraging outcomes in the double bundle ACLR cohort in the current study suggests a platform for further research.

ACLR does not guarantee the patient to return to sport, and as reported by Ardern *et al*[15] only 63% of patients may resume pre-injury level of activity participation and only 44% return to competition. Therefore, the patients ability to return to sport is often a measure of both surgical and rehabilitation success, as well as a measure of patient satisfaction[16]. The current study demonstrated that 54.9% of patients undergoing double bundle ACLR were able to return to their pre-operative level of competitive sport, and these statistics are in keeping with previous studies that have quoted a return to sport percentage of 50%-70% for double bundle ACLR[17,18].

Despite 55% of patients in the current study returning to their pre-operative level of

competitive sport, almost 89% were satisfied with their outcome at the time of follow up with a mean score of 4.27/5. This highlights the varied factors that contribute to a satisfied patient. Satisfaction rates in the current study are comparable to that reported by Günay *et al*[19] who investigated post-operative satisfaction at minimum two years follow up of 29 transphyseal ACLR patients, revealing a mean satisfaction level of 9/10, with 41% of patients returning to their pre-morbid level of sport[19]. In addition, Toritsuka *et al*[20] investigated 78 patients undergoing double bundle ACLR and reported 94% had a near normal, to normal feeling knee. While patient-reported outcomes remain a critical outcome measure in the success of an operation, there are limitations with retrospective measures of patient satisfaction. Satisfaction draws on the patient's ability to recall their pre-operative state, the surgical procedure, and the early, mid, and later post-operative phases.

While the double bundle ACLR configuration may provide a more robust graft construct, apprehension throughout the orthopedic community does exist. Firstly, it is a more technically demanding surgical procedure which may also contribute to longer operating times. Secondly, a Cochrane review by Tiamklang *et al*[8] in 2012, demonstrated no statistical differences between single and double bundle ACLR methods in patient-reported outcomes scores (Lysholm score, International Knee Documentation Committee score and Tegner score), adverse events and both short and long-term complications[8]. However, even with the limited data available, the double bundle configuration favored a better return to pre-injury level sport, anterior (KT-1000) and rotational (pivot shift) knee stability measures, and the development of newly occurring meniscal injuries[8]. While these benefits may be of higher relevance in the young active cohort, this review did not sub-categorize participants into different age groups to better evaluate the high-risk younger population.

A recent study by Sonnery-Cottet *et al*[21] in 2017 looked at anterior lateral ligament (ALL) reconstruction in conjunction with ACLR. The study concluded that graft failure was 2.5 times less likely in those with ALL and ACL reconstruction when compared with ACL reconstruction alone. The use of extra-articular ligamentous restraint may be the future direction of ACLR; however, longer term follow-up is needed. Unfortunately, young athletes with ACL ruptures are often still considered to have a career ending sporting injury. Future research should include randomized controlled trials comparing single bundle, double bundle, and ALL ACLR techniques in younger patients to better ascertain the optimal surgical technique in this high-risk population.

There are several limitations to acknowledge in the current study. Firstly, the retrospective nature of the study precludes data being collected from early post-operative time points. Secondly, while comparisons have been made to the existing literature by Webster *et al*[2] looking at young Australians undergoing single bundle ACLR using autologous hamstrings, there are limitations with cross evaluating two separate studies. This may include differences in pre-operative and post-operative demographics, management, and rehabilitation regimes, provided to patients. For example, there were discrepancies between the distribution of males and females in those < 20 years of age, with a 64% male population in the Webster *et al*[2] paper and only 49% in this sample population. Therefore, a gender bias may present in comparing those two cohorts. In addition, the current study had a patient response rate of 81%. Webster *et al*[2] reported a response rate of 89% in their young cohort, while others have reported a response rate of 79% at 2 years follow-up[2,22]. While patients over this post-operative time frame will be lost to attrition, there are always issues with missing data in the non-responder population and studies have suggested they may have worse outcomes[22]. Finally, the value in the current study presented the incidence (and timing) of ACL re-tear and contralateral ACL injury in this young cohort undergoing double bundle ACLR using autologous hamstrings. However, it was clearly underpowered to show statistical significance that a double bundle ACLR hamstring configuration would provide a reduced failure rate than single bundle configurations, in these young patients. The active nature and high failure rates in a younger population make this cohort useful in detecting differences in durability between these varied graft constructs.

In conclusion, this study presents a low ACL graft re-injury rate in young patients undergoing double bundle ACLR with a hamstring autograft, 6.6% in < 30-year old's and 9.1% in < 20-year-olds. The incidence of contralateral ACL injury was 11.1%. While underpowered to detect statistically significant differences in patients < 20-years old, these rates appear better than that reported in a similarly aged cohort undergoing single bundle ACLR[2]. Further research is required to ascertain if double bundle ACLR produces better outcomes for these high-risk patients, particularly with respect to graft longevity and longer-term knee health.

ARTICLE HIGHLIGHTS

Research background

Anterior cruciate ligament reconstruction (ACLR) is a common procedure in the young active population. Current re-rupture rates in single bundle techniques have been quoted as high as 20%-30%. While studies have shown that there are similar functional outcomes between single and double bundle ACL reconstruction techniques the re-rupture rates have not been well reported.

Research motivation

This body of research aims to investigate if double bundle ACL reconstruction techniques have lower re-rupture rates in comparison to single bundle ACL reconstruction.

Research objectives

The main objective of this research was to compare re-rupture rates of single bundle and double bundle ACL reconstruction in the young, active population. If re-rupture rates are suggestive of being lower, more research, such as a randomized control trial between the two techniques could be done to further assess the viability of double bundle ACL reconstruction, specifically in these patients.

Research methods

All patients under the age of 30 years old who underwent a double bundle ACL reconstruction at a single orthopedic clinic were assessed for eligibility for the study. Of the 112 patients, 91 (81.3%) could be contacted to complete an over the phone questionnaire. Outcomes assessed included the incidence (and timing) of subsequent re-tear and contralateral ACL tear, further surgeries, incidence and time to return to sport, and patient satisfaction. Chi-Squared tests ($P < 0.05$) were then used to compare the population in this study and a recent study by Webster *et al*[2], looking at re-rupture rates in single bundle ACL reconstructions from a similar population.

Research results

Six of the 91 patients enrolled in the study suffered from re-rupture (6.6%, 95%CI, 1.4–11.7). The mean time to re-rupture was 28 mo (range 18-24) with an additional 14 patients (15.4%) suffering from a contralateral ACL tear in the follow-up period. 14 patients (15.4%) required further surgery to their ipsilateral knee. 50 patients (54.9%) managed to return to their pre-injury level of sport, unfortunately, none of the professional level athletes returned o profession level sport. 1 patient who played amateur level netball did go on to play at a professional level with their double bundle ACL reconstruction. Comparative analysis of re-rupture rates with the Webster *et al*[2] paper, that investigated single bundle ACL reconstructions revealed a non-significant chi-squared statistic of 2.348 ($P = 0.125$).

Research conclusions

Double bundle re-rupture rates are low (6.6%). However, while there was a trend towards lower re-rupture rates in the double bundle ACL reconstruction population, there was no statistical significance in comparative testing when compared with a single bundle ACL reconstruction cohort. Double Bundle ACL reconstruction may have lower re-rupture rates that single bundle techniques but further research needs to be done to investigate these theories. The risk of re-rupture with double bundle ACL reconstruction is low in the young, active population. When compared with single bundle ACL reconstruction techniques, double bundle reconstructions have at least comparable re-rupture rates. Further research is needed to fully investigate the re-rupture rate differences between these two techniques. There is a significant paucity of knowledge regarding double bundle ACL reconstruction outcomes, with few studies investigating re-rupture rates in the young, active population. Double bundle ACL reconstruction has lower re-rupture rates than single bundle ACL reconstruction in the young, active population. Double bundle ACL reconstruction could be considered as a technique to adopt in high risk, young, active patients. Double bundle reconstructions have low re-rupture rates in the young, active, population. These rates are at least comparable with current single bundle ACL reconstruction re-rupture rates. The hypothesis that double bundle ACL reconstructions would have lower re-rupture rates in the young, active population when compared with single bundle techniques was not proven in this study. However statistical analysis reported no significant difference between the two techniques with regard to re-rupture rate. Double bundle ACL reconstruction could be considered as a technique for young, active patients with ACL tears looking for repair.

Research perspectives

Double bundle ACL reconstruction could be considered as technique in young, active patients with ACL tears looking for repair. Further research is required to investigate more deeply the differences in outcomes (in particular re-rupture rates) between these two techniques in the young, active population. A randomized control trial looking at the two techniques, double bundle *vs* single bundle ACL reconstruction, would provide the highest level of evidence.

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ORIGINAL ARTICLE

Retrospective Study

Factors associated with trigger digit following carpal tunnel release

Jacob Nosewicz, Carla Cavallin, Chin-I Cheng, Neli Ragina, Arno W Weiss, Anthony Zacharek

ORCID number: Jacob Nosewicz (0000-0003-1720-8740); Carla Cavallin (0000-0003-1729-049X); Chin-I Cheng (0000-0002-0273-8135); Neli Ragina (0000-0002-2811-1277); Arno W Weiss (0000-0002-9484-8939); Anthony Zacharek (0000-0002-7290-6122).

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Jacob Nosewicz, Carla Cavallin, Neli Ragina, Central Michigan University College of Medicine, Mt. Pleasant, MI 48858, United States

Chin-I Cheng, Department of Statistics, Actuarial and Data Science, Central Michigan University, Mt. Pleasant, MI 48858, United States

Arno W Weiss, Anthony Zacharek, Covenant Plastic Surgery, Saginaw, MI 48602, United States

Corresponding author: Jacob Nosewicz, BSc, Central Michigan University College of Medicine, 1280 E Campus Drive, Mt. Pleasant, MI 48858, United States. nosew1j@cmich.edu
Telephone: +1-989-5837918
Fax: +1-989-7747881

Abstract

BACKGROUND

Trigger digit is a common disorder of the hand associated with carpal tunnel syndrome. Carpal tunnel release (CTR) surgery may be a risk factor for trigger digit development; however, the association between surgical approach to CTR and postoperative trigger digit is equivocal.

AIM

To investigate patient risk factors for trigger digit development following either open carpal tunnel release (OCTR) or endoscopic carpal tunnel release (ECTR).

METHODS

This retrospective chart analysis evaluated 967 CTR procedures from 694 patients for the development of postoperative trigger digit. Patients were stratified according to the technique utilized for their CTR, either open or endoscopic. The development of postoperative trigger digit was evaluated at three time points: within 6 mo following CTR, between 6 mo and 12 mo following CTR, and after 12 mo following CTR. Firth's penalized likelihood logistic regression was conducted to evaluate sociodemographic and patient comorbidities as potential independent risk factors for trigger digit. Secondary regression models were conducted within each surgical group to reveal any potential interaction effects between surgical approach and patient risk factors for the development of postoperative trigger digit.

RESULTS

A total of 47 hands developed postoperative trigger digit following 967 CTR procedures (4.9%). In total, 64 digits experienced postoperative triggering. The long finger was most commonly affected. There was no significant difference between the open and endoscopic groups for trigger digit development at all three time points following CTR. Furthermore, there were no significant

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independent risk factors for postoperative trigger digit; however, within group analysis revealed a significant interaction effect between gender and surgical approach (P = 0.008). Females were more likely to develop postoperative trigger digit than males after OCTR(OR = 3.992), but were less likely to develop postoperative trigger digit than males after ECTR (OR = 0.489).

CONCLUSION
Patient comorbidities do not influence the development of trigger digit following CTR. Markedly, gender differences for postoperative trigger digit may depend on surgical approach to CTR.

Key words: Endoscopic carpal tunnel release; Open carpal tunnel release, Trigger digit; Carpal tunnel syndrome; Stenosing tenosynovitis

Core tip: Carpal tunnel syndrome and trigger digit are orthopedic hand conditions that often present concurrently. Markedly, the association between surgical treatment for carpal tunnel syndrome and trigger digit is not clear. This retrospective analysis evaluated numerous risk factors, including surgical approach, for new onset trigger digit following carpal tunnel release (CTR). We reveal that patient comorbidities do not influence the rate of trigger digit development following CTR; however, there may be a significant interaction effect between gender and surgical approach on postoperative trigger digit development. Females may be more likely to develop trigger digit following open carpal tunnel release. In contrast, males may be more likely to develop trigger digit following endoscopic carpal tunnel release.

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INTRODUCTION

Carpal tunnel syndrome (CTS) is a common entrapment neuropathy of the hand that affects 3.8% of the general population[1]. Characteristic symptoms include burning pain, numbness, and tingling in the distribution of the median nerve distal to the wrist. CTS is diagnosed by a combination of clinical signs and median nerve conduction studies, with supportive diagnostic tools including ultrasonography, magnetic resonance imaging, and diffuse tensor imaging[2]. Surgical treatment, or carpal tunnel release (CTR), involves division of the transverse carpal ligament in order to release pressure on the median nerve. Surgical decompression of the median nerve of the can be accomplished *via* two different approaches: Open carpal tunnel release (OCTR) and endoscopic carpal tunnel release (ECTR).

Trigger digit is a common disorder of the hand associated with carpal tunnel syndrome[3]. In trigger digit, the flexor tendon of the distal palm thickens, creating dysfunction between the flexor tendon and its encompassing sheath. The result is a painful locking of the affected digit in flexion or extension, most commonly due to obstruction at the A1 annular pulley[4]. Markedly, systemic inflammatory conditions that increase the risk for carpal tunnel syndrome may also predispose to trigger digit[4-6]. Current evidence also suggests that CTR surgery may be a risk factor for trigger digit development; however, the association between surgical approach to CTR and postoperative trigger digit is equivocal[6-8]. Our study aimed to investigate patient risk factors for trigger digit development following CTR and whether these risk factors varied between OCTR and ECTR.

MATERIALS AND METHODS

IRB approval was obtained. All patients over the age of 18 from a single institution

who underwent CTR from January 2013 to December 2016 were included. Two board certified surgeons from a single institution performed all procedures. One physician exclusively performed all of the OCTR procedures while the other physician exclusively performed all of the ECTR procedures.

Data collection plan and inclusion/exclusion criteria

Electronic medical record databases were queried for Current Procedural Technology codes 64721; Neuroplasty and/or transposition; median nerve at carpal tunnel (OCTR), and 29848; ECTR. This yielded 1138 carpal tunnel procedures from 800 patients for initial eligibility.

The initial list of eligible patients was merged with a query of all patients with ICD-10 Dx code "M65.3*," trigger digit. Trigger digit was clinically diagnosed as tenderness over the A1 pulley of the digit with a history of locking in the digit. Electronic medical records of patients fulfilling both the initial CTR procedural code and trigger finger diagnosis code were evaluated for inclusion eligibility. All patients with a diagnosis of trigger finger prior to ipsilateral CTR were excluded. Paper charts were collected for these patients to confirm the accuracy of the electronic medical records. 94 procedures were excluded for diagnosis of trigger finger prior to ipsilateral CTR.

Stringent exclusion criteria were employed in order to best isolate the effects of CTR. Only patients with first-time CTR for each specific hand were included. Patients undergoing recurrent CTR on the ipsilateral hand were excluded. 73 recurrent CTR procedures were excluded. Further exclusion criteria included a patient history of dupuytren's contracture, tendon repair of the finger or hand, metacarpophalangeal joint arthroplasty, and trapeziectomy prior to ipsilateral CTR. These criteria yielded 16 excluded procedures. In total, 171 CTR procedures from 106 patients were excluded.

Two authors accrued the variables of interest *via* patient electronic medical records and paper records. 967 CTR procedures from 694 patients were included in the final analysis.

Independent and dependent variables

Patients undergoing bilateral CTR were coded as two separate data units. These two procedures from the same patient were treated as independent entities for statistical analysis to account for the possibility that only one of the hands may develop trigger digit. Patient variables including age, gender, race, body mass index (BMI), hand dominance, smoking status, and the presence of diabetes mellitus, rheumatoid arthritis, and hypothyroidism at the time of CTR were also collected. Paper records were sought out to complete any input variables not available in the electronic medical records; however, some patient variables could not be found between electronic medical record and paper charts. BMI was further divided into three categories: Less than 25, between 25 and 30, and greater than 30. Smoking was defined as a patient being a "current every day smoker" within the electronic medical record at the time of CTR. The diagnosis of diabetes included both Type 1 and Type 2 diabetics.

The development of postoperative trigger digit was evaluated at three time points: within 6 mo following CTR, between 6 and 12 mo following CTR, and after 12 mo following CTR. Analysis included only the first-time point at which a patient developed trigger digit to reflect the true total of hands that ultimately developed trigger digit.

Statistical analysis

Descriptive statistics were provided including mean and standard deviation for continuous variables, and frequency and proportions for categorical variables. The two-sample *t*-test was adopted to examine differences in means for age between the two surgical approach groups. Chi-squares tests were used to test the association between categorical variables and surgical approach. Fisher's exact test was used to examine the difference in proportion of postoperative trigger digit at each time interval.

Firth's[9] penalized likelihood logistic regression was conducted to evaluate patient risk factors for postoperative trigger digit development. Patient risk factors included age, gender, BMI, diabetes mellitus, rheumatoid arthritis, smoking status, hypothyroidism, and surgical approach. Hand dominance was not included in the analysis due to the high number of missing variables. Patients were then stratified by surgical approach into an ECTR group and an OCTR group. Two more Firth logistic regression models were conducted to test the association between patient risk factors and postoperative trigger digit within each surgical group. Significant risk factors found within each surgical group were added as an interaction term to the primary logistic regression model. All of the analytical results were considered to be

significant when *P* values were less than or equal to 0.05. Data were analysed using SAS software, version 9.4 (SAS Institute Inc., Cary, NC, United States).

RESULTS

Table 1 presents the descriptive statistics for our two surgical groups. In total, we included 967 procedures in our analysis. More patients underwent ECTR (83.5%) than OCTR (16.5%). A higher percentage of women (60.3%) underwent CTR surgery than men (39.7%). The average age of patients who received endoscopic surgery (59.93 years) was higher than that of patients who received open surgery (57.24 years) (P = 0.03). Our results found that the proportion of white patients who received endoscopic or open surgery were similar at 86.9% and 87.9%, respectively; however, not all patients had race identified in their chart (P = 0.01). Both the OCTR and ECTR groups showed no significant difference in all other patient risk factors.

A total of 47 hands developed postoperative trigger digit following 967 CTR procedures (4.9%). The timing of postoperative trigger digit are reported in Table 2. Postoperative triggering occurred 36 times following 807 ECTR. 8 hands experienced trigger digit within 6 mo (22%), 10 hands between 6 and 12 mo (28%), and 18 hands after 12 mo (50%). 11 hands developed postoperative trigger digit following OCTR. Four hands developed postoperative trigger digit within 6 mo (36%), 3 hands between 6 and 12 mo (28%), and 4 hands after 12 mo (36%). There was no significant difference between the ECTR and OCTR groups to develop trigger digit at all three post-operative time markers.

A total of 64 digits experienced postoperative triggering following 967 CTR procedures as shown in Table 3. The long finger was most commonly affected (28%), followed equally by the first and fifth digit (22%), then the fourth digit (19%), with the second digit being the least commonly affected (9%).

There is insufficient evidence to conclude that independent predictors are related to postoperative trigger digit development as shown in Table 4. However, preliminary within group analysis revealed a significant interaction effect between gender and surgical approach. This significant interaction effect between gender and surgical approach was confirmed in the primary multivariable logistic regression model demonstrated in Table 4 (P = 0.008). Females were more likely to develop postoperative trigger digit than males after OCTR [Odds ratio (OR) = 3.992], but were less likely to develop postoperative trigger digit than males after ECTR (OR = 0.489).

DISCUSSION

Patients experience similar functional outcomes between OCTR and ECTR; however, the influence of CTR surgical approach on the development of other hand comorbidities, such as trigger digit, is not cohesive[6,8,10]. Furthermore, the interaction between patient comorbidities and the postoperative condition of the carpal tunnel remains unknown. Our study investigated the interaction between CTR surgical approach and patient comorbidities as risk factors for trigger digit.

The incidence rate of new-onset trigger digit development following CTR has been reported between 4%-31.3%[8,11]. Lin *et al*[12]'s meta-analysis found a collective incidence rate of 7.7% after excluding patients with a history of trigger digit prior to their CTR. Our incidence rate is at the low end of what has been reported (4.9%). Postoperative trigger digit has been reported to primarily occur in the first 6 mo following CTR[12]. In our study, postoperative trigger digit development most commonly happened after 12 mo. The extended time length for patient follow up in our study may explain why the majority of trigger digits occurred beyond one year.

There were no significant individual predictors revealed for the development of trigger digit following CTR (Table 4). Lee *et al*[13] evaluated biomechanical changes within the carpal tunnel following 497 OCTR procedures. The authors found significant differences in volar migration of the flexor tendons between those patients who developed postoperative trigger digit and those that did not. The authors suggested that this increased volar positioning of the flexor tendons resulted in increased friction upon entrance to the A1 pulley, thereby increasing the risk for trigger digit development. Karalezli *et al*[14] confirmed these findings in their study of cadavers subject to OCTR. This change was most pronounced in the third, fourth, and first digits. The frequency these digits triggered in our study support volar migration of the flexor tendons as an important factor for postoperative trigger digit development (Table 3).

Momose *et al*[15] utilized MRI to study structural changes within the carpal tunnel

Table 1 Descriptive statistics for open and endoscopic surgical groups, *n* (%)

	Total (*n* = 967)	Surgical group		Test statistics
		Open (160, 16.5%)	Endoscopic (807, 83.5%)	
Age (16-94)	59.49 (14.33)	57.24 (15.28)	59.93 (14.10)	-2.17[1]
Gender				1.31[2]
Male	384 (39.7)	70 (43.8)	314 (38.9)	
Female	583 (60.3)	90 (56.2)	493 (61.1)	
Race				6.35[2]
White	848 (87.7)	139 (86.9)	709 (87.9)	
Non-White	71 (7.3)	20 (12.5)	51 (6.3)	
Missing	48 (5.0)	1 (0.6)	47 (5.8)	
BMI				0.28[2]
< 25	126 (13.0)	22 (13.8)	104 (12.9)	
25-30	251 (26.0)	39 (24.4)	212 (26.3)	
> 30	579 (60.0)	97 (60.6)	482 (59.7)	
Missing	11 (1.1)	2 (1.2)	9 (1.1)	
Hand dominance				0.41[2]
Right	550 (56.9)	69 (43.1)	481 (59.6)	
Left	51 (5.3)	8 (5.0)	43 (5.3)	
Missing	366 (37.8)	83 (51.9)	283 (35.1)	
Diabetes mellitus				0.33[2]
Yes	219 (22.7)	39 (24.4)	180 (22.3)	
No	748 (77.4)	121 (75.6)	627 (77.7)	
Rheumatoid				3.44[2]
Arthritis				
Yes	27 (2.8)	8 (5.0)	19 (2.4)	
No	940 (97.2)	152 (95.0)	788 (97.6)	
Smoking status				3.51[2]
Yes	141 (14.6)	31 (19.4)	110 (13.6)	
No	852 (85.3)	129 (80.6)	696 (86.3)	
Missing	1 (0.1)		1 (0.1)	
Hypothyroidism				1.03[2]
Yes	113 (11.7)	15 (9.4)	98 (12.1)	
No	850 (87.9)	145 (90.6)	705 (87.4)	
Missing	4 (0.4)		4 (0.5)	

[1]Based on 2 sample *t*-test.
[2]Based on Chi-Square test excluding missing cases.
[a]*P* value < 0.05,
[b]*P* value < 0.01. Data is presented as mean (SD) for continuous variables or count (percentage) for categorical variables. BMI: Body mass index.

following 36 ECTR procedures. Similar structural changes occurred within the carpal tunnel compared to prior cadaver studies evaluating OCTR. These studies suggest that volar migration of the flexor tendons within the carpal tunnel may occur following both endoscopic and OCTR. Our results also reflect that a similar postoperative condition within the carpal tunnel may exist for both surgical techniques as surgical approach was not found to be an independent risk factor for postoperative trigger digit development.

In contrast, Goshtasby *et al*[6] reported ECTR as an independent predictor for trigger digit after CTR. The authors suggested that blunt force trauma from endoscope insertion and an earlier return to work offered by ECTR may be contributing factors for trigger digit development. These suggestions were not reflected in our results. Furthermore, prior retrospective studies in our practice have found no difference in return to work following open and ECTR, which is also reflected in the current discourse[10].

Non-enzymatic glycosylation of collagen seen in hyperglycemic states may lead to

Table 2 Frequency and proportion for trigger digit diagnosis at < 6 mo, 6-12 mo, and > 12 mo for each surgical group, *n* (%)

Post-operative time interval	Total diagnoses	Surgical group		*P* value
		Open (*n* = 160)	Endoscopic (*n* = 807)	
< 6 mo	12 (1.2)[1]	4 (2.5)[1]	8 (1.0)[1]	0.121[2]
6-12 mo	13 (1.3)[1]	3 (1.9)[1]	10 (1.2)[1]	0.461[2]
> 12 mo	22 (2.3)[1]	4 (2.5)[1]	18 (2.2)[1]	0.774[2]
Total trigger digit diagnoses	47 (4.9)[1]	11 (6.9)[1]	36 (4.5)[1]	0.225[2]

[1]Percentage represents proportion of procedures that developed trigger digit.
[2]Based on Fisher's Exact test.

connective tissue thickening, thereby lowering the threshold for trigger digit occurrence[4,8]. Grandizio *et al*[8] evaluated 1217 CTR patients, 214 of which were diabetics, and found diabetes to be a significant risk factor for the development of trigger digit following CTR. They repeated their chi-square analysis for OCTR to account for the dissimilar percentages of this procedure between their patient groups. The authors found diabetes to no longer predict trigger digit following CTR. This coincides with our study results that found no association between diabetes and trigger digit development after OCTR; however, our study did not find diabetes to be an independent risk factor for both OCTR and ECTR patients.

Goshtasby *et al*[6] reported thyroid disease as a categorical predictor of postoperative trigger digit. The authors theorized that the soft tissue swelling seen in thyroid disease may lead to flexor tendon dysfunction. Consequently, this may lower the threshold for trigger digit development when compounded with the post-operative inflammatory state of the carpal tunnel. Our study did not find an association between hypothyroidism and an increased risk of developing trigger digit. While we specifically looked at the effects of hypothyroidism on trigger digit development, Goshtasby *et al*[6] evaluated hyper- and hypothyroidism together as one independent variable.

We are the first to report gender as a potential risk factor for trigger digit following CTR. Females were as likely as males to develop trigger digit when controlling for surgical approach as an independent variable; however, the effect of gender became significant when patients were stratified into separate surgical groups. There appears to be a positive interaction between being female and receiving OCTR and a negative interaction between being female and receiving ECTR. This suggests each surgical approach may affect the carpal tunnel differently between males and females, thereby changing the threshold for trigger digit occurrence in each gender.

Current studies evaluating structural changes in the postoperative carpal tunnel do not make comparisons between genders. In contrast, imaging studies reveal gender differences in baseline carpal arch morphology. Females have a smaller cross-sectional area of the carpal tunnel and decreased palmar bowing of the carpal arch distally compared to males[16]. These baseline morphological differences may reduce the postoperative volar migration of the flexor tendons necessary for trigger digit development in females. Markedly, similar morphological changes of the carpal tunnel, including volar migration of the flexor tendons, occurs following both ECTR and OCTR[13,15,17]. Therefore, it may be expected that females are more likely than males to develop postoperative trigger digit given the smaller cross-sectional area of their carpal tunnel. This was not reflected in our study, which suggests that baseline morphological differences between genders may not contribute to postoperative trigger digit development. Gender differences in the postoperative carpal tunnel need to be further explored in order to support our findings.

Our study has a few limitations. First, our sample population was largely homogenous. Our findings may not be generalizable to more diverse populations. Second, the inconsistent coding of osteoarthritis (not included in Table 1) and hand dominance in our electronic medical records did not allow us to include these variables. Osteoarthritis and hand dominance have previously been found to be independent risk factors for trigger digit following CTR[6,18]. Third, the retrospective nature of this study dictates that our diagnosis of trigger digit be dependent on electronic medical records. Patients are educated on the potential for trigger digit occurrence; however, some patients may delay seeing a physician until they reach a subjective threshold of disability. This may explain the minority of our patients developing trigger digit in the first 6 mo following CTR.

Table 3 Trigger digit frequency and proportion by digit, *n* (%)

Digit	Frequency
Thumb	14 (21.88)
Pointed	6 (9.38)
Middle	18 (28.13)
Ring	12 (18.75)
Pinky	14 (21.88)
Total	64

Strengths of this study include a large patient population size, stringent exclusion criteria for our sample population, and a study paradigm that explored the interaction between surgical approach to CTR and patient comorbidities. One unique aspect of this paradigm was examining the interaction effect between surgical approach and gender. A prospective randomized intervention is needed to confirm the gender differences we found between the two surgical groups.

Our study reveals that patient comorbidities do not influence the development of trigger digit following CTR.

Table 4 Multivariable logistic regression analysis predicting post-operative trigger digit development

Variables	Odds ratio	95%CI for odds ratio	
		Lower	Upper
Age	1.004	0.982	1.028
Gender (Reference = male)			
Race (Reference = non-white)	1.405	0.440	7.098
BMI (Reference = BMI < 25)			
BMI: 25-30	1.392	0.488	4.740
BMI: > 30	1.389	0.542	4.480
Diabetes mellitus (Reference = no D.M.)	1.397	0.690	2.687
Rheumatoid arthritis (Reference = no R.A.)	0.372	0.003	2.811
Smoking status (Reference = non-smoker)	0.675	0.233	1.636
Hypothyroidism (Reference = euthyroid)	1.584	0.634	3.506
Surgical approach (Reference = endoscopic)			
Gender surgical approach			
Gender open	3.992[b]	1.070	21.618
Gender endoscopic	0.489[b]	0.241	0.971
Constant	0.017[b]		

[b]*P* value < 0.01. BMI: Body mass index; D.M.: Diabetes mellitus; R.A.: Rheumatoid arthritis.

ARTICLE HIGHLIGHTS

Research background

Carpal tunnel release (CTR) surgery consists of dividing the carpal tunnel ligament in order to decompress the median nerve. CTR is accomplished *via* either an open or endoscopic approach. Markedly, CTR surgery may predispose patients to trigger digit, a common orthopedic hand condition.

Research motivation

The association between surgical approach to CTR, either open or endoscopic, and postoperative trigger digit development remains equivocal.

Research objectives

Our study aimed to investigate patient risk factors for trigger digit development following CTR and whether these risk factors varied between open carpal tunnel release (OCTR) and endoscopic carpal tunnel release (ECTR).

Research methods

This retrospective chart analysis evaluated 967 CTR procedures from 694 patients for the development of postoperative trigger digit. Patients were stratified according to the technique utilized for their CTR, either open or endoscopic. The development of postoperative trigger digit was evaluated at three time points: within 6 mo following CTR, between 6 and 12 mo following CTR, and after 12 mo following CTR. Firth's penalized likelihood logistic regression was conducted to evaluate sociodemographic and patient comorbidities as potential independent risk factors for trigger digit. Secondary regression models were conducted within each surgical group to reveal any potential interaction effects between surgical approach and patient risk factors for the development of postoperative trigger digit.

Research results

There was no significant difference between the ECTR and OCTR groups to develop trigger digit at all three postoperative time markers. Furthermore, there were no significant individual predictors revealed for the development of trigger digit following CTR; however, within group analysis revealed a significant interaction effect between gender and surgical approach. This significant interaction effect between gender and surgical approach was confirmed in the primary multivariable logistic regression model ($P = 0.008$). Females were more likely to develop postoperative trigger digit than males after OCTR(OR = 3.992), but were less likely to develop postoperative trigger digit than males after ECTR (OR = 0.489).

Research conclusions

Our study found that patient comorbidities do not influence the development of trigger digit following CTR. Markedly, gender differences for postoperative trigger digit may depend on surgical approach to CTR. We are the first to report gender as a potential risk factor for trigger

digit following CTR. Females were as likely as males to develop trigger digit when controlling for surgical approach as an independent variable; however, the effect of gender became significant when patients were stratified into separate surgical groups.

Research perspectives

Current studies evaluating structural changes in the postoperative carpal tunnel do not make comparisons between genders. A prospective randomized intervention study is needed to confirm the gender differences we found between ECTR and OCTR. We also suggest the use of magnetic resonance imaging to compare changes in the morphological differences of the postoperative carpal tunnel, including volar migration.

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