Pain Management Modalities after Total Knee Arthroplasty

A Network Meta-analysis of 170 Randomized Controlled Trials

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ABSTRACT

Background: Optimal analgesia for total knee arthroplasty remains challenging. Many modalities have been used, including peripheral nerve block, periarticular infiltration, and epidural analgesia. However, the relative efficacy of various modalities remains unknown. The authors aimed to quantify and rank order the efficacy of available analgesic modalities for various clinically important outcomes.

Methods: The authors searched multiple databases, each from inception until July 15, 2016. The authors used random-effects network meta-analysis. For measurements repeated over time, such as pain, the authors considered all time points to enhance reliability of the overall effect estimate. Outcomes considered included pain scores, opioid consumption, rehabilitation profile, quality of recovery, and complications. The authors defined the optimal modality as the one that best balanced pain scores, opioid consumption, and range of motion in the initial 72 postoperative hours.

Results: The authors identified 170 trials (12,530 patients) assessing 17 treatment modalities. Overall inconsistency and heterogeneity were acceptable. Based on the surface under the cumulative ranking curve, the best five for pain at rest were femoral/obturator, femoral/sciatic/obturator, lumbar plexus/sciatic, femoral/sciatic, and fascia iliaca compartment blocks. For reducing opioid consumption, the best five were femoral/sciatic/obturator, femoral/obturator, lumbar plexus/sciatic, lumbar plexus, and femoral/sciatic blocks. The best modality for range of motion was femoral/sciatic blocks. Femoral/sciatic and femoral/obturator blocks best met our criteria for optimal performance. Considering only high-quality studies, femoral/sciatic seemed best.

Conclusions: Blocking multiple nerves was preferable to blocking any single nerve, periarticular infiltration, or epidural analgesia. The combination of femoral and sciatic nerve block appears to be the overall best approach. Rehabilitation parameters remain markedly understudied. **(ANESTHESIOLOGY 2017; 126:923-37)**

ABOUT 700,000 total knee arthroplasties (TKAs) are performed annually in the United States—a number expected to increase to 3.5 million per year by 2030.[1] TKA is a painful operation and inadequate postoperative analgesia impairs rehabilitation, prolongs hospitalization, and increases the risk of adverse events, including myocardial ischemia and infarction, pulmonary dysfunction, paralytic ileus, urinary retention, and thromboembolism.[2]

Chang and Cho[3] found that analgesia protocols for TKA vary greatly, as does postoperative pain intensity. The ideal approach would provide excellent analgesia while minimizing opioid consumption and enhancing rehabilitation.[4] There are at least 10 different pain management

What We Already Know about This Topic

- Many methods are available to provide postoperative analgesia for patients undergoing total knee arthroplasty, but it is unclear how they compare with each other

What This Article Tells Us That Is New

- Using a random-effects network meta-analysis technique, 170 trials were analyzed to identify the optimal analgesic modality that balances pain control, opioid use, and passive range of motion of the prosthetic joint
- Although functional outcomes were suboptimally studied, the combination of femoral and sciatic nerve block was judged to be the overall best approach

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modalities for TKA. It would be prohibitively expensive and impractical to conduct a randomized trial simultaneously comparing them all.

Network meta-analysis (NMA) extends the concept of the traditional meta-analysis to produce pairwise comparisons and relative treatment effects across a range of interventions through direct and indirect comparisons.[5] The method allows comparisons among treatment modalities that have never been directly compared, increases precision, and provides a relative ranking of all modalities while properly accounting for correlations between effect sizes from multiarm trials.[6,7] Experts consider NMA to be the best method for summarizing and evaluating available evidence, and many consider it to be the highest level of evidence in treatment guidelines.[8]

We thus conducted an NMA to evaluate and rank available interventional analgesic modalities for TKA in terms of efficacy and safety. We defined the optimal modality as the one that best balances low pain scores, low opioid consumption, and a large knee range of motion during the initial 72 postoperative hours.

Materials and Methods

We registered our study in the International Prospective Register of Systematic Reviews (CRD42015015870) on January 13, 2015, and the protocol was published at the "Multiple-treatments Meta-analysis" Web site (http://www.mtm.uoi.gr/index.php/material-from-publications-software-and-protocols). Our presentation follows Preferred Reporting Items for Systematic Reviews and Meta-analyses guidelines for reporting NMA.[9]

Criteria for Considering Studies for This Review

Inclusion Criteria. We included randomized clinical trials that evaluated pain management efficacy, quality of recovery (*e.g.*, nausea and vomiting), and rehabilitation profile after TKA using any of the following interventional techniques:

1. *neuraxial analgesia*: epidural analgesia (EA) and spinal analgesia
2. *peripheral nerve blocks* (single dose or continuous infusion): three-in-one nerve block or femoral nerve block (F), fascia iliaca compartment block (FIC), sciatic nerve (S), obturator nerve (O), lumbar plexus (psoas) block (LP), and adductor canal block (ACB)
3. *periarticular local anesthetic infiltration*, including intraarticular, subcutaneous, and periarticular infiltration (PA)
4. *auricular acupuncture* (*AA*)
5. *intravenous patient-controlled analgesia* (*PCA*)
6. *placebo*, including systematic opioid not given *via* PCA

Exclusion Criteria.

1. oral analgesic trials.
2. arthroscopic procedures.
3. studies that included both knee and hip arthroplasties and did not separately present the results of each.
4. studies that combined interventions from different categories such as epidural with peripheral nerve block, epidural with local infiltration, or peripheral nerve block with local infiltration; however, we included studies that evaluated more than one intervention from the same category (*e.g.*, femoral with sciatic nerve blocks)

Types of Outcome Measures

- **primary outcomes:** (1) acute postoperative pain (during rest and movement); (2) postoperative opioid consumption; and (3) quality of early postoperative rehabilitation (functional assessments)
- **secondary outcomes:** postoperative complications (*e.g.*, nausea, vomiting, falls), duration of hospitalization, blood loss, procedure failure, and patient withdrawal

Information Sources and Search Strategy

The search was conducted as recommended by the International Society for Pharmacoeconomics and Outcomes Research 2011 Task Force.[10]

The following databases were searched: MEDLINE *via* PubMed, Embase, the Cochrane Library, and Web of Science's Core Collection (excluding MEDLINE) and SciELO Citation Index with the last update on July 15, 2016. The search was not limited by language or date. We searched www.clinicaltrials.gov for ongoing studies and contacted the authors of the ongoing studies. We also searched major anesthesiology and orthopedic journals for online-first publications after the date of conducting the literature search. The search strategies are available in the supplemental digital content.

Statistical Analysis

Herein, we briefly summarized our methodology for space considerations, while further details (study selection, data collection and management, assessment for risk of bias, geometry of the network, planned methods for analysis, assessment of inconsistency, risk of bias across studies, sensitivity analysis, and the Grading of Recommendations Assessment, Development and Evaluation [GRADE] assessment) are available in our original protocol (see study protocol, Supplemental Digital Content, http://links.lww.com/ALN/B404).

A key assumption in NMA is transitivity; that is, effect modifiers are comparably distributed across treatment comparisons, making use of indirect evidence valid.[7] We used PCA as a reference treatment in all analyses. Each of the primary outcomes was measured at multiple time points. For each intervention, we synthesized the summary estimates *versus* PCA from all time points to get an overall summary estimate and to obtain a hierarchy of interventions based on these overall measures. The pooled effect sizes on different time points for each modality were further synthesized to obtain an overall weighted average using inverse variance as weights. A limitation of this approach is effect sizes between time points are inherently correlated. and this was ignored during the synthesis. We checked for inconsistency by

comparing direct and indirect estimates in each loop (loop-specific approach), using node splitting[11] and a global chi-square test[12] for inconsistency.

For all outcomes, we computed the relative effectiveness between all pairs of interventions and presented them in league tables.[13] We estimated the treatment effects of the competing interventions using standardized mean differences for continuous outcomes and odds ratios for dichotomous outcomes.

We used the surface under the cumulative ranking curve (SUCRA) values and rankograms to present the hierarchy of interventions for each outcome.[14] SUCRA values show the percentage of effectiveness each intervention achieves compared to an imaginary best intervention, which is always the best without uncertainty. Hence, a SUCRA of 0.9 means that the specific intervention achieves 90% of the effectiveness of an imaginary ideal intervention, whereas a SUCRA of 0.4 suggests it achieves only 40% of the effectiveness of the ideal intervention and there is much room for improvement. Generally, SUCRA values are interpreted as probabilities, and the larger the probability, the better the treatment. A rankogram plots the probabilities for treatments to assume any of the possible ranks. We evaluated the magnitude of heterogeneity based on the empirical distributions derived by Turner *et al.*[15] and Rhodes *et al.*[16] for dichotomous and continuous outcomes, respectively.

As a sensitivity analysis, we considered pain at rest at 24 h since we considered it the single most important outcome and was the one most often reported. Our sensitivity analyses consisted of excluding studies with an overall high risk of bias, studies that reported median instead of mean (assuming the data were not normally distributed), and studies for which we imputed SD. We originally planned metaregression analyses but were unable to use this approach because there were too few studies for most treatment modalities, thus risking an underpowered and misleading analysis.

Quality of the studies we included was evaluated using the modified GRADE tool for NMAs as developed by Salanti *et al.*[17] The quality results were classified as follows: *high quality*, further research is very unlikely to change the confidence in the estimate of effect; *moderate*, further research is likely to have an important impact on the confidence in the estimate of effect and may change the estimate; *low*, further research is very likely to have an important impact on the confidence in the estimate of effect and is likely to change the estimate; and *very low*, where any estimate of effect is highly uncertain.[18]

Results

Among 3,121 references initially identified, we included 170 randomized controlled trials with 12,530 patients (see Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram, Supplemental Digital Content, http://links.lww.com/ALN/B404). We used unpublished data from only one study.[4] These trials were conducted in 35 countries, with the United States contributing the most (31 trials; 18.2%; see countries contributing to the included trials, Supplemental Digital Content, http://links.lww.com/ALN/B404). The articles were reported in seven languages: 160 English, 3 Chinese, 2 Spanish, 2 Korean, and 1 each in Lithuanian, Russian, and Turkish. We identified 17 different treatment modalities in papers published between 1987 and 2016 (fig. 1). The basic demographic characteristics and the treatment abbreviations are presented in table 1. We explored for transitivity in the network and found no reason to believe that it was violated.

Detailed study characteristics are presented in the supplemental digital content (see studies characteristics table, Supplemental Digital Content, http://links.lww.com/ALN/B404). Only 42 (25.3%) trials described the surgical technique used; the standard medial parapatellar approach was the most commonly reported, followed by midline and mini-subvastus approaches. Only four trials mentioned using a fast-track discharge protocol, with three of them being published in 2016. Only six (3.5%) trials included patients having bilateral TKA.

One hundred (58.8%) trials used neuraxial anesthesia. The majority, 87 (51.1%), used only spinal anesthesia; 57 (33.5%) trials used general anesthesia (7 used total intravenous anesthesia and 50 used volatile anesthesia; 16 of them used nitrous oxide in the mixture), while 15% of the trials did not detail the type of anesthesia.

One hundred twenty-one trials (71.1%) included acetaminophen and/or nonsteroidal antiinflammatory adjuvants; 16 trials (9.4%) used gabapentinoids; and 24 of the trials (14.1%) did not specify whether adjuvant analgesia was used. Thirty-five trials (20.6%) were funded, only 8 of them by pharmaceutical companies (4.7%).

Risk of Bias Assessment

Risk of bias within studies is presented in the supplemental digital content (see risk of bias assessment using Cochrane tool, Supplemental Digital Content, http://links.lww.com/ALN/B404). The most common risk was incomplete blinding of participants and personnel (fig. 2) with two thirds of studies considered to be at high risk of bias, possibly explained by the difficulty of blinding personnel who are performing two different blocks in each patient. We thus exempted this parameter from scoring and classified studies to be overall at high risk of bias only when they also demonstrated a high risk of bias in at least one other domain. Comparisons having high risk of bias are shown with red edges in figure 3. The network structure for all outcomes is presented in the supplemental digital content (see network geometries, Supplemental Digital Content, http://links.lww.com/ALN/B404).

Synthesis of Results

For all outcomes at each specific time, we present league tables, SUCRA ranking, heterogeneity assessment, and inconsistency analyses in the supplemental digital content (see treatment efficacy [league] tables, SUCRA tables for primary outcomes, heterogeneity of all outcomes' NMA, and inconsistency plots and node-splitting assessment [with pairwise meta-analyses], Supplemental Digital Content, http://links.lww.com/ALN/B404). In the rest of the Results section

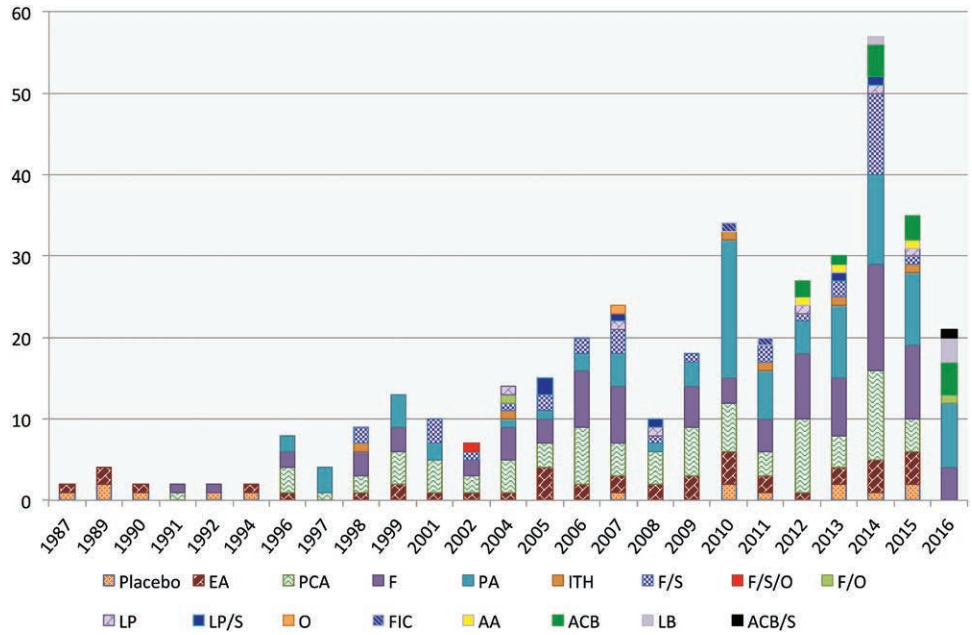

Fig. 1. History of treatment modalities appearance and frequency. *Y-axis* represents the number of groups per year. AA = auricular acupuncture; ACB = adductor canal block; ACB/S = adductor canal block plus sciatic; EA = epidural analgesia; F = femoral nerve block; FIC = fascia iliaca compartment block; F/O = femoral nerve plus obturator nerve; F/S = femoral nerve plus sciatic nerve; F/S/O = femoral plus sciatic plus obturator; ITM = intrathecal morphine; LB = liposomal bupivacaine infiltration; LP = lumbar plexus (psoas) block; LP/S = lumbar plexus (psoas) plus sciatic block; O = obturator nerve block; PA = periarticular infiltration; PCA = patient-controlled analgesia; Placebo = placebo (systemic opioids).

Table 1. Treatment Groups' Demographic Characteristics

Treatment Modality	No. of Groups	No. of Patients	Age (yr)	Male	Female	Weight (kg)	BMI (kg/m^2)	Year First RCT Published
Placebo (systemic opioids)	15	397	64.3±9.9	134	182	85.4±13.6	30.7±2.9	1987
Epidural analgesia	43	1,363	67.5±7.6	386	592	71.8±14.3	27.5±3.8	1987
Patient-controlled analgesia	83	2,515	67.8±7.6	829	1,526	69.0±11.3	28.1±3.5	1991
Femoral nerve block	83	2,509	66.7±8.8	831	1,606	76.6±10.7	28.0±3.6	1991
Periarticular infiltration	88	3,097	68.4±7.4	953	1,816	70.0±12.3	28.5±4.7	1996
Intrathecal morphine	15	382	68.1±10.3	62	83	78.2±14.6	29.2±4.5	1998
Femoral nerve + sciatic nerve	32	898	66.7±7.4	331	549	81.3±11.8	29.9±4.5	1998
Femoral + sciatic + obturator	1	24	68.9	9	15	NA	NA	2002
Lumbar plexus (psoas) block	8	254	65.1±8.3	107	144	83.5±10.4	29.3±4.6	2004
Femoral nerve + obturator nerve	2	56	71.0±8.5	19	40	NA	29.3±4.6	2004
Obturator nerve block	1	20	72.0±1.8	4	16	NA	NA	2007
Lumbar plexus (psoas) + sciatic block	4	155	70.3	40	115	73.0±10.3	28.0±4.4	2007
Fascia iliaca compartment block	2	71	66.8±5.5	29	42	NA	NA	2010
Auricular acupuncture	3	106	67.5±7.6	24	82	66.5±9.5	27.2±3.9	2012
Adductor canal block	13	499	65.6±8.8	174	246	81.3±11.8	30.9±5.1	2012
Liposomal bupivacaine infiltration*	4	163	66.3±8.0	60	103	90.0±10.6	32.2±9.4	2014
Adductor canal block + sciatic	1	21	72.0±11.8	12	9	80.0±16.3	29.0±5.9	2016
Total/summary	398	12,530	67.3±8.0	3,993	7,157	74.7±11.9	28.7±4.4	

Age, weight, and body mass index (BMI) presented as mean ± SD. Genders presented as numbers and (percentage). The treatment modalities arranged from the oldest to newest (based on the year the first randomized controlled trial [RCT] was published). Note that the sum of sex is not always identical with the total number of patients as some studies did not report the sex distribution.

*Exparel®, Pacira Pharmaceuticals, Inc., USA.

NA = not available.

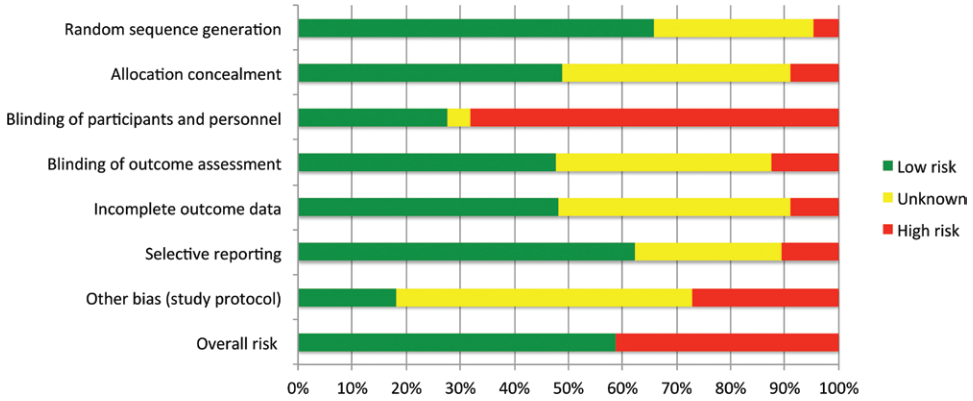

Fig. 2. Risk of bias assessment: overall risk of bias for all trials included.

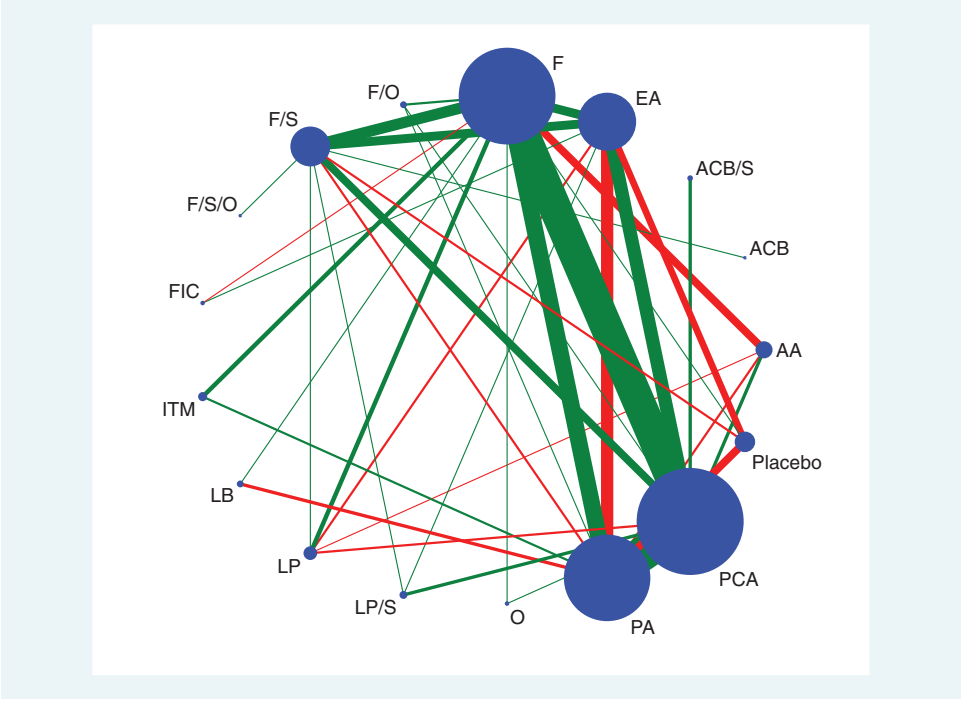

Fig. 3. Network geometry. Network of all the included treatment modalities; the size of the nodes is proportional to the number of patients randomized to each modality and the thickness of the *lines* (*edges*) to the number of direct comparisons. *Green lines* indicate overall low risk of bias in the comparison, while *red lines* indicate high risk of bias. AA = auricular acupuncture; ACB = adductor canal block; ACB/S = adductor canal block plus sciatic; EA = epidural analgesia; F = femoral nerve block; FIC = fascia iliaca compartment block; F/O = femoral nerve plus obturator nerve; F/S = femoral nerve plus sciatic nerve; F/S/O = femoral plus sciatic plus obturator; ITM = intrathecal morphine; LB = liposomal bupivacaine infiltration; LP = lumbar plexus (psoas) block; LP/S = lumbar plexus (psoas) plus sciatic block; O = obturator nerve block; PA = periarticular infiltration; PCA = patient-controlled analgesia; Placebo = placebo (systemic opioids).

we present a summary of overall estimates during the first 72 h after surgery, considering all time points combined. For all outcomes, individual treatment effects in comparison to PCA and rankograms are presented in figures 4 and 5.

Analgesia

Pain at Rest. A total of 147 trials (9,988 patients), which included 17 interventions, were included in this analysis. Treatment rankings based on SUCRA scores, from largest to smallest, were F/O (90), F/S/O (87), LP/S (83), F/S (78), FIC (68), PA (65), liposomal bupivacaine infiltration (LB; 64), ACB (55), LP (49), F (44), O (40), EA (38), ACB/S (38), intrathecal morphine (ITM; 22), AA (18), PCA (10), and finally placebo (1).

We also evaluated the effect of single-shot nerve blocks or PA *versus* continuous infusions. Unsurprisingly, continuous infusions provided better analgesia in every case, but the number of treatment modalities increased from 17 to 25 and yielded less precise and inconsistent results (data not shown).

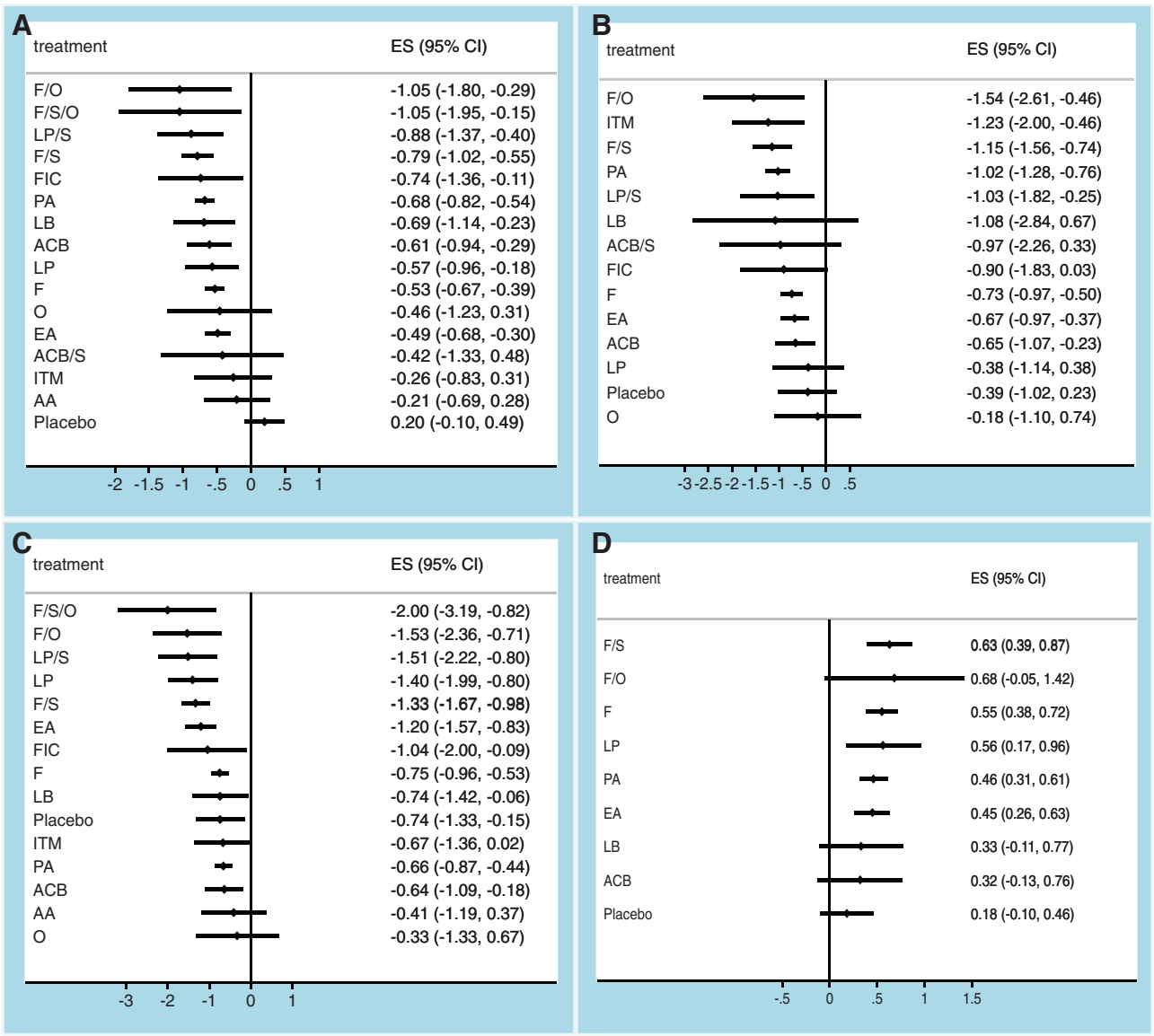

Fig. 4. Treatments effect size (ES) in comparison to patient-controlled analgesia. (*A*) Overall pain scores in the first 72 h during rest, (*B*) overall pain scores in the first 72 h during movement, (*C*) overall opioid consumption in the first 72 h, and (*D*) overall range on motion in the first 72 h. AA = auricular acupuncture; ACB = adductor canal block; ACB/S = adductor canal block plus sciatic; EA = epidural analgesia; F = femoral nerve block; FIC = fascia iliaca compartment block; F/O = femoral nerve plus obturator nerve; F/S = femoral nerve plus sciatic nerve; F/S/O = femoral plus sciatic plus obturator; ITM = intrathecal morphine; LB = liposomal bupivacaine infiltration; LP = lumbar plexus (psoas) block; LP/S = lumbar plexus (psoas) plus sciatic block; O = obturator nerve block; PA = periarticular infiltration; Placebo = placebo (systemic opioids).

Pain with Movement. A total of 85 trials (6,148 patients), which included 15 interventions, were included in this analysis. Treatment rankings based on SUCRA scores, from largest to smallest, were F/O (92), ITM (81), F/S (78), PA (69), LP/S (67), LB (63), ACB/S (60), FIC (57), F (46), EA (40), ACB (38), LP (21), placebo (21), O (12), and finally PCA (6).

Opioid Consumption

A total of 109 trials (7,857 patients), which included 16 interventions, were included in this analysis. Treatment rankings based on SUCRA scores, from largest to smallest, were F/S/O (96), F/O (85), LP/S (85), LP (80), F/S (77), EA (69), FIC (58), F (41), LB (39), placebo (39), ITM (34), PA (31), ACB (30), AA (17), O (15), and finally PCA (3).

Rehabilitation Profile

Postoperative rehabilitation assessments varied considerably. Six methods were reported: range of motion (32 studies), degree of flexion (32 studies), quadriceps strength (7 studies), straight leg rising (12 studies), maximum walking distance (6 studies), and time to get up and go (12 studies). We were therefore only able to reliably meta-analyze range

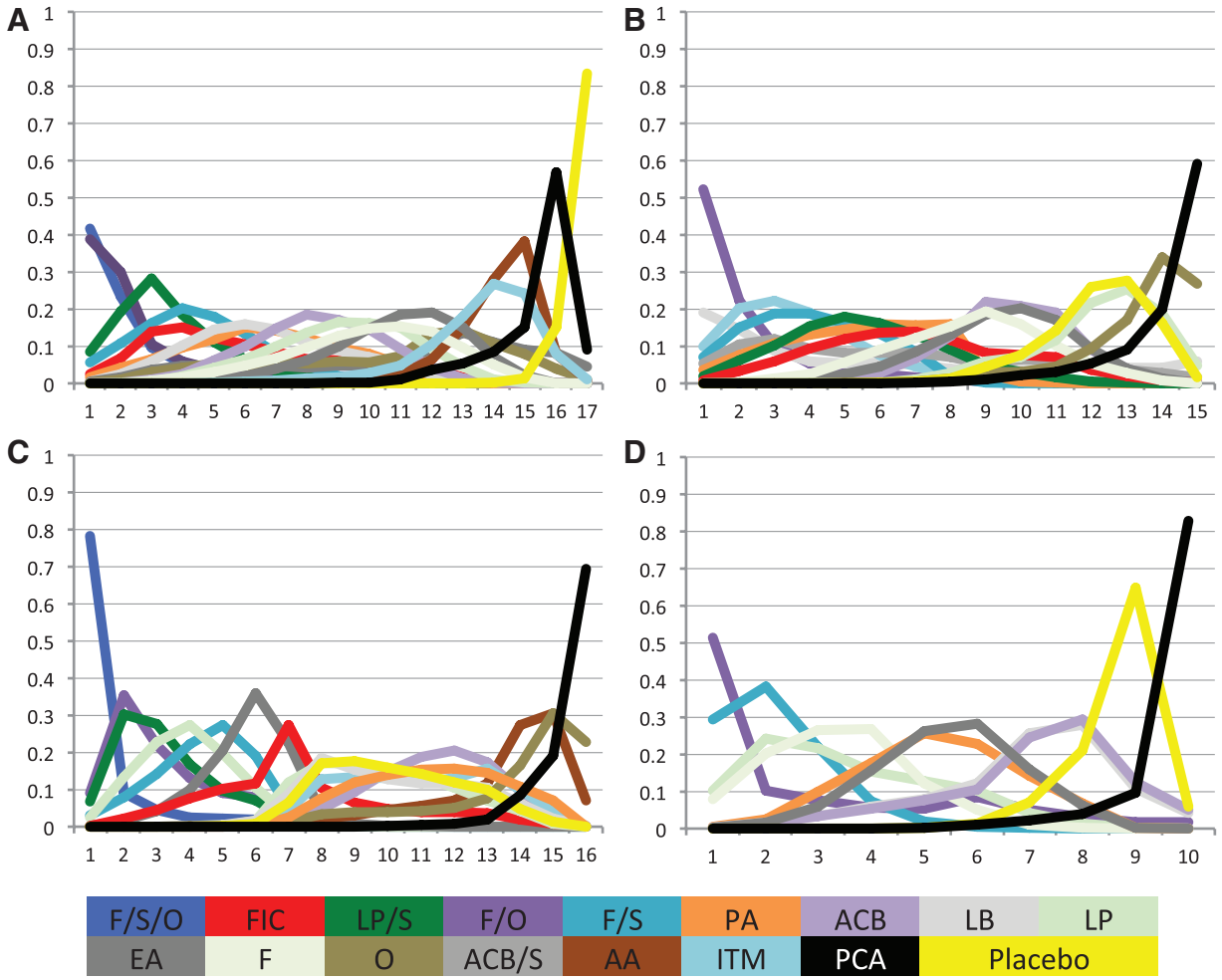

Fig. 5. Rankograms using the probability of being the best method. (*A*) Overall pain scores in the first 72 h during rest, (*B*) overall pain scores in the first 72 h during movement, (*C*) overall opioid consumption in the first 72 h, and (*D*) overall range of motion in the first 72 h. The rank of the compared modality is on the *X-axis*, while the probability of achieving that rank is on the *Y-axis*. The peak of each *line* represents the rank of the modality. For example, placebo (*yellow*) has the highest probability to rank number 17 (*i.e.*, the worst), while F/S/O has the highest probability to rank number 1 for pain at rest. Note: For visual aid, each modality is assigned a specific color. AA = auricular acupuncture; ACB = adductor canal block; ACB/S = adductor canal block plus sciatic; EA = epidural analgesia; F = femoral nerve block; FIC = fascia iliaca compartment block; F/O = femoral nerve plus obturator nerve; F/S = femoral nerve plus sciatic nerve; F/S/O = femoral plus sciatic plus obturator; ITM = intrathecal morphine; LB = liposomal bupivacaine infiltration; LP = lumbar plexus (psoas) block; LP/S = lumbar plexus (psoas) plus sciatic block; O = obturator nerve block; PA = periarticular infiltration; PCA = patient-controlled analgesia; Placebo = placebo (systemic opioids).

of motion and degree of flexion. We combined degree of flexion with range of motion to increase the number of patients. A metaregression did not identify differences between them.

A total of 55 trials (3,887 patients), which included 10 interventions, were included in range-of-motion analysis. Treatment rankings based on SUCRA scores were F/S (87), F/O (79), F (74), LP (73), PA (53), EA (50), LB (34), ACB (33), placebo (15), and finally PCA (3).

Finally, we evaluated each treatment modality combining multiple primary outcomes (pain scores, opioid consumption, and range of motion) using a cluster rankogram (fig. 6). Treatment modalities appearing in the right upper quadrant scored best on both measures: F/S (six times), F/O (six times), LP/S (three times), FIC (three times), PA (two times), F/S/O (once), and LP (once).

Secondary Outcomes (Quality of Recovery and Complications)

We were able to meta-analyze the data for incidence of nausea, vomiting, pruritus, urinary retention, and deep vein thrombosis, as well as the estimated blood loss and length of hospital stay figure 7.

Estimated blood loss. Only 26 trials (1,880 patients), which assessed 9 interventions, reported estimated blood loss (intra- and perioperative). The rankings based on SUCRA were F/S (86.3), PA (67.2), LP/S (66.5), EA (65.5), AA (50.7), F (36.7), ITM (33.1), ACB (25.2), and PCA (19).

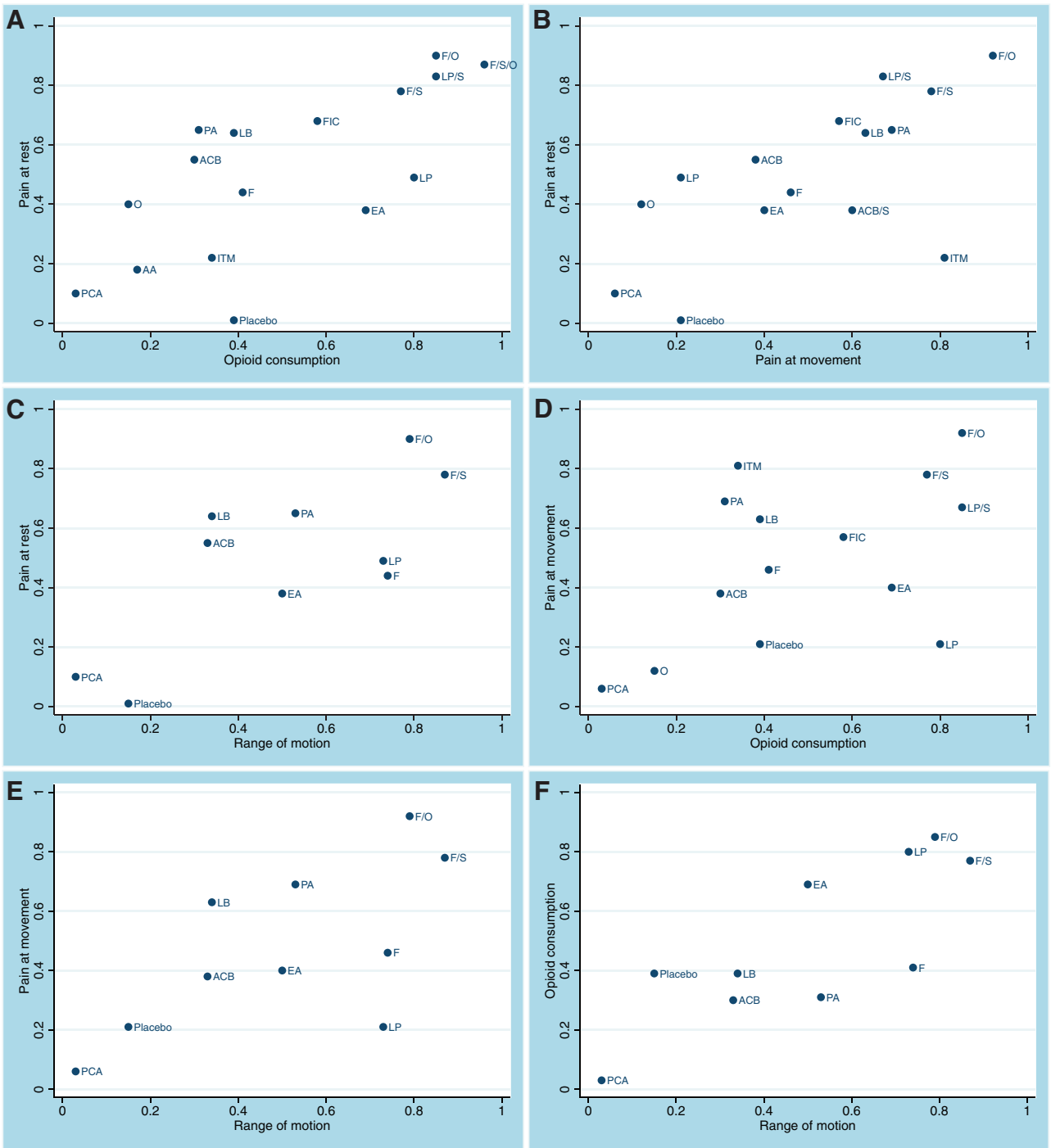

Fig. 6. Clustered ranking plots. All outcomes used for the overall estimation in the first 72 h. Each figure balances two outcomes together: (*A*) pain at rest and opioid consumption, (*B*) pain at rest and pain at movement, (*C*) pain at rest and range of motion, (*D*) pain at movement and opioid consumption, (*E*) pain at movement and range of motion, and (*F*) opioid consumption and range of motion. Modalities that worked best for both outcomes are near the *upper right parts* of each plot. AA = auricular acupuncture; ACB = adductor canal block; ACB/S = adductor canal block plus sciatic; EA = epidural analgesia; F = femoral nerve block; FIC = fascia iliaca compartment block; F/O = femoral nerve plus obturator nerve; F/S = femoral nerve plus sciatic nerve; F/S/O = femoral plus sciatic plus obturator; ITM = intrathecal morphine; LB = liposomal bupivacaine infiltration; LP = lumbar plexus (psoas) block; LP/S = lumbar plexus (psoas) plus sciatic block; O = obturator nerve block; PA = periarticular infiltration; PCA = patient-controlled analgesia; Placebo = placebo (systemic opioids).

Incidence of nausea
85 studies, 5777 patients

Rank	Treatment	SUCRA	OR	95% CI
1	AA	95.9	0.10	(0.03,0.27)
2	F/O	90.1	0.14	(0.04,0.55)
3	LP/S	66.5	0.33	(0.06,1.82)
4	F/S	65.1	0.42	(0.25,0.74)
5	ACB	61.5	0.43	(0.18,1.00)
6	F	57	0.49	(0.37,0.67)
7	PA	56.5	0.49	(0.37,0.67)
8	FIC	51.4	0.52	(0.07,4.06)
9	Placebo	49	0.55	(0.27,1.11)
10	LB	40.6	0.64	(0.22,1.82)
11	ITM	37.5	0.68	(0.33,1.35)
12	LP	35.4	0.70	(0.30,1.65)
13	PCA	17.2	Reference	
14	O	16.2	1.22	(0.33,4.95)
15	EA	10.1	1.22	(0.82,1.82)

Incidence of vomiting
34 studies, 2178 patients

Rank	Treatment	SUCRA	OR	95% CI
1	LB	83.8	0.21	(0.03,1.35)
2	F/O	82.2	0.23	(0.05,1.22)
3	PA	72.6	0.41	(0.22,0.74)
4	F	68	0.45	(0.27,0.74)
5	F/S	63.1	0.48	(0.20,1.22)
6	Placebo	60.4	0.50	(0.22,1.22)
7	ACB	35.1	0.87	(0.27,2.72)
8	LP/S	29.8	1.11	(0.15,8.17)
9	ITM	28.7	0.90	(0.33,2.46)
10	LP	28.3	1.00	(0.30,3.32)
11	EA	24.5	1.00	(0.55,1.82)
12	PCA	23.5	Reference	

Incidence of pruritus
42 studies, 2906 patients

Rank	Treatment	SUCRA	OR	95% CI
1	LP/S	96	0.07	(0.01,0.74)
2	AA	74.5	0.31	(0.02,3.67)
3	F	69	0.60	(0.30,1.22)
4	F/S	65.7	0.61	(0.20,1.82)
5	PA	65.3	0.65	(0.33,1.35)
6	ACB	52.9	0.81	(0.20,3.32)
7	PCA	42.9	Reference	
8	LP	40.7	1.11	(0.17,7.39)
9	EA	40.5	1.11	(0.50,2.23)
10	Placebo	33.4	1.35	(0.41,4.06)
11	LB	33.2	1.65	(0.20,13.46)
12	O	26	2.46	(0.15,36.60)
13	ITM	9.8	3.00	(1.11,7.39)

Length of hospital stay (days)
58 sttudies, 4383 patients

Rank	Treatment	SUCRA	SMD	95% CI
1	ACB	81.1	-0.9	(-1.7,0.0)
2	LP/S	70.8	-0.7	(-1.9,0.4)
3	PA	68.9	-0.6	(-1.0,-0.2)
4	LB	65	-0.6	(-1.6,0.4)
5	Placebo	55.7	-0.4	(-1.3,0.5)
6	F/S	54.2	-0.4	(-1.2,0.4)
7	ITM	48.8	-0.3	(-2.0,1.4)
8	F	47.4	-0.3	(-0.7,0.1)
9	EA	43	-0.3	(-0.8,0.3)
10	LP	41.1	-0.2	(-1.4,1.0)
11	PCA	22.9	Reference	
12	O	1.2	1.6	(0.1,3.2)

Incidence of urinary retention
42 studies, 2935 patients

Rank	Treatment	SUCRA	OR	95% CI
1	AA	88.9	0.21	(0.07,0.61)
2	LP	77.6	0.30	(0.06,1.49)
3	LP/S	72.5	0.25	(0.01,5.47)
4	F/S	69.9	0.45	(0.20,1.00)
5	F	61.3	0.55	(0.30,1.00)
6	ITM	54.3	0.61	(0.18,2.01)
7	PA	47.7	0.67	(0.37,1.35)
8	PCA	30.6	Reference	
9	EA	22.4	1.22	(0.61,2.72)
10	Placebo	15.5	1.82	(0.41,9.03)
11	O	9.5	2.46	(0.67,9.97)

Incidence of deep vein thrombosis
27 studies, 2408 patients

Rank	Treatment	SUCRA	OR	95% CI
1	F/S	74.3	0.22	(0.01,4.48)
2	Placebo	66.4	0.45	(0.03,5.47)
3	EA	56.8	0.74	(0.41,1.22)
4	ACB	50.9	0.74	(0.01,40.45)
5	PA	50.5	0.82	(0.45,1.49)
6	ITM	48.5	0.82	(0.01,44.70)
7	LP/S	48.4	0.82	(0.03,27.11)
8	F	39.3	1.11	(0.37,3.00)
9	PCA	38.3	Reference	
10	LP	26.7	2.46	(0.09,66.69)

Fig. 7. Secondary outcome ranking and effect size in comparison to patient-controlled analgesia (PCA). 95% CI that includes 0 is not statistically significant when compared to PCA. Note: For visual aid, each modality is assigned a specific color. AA = auricular acupuncture; ACB = adductor canal block; EA = epidural analgesia; F = femoral nerve block; FIC = fascia iliaca compartment block; F/O = femoral nerve plus obturator nerve; F/S = femoral nerve plus sciatic nerve; ITM = intrathecal morphine; LB = liposomal bupivacaine infiltration; LP = lumbar plexus (psoas) block; LP/S = lumbar plexus (psoas) plus sciatic block; O = obturator nerve block; OR = odds ratio; PA = periarticular infiltration; Placebo = placebo (systemic opioids); SMD = standardized mean difference; SUCRA = surface under the cumulative ranking curve.

Wound infection. Only 40 trials (2,945 patients), which assessed 9 interventions, reported on the incidence of wound infection. We were not able to meta-analyze them because of frequent zero events. The most common incidence was reported with PA 2.05% (n = 24 of 1,175), followed by EA 1.23% (n = 3 of 242), and then F 0.17% (n = 1 of 579), PCA 0.14% (n = 1 of 702), AA 0% (n = 0 of 30), FIC 0% (n = 0 of 51), LP 0% (n = 0 of 29), ITM 0% (n = 0 of 53), and placebo 0% (n = 0 of 114).

Falls. Only 18 trials (1,567 patients), which assessed 7 interventions, reported on the incidence of falls. We were not able to meta-analyze them because of frequent zero events. The most common fall incidence was reported with placebo 3% (n = 1 of 33), followed by F/S 2.28% (n = 7 of 306), all used infusion; and then F 0.18% (n = 1 of 554), with infusion block; ACB 0% (n = 0 of 216); EA 0% (n = 0 of 103); PA 0% (n = 0 of 243); and PCA 0% (n = 0 of 112).

Delirium. Only three trials reported postoperative delirium. The incidence of delirium was highest with placebo 24% (n = 6 of 25) with most of the data from a single study in 1994, followed by EA 12.6% (n = 11 of 87) with most patients (n = 5) from a study in 1994, then PA 9.8% (n = 7 of 71), and least with F 0% (n = 0 of 21).

Nerve injury or palsy. Nerve injury was not reported in any trial. However, five trials reported transient peroneal nerve palsy on three modalities, which recovered within days to weeks. F/S 7.6% (n = 6 of 79) presumably from the sciatic block and PA 6.4% (n = 13 of 201) presumably from the posterior knee infiltration, and finally EA 1.6% (n = 1 of 61).

Intervention failure. Only 56 trials (5,582 patients), which assessed 13 interventions, reported intervention failure. We were unable to meta-analyze them because of frequent zero events. The most common intervention failures were reported with F/S/O 20% (n = 6 of 30), all from single trial; followed by LP 7.69% (n = 11 of 143) and LP/S 7.65% (n = 15 of 196); and then EA 6.5% (n = 42 of 644); ACB/S 4.5% (n = 1 of 22), all from single trial; PA 2.7% (n = 22 of 819); F 2.7% (n = 39 of 1,437); F/S 2% (n = 14 of 682); ACB 1.6% (n = 7 of 437); PCA 0.3% (n = 3 of 987); F/O 0% (n = 0 of 33); ITM 0% (n = 0 of 47); and placebo 0% (n = 0 of 137). Most failures were related to catheter dislodgement or dysfunction.

Withdrawal from study. Only 14 trials (863 patients), which assessed 8 interventions, reported patient withdrawal from the study. We were unable to meta-analyze them because of frequent zero events. The most common withdrawals were with PA 4.5% (n = 9 of 197), followed by AA 3.3% (n = 1 of 30), ACB 3.3% (n = 3 of 91), F 2.3% (n = 4 of 172), PCA 1.8% (n = 3 of 164), F/S 1.6% (n = 2 of 120), placebo 1.6% (n = 1 of 62), and ITM 0% (0 of 27).

Patient satisfaction. Only 26 trials (1,570 patients), which assessed 10 interventions, reported patient satisfaction. We were unable to meta-analyze them because of marked heterogeneity in the methods patient satisfaction was assessed. Studies assessed satisfaction on scales of 100, 10, 6, 5, 4, and 3, making it impossible to reliably combine them for analysis.

Sensitivity Analysis

We conducted sensitivity analyses for pain at rest at 24 h by excluding studies at high risk of bias (n = 45), studies that reported median instead of mean (n = 26), and studies for which we imputed SD (n = 24). A total of 69 (from 144) remained in the analysis. Overall treatment ranking and direction were not markedly affected. The SUCRA rankings were F/S (76.3), FIC (73.6), LP (68.7), PA (65.9), ACB (64.1), LB (61.1), F (59.8), LP/S (57.1), O (44.6), EA (39.7), AA (29.4), ITM (28.9), placebo (19.5), and PCA (11.1). Inconsistency test (P = 0.85) and heterogeneity SD remained reasonable at 0.81 (see sensitivity analyses, Supplemental Digital Content, http://links.lww.com/ALN/B404).

GRADE Evaluation

GRADE evaluations were conducted only for pain at rest at 24 h (table 2). Other outcomes will have equal or worse quality.

Study Limitations (Risk of Bias)

A contribution matrix showing the contribution of each direct and indirect comparisons to the network[19] is provided in the supplemental digital content (see GRADE analyses, Supplemental Digital Content, http://links.lww.com/ALN/B404). More than 90% of the data in the NMA came from studies judged to be at low risk of bias. The majority of data contributing to the F/S modality came from low-risk studies (fig. 3).

Indirectness

Baseline characteristics did not differ across various comparisons; however, we did not have sufficient studies to properly assess the transitivity assumption for each comparison.

Inconsistency

We reported heterogeneity and inconsistency for every analysis presented in the Results section and in the supplemental digital content (see heterogeneity of all outcomes' NMA and inconsistency plots and node-splitting assessment [with pairwise meta-analyses], Supplemental Digital Content, http://links.lww.com/ALN/B404). Heterogeneity was reasonable for most outcomes. Only a few loops had inconsistent results per outcome. Neither chi-square analysis nor the node-split approach provided evidence for inconsistency.

Imprecision

Some estimates of relative effects are associated with uncertainty (table 2).

Publication Bias

We inspected for small-study effects in trials involving PCA. The comparison-adjusted funnel plot[6] is shown in the supplemental digital content (see GRADE analyses, Supplemental Digital Content, http://links.lww.com/ALN/B404), which shows signs of small study effects. Egger test also showed that smaller trials are associated with larger effects. PCA-based comparison studies contributed by 28.2% of the data in the NMA.

Discussion

Optimal pain management modalities after TKA need to provide excellent analgesia for this otherwise extremely painful procedure. Reducing postoperative opioid consumption potentially reduces opioid-related side effects, including respiratory depression, and may limit opioid tolerance.[20] Suitable analgesia may also reduce the risk of chronic postsurgical pain lasting more than 6 months after surgery, which is strongly associated with the intensity of acute postoperative pain.[21] And finally, optimal pain management modality also allows a large range of motion, which facilitates physical therapy and speedy functional recovery. All these factors need to be balanced when choosing the optimal modality.

Our systematic analysis of post-TKA pain summarizes worldwide efforts during the last three decades to identify optimal analgesic strategies for this common and painful operation. Our results suggest that the combination of femoral and sciatic nerve blocks is the best modality for almost all outcomes. Our results also indicate that modalities that provide the best analgesia and minimize opioid consumption generally perform better in other respects, including quality of rehabilitation. In contrast, PCA or systemic analgesia alone was consistently poor.

The nerve supply to the skin of the knee comes from the femoral nerve, obturator nerve, tibial nerve, and common peroneal nerves (the last two being branches of the sciatic nerve). The nerve supply of the knee joint can be divided into (1) the anterior group, consisting of the articular branches of the femoral, common peroneal, and saphenous nerves, and (2) the posterior group, consisting of the posterior articular branch of the tibial nerve and obturator nerves. Figure 8 illustrates lower extremity innervation and the site of action of each modality.

Table 2. GRADE Assessment for Pain at Rest in the First 24 h

Direct Comparisons	Number Compared Directly	Contribution to the Network (%)	Confidence	Reason for Downgrading
AA *vs.* PCA	3	4.3	Moderate	Imprecision
ACB *vs.* F	6	3	High	
ACB *vs.* LP	1	3	Moderate	Imprecision
ACB *vs.* PA	2	0.5	Moderate	Imprecision
ACB *vs.* PCA	2	2.6	Moderate	Imprecision
ACB/S *vs.* F/S	1	4.3	Moderate	Imprecision
EA *vs.* F	6	2.1	High	
EA *vs.* F/S	4	0.4	High	
EA *vs.* FIC	1	2	Moderate	Imprecision
EA *vs.* LP	2	2.2	Low	Risk of bias, imprecision
EA *vs.* LP/S	1	1.9	Moderate	Imprecision
EA *vs.* PA	9	1.1	High	
EA *vs.* PCA	7	4	High	
EA *vs.* Placebo	5	1.7	High	
F *vs.* F/O	1	2.6	Moderate	Imprecision
F *vs.* F/S	8	8.2	High	
F *vs.* FIC	2	3.2	Moderate	Imprecision
F *vs.* ITM	2	0.9	Moderate	Imprecision
F *vs.* LB	1	2.3	Moderate	Imprecision
F *vs.* LP	3	1.7	Moderate	
F *vs.* O	1	2.4	Moderate	Imprecision
F *vs.* PA	12	4.3	High	
F *vs.* PCA	24	2.8	Moderate	Publication bias
F *vs.* Placebo	1	1.3	Low	Risk of bias, imprecision
F/O *vs.* PA	1	2.5	Moderate	Imprecision
F/S *vs.* F/S/O	1	4.3	Low	Risk of bias, imprecision
F/S *vs.* LP	1	1.9	Moderate	Imprecision
F/S *vs.* LP/S	1	1.9	Moderate	Imprecision
F/S *vs.* PA	2	1.2	Moderate	Imprecision
F/S *vs.* PCA	4	4	High	
F/S *vs.* Placebo	2	0.7	Moderate	Imprecision
ITM *vs.* PA	2	3.9	Moderate	Imprecision
LB *vs.* PA	3	4.2	Moderate	Imprecision
LP *vs.* PCA	2	0.4	Moderate	Imprecision
LP/S *vs.* PCA	2	2.2	Moderate	Imprecision
O *vs.* PCA	1	2.4	Low	Imprecision, publication bias
PA *vs.* PCA	29	5.5	Moderate	Publication bias
PA *vs.* Placebo	7	2.1	High	
Ranking of treatments*			Low	Imprecision, publication bias

*Eight percent of the data in this network meta-analysis came from trials with high risk of bias. Publication bias only assessed with patient-controlled analgesia (PCA) studies.

AA = auricular acupuncture; ACB = adductor canal block; ACB/S = adductor canal block plus sciatic; EA = epidural analgesia; F = femoral nerve block; F/O = femoral nerve plus obturator nerve; F/S = femoral nerve plus sciatic nerve; F/S/O = femoral plus sciatic plus obturator; FIC = fascia iliaca compartment block; ITM = intrathecal morphine; LB = liposomal bupivacaine infiltration; LP = lumbar plexus (psoas) block; LP/S = lumbar plexus (psoas) plus sciatic block; O = obturator nerve block; PA = periarticular infiltration; Placebo = placebo (systemic opioids).

Femoral nerve blocks are among the oldest blocks used for TKA analgesia because they are easy to perform and provide good analgesia over the anteriomedial aspect of the thigh. We found that femoral nerve block alone was less effective in terms of pain control and opioid consumption than when femoral blocks were combined with other nerve blocks (*i.e.*, F/S, F/S/O, F/O, FIC, LP, LP/S). Femoral block was associated with less opioid consumption than PA, which is unsurprising considering the relevant anatomy. Recently, clinicians have become concerned that motor block consequent to femoral nerve blocks may impair active rehabilitation and increase the risk of falls.[22,23] Overall, the reported incidence of falls was low (0.18%), but most trials did not comment on the incidence of falls and falls may not have been sought in many. All falls were reported in patients given local anesthetic infusions, which is consistent with falls not being considered an outcome or sought in trials with shorter follow-up periods. Limitations of the underlying studies preclude firm conclusions about the overall incidence of falls, much less which techniques might predispose falls.

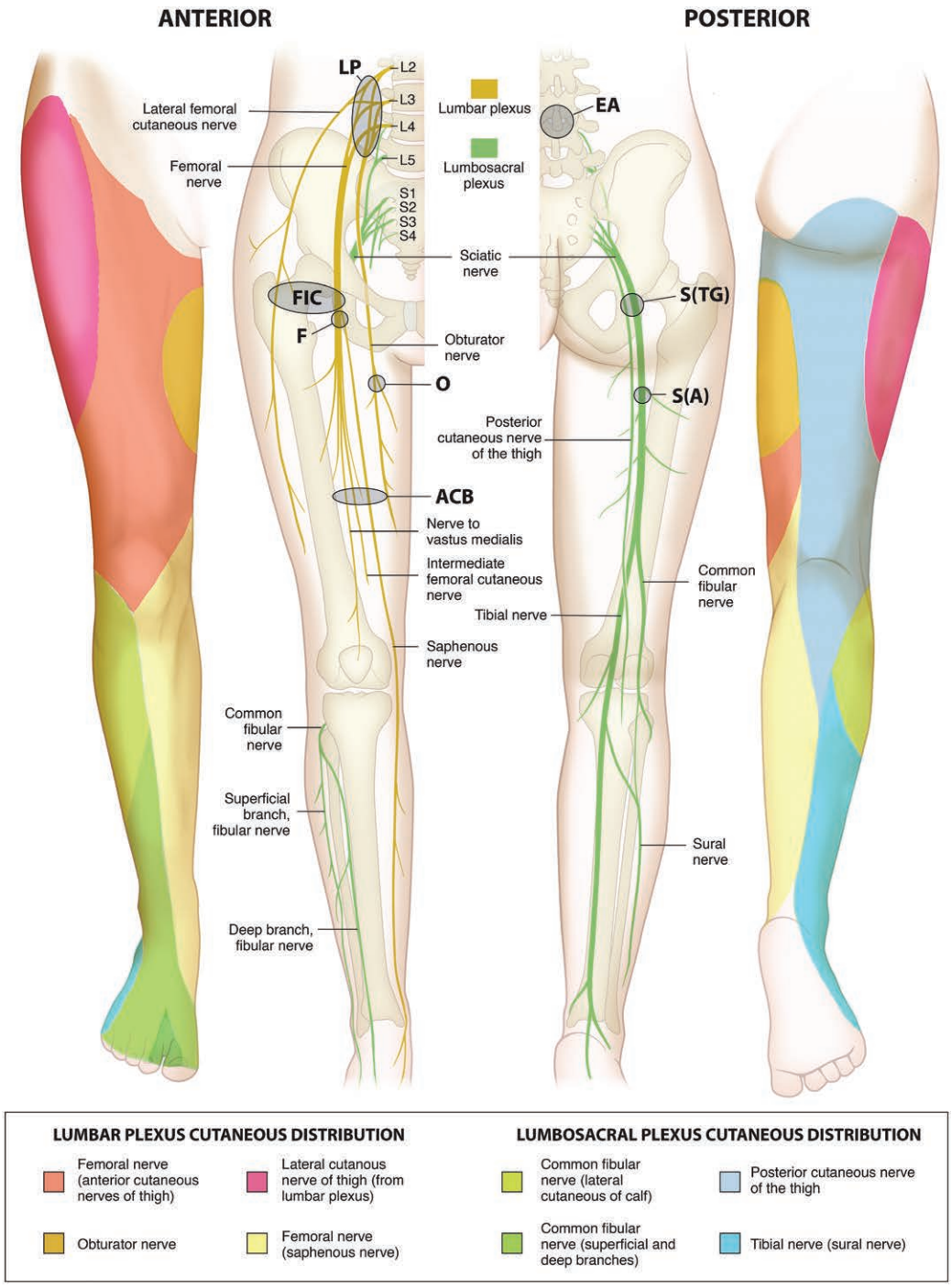

Fig. 8. Lower limb innervation and dermatomes relevant to knee surgery. *Adductor canal block* (*ACB*) involves injection of solution into the adductor canal deep to the sartorius muscle, at the mid-thigh level; it mainly involves the saphenous nerve and the nerve to vastus medialis. The canal is also known as Hunter canal or the subsartorial canal. It is an aponeurotic intermuscular tunnel in the middle third of the thigh. *Epidural analgesia* (*EA*) involves placing a catheter usually at L3–L4 level. *Fascia iliaca compartment block* (*FIC*) involves blocking both the femoral and lateral femoral cutaneous nerves, as they lie under the iliacus fascia. *Femoral nerve block* (*F*) involves blocking the femoral nerve after it passes underneath the inguinal ligament. At this point, it is usually lateral and slightly deeper than the femoral artery between the psoas and iliacus muscles. *Lumbar* (*psoas*) *plexus block* (*LP*) involves injection of solution into the compartment between the quadratus lumborum and psoas major muscles. It leads to blocking the femoral, lateral femoral cutaneous, and obturator nerves as they run within the psoas major muscle. *Obturator nerve block* (*O*) involves blocking the nerve about 5 to 10 cm beneath the pubic tubercle directly lateral to the tendon of the long adductor muscle. *Sciatic nerve block* (*S*): as the sciatic nerve is large (the largest nerve in the body), it can be blocked at several different locations. Most common approaches are the transgluteal (TG; posteriorly) and the anterior (A) while the patient is in supine position. Note: Common fibular nerve is also known as common peroneal nerve, external popliteal nerve, or lateral popliteal nerve.

The efficacy of adding sciatic nerve blocks to a femoral block remains controversial.[24] Two previous studies, a systematic review,[25] and a pairwise meta-analysis[26] failed to prove that there is a significant advantage to combining the two. In contrast, our study shows that combining sciatic nerve and femoral blocks markedly improved all outcomes. Indeed, the combination of femoral and sciatic blocks was among the best approaches when considering overall outcomes and the underlying quality of evidence. Improvement presumably resulted from providing adequate analgesia to the posterior component of knee pain.

Adding obturator blocks to femoral or femoral and sciatic blocks improved their ranking for pain scores and opioid consumption; however, the obturator block alone was not even superior to PCA. Thus, there is little advantage to an obturator block alone; however, an obturator nerve block may be a useful supplement to a femoral or femoral and sciatic block.

Adductor canal blocks were thought to target the saphenous nerve, articular branches of the obturator nerve, the medial retinacular nerve, and the nerve to the vastus medialis. However, Burckett-St Laurant *et al.*[27] found that both the saphenous nerve and the nerve of the vastus medialis contribute to the innervation of the knee capsule, while the obturator nerve is rarely involved in capsule innervation. The ACB typically covers the anteriomedial aspect of the knee and preserves quadricep function, which presumably enhances postoperative rehabilitation by allowing patients to actively participate in knee movement. Although many studies show that ACBs preserve quadriceps function, it remains unclear whether these blocks reduce the risk of falls after TKA[28] or decrease the time to overall discharge readiness.[29] In our analysis, we found ACB to be similar to femoral blocks alone on pain control and opioid consumption. ACB was not among the top 5 modalities on pain control and opioid consumption, but along with LB, it was one of the highest ranking in terms of hospital duration. We note, though, that hospital length of stay has been decreasing rapidly (see mean duration of hospital stay by year, Supplemental Digital Content, http://links.lww.com/ALN/B404), largely consequent to fast-track programs. For instance, the mean length of stay in 1990 was more than 10 days while it was 2.5 days in 2016—although both ACB and LB were only introduced into clinical practice in 2012. Some of the benefit attributed to ACB and LB may thus result from the overall marked improvement in length of stay in recent years.

The LP is a field approach that consistently blocks the femoral, lateral femoral cutaneous, and obturator nerves as they run within the psoas major muscle.[30] LP block alone was not from the top 5 modalities for pain scores, but it was for opioid consumption. When combined with sciatic block, its efficacy was markedly increased for pain scores, which again highlights the importance of providing posterior analgesia. We note, though, that LP was associated with more block failures than other modalities, highlighting its technical complexity.

Fascia iliaca compartment block is another field approach that targets the femoral and lateral femoral cutaneous nerve.[31] We found the FIC was within the top 5 modalities for pain scores and ranked better than any single nerve block, PA, or EA. This finding is curious since the lateral femoral cutaneous nerve is not known to innervate the knee, making it unclear why blocking the lateral femoral cutaneous nerve reduced both pain scores and opioid consumption. Possibly there is a nonincisional source of pain (*e.g.*, tourniquet site and tissue manipulation). But given the limited number of studies, this intriguing finding should be interpreted with caution.

Epidural analgesia has been considered the definitive standard analgesic modality for TKA,[4] although the method is losing favor because it promotes hypotension, urinary retention, and pruritus.[32] We nonetheless found the EA ranked below various combined nerve blocks for both pain control and opioid consumption and below almost all other modalities for most secondary outcomes. Presumably, poor analgesia results from the dilute local anesthetic (*e.g.*, 0.0625%) that is usually used in an effort to preserve motor function. In contrast, much higher concentrations are used for peripheral nerve block and PA. Our results support the current trend toward alternative analgesic approaches, especially various nerve blocks.

Periarticular infiltration is appealing because it is easier to implement than specialized blocks. Many studies found PA to be superior to other methods during the first 24 h. But during the initial 72 postoperative hours—a more relevant period—we found PA to be better than single nerve blocks for analgesia but not for opioid consumption or range of motion. Combination blocks (*e.g.*, F/S) thus proved better for nearly all outcomes. PA also had the highest rate of joint infection (2%) and study withdrawal (4.5%). Single-injection PA has been criticized for causing rebound pain after the medication wears off,[33] which is consistent with our analysis. Another disadvantage of PA is the possibility of transient foot drop, presumably resulting from posterior popliteal infiltration. For example, Tsukada *et al.*[34] reported that 12% of patients infiltrated with 100 ml (20 ml posterior to the capsule) experienced transient peroneal nerve palsy.

Liposomal bupivacaine (Exparel®, Pacira Pharmaceuticals, Inc., USA) is a relatively new product. We only included four trials that used liposomal bupivacaine for PA. Although any firm conclusion would be premature at this point, LB did not appear to be superior to traditional PA during the initial 72 h. Possible explanations include (1) the volume of LB that can be given safely is relatively small[35] and (2) LB cannot be mixed with other nonliposomal-based anesthetics, as doing so might provoke rapid release of the encapsulated bupivcaine.[36]

We considered three trials of AA at the sympathetic, Shen Men, stomach, and occipital points. While we found AA to be better than placebo and PCA in all tested outcomes, AA was worse than all peripheral nerve blocks, PA, and epidurals

on pain management. AA was, however, among the best ways to prevent postoperative nausea and vomiting.

We were not able to study the local anesthetic adjuvant effects in our study. But there is at least some evidence that opioids (*e.g.*, fentanyl),[37] dexamethasone,[38] and ketorolac (used in PA only so far)[39] enhance block efficacy and duration.

Limitations

By the nature of meta-analysis, our results are limited by the quality of available studies. To the extent that included studies were suboptimally conducted or suffer various biases, the resulting errors will be included in our analysis. Many included studies had small sample sizes and high (or unclear) risk of bias.

We were limited to available studies; many important comparisons have never been studied, and an NMA is only a partial substitute for comparisons that have never been attempted. Some comparisons were based on sparse results and thus lacked power, thus having wide CIs and uncertain ranking.

Rehabilitation remains poorly studied, as its importance has only recently become apparent to investigators. We thus restricted our analysis to passive range of motion, which probably is not the best method of assessing functional recovery. However, it was the only functional outcome reported sufficiently often to include in our analysis.

We found that the best modality for a given outcome was not necessarily the best for others. Consequently, focusing on one outcome could easily lead to selection of a modality that performs poorly with regard to other important outcomes. More comprehensive tools that wisely combine multiple outcomes may be better endpoints for future studies. For example, there are already two nonspecific recovery assessment tools that take a broad approach: the Postoperative Quality Recovery Score[40] and the Postoperative Quality Recovery Scale.[41] Recently, a new composite outcome, "discharge readiness," specific to TKA, was introduced. It includes four parameters: adequate analgesia, intravenous opioid dependence, ability to stand, walk 3 m and sit down, and ability to ambulate 30 m.[29]

Conclusions

Multiple nerve blocks (F/S, F/S/O, F/O, FIC, and LP/S) performed better than single nerve blocks, PA, and EA. Based on the available evidence, the combination of femoral and sciatic nerve block appears be the best overall modality. Although F/S/O and F/O also appear effective, less evidence supports them. Blocking posterior innervation of the knee seems to be more important than previously thought and improves analgesia and overall outcomes.

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Competing Interests

The authors declare no competing interests.

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