ANESTHESIOLOGY

Anesthesia Method, Tourniquet Use, and Persistent Postsurgical Pain after Total Knee Arthroplasty: A Prespecified Secondary Analysis of a Randomized Trial

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EDITOR'S PERSPECTIVE

What We Already Know about This Topic

- Persistent pain after total knee arthroplasty is common and adversely affects outcomes
- The choice of anesthesia and use of a tourniquet during knee arthroplasty may have an impact on complication rates, but the effects on persistent pain are poorly known

What This Article Tells Us That Is New

- In a secondary analysis of a study involving 404 patients, no clinically important differences in pain scores 1 yr after arthroplasty were found between the spinal and general anesthesia groups
- In the same study, no clinically meaningful differences in 1-yr pain scores were found between the no-tourniquet and tourniquet use groups

ABSTRACT

Background: Persistent postsurgical pain after total knee arthroplasty is a common problem and a major reason for patient dissatisfaction. This secondary analysis aimed to investigate the effects of anesthesia (spinal *vs.* general) and tourniquet use on persistent pain after total knee arthroplasty.

Methods: In this secondary analysis of a previously presented parallel, single-center, randomized trial, 404 patients scheduled for total knee arthroplasty were randomized to spinal *versus* general anesthesia and no-tourniquet *versus* tourniquet groups. Patients assessed pain using the Brief Pain Inventory–short form preoperatively and 3 and 12 months postoperatively. The prespecified main outcome was the change in "average pain" measured with numerical 0 to 10 rating scale 1 yr postoperatively. The threshold for clinical importance between groups was set to 1.0.

Results: The change in average pain scores 1 yr postoperatively did not differ between the spinal and general anesthesia groups (–2.6 [SD 2.5] *vs.* –2.3 [SD 2.5], respectively; mean difference, –0.4; 95% CI, –0.9 to 0.1; $P = 0.150$). The no-tourniquet group reported a smaller decrease in the average pain scores than the tourniquet group (–2.1 [SD 2.7] *vs.* –2.8 [SD 2.3]; mean difference, 0.6; 95% CI, 0.1 to 1.1; $P = 0.012$). After 1 yr, the scores concerning the mean of four pain severity variables (numerical rating scale) decreased more in the spinal than in the general anesthesia group (–2.3 [SD 2.2] *vs.* –1.8 [SD 2.1]; mean difference, –0.5; 95% CI, –0.9 to –0.05; $P = 0.029$) and less in the no-tourniquet than in the tourniquet group (–1.7 [SD 2.3] *vs.* –2.3 [SD 2.0]; mean difference, 0.6; 95% CI, 0.2 to 1.0; $P = 0.005$). None of the differences in pain scores reached the threshold for clinical importance.

Conclusions: The type of anesthesia (spinal *vs.* general) or tourniquet use has no clinically important effect on persistent postsurgical pain after total knee arthroplasty.

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Total knee arthroplasty is a common procedure with good long-term outcomes.[1,2] Despite its benefits, moderate to severe persistent postsurgical pain remains a challenge, affecting 13 to 31% of patients.[3–9] Persistent postsurgical pain after total knee arthroplasty is a major reason for patient dissatisfaction.[3,10] Moreover, pain is an independent risk factor for revision surgery.[11]

Several studies have investigated factors that may affect the risk of persistent postsurgical pain.[7–9,12–19] However, data on the effects of spinal and general anesthesia on persistent pain after total knee arthroplasty are highly limited. A retrospective, multicenter study including patients who underwent hip or knee arthroplasty found no difference in the prevalence of persistent postsurgical pain between the regional and general anesthesia groups.[13] In this study, however, regional anesthesia methods and perioperative

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pain management were variable, and most general anesthesia patients underwent a hip replacement.[13] Similarly, in a recent prospective cohort study, the anesthesia type was not a predictor for persistent postsurgical pain after total knee arthroplasty; however, only 11% of patients received other than neuraxial anesthesia.[8] Nevertheless, spinal anesthesia is recommended over general anesthesia for total knee arthroplasty mainly because of its lower risk of complications.[20–22]

The effects of no-tourniquet *versus* tourniquet use on persistent postsurgical pain after total knee arthroplasty have been investigated in three randomized controlled trials.[12] Only two of these trials reported separate pain scores, with no significant differences 6 to 12 months after surgery.[14,15]

The increasing annual number of total knee arthroplasties underlines the need for adequately sized randomized investigations targeted at comparing the effects of spinal and general anesthesia and no-tourniquet and tourniquet use on persistent postsurgical pain. In addition, the overall prevalence of persistent postsurgical pain after total knee arthroplasty should be reassessed, given that some of the previous results might not reflect the current situation due to the implementation of fast-track protocols, such as multimodal analgesia, which appear to improve outcomes after total knee arthroplasty.[23,24]

In this secondary analysis of a previously presented randomized trial, we investigated whether spinal *versus* general anesthesia and no-tourniquet *versus* tourniquet use would lead to differences in persistent postsurgical pain after total knee arthroplasty.[25] We also explored possible interaction effects between these anesthesia and tourniquet regimens. The primary in-hospital results concerning the same patients and study groups have been published previously.[25] In the current study, we further evaluated the overall prevalence of moderate to severe persistent postsurgical pain after total knee arthroplasty and possible major differences in long-term pain management by investigating analgesic prescriptions. We hypothesized that anesthesia and tourniquet methods would not differ in their effects on the outcomes.

Materials and Methods

This study was a secondary analysis of a trial that was approved by the ethics committee of HUS Helsinki University Hospital, Surgery (Helsinki, Finland) (June 8, 2016; reference No. HUS1703/2016) and the Finnish Medicines Agency Fimea (Kuopio, Finland) (May 20, 2016; reference No. KL72/2016). The study was registered to EudraCT (reference No. 2016-002035-15, principal investigator: Anne Vakkuri) on May 12, 2016. We obtained written informed consent from every participant.

Study Setting and Participants

This study was a secondary analysis of an open-label, parallel, longitudinal, single-center, randomized controlled trial conducted at the Arthroplasty Center of HUS Helsinki University Hospital, Vantaa, Finland. A separate study description and in-hospital results, including the primary outcome concerning the use of intravenous (IV) oxycodone with a patient-controlled analgesia device, have been published.[25,26]

Patients aged 18 to 75 yr with a body mass index of 40 kg/m^2 or less and who were referred for primary total knee arthroplasty due to Kellgren–Lawrence grade III to IV knee arthritis were included in the study. We excluded patients with severe malalignment, extension or flexion deficit, or previous major surgery of the same knee. In addition, we excluded patients with American Society of Anesthesiologists (Schaumburg, Illinois) physical status class IV or higher, those with contraindications to the study medications or to either anesthesia method, those with a need for bridging anticoagulation, those who underwent a bilateral operation, or those with ongoing usage of strong opioids.[26]

Randomization and Blinding

Sealed and opaque randomization envelopes were created in blocks of 20 by a nonparticipating physician. The patients were randomized into the following four groups in a 1:1:1:1 allocation ratio: spinal anesthesia + no tourniquet, spinal anesthesia + tourniquet, general anesthesia + no tourniquet, and general anesthesia + tourniquet. The envelopes were opened at the earliest 2 h before the operation by a nurse not associated with the study. Blinding the medical staff or patients was infeasible.

Perioperative Care

Premedication included 5 mg oral diazepam, 1 g acetaminophen, and 400 to 800 mg ibuprofen according to the ideal body weight.[26] Induction of spinal anesthesia was performed with 15 mg isobaric bupivacaine, and patients received propofol infusion for light sedation. Target-controlled infusions of propofol and remifentanil were used for general anesthesia. At the end of the surgery, the patients under general anesthesia received 0.1 mg/kg IV oxycodone based on their ideal body weight. When used, tourniquets were maintained at 250 mmHg and applied for no more than 2 h. Surgeons injected local infiltration analgesia with 30 mg ketorolac, 300 mg ropivacaine, and 0.5 mg epinephrine to every patient with an organized multipuncture method and 100 mg of ropivacaine to subcutaneous wound edges. Surgeons used a single type of cemented implant with patellar resurfacing and operated through a midline incision and with a medial parapatellar approach.[26]

Postoperatively, acetaminophen and ibuprofen were administered three times daily with premedication doses. A patient-controlled analgesia device was used with no baseline infusion and a preset dose of 0.04 mg/kg IV oxycodone for a maximum of four doses per hour for the first 24 h. Subsequently, the patients received one extended-release

oxycodone tablet of 5 to 15 mg. Repeated immediate-release oxycodone (5 to 15 mg orally or 4 to 12 mg intramuscularly) was allowed upon request. All oxycodone doses were predefined according to the ideal body weight.[26] From the second postoperative morning, the patients received 50 mg oral tramadol or a combination of 500 mg acetaminophen and 30 mg codeine (one to two tablets up to three times daily). If the immediate-release oxycodone was insufficient, 75 to 300 mg pregabalin orally twice daily was allowed as a rescue analgesic. Peripheral nerve block was allowed if treatment with analgesics proved insufficient.

Prescriptions for Pain Management after Discharge

Patients received prescriptions for acetaminophen, a nonsteroidal anti-inflammatory drug, and either tramadol or a combination of acetaminophen and codeine. Possible contraindications, such as the permanent use of anticoagulants, were noted. Strong opioids or gabapentinoids were prescribed only if the surgeon or anesthesiologist assessed that routine medication was insufficient. Once discharged, patients were allowed to obtain prescriptions from other physicians and healthcare organizations.

Data Collection

The patients completed the Brief Pain Inventory–short form[27] and Oxford Knee Score[28,29] questionnaires median 7 days preoperatively and 3 and 12 months postoperatively. The Brief Pain Inventory–short form is a self-administered, validated, and widely used questionnaire in clinical studies for assessing pain. Patients evaluate four pain severity variables (average pain, worst and least pain in the last 24 h, and current pain) and seven pain interference variables with a numerical rating scale (0 = no pain/pain interference, and 10 = worst imaginable pain/pain interference). The Oxford Knee Score is a self-administered and validated questionnaire designed to measure knee pain and function after total knee arthroplasty. From the Oxford Knee Score questionnaire, we extracted responses to the question concerning the description of usual knee pain during the past 4 weeks. The responses were rated on a 5-point scale (none, very mild, mild, moderate, and severe).[28]

We obtained information on opioid and gabapentinoid prescriptions up to 12 months after the operation from the National Prescription Center. This database includes all prescriptions concerning these analgesics. If additional information was necessary to check the indications on prescriptions, we investigated the electronic patient records.

Outcomes

The prespecified main outcome of this secondary analysis was the change in the "average pain" 12 months postoperatively, measured using the Brief Pain Inventory–short form (numerical rating scale).[26] Other prespecified secondary outcomes included the change in the average pain 3 months postoperatively and the change in the other three (worst and least pain in the last 24 h and current pain) Brief Pain Inventory–short form pain severity variables, in the arithmetic mean of the four pain severity variables, and in the arithmetic mean of the seven pain interference variables 3 and 12 months postoperatively. The scores of the respective Brief Pain Inventory–short form pain variables at 3 and 12 months were also explored in a *post hoc* sensitivity analysis.

The prevalence of moderate to severe knee pain at 3 and 12 months postoperation, as defined by the Oxford Knee Score question, was added as a secondary outcome *post hoc*.[28] Given the wide variations in the presented cutoff values for moderate to severe pain, we further included the prevalence of average pain (Brief Pain Inventory–short form) with three different cutoffs (numerical rating scale of 3 or higher, 4 or higher, and 5 or higher) at 3 and 12 months as secondary outcomes *post hoc*.[4,9,30] In addition, the secondary *post hoc* outcomes included the number of patients who were prescribed gabapentinoids or opioids (except tramadol and codeine) because of the study operation during the 12-month follow-up.

Statistical Analysis

We conducted sample size calculations of the primary trial with parametric methods to address the prespecified main outcome of this secondary analysis, "average pain" of the Brief Pain Inventory–short form, with the estimated mean numerical rating scale of 5.5 (SD 2.2) and used two-tailed tests with an α level of 0.05 and a power of 80%.[26] Subsequently, we increased sample sizes by 16% to adjust for possible nonparametric analyses. We set numerical rating scale 1.0 as the minimal clinically important difference between groups, for which a sample size of at least 90 patients/group was required for nonparametric comparisons.[26]

Categorical data were expressed as frequencies with percentages, normally distributed data as means with standard deviations, and nonnormally distributed data as medians with interquartile ranges. The analysis plan was finalized after the completion of data collection. Comparisons of patient characteristics between the four randomization groups were conducted using the chi-square test or Fisher's exact test and Bonferroni adjustments in further pairwise comparisons for categorical data and one-way ANOVA for continuous data. The prespecified main outcome of this secondary analysis, the change in average pain 12 months after the operation, and changes in other continuous pain outcome variables at 3 and 12 months after the operation were analyzed using the two-way ANOVA, with the main effects for anesthesia (spinal *vs.* general) and tourniquet (no tourniquet *vs.* tourniquet) and an interaction effect between anesthesia and tourniquet. *Post hoc* sensitivity analyses concerning pain scores at 3 and 12 months after surgery were conducted using the analysis of covariance, with the main

effects for anesthesia and tourniquet, an interaction effect between anesthesia and tourniquet, and the preoperative pain score of the respective postoperative score as a covariate. The results from the two-way ANOVA and analysis of covariance were reported as estimated marginal mean differences (95% CI). The comparisons concerning dichotomous secondary outcome data were conducted using binary logistic regression, and the results were presented as odds ratios (95% CI). All statistical tests were two-sided, and *P* values less than 0.05 were considered statistically significant.

We reported mean pain interference scores if data were available on at least four of the seven items.[27] We imputed the scores concerning the mean of four pain severity variables if at least three of the four items were reported. We did not analyze data on patients with randomization deviations because of their low number. Statistical analyses were performed using IBM SPSS Statistics 26 (IBM Corp., USA).

Results

Patient recruitment began in October 2016. A total of 2,783 patients referred for knee arthroplasty were evaluated, 413 patients signed informed consent forms, and 404 were randomized. Preoperative data were eventually analyzed from 395 patients (table 1). The 3- and 12-month follow-ups of this secondary analysis ended in March and December 2019 with data from 391 and 387 patients, respectively (fig. 1). Pain scores of the randomization groups at different time points are presented in table 2. We derived information on prescriptions from 390 patients.

Spinal *versus* General Anesthesia

The change in average pain scores (Brief Pain Inventory–short form) 1 yr after the operation did not differ significantly between the anesthesia groups (tables 3 and 4; fig. 2). At 12 months, the spinal anesthesia group reported greater decreases in scores concerning least pain in the last 24 h and arithmetic means of the four pain severity variables and seven pain interference variables, compared with the general anesthesia group (tables 3 and 4). These differences, however, did not reach the predefined threshold (numerical rating scale of 1.0 or more) for clinical importance. The interaction effect between anesthesia and tourniquet was not significant in any pain variable at 3 or 12 months after total knee arthroplasty, indicating that the effect of anesthesia on pain variables was not different in the no-tourniquet and the tourniquet groups (table 4).

In the *post hoc* sensitivity analysis, the differences between the anesthesia groups in pain scores at 3 and 12 months were consistent with the main analysis, except for the scores concerning the mean of four pain severity variables, which did not differ significantly between the groups (Supplemental Digital Content 1, http://links.lww.com/ALN/C663).

Table 1. Patient Characteristics by Randomization Group

	Spinal Anesthesia		General Anesthesia		
Characteristic	**No Tourniquet (n = 99)**	**Tourniquet (n = 101)**	**No Tourniquet (n = 96)**	**Tourniquet (n = 99)**	**Total (n = 395)**
Age, yr	63 ± 8	64 ± 7	65 ± 7	63 ± 7	64 ± 7
Sex, female	58 (59)	73 (72)	59 (61)	61 (62)	251 (64)
Height, cm	172 ± 9	169 ± 8	170 ± 10	171 ± 9	170 ± 9
Weight, kg	90 ± 15	87 ± 15	86 ± 15	89 ± 15	88 ± 15
Medication for hypertension	46 (46)	64 (63)	51 (53)	55 (56)	216 (55)
Coronary artery disease	4 (4)	2 (2)	9 (9)*	0	15 (4)
Diabetes mellitus	14 (14)	16 (16)	13 (14)	22 (22)	65 (16)
Asthma or COPD	14 (14)	16 (16)	13 (14)	11 (11)	54 (14)
Current smoking	13 (13)	13 (13)	10 (10)	9 (9)	45 (11)
Depression	7 (7)	7 (7)	5 (5)	8 (8)	27 (7)
Rheumatological disease	7 (7)	9 (9)	9 (9)	5 (5)	30 (8)
Previous minor surgery of the target knee	42 (42)	39 (39)[2]	39 (41)[1]	37 (37)	157 (40)[3]
Reason for operation					
Primary osteoarthritis	91 (92)	93 (92)	92 (96)	93 (94)	369 (93)
Rheumatoid or psoriatic arthritis	4 (4)	5 (5)	2 (2)	1 (1)	12 (3)
Posttraumatic osteoarthritis	3 (3)	1 (1)	1 (1)	3 (3)	8 (2)
Other	1 (1)	2 (2)	1 (1)	2 (2)	6 (2)
ASA physical status classification					
I	8 (8)	10 (10)	8 (8)	10 (10)	36 (9)
II	63 (64)	57 (56)	62 (65)	62 (63)	244 (62)
III	28 (28)	34 (34)	26 (27)	27 (27)	115 (29)

The values present the means ± SD or the number of patients (%). Superscript numbers present the number of missing values.

*$P = 0.008$ for the comparison with the general anesthesia + tourniquet group.

ASA, American Society of Anesthesiologists; COPD, chronic obstructive pulmonary disease.

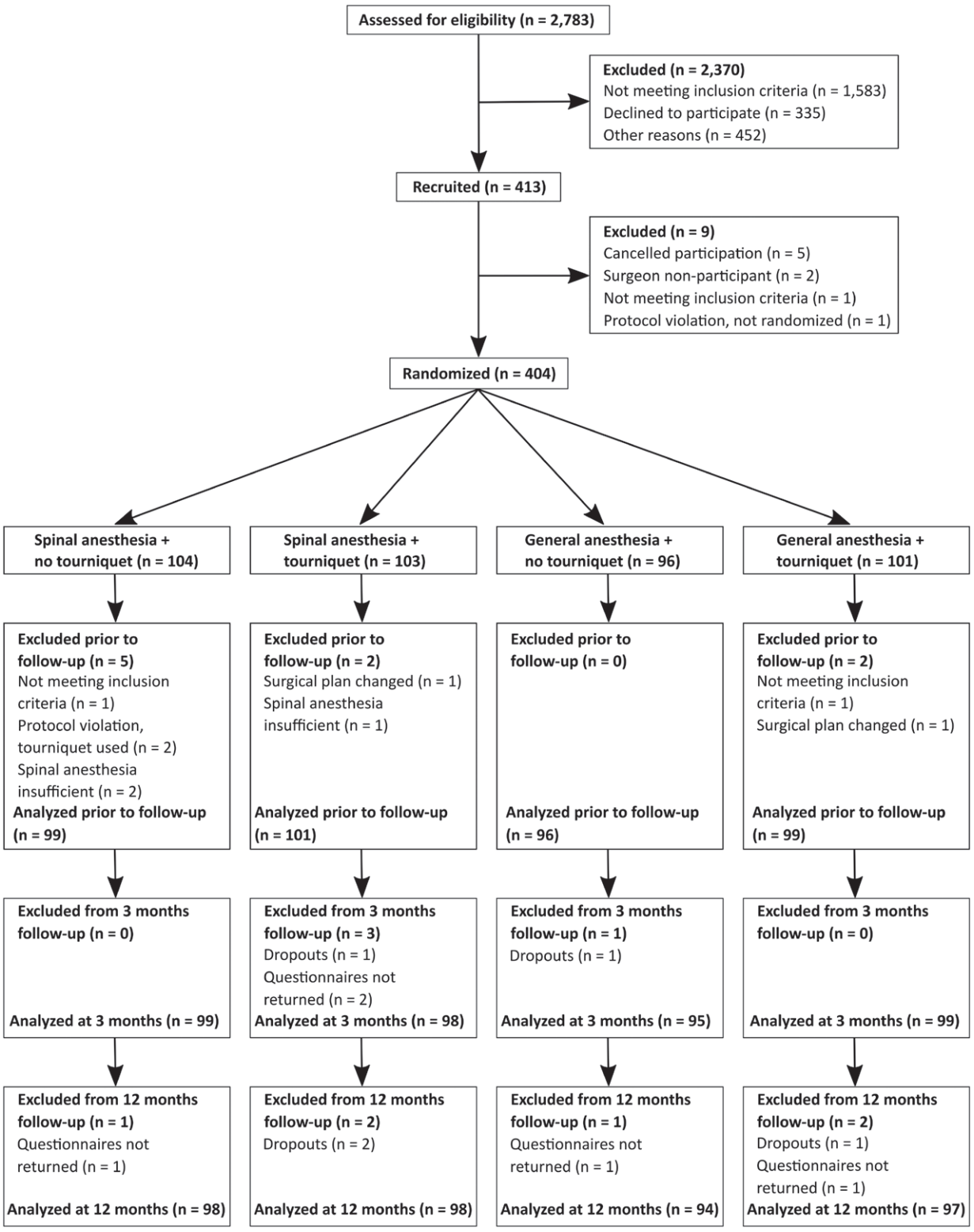

Fig. 1. Consolidated Standards of Reporting Trials flow diagram.

Table 2. Pain before and after Total Knee Arthroplasty in the Randomization Groups

	Spinal Anesthesia		General Anesthesia	
Pain Assessment	**No Tourniquet**	**Tourniquet**	**No Tourniquet**	**Tourniquet**
Before operation				
n	99	101	96	99
Average pain	4.3 ± 1.7[1]	4.8 ± 2.2[1]	4.3 ± 1.9[1]	4.7 ± 2.0[1]
Worst pain in 24 h	5.5 ± 2.1[1]	5.9 ± 2.1[1]	5.4 ± 2.4	6.1 ± 2.1[1]
Least pain in 24 h	2.0 [1.0, 3.0][1]	2.0 [1.0, 3.8][1]	2.0 [0.0, 3.0][1]	2.0 [0.0, 3.0][1]
Current pain	3.1 ± 2.3[1]	3.4 ± 2.2[1]	2.9 ± 2.1[1]	3.2 ± 2.5[1]
Pain severity	3.7 ± 1.6[1]	4.1 ± 1.8[1]	3.6 ± 1.8[1]	3.9 ± 1.7[1]
Pain interference	4.4 ± 2.0[1]	4.5 ± 2.2[4]	4.2 ± 2.4[1]	4.4 ± 2.1[1]
3 months after operation				
n	99	98	95	99
Average pain	2.4 ± 2.1	2.4 ± 1.8[1]	2.6 ± 2.2[2]	2.7 ± 2.0
Worst pain in 24 h	3.5 ± 2.6	3.7 ± 2.6	3.7 ± 2.7	3.9 ± 2.7[1]
Least pain in 24 h	0.0 [0.0, 2.0]	1.0 [0.0, 2.0][1]	1.0 [0.0, 2.0]	0.0 [0.0, 2.0]
Current pain	1.0 [0.0, 2.0][1]	1.0 [0.0, 2.0]	1.0 [0.0, 2.0][2]	1.0 [0.0, 3.0]
Pain severity	1.5 [0.5, 3.0]	2.0 [0.9, 3.1]	2.0 [0.8, 3.3][1]	2.3 [0.8, 3.8]
Pain interference	1.5 [0.5, 3.6][1]	1.3 [0.3, 3.3][1]	1.9 [0.3, 4.7]	2.0 [0.6, 3.9]
12 months after operation				
n	98	98	94	97
Average pain	2.0 [0.0, 3.3]	1.0 [0.0, 3.5][1]	2.0 [0.0, 4.0]	2.0 [0.0, 3.0]
Worst pain in 24 h	3.0 [0.0, 5.3]	2.0 [0.0, 4.0]	3.0 [0.0, 6.0]	3.0 [1.0, 5.0]
Least pain in 24 h	0.0 [0.0, 1.0]	0.0 [0.0, 1.0]	0.0 [0.0, 2.0]	0.0 [0.0, 1.0]
Current pain	0.0 [0.0, 3.0]	0.0 [0.0, 2.0]	0.0 [0.0, 3.0]	0.0 [0.0, 2.0]
Pain severity	1.4 [0.0, 3.1]	1.0 [0.0, 2.6]	1.5 [0.0, 3.6]	1.5 [0.3, 3.0]
Pain interference	0.7 [0.0, 1.9][1]	0.3 [0.0, 1.9]	1.0 [0.0, 3.3]	1.0 [0.0, 3.1]

The values present the means ± SD or median [interquartile range]. Patients assessed pain and pain interference using a numerical rating scale, where 0 = no pain/interference, and 10 = worst imaginable pain/interference. Pain severity is an arithmetic mean of four variables: average pain, worst and least pain in the last 24 h, and current pain. Pain interference is an arithmetic mean of seven variables: general activity, mood, walking, relations with others, working, sleep, and enjoyment of life during the last 24 h. Superscript numbers present the number of missing values.

Regardless of the cutoff value (numerical rating scale of 3 or higher, 4 or higher, and 5 or higher), no significant differences in the prevalence of moderate to severe average pain at 3 and 12 months emerged between the groups (Supplemental Digital Content 2, http://links.lww.com/ALN/C664). However, the prevalence of Oxford Knee Score–derived moderate to severe knee pain at 12 months appeared lower in the spinal than in the general anesthesia group (Supplemental Digital Content 2, http://links.lww.com/ALN/C664). The number of patients who received prescriptions for gabapentinoids or oxycodone did not differ significantly between the two groups (Supplemental Digital Content 3, http://links.lww.com/ALN/C665).

No Tourniquet *versus* Tourniquet

The average pain scores decreased less in the no-tourniquet than in the tourniquet group during the 12-month follow-up (tables 4 and 5; fig. 2). In addition, all other pain severity scores and the scores concerning the arithmetic mean of the four pain severity variables in 12 months decreased less in the no-tourniquet than in the tourniquet group (tables 4 and 5). Nevertheless, these differences did not reach the level of minimal clinical importance. The interaction effect between anesthesia and tourniquet was not significant in any pain variable at 3 or 12 months after surgery, indicating that the effect of tourniquet on pain variables was not different in the spinal and the general anesthesia groups (table 4). In the *post hoc* sensitivity analysis, none of the differences in pain scores between the tourniquet groups at 3 and 12 months were statistically significant (Supplemental Digital Content 1, http://links.lww.com/ALN/C663).

The number of patients with moderate to severe average pain with different cutoff values or knee pain at 3 or 12 months did not differ significantly between the groups (Supplemental Digital Content 4, http://links.lww.com/ALN/C666). Furthermore, the groups did not differ regarding the number of patients receiving prescriptions for oxycodone and gabapentinoids (Supplemental Digital Content 3, http://links.lww.com/ALN/C665).

Total Rates of *Post Hoc* Outcomes

The total prevalence of moderate to severe knee pain, as defined by the Oxford Knee Score question, was 77% (303 of 395 patients) preoperatively, 24% (93 of 389 patients) 3 months after surgery, and 7% (27 of 387 patients) 12 months after surgery. At the cutoff values (numerical rating scale) of 3 or higher, 4 or higher, and 5 or higher, the total prevalence

Table 3. Preoperative Pain Scores and Change Scores 3 and 12 Months after Total Knee Arthroplasty in the Spinal and General Anesthesia Groups

Pain Assessment	Spinal Anesthesia	General Anesthesia
Preoperative pain scores		
n	200	195
Average pain	4.5 ± 2.0[2]	4.5 ± 1.9[2]
Worst pain in 24 h	5.7 ± 2.1[2]	5.8 ± 2.3[1]
Least pain in 24 h	2.0 [1.0, 3.0][2]	2.0 [0.0, 3.0][2]
Current pain	3.2 ± 2.2[2]	3.0 ± 2.3[2]
Pain severity	3.9 ± 1.7[2]	3.8 ± 1.8[2]
Pain interference	4.4 ± 2.1[5]	4.3 ± 2.2[2]
Change in pain scores 3 months after operation		
n	197	194
Average pain	−2.1 ± 2.4[3]	−1.9 ± 2.2[4]
Worst pain in 24 h	−2.1 ± 2.8[2]	−2.0 ± 2.9[2]
Least pain in 24 h	−1.1 ± 1.9[3]	−0.8 ± 1.6[2]
Current pain	−1.7 ± 2.4[3]	−1.4 ± 2.4[4]
Pain severity	−1.8 ± 2.0[2]	−1.5 ± 1.9[3]
Pain interference	−2.3 ± 2.5[7]	−1.6 ± 2.7[2]
Change in pain scores 12 months after operation		
n	196	191
Average pain	−2.6 ± 2.5[3]	−2.3 ± 2.5[2]
Worst pain in 24 h	−3.0 ± 3.1[2]	−2.6 ± 2.9[1]
Least pain in 24 h	−1.4 ± 1.9[2]	−0.9 ± 1.8[2]
Current pain	−2.0 ± 2.6[2]	−1.5 ± 2.5[2]
Pain severity	−2.3 ± 2.2[2]	−1.8 ± 2.1[2]
Pain interference	−3.1 ± 2.5[6]	−2.4 ± 2.5[2]

The values present the means ± SD or the median [interquartile range]. Patients assessed pain and pain interference using a numerical rating scale, where 0 = no pain/interference, and 10 = worst imaginable pain/interference. Pain severity is an arithmetic mean of four variables: average pain, worst and least pain in the last 24 h, and current pain. Pain interference is an arithmetic mean of seven variables: general activity, mood, walking, relations with others, working, sleep, and enjoyment of life during the last 24 h. Superscript numbers present the number of missing values.

of moderate to severe pain was 45% (175 of 388 patients), 28% (108 of 388 patients), and 18% (71 of 388 patients), as defined by the Brief Pain Inventory–short form 3 months after surgery, and 37% (144 of 386 patients), 24% (94 of 386 patients), and 15% (58 of 386 patients) 12 months after surgery, respectively.

Only one patient was prescribed buprenorphine, and eight patients (2%) were prescribed oxycodone for postoperative knee pain. No other strong opioids were prescribed. In addition, because of knee pain after the study operation, 40 patients (10%) were prescribed gabapentinoids.

Discussion

In this secondary analysis of a previously presented randomized trial, the change in average pain scores 1 yr after total knee arthroplasty did not differ between the spinal and general anesthesia groups. The no-tourniquet group reported a smaller decrease in the average pain scores 1 yr after surgery than the tourniquet group; however, this difference was not clinically important. The scores concerning the arithmetic means of the four pain severity variables and seven pain interference variables decreased more in the spinal anesthesia group during the 12-month follow-up compared with the general anesthesia group, although the differences remained below the borderline of clinical importance. In addition to average pain, the no-tourniquet group had smaller decreases in the scores of the other three pain severity variables (worst and least pain in the last 24 h and current pain) and in the arithmetic mean of all four severity variables 12 months after total knee arthroplasty compared with the tourniquet group, but without clinical importance. No interaction effects between anesthesia and tourniquet methods were detected in the pain variables.

In the *post hoc* sensitivity analysis with the analysis of covariance, the differences in pain scores between the anesthesia groups were mostly in line with the main analysis. However, in the comparison of the no-tourniquet and tourniquet groups, no differences in pain scores at 3 and 12 months were observed. In the other *post hoc* analyses, the spinal anesthesia group had a lower prevalence of Oxford Knee Score–based moderate to severe knee pain 12 months after total knee arthroplasty compared with the general anesthesia group. However, the prevalence of Brief Pain Inventory–short form–based moderate to severe average pain did not differ between these groups at any time point. Comparing the no-tourniquet and tourniquet groups, the prevalence rates of moderate to severe pain did not differ significantly at 3 or 12 months. The number of patients receiving prescriptions for oxycodone or gabapentinoids for postoperative knee pain did not differ in either comparison.

This secondary analysis of a previously presented trial included both prespecified and *post hoc* outcomes. Our previously published primary in-hospital results from the same patient cohort revealed that during the hospital stay (median of 2.2 days after surgery), pain management did not differ between the study groups.[25] In addition, even though general anesthesia patients reported more pain during the immediate postoperative phase in the recovery room, the differences in pain scores were not clinically important 24 h after surgery.[25]

Previous cohort studies have suggested no differences in the prevalence of persistent postsurgical pain after total knee arthroplasty between regional and general anesthesia groups.[8,13] The main results of this secondary analysis are in line with these studies. Thus, the recommendations to use spinal anesthesia as the primary method in total knee arthroplasty seem to remain unaffected by the outcomes concerning persistent pain.[20–22]

Our results seem consistent with two smaller randomized trials showing no significant differences in persistent postsurgical pain after total knee arthroplasty between tourniquet and no-tourniquet groups.[14,15] Compared with the Brief Pain Inventory–short form–based results of the current trial, some prospective studies have presented lower prevalence rates for moderate to severe or for "significant" persistent postsurgical pain 1 yr after total knee arthroplasty.[4,6,8]

Table 4. Comparisons of Change Scores 3 and 12 Months after Total Knee Arthroplasty in the Spinal and General Anesthesia and in the No-Tourniquet and Tourniquet Groups

Pain Assessment	Spinal *vs.* General Anesthesia Difference (95% CI)	*P* Value	No-Tourniquet *vs.* Tourniquet Difference (95% CI)	*P* Value	Anesthesia–Tourniquet Interaction Effect *P* Value
Change in pain scores 3 months after operation					
Average pain	–0.3 (–0.7 to 0.2)	0.240	0.4 (–0.1 to 0.8)	0.128	0.617
Worst pain in 24 h	–0.2 (–0.8 to 0.4)	0.519	0.3 (–0.3 to 0.9)	0.300	0.614
Least pain in 24 h	–0.3 (–0.7 to 0.03)	0.075	0.1 (–0.2 to 0.5)	0.513	0.070
Current pain	–0.3 (–0.8 to 0.2)	0.206	0.4 (–0.1 to 0.8)	0.146	0.760
Pain severity	–0.3 (–0.7 to 0.1)	0.165	0.3 (–0.1 to 0.7)	0.154	0.641
Pain interference	–0.7 (–1.2 to –0.1)	0.014	0.3 (–0.3 to 0.8)	0.328	0.951
Change in pain scores 12 months after operation					
Average pain	–0.4 (–0.9 to 0.1)	0.150	0.6 (0.1 to 1.1)	0.012	0.551
Worst pain in 24 h	–0.5 (–1.1 to 0.1)	0.136	0.8 (0.2 to 1.4)	0.014	0.456
Least pain in 24 h	–0.6 (–0.9 to –0.2)	0.003	0.4 (0.03 to 0.8)	0.036	0.239
Current pain	–0.5 (–1.0 to 0.04)	0.069	0.6 (0.1 to 1.1)	0.016	0.779
Pain severity	–0.5 (–0.9 to –0.05)	0.029	0.6 (0.2 to 1.0)	0.005	0.466
Pain interference	–0.8 (–1.3 to –0.3)	0.003	0.3 (–0.2 to 0.8)	0.190	0.698

The results are from the two-way ANOVA for the changes in the preoperative pain scores. Patients assessed pain and pain interference using a numerical rating scale, where 0 = no pain/interference, and 10 = worst imaginable pain/interference. Pain severity is an arithmetic mean of four variables: average pain, worst and least pain in the last 24 h, and current pain. Pain interference is an arithmetic mean of seven variables: general activity, mood, walking, relations with others, working, sleep, and enjoyment of life during the last 24 h.

Studies of 63 and 116 patients reported prevalence rates of 27% (numerical rating scale of 3 or higher) and 13% (visual analog scale greater than 40 of 100).[4,6] Furthermore, a recent study of 288 patients reported that 16% suffered from moderate to severe persistent postsurgical pain (Western Ontario McMaster Universities Osteoarthritis Index pain score of 30 of 100 or higher).[8] However, based on the Oxford Knee Score question, the prevalence of

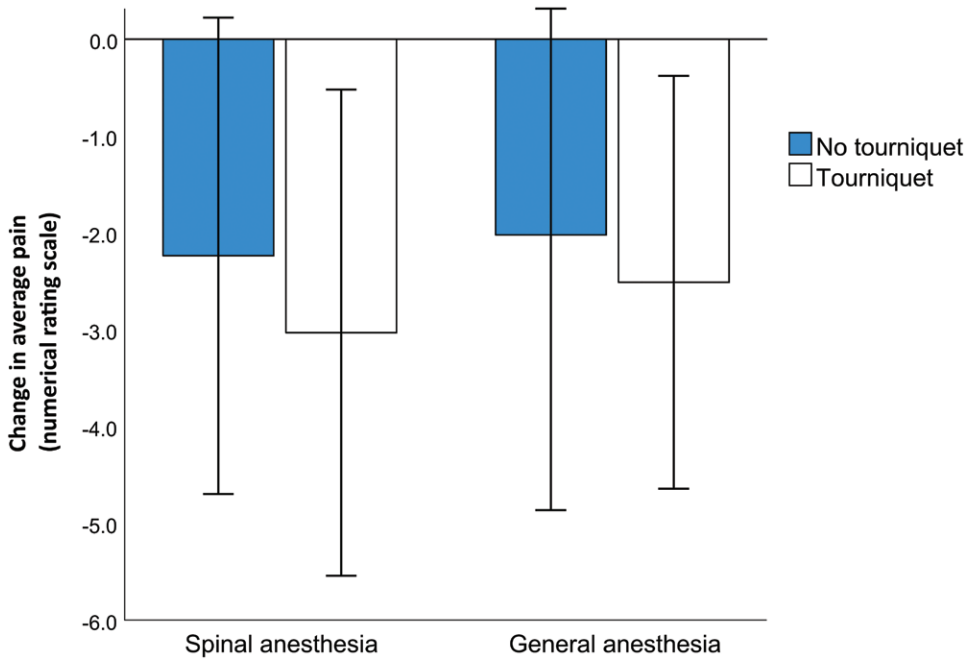

Fig. 2. Bar charts of changes in preoperative average pain scores 12 months after total knee arthroplasty by study groups. The values present means (SD). $P = 0.150$ for spinal *versus* general anesthesia, $P = 0.012$ for no tourniquet *versus* tourniquet, and $P = 0.551$ for anesthesia × tourniquet interaction from the two-way ANOVA.

Table 5. Preoperative Pain Scores and Change Scores 3 and 12 Months after Total Knee Arthroplasty in the No-Tourniquet and Tourniquet Groups

Pain Assessment	No Tourniquet	Tourniquet
Preoperative pain scores		
n	195	200
Average pain	4.3 ± 1.8[2]	4.7 ± 2.1[2]
Worst pain in 24 h	5.5 ± 2.2[1]	6.0 ± 2.1[2]
Least pain in 24 h	2.0 [0.0, 3.0][2]	2.0 [1.0, 3.0][2]
Current pain	3.0 ± 2.2[2]	3.3 ± 2.4[2]
Pain severity	3.7 ± 1.7[2]	4.0 ± 1.8[2]
Pain interference	4.3 ± 2.2[2]	4.4 ± 2.2[5]
Change in pain scores 3 months after operation		
n	194	197
Average pain	−1.8 ± 2.3[4]	−2.2 ± 2.3[3]
Worst pain in 24 h	−1.9 ± 2.9[1]	−2.2 ± 2.8[3]
Least pain in 24 h	−0.9 ± 1.7[2]	−1.0 ± 1.8[3]
Current pain	−1.3 ± 2.3[5]	−1.7 ± 2.5[2]
Pain severity	−1.5 ± 2.0[3]	−1.8 ± 1.9[2]
Pain interference	−1.8 ± 2.7[3]	−2.1 ± 2.6[6]
Change in pain scores 12 months after operation		
n	192	195
Average pain	−2.1 ± 2.7[2]	−2.8 ± 2.3[3]
Worst pain in 24 h	−2.4 ± 3.2[1]	−3.2 ± 2.8[2]
Least pain in 24 h	−1.0 ± 1.9[2]	−1.3 ± 1.8[2]
Current pain	−1.4 ± 2.7[2]	−2.1 ± 2.4[2]
Pain severity	−1.7 ± 2.3[2]	−2.3 ± 2.0[2]
Pain interference	−2.6 ± 2.7[3]	−2.9 ± 2.3[5]

The values present the means ± SD or medians [interquartile range]. Patients assessed pain and pain interference using a numerical rating scale, where 0 = no pain/interference, and 10 = worst imaginable pain/interference. Pain severity is an arithmetic mean of four variables: average pain, worst and least pain in the last 24 h, and current pain. Pain interference is an arithmetic mean of seven variables: general activity, mood, walking, relations with others, working, sleep, and enjoyment of life during the last 24 h. Superscript numbers present the number of missing values.

persistent postsurgical pain appeared much lower in our analysis. These differences may have arisen from differences in the definitions of persistent postsurgical pain, surgery and anesthesia protocols, sample sizes, and patient characteristics. Questionnaires also play a crucial role, as observed in our results. Oxford Knee Score and Brief Pain Inventory–short form questionnaires involve different time frames. Furthermore, the Oxford Knee Score focuses on the knee, whereas the Brief Pain Inventory–short form is a universal instrument for assessing pain.

Our findings on prescriptions are in line with a recent study reporting a very low proportion of patients receiving postoperative prescriptions for strong opioids.[31] This result suggests that prescribing strong opioids routinely for pain after total knee arthroplasty may be unnecessary, at least in some populations.

The strengths of this study include its randomized design, adequate sample size, and very low (2%) dropout rate during the follow-up. In addition, this study was conducted in a publicly funded, high volume, tertiary hospital, and numerous arthroplasty surgeons and anesthesiologists treated patients who underwent total knee arthroplasty with modern fast-track protocols.

Among the limitations of this study, its open-label design is the most obvious. Blinding, however, was not feasible. Personnel had either first-hand knowledge or free access to information on operating room events, and patients were undoubtedly aware of the anesthesia method. In addition, we regarded blinding the tourniquet use in the spinal anesthesia group as unreliable. The single-center design and high exclusion rate are also noteworthy limitations. Of 1,583 patients who failed to meet the inclusion criteria, 51% were either over 75 yr, referred for a unicompartmental knee replacement, underwent a bilateral operation, or received a nonprotocol prosthesis, such as a hinge prosthesis.[25] In addition, due to randomization deviations, five patients were excluded from the analyses, which might have biased the results.

A further limitation concerns the type of pain. A recent definition for chronic postsurgical pain refers to pain that develops after surgery and persists longer than 3 months.[32] In this study, we used the term "persistent postsurgical pain" to describe the combination of residual pain from the preoperative period and possible chronic pain caused by the surgery. Estimating the proportions of these two pain modalities or their precise nature was not possible with the questionnaires used in this study, and this should be noted in interpreting the results.

In the current analysis, we used numerical rating scale 1.0 as the threshold for minimal clinically important differences between the groups. This was consistent with previous studies assessing the minimal clinically significant changes in pain scores.[33,34] However, for persistent pain after total knee arthroplasty, the optimal threshold for clinically important differences between groups remains to be established. In addition, for data comparability, a consensus should be reached on time points for measuring persistent pain after total knee arthroplasty. We suggest 1 yr as the primary timepoint for future studies, given the current and previous results, which strongly indicate that pain continues to decrease up to 12 months after the operation.[4,6,8] Furthermore, studies with longer follow-up times have not presented lower prevalence rates for persistent postsurgical pain.[3,7,35]

In conclusion, the results from this secondary analysis of a randomized trial concerning total knee arthroplasty suggest that spinal and general anesthesia do not lead to clinically important differences in persistent postsurgical pain. Similarly, operating with or without a tourniquet has no clinically important impact on persistent pain. Prescriptions for strong opioids may be rarely necessary after total knee arthroplasty.

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Competing Interests

Dr. Madanat has received fees for consultancy and lectures from Pfizer (Helsinki, Finland) and Stryker (Vantaa, Finland) and holds stock options and is a medical advisor for Osgenic Ltd. (Helsinki, Finland). Dr. Reponen has received personal grants from the Foundation for Economic Education, Pulsus Foundation, Finnish Medical Association, and Finnish Society of Anaesthesiologists (all in Helsinki, Finland). Dr. Linko has received a fee from Fisher&Paykel (Helsinki, Finland) for a lecture concerning nasal high flow therapy. The other authors declare no competing interests.

Reproducible Science

Full protocol available at: riku.palanne@ksshp.fi. Raw data available at: riku.palanne@ksshp.fi.

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ANESTHESIOLOGY REFLECTIONS FROM THE WOOD LIBRARY-MUSEUM

Luck, Pluck, and the Making of the Macintosh Laryngoscope

British anaesthetist Sir Robert Macintosh (1897 to 1989, *right*) was born in New Zealand under a lucky star. The son of a mayor and newspaper editor, young Macintosh shone as a student and athlete. In 1937, automotive magnate Lord Nuffield beamed as Oxford University officials installed Macintosh as Britain's first (Nuffield) Professor of Anaesthetics. Honorary doctorates and fellowships followed, along with knighthood by Queen Elizabeth II. Fortune indeed favored him, but adversity had forged his mettle. His beloved mother died in his youth. During World War I, German soldiers shot down his fighter plane and took him as a prisoner of war. To invent his namesake laryngoscope in 1943, Macintosh would fuse pluck with luck. While helping a surgeon insert a Boyle-Davis gag (*lower left*) prior to a tonsillectomy, the tip overreached into the patient's vallecula. Serendipity revealed a glorious glottic view. After extensive experimentation, Macintosh and his technician, Richard Salt, fashioned a prototype (*upper left*) that also lifted the sensitive epiglottis *indirectly*. Facilitating visualization and endotracheal intubation (pre-curare) under lighter anesthesia, the Macintosh laryngoscope—like its creator—gained respect and affection everywhere. (Copyright © the American Society of Anesthesiologists' Wood Library-Museum of Anesthesiology.)

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