

Comparison of the major intraoperative and postoperative complications between unilateral and sequential bilateral total knee arthroplasty in a high-volume community hospital

Erin Spicer, MSc*†‡
Garry Robert Thomas, MSc*†‡
Edward John Rumble, MD[†]

From the *Faculty of Medicine, University of Toronto, Toronto, Ont. and the †Division of Orthopaedic Surgery, North York General Hospital, Toronto, Ont.

‡Co-first authors

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Correspondence to:
E.J. Rumble
5 Fairview Mall Dr. Suite 377
North York ON M2J 2Z1
ejrubble@gmail.com

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Background: Total knee arthroplasty (TKA) is a common surgical treatment for arthritis. In the event of bilateral knee symptoms, a patient may elect for bilateral TKA (BTKA) under 1 anesthetic or 2 separate unilateral TKAs (UTKA). Controversy exists in the literature regarding the safety of BTKA versus UTKA. We compared the rate of major intraoperative and postoperative complications for BTKA versus UTKA at a high-volume community hospital.

Methods: We compared 373 patients who underwent BTKA with 966 who underwent UTKA between May 2008 and May 2011. Health records were used to determine patient characteristics and major intraoperative and postoperative complications. The BTKA and UTKA cohorts were matched for demographic characteristics and comorbidities with the exception of previous transient ischemic attack and previous knee surgery (UTKA > BTKA).

Results: Rates of intraoperative and postoperative complications, including cardiovascular, thromboembolic and neurologic complications; deep wound infections; and mortality, did not differ significantly between groups. Bilateral TKA was associated with a greater proportion of patients requiring blood transfusion than UTKA (29.8% v. 8.9%, $p < 0.001$). Among those transfused, there was no significant difference between the groups in the mean number of units required (1.72 ± 0.77 v. 1.53 ± 0.85 units, $p = 0.68$).

Conclusion: Bilateral TKA was not associated with statistically greater rates of intraoperative and postoperative complications than UTKA, barring the proportion of patients requiring transfusion. Our results support the use of BTKA to treat bilateral knee arthritis in a high-volume community hospital setting.

Contexte : La prothèse (ou arthroplastie) totale du genou (PTG) est un traitement chirurgical courant contre l'arthrite. Quand les 2 genoux sont atteints, le patient peut choisir entre une PTG bilatérale (PTGB), qui ne nécessitera qu'une seule anesthésie, ou 2 interventions unilatérales distinctes (PTGU). Dans la littérature, on ne semble pas s'entendre sur l'innocuité de la PTGB contre la PTGU. Nous avons comparé les taux de complications peropératoires et postopératoires majeures associées aux PTGB et aux PTGU dans un hôpital communautaire où s'effectue un volume élevé de telles interventions.

Méthodes : Nous avons comparé 373 patients qui ont subi une PTGB à 966 qui ont subi une PTGU entre mai 2008 et mai 2011. Nous avons consulté les dossiers médicaux pour établir les caractéristiques des patients et relever les complications peropératoires et postopératoires majeures. Les cohortes soumises à la PTGB et à la PTGU ont été assorties en fonction des caractéristiques démographiques et des comorbidités, à l'exception des antécédents d'accidents ischémiques transitoires et d'interventions chirurgicales du genou (PTGU > PTGB).

Résultats : Les taux de complications peropératoires et postopératoires, y compris cardiovasculaires, thromboemboliques et neurologiques, les infections de plaies profondes et la mortalité n'ont pas varié significativement entre les groupes. Une proportion plus grande de patients soumis à la PTGB a nécessité une transfusion sanguine comparative aux patients soumis à la PTGU (29,8 % c. 8,9 %, $p < 0,001$). Parmi les receveurs de transfusions, on n'a noté aucune différence significative entre les groupes quant au nombre moyen d'unités requises ($1,72 \pm 0,77$ c. $1,53 \pm 0,85$ unité, $p = 0,68$).

Conclusion : La PTGB n'a pas été associée à des taux statistiquement plus élevés de complications peropératoires et postopératoires comparativement à la PTGU, à l'exception de la proportion de patients ayant nécessité une transfusion. Nos résultats appuient le recours à la PTGB pour traiter l'arthrite bilatérale du genou dans le contexte d'un hôpital communautaire ou le volume de ces interventions est élevé.

Total knee arthroplasty (TKA) is the most commonly performed joint replacement surgery in Canada.^{1,2} It is considered a safe and reliable procedure for providing pain relief, correcting limb alignment and improving quality of life in patients with moderate to severe arthritis.³ A substantial proportion of these patients present with bilateral symptomatic joint disease and may benefit from bilateral replacements. In these circumstances, the patient and orthopaedic surgeon must together decide whether to pursue a bilateral knee replacement under a single anesthetic (BTKA) or 2 separate unilateral TKAs (UTKA).³

Critics of BTKA argue that the procedure increases the risk for serious complications.³⁻⁹ The TKA complications most often referenced in the literature are cardiovascular (i.e., new-onset arrhythmia, myocardial infarction, congestive heart failure), thromboembolic (i.e., deep vein thrombosis, pulmonary embolism), neurologic (i.e., transient ischemic attack, stroke, delirium), blood loss measured directly or indirectly through blood transfusion requirements and mortality.⁶ The true risk associated with BTKA remains controversial, as many studies opposing the procedure have reported predominantly nonstatistical differences in complication rates between BTKA and UTKA.^{3,10-13}

Proponents of BTKA, however, report numerous advantages, including decreased total anesthetic, total rehabilitation time, length of hospital stay and institution costs. These patients have also been found to have lower rates of superficial wound infections and to report increased convenience and satisfaction.¹¹⁻¹⁹ One study also found that at 10 years postoperatively the BTKA group had a significantly higher rate of survival than the UTKA group, independent of other contributing factors.¹⁰

The number of TKAs being performed in Canada is projected to continue rising given the prevalence of degenerative osteoarthritis in the aging population. While most TKAs are performed in community hospitals, we are not aware of any literature comparing the rates of major complications of BTKA with UTKA within the context of a community hospital.²⁰

Our objective was to compare the rates of major intraoperative and postoperative complications between patients undergoing BTKA and those undergoing UTKA at a high-volume community hospital.

METHODS

Study population

We searched the surgical database to retrospectively iden-

tify all patients who had undergone a BTKA or a UTKA between May 2008 and May 2011. Patients who had an incomplete charted medical history, multiple procedures under the same anesthetic or a revision TKA were excluded from the analysis. Patients who underwent staged TKA (2 distinct surgeries on both knees within a 1-year period) were excluded from the study because of the small population size and owing to suggestions in the literature that retrospective analysis of staged procedures can be misleading.²¹ Furthermore, patients who were subject to blood conservation techniques, including autologous blood transfusion, erythropoietin, and tranexamic acid (TXA) were excluded from the study. All patients underwent a preoperative assessment by an anesthesiologist to ensure suitability for surgery, and those patients who were found to need optimization of their comorbidities were referred to internal medicine. All candidates with bilateral knee symptoms who were deemed eligible for surgery were given the option of BTKA or 2 UTKAs. Our institution's research ethics board approved our study protocol.

Operative and postoperative procedures

A pool of 7 staff surgeons performed the TKAs using a standardized approach. Whereas in some centres, 2 surgeons operate in parallel in patients undergoing BTKA,²² the BTKAs in our study were performed sequentially by a single surgeon, with the patient under a single anesthetic. The patients received either general or regional anesthetic with sedation and were given routine preoperative intravenous antibiotics. Procedures were performed under tourniquet control. All TKAs were done with intramedullary femoral alignment and extramedullary tibial alignment. The prostheses were produced by Zimmer or Biomet and were either cruciate-sparing or posterior stabilized.

Postoperatively, all patients were under the care of the same hospitalist. Supplemental oxygen was administered until oxygen saturation was maintained at a minimum of 92% on room air. Pain control was achieved using oral analgesics supplemented by patient-controlled analgesia. All patients received routine thromboprophylaxis for 2-3 weeks. Continuous passive motion was started within 24 hours of surgery. On the first postoperative day, patients were mobilized, fully weight bearing, under the supervision of physiotherapists. Patients were typically discharged by the fourth day or transferred to a rehabilitation institution as required.

Medical records

Two of us (E.S. and G.R.T.) collected and independently reviewed and verified all data from the patients' hospital records. Patient demographic characteristics and medical history were determined by reviewing all standard preoperative orthopedic, anesthesiology and internal medicine records. Intraoperative complications, if any, were identified in operative and/or consultation notes. Patient progress notes, consultation notes, discharge summaries, readmission records and follow-up appointment notes for up to 3 months were screened to identify any postoperative complications. Transfusion data were obtained from the institution blood bank records.

Statistical analysis

Continuous variables are expressed as means \pm standard deviation. We compared these data with an unpaired, 2-tailed Student *t* test using Microsoft Excel software. Dichotomous variables are expressed as numbers and percentages, and we analyzed these data with a 2-tailed Fisher exact test using GraphPad Prism. We considered results to be significant at $p < 0.05$. We calculated odds ratios (OR) and 95% confidence intervals (CIs) for all data.

RESULTS

Based on our study criteria, we excluded 36 patients from the UTKA group and 12 from the BTKA group. Of those patients who met our inclusion criteria, 966 underwent UTKA (65.9% women v. 34.1% men, mean age 69.6 ± 10.2 yr) and 373 underwent BTKA (71.0% women v. 29.0% men, mean age 69.1 ± 9.1 yr). No patients were lost to follow-up. There were no significant differences between the cohorts in terms of sex, age, body mass index (BMI) or smoking history. In both cohorts, there were nearly twice as many women as men (Table 1).

We compared the groups for preoperative comorbidities, including hypertension, arrhythmia, coronary artery disease (CAD), myocardial infarction (MI), congestive heart failure (CHF), deep vein thrombosis (DVT), pulmonary embolism (PE), stroke, transient ischemic attack

(TIA), dementia, asthma, chronic obstructive pulmonary disease (COPD), renal disease, diabetes mellitus, previous knee surgery, preoperative hemoglobin and anemia (hemoglobin < 130 g/L).²³ No significant differences existed between cohorts except for incidence of TIA and previous knee surgery. A greater proportion of patients undergoing UTKA had a history of TIA than those undergoing BTKA (3.4% v. 1.1%, $p = 0.015$). The patients undergoing UTKA had significantly more previous knee operations, including arthroscopic débridement, than patients undergoing BTKA (20.3% v. 5.6%, $p < 0.001$; Table 2).

There were no significant differences between the UTKA and BTKA cohorts for intraoperative and postoperative cardiovascular, thromboembolic or neurologic complications; deep wound infections; or mortality. In addition, there were no significant differences in the rates of respiratory failure, renal failure or length of hospital stay between cohorts. The sole significant difference identified between cohorts was the greater proportion of BTKA patients requiring blood transfusions (29.8% v. 8.9%, $p < 0.001$). Among those patients in the BTKA and UTKA cohorts who were transfused, there was no significant difference in the number of blood units required (1.72 ± 0.77 v. 1.53 ± 0.85 units, $p = 0.68$; Table 3).

As part of a further analysis, we assessed the UTKA and BTKA cohorts to identify factors that may have predisposed patients to transfusion. All patients who received transfusion had preoperative anemia ($p < 0.001$). Previous MI was significantly more common among transfused than nontransfused patients in the UTKA cohort (14.0% v. 5.5%, $p = 0.008$); we did not observe a similar trend in the BTKA cohort. Transfused patients were significantly older than nontransfused patients in the UTKA cohort (76.1 ± 8.60 yr v. 69.2 ± 10.12 yr, $p < 0.001$); again, we did not observe a similar trend in the BTKA cohort.

DISCUSSION

The number of TKAs being performed in Canada is projected to continue rising, given the aging population.¹² The literature regarding the relative safety of BTKA remains controversial. While some studies supporting the use of BTKA have shown comparable complication rates to that

Table 1. Demographic characteristics of patients undergoing bilateral or unilateral total knee arthroplasty

Characteristic	UTKA, <i>n</i> = 966	BTKA, <i>n</i> = 373	<i>p</i> value	OR (95% CI)
Sex				
Male, no. (%)	329 (34.1)	108 (29.0)	0.08	1.3 (1.0–1.6)
Female, no. (%)	637 (65.9)	265 (71.0)	0.08	0.8 (0.6–1.0)
Age, mean \pm SD yr	69.6 ± 10.2	69.1 ± 9.1	0.26	1.01 (0.99–1.02)
BMI, mean \pm SD	32.5 ± 7.0	32.2 ± 6.0	0.38	1.01 (0.99–1.03)
Smoking, no. (%)	86 (8.9)	24 (6.2)	0.12	1.4 (0.9–2.3)

BMI = Body Mass Index; BTKA = bilateral total knee arthroplasty; CI = confidence interval; OR = odds ratio; SD = standard deviation; UTKA = unilateral total knee arthroplasty.

of UTKA, critics of BTKA maintain that the procedure increases the risk of serious complications, including cardiovascular, thromboembolic and neurologic events and death.^{3-9,13,14,24,25} Therefore, we conducted the present study to determine whether it is safe to perform BTKA at a high-volume community hospital.

Our study demonstrated no significant differences in intraoperative and postoperative complications between patients undergoing BTKA and those undergoing UTKA with the exception of an increased proportion of patients in the BTKA cohort requiring blood transfusions. It has been suggested that patients undergoing BTKA are at increased risk for cardiovascular complications due to greater intraoperative blood loss leading to substantial hemodynamic shifts and ischemia.⁴ A potential explanation for the comparable cardiovascular outcomes between cohorts in our study may be that the blood loss experienced by patients in the BTKA group was not substantial enough to precipitate more cardiovascular events. Support for this explanation may lie in the fact that the mean transfusion requirement for our patients undergoing BTKA was 1.72 ± 0.77 units, whereas the literature reports requirements of 3.9 units for these patients.²⁶ Furthermore, 1 study that identified a greater proportion of postoperative CHF in the BTKA cohort examined a population aged older than 80 years,⁴ which was markedly older than the mean age of both cohorts in the present

study (69.6 ± 10.2 yr in the UTKA group and 69.1 ± 9.1 yr in the BTKA group).

The reported incidence of thromboembolic events following a TKA procedure varies widely in the literature, ranging from 0.4% to 71% for DVT and 0% to 3% for PE.⁶ Studies demonstrating high rates, however, used radiological imaging to detect thromboembolism. Radiological imaging often detects clinically asymptomatic thrombosis, whereas our study considered only symptomatic events. Consistent with our findings, several studies considering only symptomatic DVT or PE have demonstrated no statistically significant differences between UKTA and BTKA cohorts.^{4,15} One possible explanation for this may be that while BTKA increases recovery time and predisposes patients to immobility-related thromboembolic risk, patients undergoing BTKA tend to be more hypocoagulable in the postoperative period due to a greater intraoperative consumption of coagulation factors.²⁷

The literature reports a 3-month mortality of 0.46% associated with TKA.²⁸ In addition, 1 study of in-hospital mortality found that 0.5% of patients who had BTKA died compared with 0.3% of patients who had UTKA.²⁹ In contrast, our study identified lower mortality among patients who had UTKA, with no significant difference between cohorts (0.3% in the BTKA group v. 0.1% in the UTKA group, $p = 0.48$). Although the literature predominantly reflects higher mortality in patients who had BTKA, many

Table 2. Comorbidities of patients undergoing bilateral or unilateral total knee arthroplasty

Comorbidity	Group, no. (%) [*]		p value	OR (95% CI)
	UTKA, n = 966	BTKA, n = 373		
Cardiovascular				
Hypertension	553 (57.2)	222 (59.5)	0.46	0.9 (0.7-1.2)
Arrhythmia	107 (11.1)	29 (7.8)	0.09	1.5 (1.0-2.3)
Coronary artery disease	108 (11.2)	38 (10.2)	0.63	1.1 (0.8-1.6)
Myocardial infarction	60 (6.2)	25 (6.7)	0.71	0.9 (0.6-1.5)
Chronic heart failure	14 (1.4)	4 (1.1)	0.79	1.4 (0.4-4.2)
Thromboembolic				
Deep vein thrombosis	23 (2.4)	11 (2.9)	0.56	0.8 (0.4-1.7)
Pulmonary embolism	8 (0.8)	3 (0.8)	> 0.99	1.0 (0.3-3.9)
Neurologic				
Transient ischemic attack	33 (3.4)	4 (1.1)	0.015	3.3 (1.1-9.3)
Stroke	25 (2.6)	7 (1.9)	0.55	1.4 (0.6-3.2)
Dementia	8 (0.8)	1 (0.3)	0.46	3.1 (0.4-24.9)
Respiratory				
Asthma	97 (10.0)	34 (9.1)	0.68	1.1 (0.7-1.7)
COPD	40 (4.1)	10 (2.7)	0.26	1.6 (0.8-3.2)
Renal failure	32 (3.3)	6 (1.6)	0.10	2.1 (0.9-5.1)
Diabetes	172 (17.8)	72 (19.3)	0.53	0.9 (0.7-1.2)
Previous knee surgery	196 (20.3)	21 (5.6)	< 0.001	4.3 (2.7-6.8)
Preop Hb status				
Preop Hb, mean \pm SD, g/L	134.7 \pm 13.5	133.1 \pm 13.7	0.21	1.01 (1.0-1.02)
Preop anemia,† mean \pm SD, g/L	320.0 \pm 33.1	118.0 \pm 31.6	0.65	1.1 (0.8-1.4)

BTKA = bilateral total knee arthroplasty; CI = confidence interval; COPD = chronic obstructive pulmonary disease; Hb = hemoglobin; OR = odds ratio; SD = standard deviation; UTKA = unilateral total knee arthroplasty.
^{*}Unless otherwise indicated.
[†]Hb < 130 g/L.

authors have acknowledged that there may be no difference between procedures if performed at high-volume institutions with specialized TKA surgeons.^{29,30} At our institution, 500–600 BTKAs and UTKAs are collectively performed each year, making it a high-volume, specialized facility.³¹ Furthermore, critics of BTKA claim that the studies demonstrating no difference in mortality between cohorts are misleading, as BTKA candidates are often selected for their benign medical history, thereby introducing a selection bias.³² Both populations in the present study, however, were comparable in terms of demographic characteristics and comorbidity profiles. In addition, our patients were not assigned to a particular procedure based on comorbidities; rather, they chose the procedure they would undergo.

The only significant difference between the BTKA and UTKA cohorts in the present study was the proportion of patients requiring blood transfusion of at least 1 unit (8.9% v. 29.8%, $p < 0.001$). All transfused patients, regardless of cohort, had preoperative anemia, which is the strongest predictor of transfusion.²³ Studies show that the blood loss associated with TKA can be as high as 2.2 units per knee replaced due to extensive bone and soft tissue cuts; therefore, it would be expected that operating on 2 knees rather than 1 knee predisposes the patient to a greater risk of blood loss and the need for transfusion.^{9,33} In fact, it has been reported that during BTKA, the blood loss from the second knee replacement is greater than that from the first,

likely due to decreased tissue clotting factors associated with intraoperative tissue trauma, hypothermia or hypoxemia.³⁴ Interestingly, our study demonstrated that among patients being transfused, those in the BTKA cohort required a greater number of blood units than those in the UTKA cohort, but this finding was not significant (1.72 ± 0.77 v. 1.53 ± 0.85 units, $p = 0.68$). While this outcome may seem paradoxical, it is important to note that transfusion requirement is a useful, albeit imperfect, substitute measurement for blood loss. Blood transfusion is a second line treatment for hemodynamically unstable patients owing to transfusion-related risks; therefore, the trigger for transfusion is often reserved for patients with a hemoglobin level of less than 70 g/L, and patients are often transfused until stable rather than euvolemic.³⁵ Prophylactically, the use of antifibrinolytics has been shown to markedly reduce blood loss and transfusion requirements during TKA.³⁶ Intraoperative use of antifibrinolytic TXA has recently been incorporated into the TKA procedures at our institution to address the need for blood transfusion, particularly in patients undergoing BTKA. Preliminary data demonstrate that use of TXA has resulted in lowered transfusion rates for patients undergoing BTKA.

In contrast to the present study, several larger bodies of work have found that while the absolute number of complications associated with any TKA procedure is small, the relative risk of cardiovascular complications, PE and death is greater for BTKA.^{32,37} The results of our community

Table 3. Procedure-related complications in patients who had bilateral or unilateral total knee arthroplasty

Complication	Group, no. (%)*		<i>p</i> value	OR (95% CI)
	UTKA, <i>n</i> = 966	BTKA, <i>n</i> = 373		
Cardiovascular				
Arrhythmia	8 (0.8)	1 (0.3)	0.46	3.1 (0.4–24.9)
Myocardial infarction	4 (0.4)	4 (1.0)	0.23	0.4 (0.1–1.5)
Chronic heart failure	10 (1.0)	0 (0)	0.07	NA
Total	22 (2.3)	5 (1.3)	0.39	1.7 (0.6–4.6)
Thromboembolic				
Deep vein thrombosis	5 (0.5)	2 (0.5)	> 0.99	1.0 (0.2–5.0)
Pulmonary embolism	3 (0.3)	1 (0.3)	> 0.99	1.2 (0.1–11.2)
Total	8 (0.8)	3 (0.8)	> 0.99	1.0 (0.3–3.9)
Neurologic				
TIA/stroke	2 (0.2)	0 (0.0)	> 0.99	NA
Delirium	12 (1.2)	3 (0.8)	0.77	1.6 (0.4–5.5)
Total	14 (1.4)	4 (1.1)	0.79	1.4 (0.4–4.1)
Respiratory failure	4 (0.4)	2 (0.5)	0.67	0.8 (0.1–4.2)
Renal failure	1 (0.1)	0 (0.0)	0.28	NA
Deep infection	4 (0.4)	1 (0.3)	> 0.99	1.5 (0.2–13.9)
Mortality	1 (0.1)	1 (0.3)	0.48	0.4 (0–6.2)
Hospital stay, mean \pm SD, d	4.9 \pm 2.9	5.3 \pm 2.1	0.36	0.92 (0.88–0.98)
Transfusion				
Transfused	86 (8.9)	111 (29.8)	< 0.001	0.2 (0.2–0.3)
Units, mean \pm SD	1.53 \pm 0.85	1.72 \pm 0.77	0.68	0.89 (0.84–0.94)

BTKA= bilateral total knee arthroplasty; CAD = coronary artery disease; CI = confidence interval; NA = not available; OR = odds ratio; SD = standard deviation; TIA = transient ischemic attack; UTKA= unilateral total knee arthroplasty.
*Unless otherwise indicated.

hospital-based study may therefore not be universally applicable to all centres where BTKA is performed. Given the controversial status of BTKA safety in the literature, patients should be made aware of the major intraoperative and postoperative complications identified in the larger cohort studies when deciding whether to undergo elective bilateral or unilateral knee replacement surgery.

Limitations

Our study had several limitations that should be acknowledged. First, despite having a standard TKA approach at our institution, our study was based on the data of 7 surgeons, each of whom may have introduced a minor degree of procedure variability. Nevertheless, we felt that combining the results from different surgeons yielded a more accurate representation of TKA outcomes at a community hospital and would enhance the external validity of our study. Second, reviewing only hospital records may not identify all patient complications that occurred after discharge. For instance, if a patient visited another hospital with an acute complication, our institution database may not have a record of that visit. The potential for this error was minimized, however, as no study patient was lost to follow-up and all patients were seen within the first 3 postoperative months to monitor knee progress and screen for complications. Finally, it may be suggested that a comparison between BTKA and staged TKA is more valuable than a comparison of BTKA and UTKA. We initially incorporated staged TKA, but the sample size was too small for the analysis to have adequate statistical power. In addition, staged TKA introduces confounding factors, such as 2 distinct anesthetic exposures and 2 distinct postoperative recovery periods, that do not exist in a comparison between BTKA and UTKA. In addition, the literature suggests that the operative risk of staged TKA is underestimated in retrospective studies, as patients who experience complications during the first surgery may be unlikely to participate in a second surgery and thereby become a UTKA patient.²¹ Individuals who decline the second operation are likely to continue experiencing symptoms of arthritis, which suggests that they may have been better served by a 1-step BTKA.

This study has several strengths compared with the existing body of literature. First, having the study based at a high-volume hospital generated a large number of eligible patients in both cohorts for comparison. Second, this study uniquely examined the TKA outcomes at a community institution where all surgeries are performed by staff surgeons, whereas most studies in the literature were conducted at academic centres where trainees also participated in operations. Finally, the same hospitalist managed all patients in the postoperative setting at our institution, minimizing the possibility that variability in postoperative care influenced complication rates.

CONCLUSION

The purpose of our study was to determine the safety of performing BTKA procedures at a high-volume community hospital. While several large scale studies, which used data from academic centres, have identified relative risks correlated with BTKA, our study did not find BTKA to be associated with increased cardiovascular, thromboembolic, or neurologic complications; deep wound infection; or death compared with UTKA. The proportion of patients requiring blood transfusions was significantly greater in the BTKA cohort, but the number of units required per transfused patient was not significantly different. Recent efforts have been made at our institution to effectively reduce the need for transfusion by introducing the use of TXA. We conclude that BTKA can be a safe treatment for bilateral knee arthritis in the context of a high-volume community hospital with experienced TKA surgeons, hospitalists, paramedical staff and ready access to postoperative inpatient rehabilitation.

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Contributors: E. Spicer and G.R. Thomas contributed to all aspects of this work. E.J. Rumble designed the study, analyzed the data, reviewed the article and approved the final version for publication.

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