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Total Knee Arthroplasty for Knee Osteoarthritis: Support for a Foregone Conclusion?

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Abstract Total knee arthroplasty (TKA) is generally accepted as the definitive treatment for advanced knee arthritis after patients fail nonoperative treatments; however, the safety and efficacy of TKA compared to continued nonoperative treatment has never been proven in high-quality, randomized controlled trials. Recently, a 2015 Danish study published a 12-month follow-up on a cohort of patients randomized to either a TKA or continued nonsurgical management for advanced knee osteoarthritis (OA). The authors reported significantly greater improvement in the TKA group in functional outcome scores such as the overall Knee Injury and Osteoarthritis Outcome Score ($KOOS_4$ score), the KOOS subscales, EQ-5D descriptive index, and timed get up-and-go and 20-m walk tests; however, patients in the TKA did suffer significantly more serious adverse events (SAE). The authors concluded that TKA combined with additional nonoperative care postoperatively is more efficacious than nonsurgical treatment alone in terms of improving pain, function, and quality of life at 12 months but is associated with more SAE. The purpose of this review is to identify the strengths and weaknesses of this trial, interpret its outcomes within the context of prior literature, and evaluate the validity of its conclusions.

Keywords total knee replacement · outcomes · osteoarthritis

This work was performed at Hospital for Special Surgery.

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Introduction

Total knee arthroplasty (TKA) has become one of the most commonly performed surgical procedures in the United States [4]. In 2009, a total of 619,000 primary TKAs were performed, and by 2020, the demand for primary TKA is projected to grow to 1.4 million (M), with up to 3.5M by 2030 [4, 10, 11]. At an estimated lifetime cost of $20,000 more than nonsurgical treatment, TKA potentially carries considerable financial burden [16]. Despite these substantial and rising costs, several studies have demonstrated the cost-effectiveness of TKA [9, 13], with an estimated societal savings of $12 billion in 2009 attributed to TKA annually [16].

Previous studies have demonstrated clinical benefits of total knee replacement. A recent 5-year prospective study of patients with knee OA by Nilsdotter et al. demonstrated significant improvements in Knee Injury and Osteoarthritis Outcome Score (KOOS) and SF-36 scores in patients undergoing TKA, with improvements sustained over 5 years [14]. A previous meta-analysis by Callahan et al. analyzed the results of 130 studies, concluding that TKA was both safe and effective [2]. On the other hand, several studies have also demonstrated the benefits of continued nonsurgical management [7, 19]. Though it is generally accepted that TKA is the definitive treatment of choice for knee arthritis after failing nonoperative treatment, no high-quality, randomized controlled trial has previously shown TKA to be safe and effective compared to nonsurgical management alone [12]. In an increasingly cost-conscious healthcare environment, combined with the rising demand of TKA, demonstrating the efficacy of TKA over nonsurgical management is imperative in order to justify our continued spending.

The article by Skou et al. reported the 12-month follow-up on a cohort of patients randomized to TKA plus postoperative nonsurgical interventions compared to continued nonsurgical management alone for advanced osteoarthritis of the knee. In this randomized trial of 100 patients with OA, the investigators' primary research question was: What are the differences in patient-reported outcomes between TKA

plus postoperative nonsurgical management compared to nonsurgical management alone? As a secondary outcome, the authors also sought to examine the differences in serious adverse events (SAE) between the two cohorts. The purpose of this review is to identify the strengths and weaknesses of this trial, interpret its outcomes within the context of prior literature, and evaluate the validity of its conclusions.

The Article

A Randomized, Controlled Trial of Total Knee Replacement *Soren T. Skou, Ewa M. Roos, Mogens B. Laursen, Michael S. Rathleff, Lars Arendt-Nielsen, Ole Simonsen, Sten Rasmussen. NEJM 2015;373:1597–606. October 22.*

This parallel-group, randomized, two-center, superiority study compared surgical to nonsurgical treatment of knee osteoarthritis in 100 adults. Eligible patients had radiographically confirmed knee OA (score of ≥2 on the Kellgren-Lawrence scale) and were determined to be eligible for TKA by one of nine experienced orthopedic surgeons at two public outpatient clinics in Denmark. Patients with prior ipsilateral or bilateral TKA and knee pain rated higher than 60 mm on a 100-mm visual analogue scale (VAS) during the previous week were excluded. Patients were randomized in a 1:1 ratio to undergo TKA followed by 12 weeks of nonsurgical treatment or to receive 12 weeks of nonsurgical treatment only. A cemented total knee prosthesis with patellar resurfacing (NexGen CR-Flex or LPS-Flex Fixed Bearing Knee, Zimmer) was used in the TKA group; the 12-week standardized nonsurgical treatment consisted of exercise, education, dietary advice, use of insoles, and pain medication. To calculate sample size, the authors used an effect size of 10-point improvement in $KOOS_4$ score as the minimal clinically important difference and 90% power, determining that they would need 41 patients using these parameters. This meaningful difference was determined based on the WOMAC index [5] as well as a study of statistically significant changes in subscale scores after ACL reconstruction [15]. To account for missing data and crossovers, 100 patients were enrolled.

In the TKA group ($N = 50$), the mean age was 65.8 years, mean BMI was 32.3 kg/m^2, and included 32 females; the nonsurgical treatment group ($N = 50$) had a mean age of 67.0 years, BMI of 32.0 kg/m^2, and included 30 females. Follow-up assessments were performed at 3, 6, and 12 months after the initiation of nonsurgical treatment. The primary outcome measure was the between-group difference in change from baseline to 12 months in the mean score on four KOOS subscales (pain, symptoms, activities of daily living, and quality of life) and the overall $KOOS_4$ score. Secondary outcomes included change from baseline to 12 months in all five KOOS subscales (function in sports and recreation, in addition to the $KOOS_4$); timed up-and-go and two 20-m walk tests; EQ-5D general health assessment; weight; and type, dose, and quantity of previous week's pain medication. Serious adverse events (SAE) before the 12-month follow-up were gathered from hospital records, self-report, and physiotherapist report and were defined as events that have the potential to compromise the clinical outcome, result in disability or incapacity, or require hospital care, or those considered to prolong hospital care, to be life-threatening or to result in death. The small sample size ($N = 100$) and short-term nature (12 months) are notable limitations, as many of the differences in outcome benefits and adverse events might be expected to appear following the 12-month time horizon of this study. Of the 50 patients assigned to the nonsurgical group only, 13 underwent TKA prior to the 12-month follow-up; of the 50 patients in the surgical group, one did not undergo TKA before the 12-month follow-up. Ultimately, 100 patients were included in the intention-to-treat (ITT) analysis and 51 (25 nonsurgical, 26 TKA) were included in the per-protocol analysis (defined as attending ≥ 75% of exercise sessions, excluding crossovers).

In the ITT analysis, the authors found a significantly greater improvement in the KOOS in the TKA group compared to the nonsurgical group (mean difference of 16.5). Additionally, the TKA group had significantly greater improvements in scores on all KOOS subscales and EQ-5D descriptive index, as well as times on the up-and-go and 20-m walk tests. However, SAE were significantly more common in the TKA group, both involving the index knee and overall. The per-protocol analysis showed similar findings, with the exceptions of a significant difference on the EQ-5D VAS and no difference in the symptoms subscale of the KOOS.

From these results, the authors concluded that TKA followed by nonsurgical treatment is more efficacious than nonsurgical treatment alone for improving pain, function, and quality of life at 12 months but is associated with a higher rate of serious adverse events.

Commentary

The trial by Skou et al. suggests that, for patients with osteoarthritis of the knee, TKA is more efficacious than nonsurgical management alone in improving pain, function, and quality of life. Although this is a commonly held belief in the orthopedic community, which in part drives the substantial volume of TKAs performed annually, this study is valuable in providing objective data to support current practices. However, an equally important conclusion is that TKA does carry a significantly higher risk of serious adverse events and patients should be counseled accordingly.

The study by Skou et al. has several strengths. Most importantly, the study was designed to examine a question of utmost clinical relevance utilizing the gold standard in clinical research, a randomized, controlled clinical trial (RCT). Patients were successfully randomized to the two treatment groups with similar baseline demographics, with the two groups having similar symptom duration (68–74% 2+ years), radiographic OA severity (86–90% K–L grade 3 or 4), Charlson Comorbidity Index (72–78% index 0 or 1), as well as prior treatment and baseline KOOS/EQ-5D scores. In addition, the analytics were sound with both ITT and per-protocol analyses performed, and results were

adjusted for time of assessment, location of the clinic, baseline outcome values, and interaction between time of assessment and study group. The nonsurgical regimen was delivered identically, adherence was moderate to high for both groups, with roughly similar rates of compliance with exercise sessions (15 to 17 out of 24 sessions), aspects learned in education (62–63% using it every day or all the time), aspects learned from the dietician (65% using it every day or all the time), and attendance at two patient education sessions (74–82%) and four dietary sessions (74–86%), although considerably more patients in the TKR group never used insoles (40 vs. 21% in the nonsurgical group). Follow-up was excellent with 98% and 92% of patients in the TKA and nonsurgical groups, respectively, completing the 12-month assessment. Finally, the authors employed the KOOS outcome, a validated patient-reported measure for patients with knee osteoarthritis and TKA [3].

However, several limitations exist. First, the authors excluded patients with VAS pain ≥ 60 mm. In their conclusions, the authors claim their findings are applicable to patients with "moderate-to-severe" knee osteoarthritis; however, we would imagine that many of the patients who were excluded for this study based on their VAS pain threshold are likely to have been classified as having moderate-to-severe osteoarthritis; further, patients with greater amounts of preoperative pain are theoretically even more likely to benefit from surgery. Thus, selection bias may exist and, further, the effect of the intervention of TKA may have been diluted, at least in terms of pain improvement. In addition, this was a two-center study of Danish patients, which may limit its generalizability, particularly given the intensive nonsurgical regimen which has demonstrated greater efficacy than usual care in a similar population [19]. Moreover, while the majority of baseline demographics were similar between the two groups, the authors report that patients assigned to the TKA group were significantly more likely to be living alone and be on sick leave from work, both of which could act as confounding variables when interpreting the study results. There was also a considerable crossover rate of 26% (13/50) for the nonsurgical group, which may limit the study's internal validity; however, the inclusion of a per-protocol analysis may reduce this drawback.

Furthermore, conclusions about many of the SAE may not truly reflect differences between the surgery and nonsurgery groups. The reported adverse event rate was extremely high (48% in the surgery group), and many of the documented SAE are not regarded as complications related to surgery. Of the not index knee-related events listed, very few could be considered to have any correlation with TKR. Specifically, listed events such as melanoma, carcinoid tumor, breast cancer, hiatal hernia, and retinal detachment, among others, likely cannot be attributed to knee arthroplasty. Even for those that might be related to surgery (e.g. atrial fibrillation, pneumonia, trauma after a fall), the timing of these events (i.e. whether they occurred in the acute postoperative period) would be relevant but was not provided by the authors. Regarding the events related to the index knee, several of these may represent institutional bias and may not be generalizable to the broader community. It is not known, for example, what limitation in range of motion led the authors to perform manipulation under anesthesia, what kind of prophylaxis for deep vein thrombosis (DVT) was used, what criteria were used to determine whether a DVT required anticoagulation, or whether the nonsurgical and TKR groups underwent equal monitoring for asymptomatic DVT. These results could be affected by considerable bias, limiting the validity of these data. That the study's reported serious adverse event rate (48%) is much higher than others (6–6.5% at 30–90 days) [6, 17] provides further evidence to support the idea that this rate is quite inflated. Including only events related to the index knee, these authors found a 16% complication rate for TKR at 1 year, which while still quite high is much more in line with these prior reports.

Additionally, the sample size of 100 is quite small and the 12-month time horizon too short, precluding subgroup analyses or conclusions about the long-term benefits and risks of the two treatments. While a study by Nilsdotter et al. reported the best outcomes at one year following TKA [14], the true long-term advantages of TKA *over* nonsurgical management are likely accrued and extend beyond 12 months postoperatively. And, as noted by the authors, their results could be limited by placebo effects, which can impact both surgical and nonsurgical treatments [1, 18, 20, 22]. Finally, in most orthopedic surgery practices, patients will usually attempt a trial of nonoperative management prior to considering TKA. Given that the patients in this trial did not fail conservative management prior to undergoing TKA, the perceived impact of nonoperative treatment may be inflated. It is our opinion that if patients had already trialed nonoperative treatments prior to total knee replacement and had plateaued in terms of improvement, the difference in outcomes between the pre-intervention and the post-intervention would likely have been greater in the TKA group than in the continued nonoperative treatment group.

Some orthopedic surgeons may wonder whether the study by Skou et al. added to the literature. However, we believe that while most orthopedic surgeons agree on the potential benefit of TKA, not all healthcare providers agree that surgery is more beneficial than continued nonoperative treatment alone, especially since risks are inherent to TKA. Supported by the literature, although surgery has demonstrated benefit in patients with knee osteoarthritis, nonsurgical management alone has also shown efficacy in this population. In a study of patients with knee OA who were ineligible for TKA, Skou et al. found that an intensive nonsurgical regimen resulted in substantial improvements in the $KOOS_4$, without serious adverse events, compared to usual care [19]. Similarly, a systematic review by Jansen et al. found significant improvements in pain and physical function in patients undergoing nonoperative treatments for knee OA, with patients undergoing exercise therapy plus manual mobilization achieving the greatest effect size [7]. In line with this prior literature, patients assigned to the nonsurgical management group demonstrated a 16-point improvement in $KOOS_4$ from baseline to 12 months after initiation of treatment, which is both statistically and clinically significant. Furthermore, as the current study highlights, the surgery itself entails risks that are not typically

posed by nonsurgical management. The authors report SAE rates of 16% involving the index knee and of 48% overall for TKR, compared to rates of 2 and 12%, respectively, for the nonsurgical only group. The SAE related to the index knee are more applicable, as the overall event rate included complications unrelated to the surgery itself, as discussed above. The AE rates reported by Skou et al. (2% infection, 6% deep vein thrombosis, 2% fracture) are greater than prior studies that report rates of death, infection, deep vein thrombosis/pulmonary embolism, and periprosthetic fracture to range from 0.4 to 1.6% within 90 days of discharge [8, 21]; however, the discrepancy may be related to the longer follow-up (12 months) in this study, compared to the shorter period of follow-up (within 90 days after discharge) typically reported in the literature.

Despite the limitations of the study, Skou et al. provide a valuable contribution to the literature. The authors demonstrated that, in spite of factors which may bias the results in favor of nonsurgical management, TKA resulted in significant improvement in patient outcomes compared to nonsurgical management alone. This trial is the first randomized study to evaluate the efficacy of TKA in knee OA, allowing us to justify the considerable societal resources allocated to TKA. It also serves as a reminder of the benefits of nonsurgical management, which should be employed in all patients prior to considering surgical intervention.

Compliance with Ethical Standards

Conflict of Interest: Michael E. Steinhaus, MD, and Alexander B. Christ, MD, have declared that they have no conflict of interest. Michael B. Cross, MD, reports personal fees from Acelity, Intellijoint, Link Orthopedics, and Exactech, Inc.; others are from Bone and Joint Journal 360, Journal of Orthopedics and Traumatology, Techniques in Orthopedics, and grants and personal fees from Smith & Nephew from outside the work.

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