Systematic Review

Tranexamic acid reduces perioperative blood loss and postoperative hemoglobin loss during total ankle arthroplasty: A systematic review and meta-analysis of clinical comparative studies

James J. Butler a,**, Ragul Rajivan b, Kishore Konar b, Utkarsh Anil a, Mohammad T. Azam a, Raymond Walls a, John G. Kennedy a,*

a Foot and Ankle Division, Department of Orthopaedic Surgery, NYU Langone Health, New York City, 10002, USA
b University of Buckingham, Buckingham, England, MK18 1EG, United Kingdom

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ABSTRACT

Importance: Peri-operative blood loss during joint replacement procedures is a modifiable risk factor that impacts wound complications, hospital stay and total costs. Tranexamic acid (TXA) is an anti-fibrinolytic that has been widely used in orthopedic surgery, but its efficacy in the setting of total ankle arthroplasty (TAA) has not been quantified to date.

Aim: The purpose of this systematic review and meta-analysis was to evaluate the efficacy and safety of administering TXA in patients undergoing TAA.

Evidence review: The Medline, Embase and Cochrane library databases were systematically reviewed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. Five comparative studies examining blood loss following administration of TXA for patients undergoing TAA were included. The outcome measures of interest were blood loss, reduction in hemoglobin concentration, transfusion requirements, total complications and wound complications.

Findings: In total, 194 patients received TXA and 187 patients did not receive TXA while undergoing TAA. Based on the common-effects model for total blood loss for the TXA group versus control, the standardized mean difference (SMD) was \( -0.7832 \) (95% CI, \( -1.1544, -0.4120 \); \( P < 0.0001 \)), in favor of lower total blood loss for TXA. Based on the random-effects model for reduction in hemoglobin for the TXA group versus control, the SMD was \( -0.9548 \) (95% CI, \( -1.7850, -0.1246 \); \( P = 0.0242 \)) in favor of lower hemoglobin loss for TXA. Based on the random-effects model for total complications for the TXA group versus control, the risk ratio was 0.512 (95% CI, 0.1588, 1.6512; \( P = 0.1876 \)), in favor of lower total complications for TXA but this was not statistically significant.

Conclusions: This current review demonstrated that administration of TXA led to a reduction in blood loss and hemoglobin loss without an increased risk of the development of venous thromboembolism in patients undergoing TAA. No difference was observed with respect to total complication rates between the TXA cohort and the control group. TXA appears to be an effective hemostatic agent in the setting of TAA, but further studies are necessary to identify the optimal timing, dosage and route of TXA during TAA.

Level of Evidence: III.

What is already known

- Tranexamic acid (TXA) is a safe and efficacious anti-fibrinolytic agent in the setting of total hip arthroplasty and total knee arthroplasty
- In recent years, increased attention has been directed towards the use of TXA during total ankle arthroplasty (TAA)

* Corresponding author. 171 Delancey Street, 2nd Floor, New York, NY 10002, USA
** Corresponding author.

E-mail addresses: jamesbutler@rcsi.com (J.J. Butler), john.kennedy@nyulangone.org (J.G. Kennedy).

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What are the new findings

- TXA led to a statistically significant reduced total blood loss and reduction in hemoglobin following TAA
- No increase in venous thromboembolic events were encountered in the TXA cohort
- No difference in wound complications were found between the 2 cohorts
- TXA is a safe and effective hemostatic agent during TAA

INTRODUCTION

End-stage ankle osteoarthritis is a degenerative, debilitating condition the majority of which is post-traumatic in origin [1]. The mainstay treatment option for end-stage ankle osteoarthritis is surgical intervention via ankle arthrodesis or total ankle arthroplasty (TAA) [2]. The emergence of third and fourth generation TAA implants have been associated with significantly improved outcomes compared to their predecessors and are now an attractive operation for both the patient and the surgeon [3]. As the utility of TAA has increased in recent years, more attention has been directed towards optimising perioperative factors to reduce complication rates, length of hospital stay and improve patient satisfaction. In the setting of total knee arthroplasty (TKA) and total hip arthroplasty (THA), the management of perioperative blood loss has been demonstrated to be a modifiable risk factor that has significant impact on postoperative hemorrhaxis rates, wound complication rates, and hospital costs associated with allogenic blood transfusions [4,5].

Multiple strategies aimed at reducing perioperative blood loss have been developed including intraoperative blood salvage, hypothermic anesthesia, and antifibrinolytic agents such as tranexamic acid (TXA) [5–7]. TXA is a synthetic lysine analog that inhibits fibrinolysis via blockade of the lysine-binding sites of plasminogen [8]. TXA stabilises blood clot formation without promoting a systemic hyper-coagulable state [8]. TXA has an excellent safety profile, being utilized throughout a multitude of surgical specialties in the settings of dental extraction, heavy menstrual bleeding, prostate surgery and tonsillectomies [9]. TXA has also been studied extensively in patients undergoing TKA and THA, reducing drain output, wound complication rates and transfusion rates without an associated increase in postoperative morbidity or mortality [10–12].

Recently, growing interest has been directed towards the use of TXA in patients undergoing TAA [13,14]. However, no definitive consensus has been reached regarding the effectiveness of TXA for TAA. The objective of this article is to evaluate the evidence currently available regarding blood loss, transfusion and complications during TAA and its association with the use of TXA.

METHODS

Search Strategy

During January 2023, a systematic review of the MEDLINE, EMBASE and Cochrane Library databases was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The following search terms were used: (tranexamic acid) and (ankle or talus or talar) and (arthroplasty or replacement or prosthesis). Clinical comparative studies that evaluated the use of TXA during TAA published in English in a peer review journal were included. Non-clinical studies, clinical studies with less than 5 patients and case reports were excluded (supplemental file 1). The titles, abstracts and full text articles of all of the searched studies were screened by 2 independent reviewers by applying the inclusion and exclusion criteria. The senior author of this article was consulted to arbitrate any discrepancies that arose. No study approval nor ethical approval was required for this study. This study was not registered with an online database.

Assessment of Level of Evidence and Methodological Quality

The level of evidence (LOE) was assessed based on the guidelines published by The Journal of Bone & Joint Surgery [15]. The methodological quality of clinical evidence and risk of bias for non-randomised studies was assessed using the Risk Of Bias In Non-randomised Studies-of Interventions (ROBINS-I) tool [16]. This tool evaluates seven domains through which bias might be introduced. The first two domains address potential confounders and the selection process of participants into the study. The third domain addresses classification of the interventions. The other 4 domains evaluate potential bias due to deviations from intended interventions, missing data, measurement of outcomes, and selection of the reported result. There is a final domain is an overall assessment of bias of the study. The options for a domain-level risk-of-bias judgment are “low,” “moderate,” “serious” or “critical” risk of bias, with an additional option of “no information”. The ROBINS-I score for each study was determined by two independent reviewers. If any discrepancy existed, the senior author was consulted, evaluated the available data and a consensus was reached.

Data Extraction and Evaluation

Two independent reviewers independently extracted and assessed the data from each individual study. Data on the characteristics of the surgical procedure was collected. Blood loss, transfusion requirements, total complications and wound complications were evaluated.

Statistical Analysis

All other statistical analyses were performed using RStudio software (version 4.2.0). Descriptive statistics were calculated for all continuous and categorical variables. Continuous variables were reported as weighted mean and estimated standard deviation, whereas categorical variables were reported as frequencies with percentages. The outcome measures of interest were blood loss, reduction in hemoglobin concentration, transfusion requirements, total complications and wound complications. Statistical analysis was performed with RStudio (version 4.2.0). Heterogeneity among studies was quantified with the I² statistic. An I² statistic less than 25% is considered to represent low heterogeneity, thus a common effects model was utilised in this setting. If the I² value was greater than 25%, a random-effects model was utilised. For continuous outcomes, standardized mean differences (SMD) were calculated with a 95% confidence interval (CI). For dichotomous outcomes, the log-risk ratio (RR) was calculated with a 95% CI. A value of P < 0.05 was considered statistically significant.

RESULTS

The search 61 generated studies. Of these, 5 studies met the inclusion and exclusion criteria (Fig. 1) and were included.

Study Characteristics and Patients Demographics

Study characteristics and patient demographic data are listed in Table 1. One study was LOE II [17] and 4 studies were LOE III [13,14,18,19]. Four studies were “moderate” level of bias and 1 study was “serious” risk of bias (Supplemental File 2).

Table 1. One study was LOE II [17] and 4 studies were LOE III [13,14,18,19]. Four studies were “moderate” level of bias and 1 study was “serious” risk of bias (Supplemental File 2).
In total, 194 patients received TXA during TAA and 187 patients did not receive TXA during TAA. The weighted mean postoperative follow-up time in the TXA cohort was 18.6 ± 7.8 months (range, 9.3–28.0) and the weighted mean postoperative follow-up time in the control cohort was 23.5 ± 6.8 months (range, 18.4–28.0). There was no significant differences between the cohorts with regards to patient demographics and preoperative hematocrit.

Treatment Characteristics

Treatment characteristics are listed in Table 2. TXA was administered intravenously prior to pneumatic tourniquet inflation across 4 studies and the route of administration was not recorded in 1 study [19]. The dosage of TXA was recorded in all studies [14,19], which ranged from 1 g to 2 g. Deep vein thrombosis prophylaxis was reported in 2 studies which included aspirin [13], heparin and rivaroxaban [17]. The Salto-Talaris™ implant was used in 2 studies (169 ankles) [13,14], the INBONE II™ implant was used in 1 study (71 ankles) [17], the Infinity™ implant was used in 1 study (72 ankles) [18], the Integra™ implant was used in 1 study (26 ankles) [19] and the Cadence™ implant was used in 1 study (43 ankles) [19].

Total Blood Loss

The mean total blood loss in the TXA cohort was 397.4 ± 333.0 mls and the mean total blood loss in the control cohort was 525.9 ± 456.4 mls. Two studies adequately reported data which could be extracted regarding total blood loss. Administration of TXA resulted in a significant decrease in total blood loss compared with controls (SMD, −0.7832; 95% CI, −1.1544, −0.4120; P < 0.0001), with low heterogeneity (I² = 0%) (Fig. 2).

Intraoperative Blood Loss

The mean intraoperative blood loss in the TXA cohort was 80.7 ± 12.8 mls and the mean intraoperative blood loss in the control cohort was

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### Table 1

<table>
<thead>
<tr>
<th>Author</th>
<th>LOE</th>
<th>N patients</th>
<th>Follow-up</th>
<th>Age (years)</th>
<th>Sex (M/F)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan et al., 2022 [17]</td>
<td>2</td>
<td>38</td>
<td>28</td>
<td>65.8</td>
<td>17/21</td>
<td>25.7</td>
</tr>
<tr>
<td>Nodzo et al., 2018 [14]</td>
<td>3</td>
<td>25</td>
<td>9.3</td>
<td>65.8</td>
<td>14/11</td>
<td>31.6</td>
</tr>
<tr>
<td>Steinmetz et al., 2020 [13]</td>
<td>3</td>
<td>55</td>
<td>Can not extract</td>
<td>63.5</td>
<td>29/26</td>
<td>22.7</td>
</tr>
<tr>
<td>Moore et al., 2022 [18]</td>
<td>3</td>
<td>43</td>
<td>15.8</td>
<td>59.4</td>
<td>Can not extract</td>
<td>31.8</td>
</tr>
<tr>
<td>Ali et al., 2022 [19]</td>
<td>3</td>
<td>33</td>
<td>Can not extract</td>
<td>Can not extract</td>
<td>Can not extract</td>
<td>N/R</td>
</tr>
</tbody>
</table>

TXA, tranexamic acid; LOE, level of evidence; N/R, not recorded.
Two studies adequately reported data which could be extracted regarding intraoperative blood loss. Administration of TXA resulted in a statistically significant decrease in intraoperative blood loss compared with controls across 2 studies (SMD, 1.1453; 95% CI, −1.5327, 0.7578; \( P < 0.0001 \)), with low heterogeneity (I² = 0\%). (Fig. 3).

**Change in Hemoglobin**

The mean change in hemoglobin in the TXA cohort was 1.4 ± 0.3 g/dL and the mean change in hemoglobin in the control cohort was 1.8 ± 0.5 g/dL. Four studies adequately reported data which could be extracted regarding change in hemoglobin. Administration of TXA resulted in a statistically significant decrease in haemoglobin loss compared with controls across 4 studies (SMD, 0.9548; 95% CI, −1.7850, −0.1246; \( P = 0.0242 \)), with high heterogeneity (I² = 90\%) (Fig. 4).

**Transfusion Requirements**

Four studies adequately reported data which could be extracted regarding transfusion requirements. Although administration of TXA resulted in a decrease in transfusion requirements compared with controls across 4 studies (SMD, 0.335; 95% CI, 0.0533, 2.1062; \( P = 0.0837 \)), with high heterogeneity (I² = 90\%), this was not statistically significant. All transfusions occurred in the control cohort.

**Total Complications**

In total, 24 complications (12.4\%) were observed in the TXA cohort and 51 complications (27.3\%) were observed in the control cohort. Although it was not statistically significant, there appears to be a decrease in the incidence of complications in the group treated with TXA compared to controls (SMD, 0.512; 95% CI, 0.1588, 1.6512; \( P = 0.1876 \)).

**Table 2**

<table>
<thead>
<tr>
<th>Author</th>
<th>Number of TXA Cohort</th>
<th>Number of Control Cohort</th>
<th>Implant</th>
<th>TXA regimen</th>
<th>Thromboprophylaxis regimen</th>
<th>Drain clamping</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tan et al., 2022 [17]</td>
<td>38</td>
<td>33</td>
<td>INBONE II</td>
<td>15 mg/kg intravenous TXA, 5–10 min prior to skin incision</td>
<td>0.2 ml subcutaneous LMWH at 12 h after surgery and then 0.4 ml every 24 h or 10 mg of oral Rivaroxaban once a day for 35 days to prevent VTE if no bleeding events occurred</td>
<td>Nil</td>
</tr>
<tr>
<td>Nodzo et al., 2018 [14]</td>
<td>25</td>
<td>25</td>
<td>Salto-Talaris</td>
<td>1 g intravenous TXA, 20 min prior to tourniquet inflation</td>
<td>N/R</td>
<td>Nil</td>
</tr>
<tr>
<td>Steinmetz et al., 2020</td>
<td>55</td>
<td>64</td>
<td>Salto-Talaris</td>
<td>1 g intravenous TXA before tourniquet inflation and 1 g intravenous TXA after tourniquet release</td>
<td>Aspirin</td>
<td>Nil</td>
</tr>
<tr>
<td>Moore et al., 2022 [18]</td>
<td>43</td>
<td>29</td>
<td>Infinity</td>
<td>20 mg/kg intravenous TXA, before skin closure and before tourniquet deflation</td>
<td>N/R</td>
<td>Nil</td>
</tr>
<tr>
<td>Ali et al., 2022 [19]</td>
<td>33</td>
<td>36</td>
<td>Integra, Cadence</td>
<td>1–2 g of TXA, route not recorded</td>
<td>N/R</td>
<td>Nil</td>
</tr>
</tbody>
</table>

TXA, tranexamic acid; LMWH, low molecular weight heparin; VTE, venous thromboembolism.

**Fig. 2.** Meta-analysis of total blood loss between tranexamic acid cohort and control group.

**Fig. 3.** Meta-analysis of intraoperative blood loss between tranexamic acid cohort and control group.

149.7 ± 71.4 mls. Two studies adequately reported data which could be extracted regarding intraoperative blood loss. Administration of TXA resulted in a statistically significant decrease in intraoperative blood loss compared with controls across 2 studies (SMD, −1.1453; 95% CI, −1.5327, −0.7578; \( P < 0.0001 \)), with low heterogeneity (I² = 0\%) (Fig. 3).
with moderate heterogeneity ($I^2 = 61\%$) (Fig. 6). The most common complication both cohorts were wound complications.

**Wound complications**

Although administration of TXA resulted in a decrease in wound complications compared with controls across 5 studies (SMD, $0.5403; 95\%$ CI, $0.1001, 2.9174; P = 0.3681$), with moderate heterogeneity ($I^2 = 56\%$), this was not statistically significant (Fig. 7).

**DISCUSSION**

The most important finding of this systematic review was that administration of TXA led to a reduction in blood loss and hemoglobin loss without an increased risk of the development of VTEs. Interestingly, no difference in complication rates existed between patients who received TXA and those who did not. This data is encouraging but should be interpreted with discretion in light of the heterogeneity and under-reporting of data of the included studies.

Optimal management of perioperative blood loss during joint sacrificing procedures such as TAA, TKA and THA is crucial to reduce the incidence of postoperative hemorrhage and subsequent wound complications. Multiple perioperative and postoperative strategies have been proposed to mitigate against significant blood loss including the use of antifibrinolytic medications, blood salvage, hypotensive anesthesia, minimally invasive surgical techniques, topical fibrin sealants and optimal tourniquet strategies [5–7]. The utilization of antifibrinolytic agents such as TXA is an attractive strategy due to the relatively low cost-per unit together with the promotion of clot stabilization without the concurrent increased risk of thromboembolic events [9]. TXA has been demonstrated to be a highly efficacious hemostatic agent in the perioperative period during TKA and THA procedures [12]. A meta-analysis by Wei et al. examined the impact of TXA on perioperative blood loss, thromboembolic events and allogenic blood transfusion requirements across 2720 cases of TKA and THA in 39 studies [12]. The authors found statistically significant reduced blood loss, VTEs and allogenic blood transfusions in the TXA cohort compared to the control cohorts.

The inherent anatomy of the ankle joint predisposes patients to a high risk of postoperative hemorrhage formation. The ankle joint is surrounded by a thin, fragile soft tissue envelope that lacks highly adaptable elastic properties [20]. The ankle receives a rich vascular supply via the branches of the anterior tibial artery that is located within the fascia that is continuous with the distal tibial periosteum. Bleeding into the ankle joint can occur at numerous stages during TAA: (a) during the anterior or transfibular approach and soft tissue release, and (b) during dislocation
and subluxation of the joint which places significant tearing shear forces across the anterior tibial artery [21]. The blood that accumulates in the small intra-articular volumetric space of the ankle joint will inevitably extravasate into the surrounding soft tissue structures which may not be able to accommodate this increased blood volume. The compromised soft tissue envelope leads to the formation of a postoperative hemarthrosis which can precipitate wound infection, wound necrosis and wound dehiscence. Therefore, it is imperative that strategies are taken to reduce perioperative blood loss and hemarthrosis formation during TAA. This current systematic review found that TXA was a highly effective hemostatic agent in the setting of TAA. There was a statistically significant reduced volume of total blood loss in favor of patients who received TXA compared to patients who did not receive TXA during TAA (SMD: −0.7832; 95% CI -1.1544, −0.4120; P < 0.0001). Additionally, a statistically significant reduced volume of intraoperative blood loss between the TXA cohort and the control cohort was also observed in favor of the TXA cohort (SMD: −1.14; −1.5372; −0.7578; P < 0.0001). Finally, administration of TXA resulted in statistically significant lower hemoglobin loss compared with controls (SMD, −0.9548; 95% CI, −1.7850, −0.1246; P = 0.0242).

Perioperative allogenic blood transfusion has been determined to be a harbinger of poor outcomes in the setting of THA and TKA [22,23]. Specifically, higher mortality rates, higher infection rates, higher financial costs and longer hospital stays are associated with allogenic blood transfusion following THA and TKA [22,23]. Although, the consequences of perioperative allogenic blood transfusion during TAA have not been extensively studied, emerging evidence indicates that allogenic blood transfusion is a predictor of inferior outcomes. An analysis of 25,412 patients who underwent TAA from the Nationwide Inpatient Sample database found approximately 50% higher financial costs and 3 days longer hospital stay compared to patients who did not receive an allogenic blood transfusion [24]. This current review found that all incidences of allogenic blood transfusions occurred in the non-TXA cohorts. However, the overall number of allogenic blood transfusions were low [2] and there was no statistically significant pooled transfusion rates between the 2 cohorts (P = 0.0837). Nevertheless, TXA should be utilized prophylactically in an effort to reduce allogenic blood transfusion rates in patients at a high risk of requiring allogenic blood transfusions including patients with diabetes, heart failure, peripheral vascular disease, anemia, hypothyroidism and coagulation disorders [24].

In total, 24 complications (12.4%) were observed in the TXA cohort and 51 complications (27.3%) were observed in the control cohort. Interestingly, this systematic review found that there was no statistically significant difference in the total complication rates nor the wound complication rates between the TXA cohort and the control group. This conflicts with previously published studies which found lower complication rates following TXA administration in TKA and THA cohorts. This discrepancy can be accounted for by the results in Steinmetz et al.’s study which reported a 16.4% complication rate in the TXA cohort and a 7.8% complication rate in the control group, but this was not statistically significant (P = 0.09) [13]. The other 4 studies included in this review all reported lower total complication rates and wound complication rates in the TXA cohort compared to the control group, indicating that TXA adequately reduces the risk of postoperative wound complications. Although the rates of VTEs were low between both cohorts, no VTEs were recorded in the TXA cohort suggesting that TXA may be a potent strategy to mitigate against the development of VTEs. Further studies with more robust scientific methodology are warranted to elucidate the effects of TXA on complications following TAR.

The optimal method of TXA delivery in the setting of joint arthroplasty remains controversial. Three routes of administration of TXA exist: intravenous, oral and topical [25]. Intravenous TXA is an efficacious delivery method that has routinely been shown to reduce perioperative blood loss and postoperative transfusion requirements across numerous studies [10–12]. Benefits of oral TXA include low cost, ease of administration and lack of equipment needed for administration [26]. The application of topical TXA provides a simple method of drug delivery, maximal drug concentration at the operative site and minimal systemic absorption thus, theoretically, decreasing the risk of thromboembolic events in comparison to intravenous and oral therapies [27]. A meta-analysis of randomized control trials (RCT) by Sun et al. compared blood loss, transfusion rates and length of hospital stay between patients who received intravenous TXA and oral TXA in TKA and THA procedures [28]. There was no statistically significant difference between the 2 methods of drug delivery with regards to blood loss, transfusion rates, length of hospital stay and development of VTEs, suggesting that oral administration may be a more optimal route of TXA delivery. A blinded RCT by Ors et al. found that combined administration of intravenous and topical TXA led to lower transfusion requirements compared to single intravenous and topical TXA administration [29]. Although the absolute costs of combined TXA administration was higher than single route TXA administration, combined intravenous and topical TXA administration was more cost-effective due to the expenses related to blood transfusions, additional nursing care and laboratory costs. The 4 studies included in this systematic review that reported the method of administration of TXA reported the use of intravenous TXA, with no oral nor topical TXA administered. Topical TXA may be more favorable than intravenous TXA in the setting of TAA as a high drug concentration can be delivered to the small intra-articular volume without any systemic absorption. Thus, further comparative studies are warranted to determine the optimal route of delivery of TXA during TAA.

Several limitations exist with regards to this review. Firstly, this study is limited by the lack of high quality LOE I studies together with small patient cohorts. Secondly, there was marked heterogeneity and under-reporting of data across numerous domains: only 2 studies recorded the frequency and dosage of TXA administered, 2 studies reported the use of intraoperative drains, and 2 studies described anti-thrombotic prophylactic regimens including oral aspirin [13] and oral rivaroxaban with subcutaneous heparin [17]. A pneumatic tourniquet was utilized across all 5 studies, but the duration of use was not stated. Thus it is unclear if the pneumatic tourniquet and its duration had a synergistic effect on the efficacy of TXA. Studies published in databases other than MEDLINE and
EMBASE are not represented in this review. Future higher quality studies with larger patient cohorts are necessary to identify the role and effects of TXA following TAR.

Conclusion

This current systematic review and meta-analysis demonstrated that administration of 1–2 g of intravenous TXA led to a reduction in blood loss and hemoglobin loss without an increased risk of the development of VTEs in patients undergoing TAA. No difference was observed with respect to total complication rates nor wound complication rates between patients who received TXA and the control cohort. TXA appears to be an effective hemostatic agent in the setting of TAA, but RCTs are necessary to identify the optimal timing, dosage and route of TXA during TAA.

Ethical approval statement

Ethical approval was not sought for the present study because this is a systematic review where we did not obtain access to any patient records.

Declaration of competing interest

The authors declare the following financial interests/personal relationships that may be considered as potential competing interests:

John G. Kennedy reports a relationship with Arthrex Inc that includes: consulting or advisory. Dr John G Kennedy receives financial interests/personal relationships that may be considered as potential competing interests:

References