SYSTEMATIC REVIEW

Analgesic efficacy of adding the IPACK block to multimodal analgesia protocol for primary total knee arthroplasty: a meta-analysis of randomized controlled trials

Xiumei Tang, Yahao Lai, Siwei Du and Ning Ning*

Abstract
Background: Total knee arthroplasty (TKA) is a standard treatment for end-stage degenerative knee disease. Most patients will experience moderate-to-severe postoperative knee pain, significantly affecting rehabilitation. However, controversy remains regarding the efficacy of adding the interspace between the popliteal artery and capsule of the knee (IPACK) into multimodal analgesia protocol.

Methods: PubMed, Medline, Embase, Cochrane Library, and other databases were searched from inception to February 1, 2021. Studies comparing patients receiving IPACK to patients not receiving IPACK were included. The primary outcome was the ambulation pain score on a visual analogue scale (VAS) of 0–10. Secondary outcomes included pain score at rest, morphine usage, functional recovery, clinical outcomes, and complications.

Results: Thirteen RCTs involving 1347 knees were included. IPACK was associated with lower ambulation pain scores (weight mean difference [WMD] −0.49, 95% confidence interval [CI] −0.72 to −0.26). The benefits were observed from 2 to 4 h, 6 to 12 h, and beyond one week. IPACK also significantly reduced rest pain scores (WMD −0.49, 95% CI −0.74 to −0.24), and the benefits were observed from 6 to 12 h and beyond one week. IPACK reduced the overall morphine consumption (WMD −2.56, 95% CI −4.63 to −0.49). Subgroup analysis found reduced oral morphine consumption from 24 to 48 h (WMD −2.98, 95% CI −5.71 to −0.24) and reduced rate of morphine requirement from 12 to 24 h (relative risk [RR] = 0.51, 95% CI 0.31 to 0.83). Functional recovery outcomes regarding ambulation distances (on the second postoperative day [POD2]) (WMD = 1.74, 95% CI 0.34 to 3.15) and quadriceps muscle strength (at 0 degree) (WMD = 0.41, 95% CI 0.04 to 0.77) favored IPACK. And IPACK reduced the rate of sleep disturbance (on POD 1) (RR = 0.39, 95% CI 0.19 to 0.81). There was no significant difference in the other outcomes.

Conclusions: Moderate-level evidence confirmed that IPACK was related to better results in pain scores, morphine usage, and functional recovery without increasing the risk of complications.

Registration: CRD42021252156.

*Correspondence: ningning6405@163.com

West China School of Nursing, Sichuan University / Department of Orthopaedics, West China Hospital, Sichuan University, Chengdu 610041, P.R. China

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Key points

**Question** Can IPACK as an additional analgesic method provide better results on postoperative knee pain and function recovery for patients after TKA?

**Findings** Moderate evidence suggested that the addition of IPACK to the multimodal analgesia programs had better results on postoperative knee pain VAS scores, morphine usage, ambulation distances, muscle strength, and sleep disturbance without increasing the risk of complications, compared to those without IPACK. However, these differences in pain VAS scores, ambulation distances, and muscle strength were minor and had relative clinical significance. The reduced morphine consumption significantly confirmed the benefits of IPACK.

**Meaning** The combinations of IPACK with other regional analgesia techniques (e.g., PAI, ACB) are recommended as an integral part of multimodal analgesia programs. More trials were needed to confirm the benefits of IPACK in different combinations.

**Keywords:** IPACK block, Total knee arthroplasty, Randomized controlled trial, Meta-analysis

Background

Total knee arthroplasty (TKA) is an effective intervention for end-stage knee diseases and could relieve pain, restore function, and improve patients’ quality of life [1]. However, patients usually experience moderate-to-severe postoperative knee pain [2]. Due to osteophytes removal and soft tissue release on the backside of the knee, posterior knee pain is also a significant issue [3]. Insufficient pain control may hinder early ambulation, hamper the quality of recovery, and increase the utilization of opioids [4].

The interspace between the popliteal artery and capsule of the knee (IPACK) is a novel regional anesthetic approach that could supply analgesic effects on the posterior capsule without compromising muscle strength [5]. Cadaveric data demonstrated that IPACK mainly anesthetizes the articular branches from the tibial and obturator nerves [6]. Several randomized controlled trials (RCTs) reported the benefits of IPACK complemented many regional anesthesia modalities [3, 7–12]. However, these studies yielded conflicting results regarding the use of IPACK for analgesia after TKA. Three studies [7, 10, 13] reported lower pain visual analogue scale (VAS) scores, while the other two studies [3, 14] found similar pain scores with the addition of IPACK. Two studies [12, 15] found longer postoperative ambulation distances in the IPACK group, while the other three studies had contract results [3, 11, 16]. IPACK has been adopted into clinical practice, but the efficacy of IPACK has not been confirmed by synthesized evidence. Two reviews discussed the efficacy of IPACK in the practice of multimodal pain management. However, their conclusions lacked the support of quantity information, and the certainty of evidence cannot be measured. Moreover, previous studies found that the analgesic effect of IPACK usually disappeared within 24 h, while the long-term effects were unclear.

Therefore, we conducted a systematic review and meta-analysis to ascertain the benefit of IPACK in combination with other analgesic methods concerning (1) pain scores (at rest, at ambulation); (2) morphine consumption (amount and frequency); (3) functional recovery (range of motion, muscle strength, ambulation distances, time-up-and-go test time); (4) complications (needle puncture, postoperative nausea, vomiting, sleep disturbance); and (5) clinical outcomes (length of stay, operation duration, patients satisfaction).

Methods

This review was reported according to the criteria of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Additional file 1) [17]. The protocol for this review was registered with the International Prospective Register of Systematic Reviews (PROSPERO—CRD42021252156).

Search strategy

We searched for databases including PubMed, Medline, Embase, the Cochrane Library, Ovid, Web of Science, and websites including Clinicaltrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), and Google Scholar till February 1, 2021. The following terms were used: (IPACK OR “interspace between the popliteal artery and posterior capsule of the knee”) AND (total knee arthroplasty OR knee arthroplasty OR total knee replacement OR knee replacement OR TKA OR TKR) AND ((randomize* control* trial*) OR RCT). No language or date limits were placed on the search. We also used a manual search strategy, checked references,
and contacted authors to identify additional studies. Two authors screened studies with a third author adjudicating in case of disagreement.

**Trial selection**

The studies had to be RCTs comparing TKA patients with IPACK. Any non-RCTs, quasi-RCTs, retrospective studies, cadaver studies, comments, letters, editorials, protocols, guidelines, surgical registries, and review papers were excluded. Follow-up reports at different time points or different comparisons in one trial will be extracted separately. Studies with multiple arms were eligible, as were studies in which multiple regional anesthetic techniques were performed, so long as an IPACK was one of the arms or one of the used techniques. There was no restriction on language or publishing year. Two investigators independently screened titles and abstracts to exclude non-relevant trials. Discrepancies were resolved by a third author. Relevant full-text articles were retrieved and analyzed for eligibility using the pre-defined inclusion criteria.

**Data extraction**

Data were extracted via a standardized spreadsheet according to a pre-agreed protocol. The following information was collected: first author, publication year, country, number of participants in each group, patient demographics, inclusion and exclusion criteria, and conclusions. We collected: interventions, dosages, and types of anesthesia drug administered, the method of analgesia, pain rescue methods, multimodal analgesia protocol, surgeons, prosthesis, approach, follow-up duration, and numbers of patients lost to follow. If data cannot be extracted directly or missing, we will contact the authors by email or calculate data with the Cochrane Review Manager calculator [18]. Two authors independently extracted the information, and any discrepancies were resolved by a third author. Pain scores reported on visual, verbal, or numerical rating scales were converted to a standardized 0–10 scale. All opioids were converted to oral milligram morphine equivalents via an online website (http://opioidcalculator.practicalpainmanagement.com/).

**Outcomes**

The primary outcome was the ambulation pain score. The secondary outcomes were rest pain score, morphine consumption, functional recovery outcomes, clinical outcomes, and complications. The morphine consumption was collected as a continuous variable (amount) and category variable (used or not). The functional recovery outcomes included the range of motion (ROM), quadriceps muscle strength (QMS), ambulation distances, and time-up-and-go test (TUG) time. The clinical outcomes included the length of hospital stay, operation time, and patient satisfaction. The complications were postoperative nausea and vomiting (PONV) and sleep disturbance.

**Subgroup analyses**

Our pre-defined subgroup analysis was based on multiple time points. The subgroups were as closest to 6, to 12, to 24, to 48 h and beyond one week or as the postoperative day (POD) 0, 1, and 2 described in original studies.

**Trial sequential analysis**

We performed Trial Sequential Analysis (TSA) using the TSA program (www.ctu.dk/tsa.) on the three critical outcomes (pain at rest, pain at ambulation, morphine consumption). TSA tests the credibility of the results by combining the estimation of information size (a cumulative sample size of included RCTs) with an adjusted threshold of statistical significance for the cumulative meta-analysis. The required information size (RIS) and meta-analysis monitoring boundaries (Trial Sequential Monitoring Boundaries) were quantified, alongside adjusted 95% confidence intervals. Diversity adjustment was performed according to an overall type I error of 5% and power of 80%.

**Meta-regression**

High heterogeneity not fully explained by subgroup analysis was further investigated with a post hoc mixed-model meta-regression on the primary outcome (pain at ambulation). To avoid overfitting, meta-regression was performed only in the following clinically meaningful and explanatory variables: patient number, the multimodal analgesia protocol, types of other nerve blocks, anesthesia drug.

**Risk of bias assessment and publication bias**

The methodology quality was independently evaluated by two reviewers using the Cochrane Collaboration’s Risk of Bias Tool [19]. The following domains were assessed and evaluated: randomization process, deviation from intended interventions, missing outcome data, measurement of outcomes, and selection of reported results. Each domain can be judged as low risk of bias, high risk of bias, or unclear, and overall risk of bias is expressed on a three-grade scale (low risk of bias, high risk of bias or unclear).

The funnel plots were used to assess publication bias when the included studies were more than 10 in the outcome, and the Egger test was further performed (when visual asymmetry was observed).
Quality of evidence
We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the certainty of the evidence in key outcomes. Study design, risk of bias, imprecision, inconsistency, indirectness, and magnitude of effect were considered. The level of evidence could be divided into four degrees: high, moderate, low, and very low. The rules for downgrade evidence were referenced in Guyatt’s studies [20–25]. We defined the following as critical outcomes: pain at ambulation, pain at rest, morphine consumption amount, the rate of rescue morphine use.

Statistical analysis
Weight mean difference (WMD) for continuous variables (Mantel–Haenszel method) and risk ratios (RR) for dichotomous variables (inverse variance method) with 95% confidence intervals (95% CIs) were used. P values of < 0.05 were considered statistically significant. A random-effect model was used in the study. The heterogeneity was reported by $I^2$ statistics. ($I^2 > 70\%$ was considered as high heterogeneity.) Sensitivity analysis will be applied to examine the effect of deleting one single study on the overall estimate when observed high heterogeneity, and Publication bias was evaluated both by a visual inspection of funnel plots and by Egger test ($p < 0.05$ indicating a possible publication bias) using Egger’s regression intercept to quantify publication bias. The Review Manager 5.3 was used for drafting figures of risk of bias, and STATA 13.0 was used for data analysis.

Results
Study selection, data retrieval, and characteristics
Our search initially yielded 310 potentially relevant papers and 181 articles remaining after duplicates. After title and abstract screening, 33 relevant papers were identified and remained full-text selection (Fig. 1). After reading the full text, we included 13 RCTs with 1347
### Table 1 The results of meta-analysis

| Variables                              | N (comparisons) | N (IPACK) | N (non-IPACK) | Pooled data WMD/RR (95% CI) | P | Heterogeneity I² (%) Ph |
|----------------------------------------|-----------------|-----------|---------------|----------------------------|---|------------------------|
| **Pain scores**                        |                 |           |               |                            |   |                        |
| Overall                                | 52              | 2047      | 2062          | −0.487 (−0.719, −0.255)     | <0.0001* | 92.4% <0.0001          |
| By subgroup (Follow-up time)           |                 |           |               |                            |   |                        |
| Pain at rest (2–4 h)                   | 9               | 349       | 348           | −0.483 (−0.958, −0.008)     | 0.046* | 90.3% <0.0001          |
| Pain at rest (6–12 h)                  | 13              | 612       | 611           | −0.691 (−1.064, −0.318)     | <0.0001* | 91.1% <0.0001          |
| Pain at rest (16–24 h)                 | 8               | 345       | 344           | −0.508 (−1.273, 0.258)      | 0.194 | 94.6% <0.0001          |
| Pain at rest (32–48 h)                 | 10              | 410       | 422           | −0.203 (−0.811, 0.404)      | 0.512 | 95.1% <0.0001          |
| Pain at rest (> 1w)                    | 12              | 371       | 377           | −0.586 (−0.951, −0.220)     | 0.002* | 65.2% 0.001           |
| **Morphine consumption**               |                 |           |               |                            |   |                        |
| Oral morphine consumption (overall)    | 34              | 1296      | 1292          | −2.559 (−4.625, −0.494)     | 0.015* | 62.0% <0.0001          |
| By subgroup (Follow-up time)           |                 |           |               |                            |   |                        |
| Morphine consumption (0–12 h)          | 7               | 273       | 269           | −2.019 (−9.989, 5.950)      | 0.619 | 63.8% 0.400           |
| Morphine consumption (12–24 h)         | 10              | 406       | 401           | −4.936 (−11.517, 1.646)     | 0.142 | 75.7% <0.0001          |
| Morphine consumption (24–48 h)         | 10              | 405       | 407           | −2.979 (−5.714, −0.244)     | 0.033* | 0% 0.441              |
| Morphine consumption (48–72 h)         | 4               | 212       | 215           | −0.579 (−2.892, 1.734)      | 0.624 | 61.4% 0.051           |
| **Morphine requirement (overall)**     |                 |           |               |                            |   |                        |
| By subgroup (Follow-up time)           |                 |           |               |                            |   |                        |
| Morphine requirement (0–12 h)          | 2               | 66        | 64            | 0.813 (0.377, 1.755)        | 0.599 | 0% 0.608              |
| Morphine requirement (12–24 h)         | 4               | 142       | 139           | 0.506 (0.309, 0.829)        | 0.007* | 3.8% 0.374            |
| Morphine requirement (24–48 h)         | 5               | 157       | 155           | 0.841 (0.626, 1.131)        | 0.252 | 0% 0.825             |
| Morphine requirement (48–72 h)         | 2               | 32        | 14            | 2.336 (0.953, 5.730)        | 0.064 | 54.3% 0.139           |
| **Functional outcomes**                |                 |           |               |                            |   |                        |
| ROM (Overall)                          | 11              | 400       | 397           | 1.090 (−3.740, 5.921)       | 0.658 | 90.2% <0.0001         |
| By subgroup (Follow-up time)           |                 |           |               |                            |   |                        |
| ROM (POD0)                             | 1               | 34        | 35            | −2.700 (−7.959, 2.559)      | 0.314 | N/A N/A               |
| ROM (POD1)                             | 4               | 160       | 159           | 1.002 (−6.683, 8.687)       | 0.798 | 87.1% <0.0001         |
| ROM (POD2)                             | 4               | 140       | 139           | 4.221 (−4.816, 13.258)      | 0.360 | 92.2% <0.0001         |
| ROM (POD3)                             | 2               | 66        | 64            | −3.200 (−7.180, 0.780)      | 0.115 | 0% 1.000              |
| TUG (Overall)                          | 18              | 830       | 821           | −0.735 (−3.352, 1.881)      | 0.582 | 74.6% <0.0001         |
| By subgroup (Follow-up time)           |                 |           |               |                            |   |                        |
| TUG (POD0)                             | 1               | 34        | 35            | −18.60 (−45.428, 8.228)     | 0.174 | N/A N/A               |
| TUG (POD1)                             | 3               | 127       | 126           | −4.901 (−15.554, 5.753)     | 0.367 | 19.2% 0.290           |
| TUG (POD2)                             | 5               | 238       | 236           | −1.701 (−9.572, 6.170)      | 0.672 | 91.8% <0.0001         |
| TUG (POD3)                             | 4               | 166       | 164           | −0.585 (−5.641, 4.471)      | 0.821 | 42.8% 0.154           |
| TUG (> 1w)                             | 6               | 232       | 228           | −0.260 (−1.812, 1.293)      | 0.743 | 0% 0.523              |
| Ambulation distance (Overall)          | 15              | 662       | 660           | 1.122 (0.365, 1.878)        | 0.004* | 0% 0.869              |
| By subgroup (Follow-up time)           |                 |           |               |                            |   |                        |
| Ambulation distance (POD0)             | 2               | 75        | 77            | 3.503 (−6.804, 13.810)      | 0.505 | 0% 0.722              |
| Ambulation distance (POD1)             | 6               | 266       | 265           | 0.798 (−0.122, 1.718)       | 0.089 | 0% 0.633              |
| Ambulation distance (POD2)             | 5               | 221       | 218           | 1.743 (0.339, 3.147)        | 0.015* | 0% 0.563              |
| Ambulation distance (POD3)             | 2               | 100       | 100           | 2.013 (−2.476, 6.503)       | 0.379 | 0% 0.610              |
patients (675 with IPACK; 672 without IPACK) [3, 7–16, 26, 27]. The overall analysis is summarized in Table 1. The sample size ranged from 56 to 120 patients. All studies were published between 2018 and 2020, and the mean follow-up period ranged from 2 days to 3 months. A detailed description of all included studies can be found in Tables 2 and 3. More confounding information can be found in Table 3.

**Methodological quality**

According to the risk of bias evaluation, twelve studies clearly described randomization methods except one [27]. In eleven studies, appropriate methods were used to describe allocation concealment [3, 7–13, 15, 16, 26]. Blinding of the participants and personnel in eight studies was well described [3, 7, 10–13, 15, 16, 26]. The blinding of outcome assessors in nine studies was well performed [3, 7, 9–12, 15, 16, 26]. The proportion of patients lost to follow-up was less than 10% in all studies, indicating low attrition bias. All studies reported satisfactory outcomes, and the risk of reporting bias was low. No other bias was detected. The risk of bias overall and in each domain can be seen in Fig. 2.

**Pain scores at ambulation**

IPACK reduced ambulation pain scores (WMD = −0.49 VAS, 95% CI −0.72 to −0.26, p < 0.0001). Subgroup analysis suggested that IPACK had lower scores within 12 h (2–4 h, WMD = −0.48, 95% CI −0.96 to −0.008, p = 0.046; 6–12 h, WMD = −0.69, 95% CI −1.06 to −0.32, p < 0.0001), and beyond 1 week (WMD = −0.59 95% CI −0.95 to −0.22, p < 0.0001). T.S.A. confirmed the effect of IPACK when performed at a power of 80%. The cumulative z-score crossed the monitoring boundary for the benefit and reached the required sample size (Fig. 3). Due to the inconsistency, the certainty of the evidence was evaluated as moderate (Table 4).

**Pain scores at rest**

IPACK was associated with lower pain scores at rest (WMD = −0.49 VAS, 95% CI −0.74 to −0.24, p < 0.0001). Subgroup analysis suggested lower rest pain scores with IPACK between 6 and 12 h (WMD = −0.96, 95% CI −1.47 to −0.45, p < 0.0001), and beyond 1 week (WMD = −0.31, 95% CI −0.62 to −0.02, p = 0.039). T.S.A. confirmed the effect of IPACK, and the cumulative z-score crossed the monitoring boundary for the benefit and reached the required sample size (Fig. 4). Due to the inconsistency, the certainty of the evidence was evaluated as moderate (Table 4).

**Morphine consumption**

IPACK was associated with a reduction in overall oral morphine consumption (WMD = −2.56 mg, 95% CI
Table 2: The baseline characteristics

| Study                     | Country  | Period          | Comparison                      | No. of Patients | Age† (years) | Women‡ (no. [%]) | BMI† (kg/m²) | Inclusion                                                                 |
|---------------------------|----------|-----------------|---------------------------------|-----------------|--------------|------------------|--------------|--------------------------------------------------------------------------|
| El-Emam2020               | Egypt    | N/A             | IPACK + SACB                    | 28              | 52 (15)      | 8 (28.57%)       | 29.1 (2.7)   | Age > 45 years; ASA I–III; Be competent to understand the study protocol; Radio-graphic evidence of OA; Chronic pain for at least 6 months; Conservative therapies were useless during the last 6 months; Patient refusal; Bleeding or coagulation disorders; Local skin infection or any other medical problem in the affected limb; Psychiatric problems lead to difficult communication with the patients; Previous chronic opioid use; Contraindications to steroid injection as diabetes or hypertension |
| Hu2020                    | China    | N/A             | IPACK + SACB                    | 40              | 74.7 (6.3)   | N/A              | 21.2 (1.9)   | Age between 65 to 89; ASA I–III; BMI 18.5 – 23.7 kg/m²; Selective unilateral primary TKA; Severe cardiovascular disease; Severe pulmonary dysfunction; Diseases of the central nervous system; Fail to communicate and cooperate; Coagulation disorders; Puncture site infection; Allergic to local anesthetic drugs; IPACK group decreased post-operative remedial analgesia and the use of vasoactive drugs, but the postoperative VAS scores are similar after 24 h and 48 h; Ultra-guided IPACK and ACB are safe and effective in old patients with primary TKA; |
| Study                  | Country     | Period            | Women (no. [%]) | BMI (kg/m²) | Inclusion                                                                                                                                  | Exclusion                                                                                                                                  | Conclusion                                                                                                                                  |
|-----------------------|-------------|------------------|-----------------|-------------|------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------|
| Kim2019               | America     | 2017.03–2017.10  | 23 (53.48%)     | 28.3 (4.1)  | Patients with OA scheduled for primary unilateral TKA with a participating surgeon; Age 18–80 years old, planned use of regional anesthesia, able to follow study protocol, and English speaking; | Hepatic or renal insufficiency, age < 18 or > 80 years old, patients undergoing general anesthesia, allergy or intolerance to one of the study medications, BMI > 40, diabetes mellitus, ASA IV, chronic gabapentin or pregabalin use (regular use for > 3 months), chronic opioid use (taking opioids for > 3 months, or daily oral morphine equivalent of > 5 mg/d for 1 month), and patients with severe valgus deformity and flexion contracture | We conclude that the addition of IPACK and ACB to PAI for pain management in TKA patients improves postoperative pain, opioid consumption, and measures of pain-related patient satisfaction |
| Kertkaiatkachorn2020  | Thailand    | 2019.05–2019.11  | 29 (85.29%)     | 27.2 (3.8)  | Ages between 18 and 80 years; ASA I to III; Scheduled to undergo the first two elective TKAs of the day were screened for eligibility     | Exclusion criteria were a varus-valgus deformity of > 20°, knee flexion deformity > 30°, known allergy to the drugs used in this trial, body mass index < 18 or > 40 kg/m², contraindication for neuraxial or regional anesthesia, contraindication for NSAIDs, chronic opioid use (defined as a history of regular opioid use for more than 3 months or a history of oral morphine use equivalent of > 60 mg/month), failure to perform the Timed Up and Go test and, inability to communicate or unwilling to give informed consent | The combination of ACB and iPACK block provides non-inferior analgesia compared with PAI when combined with CACB during part of postoperative multimodal analgesia regimens for patients undergoing TKA. However, the ACB + iPACK block may be associated with a higher level of opioid consumption and lower ambulatory ability on the day of surgery |
| Study                  | Country | Period               | Women (no. [%]) | BMI (kg/m²) | Inclusion                              | Exclusion                                               | Conclusion                                                                 |
|-----------------------|---------|----------------------|-----------------|-------------|----------------------------------------|----------------------------------------------------------|--------------------------------------------------------------------------|
|                       |         |                      | IPACK           | Non-IPACK   | IPACK        | Non-IPACK                               |                                                                          |                                                                          |
|                       |         |                      |                 |             | 27.6 (4.2) | 28.6 (3.9)                              | Exclusion criteria were age > 18 years; ASA I–III; BMI:18–40 kg/m²        | Distal IPACK block were better able to preserve the normal motor function |
| Kamptak2020(Comparison A) | Thailand | 2018.02–2019.01      | 28 (84.84%)     | 28 (87.5%) | 28.6 (3.9) | 28.6 (3.9)                              | Exclusion criteria were inability to cooperate, allergy to any drug       |                                                                          |
|                       |         |                      |                 |             |             |                                          | administered in this study, contraindications to neuraxial and/or regional |
|                       |         |                      |                 |             |             |                                          | anesthesia. Lower limb neuropathy involving the operative site, intolerance|                                                                          |
|                       |         |                      |                 |             |             |                                          | to non-steroidal anti-inflammatory drugs, chronic opioid drug use (daily  |                                                                          |
|                       |         |                      |                 |             |             |                                          | or almost daily use of opioid drugs for at least 3 months or morphine use  |                                                                          |
|                       |         |                      |                 |             |             |                                          | greater than or equal to 60 mg/day for at least 1 month, or diagnosis    |                                                                          |
|                       |         |                      |                 |             |             |                                          | of neuropathic pain), and inability to perform the timed up- and-go (TUG)  |                                                                          |
|                       |         |                      |                 |             |             |                                          | test                                                                        |                                                                          |
|                       |         |                      |                 |             |             |                                          | See in Kampitak2020 (Comparison A)                                    |                                                                          |
|                       |         |                      | 21 (70%)         | 16 (53.33%) | 21.9 (2.2) | 21.7 (2)                                | Exclusion criteria were cardiovascular disease; Severe pulmonary dysfunction; |                                                                          |
| Li2019                 | China   | 2017.11–2018.04      |                 |             |             |                                          | Diseases of the central nervous system; Failure to communicate and        |                                                                          |
|                       |         |                      |                 |             |             |                                          | cooperate; Coagulation disorders; Puncture site infection; Allergic to    |                                                                          |
|                       |         |                      |                 |             |             |                                          | local anesthetic drugs                                                   |                                                                          |
|                       |         |                      |                 |             |             |                                          | See in Kampitak2020 (Comparison A)                                    |                                                                          |
|                       |         |                      |                 |             |             |                                          | IPACK plus SACB added to multimodal analgesic methods could provide       |                                                                          |
|                       |         |                      |                 |             |             |                                          | satisfied effect                                                          |                                                                          |
| Study               | Country | Period          | Women\(^a\) (no. [%]) | BMI\(^b\) (kg/m\(^2\)) | Inclusion                                                                 | Exclusion                                                                 | Conclusion                                                                 |
|--------------------|---------|-----------------|------------------------|--------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------|
| Li2020(Comparison A) | China   | 2018.05–2019.04 | 33 (66%)               | 24.82 (2.58)             | Aged between 50 and 80 years; BMI 19–30 kg/m\(^2\); ASA I-III; Scheduled to have primary unilateral TKA for osteoarthritis; | Exclusion criteria included the following: (1) knee flexion deformity \(\geq 30^\circ\), varus-valgus deformity \(\geq 30^\circ\), and inability to walk; (2) allergy to morphine or had a past history of opioid consumption; (3) had any contraindications to regional anesthesia, local infiltration, general anesthesia, and the drugs used in this study; (4) diagnosis of septic arthritis, rheumatic arthritis, traumatic arthritis, and other non-OA; and (5) patients with a medical history of psychiatric illness, cognitive impairment, recognized neuromuscular disorder, narcotic dependency, knee infection, knee surgery, or thromboembolic event including myocardial infarction, cerebrovascular accident, deep vein thrombosis, and pulmonary embolus. Additionally, patients with a language barrier, or those who refused to sign informed consent, were also excluded | ACB with IPACK block and LFCNB may decrease the early postoperative pain scores and prolong analgesic duration following TKA. Compared to ACB with IPACK, ACB with LFCNB, or ACB alone, this method produced optimal outcomes without increased complications |
| Li2020(Comparison B) | China   | 2018.05–2019.04 | 40 (80%)               | 24.68 (2.60)             | see in Li (Comparison A)                                                                                      | see in Li (Comparison A)                                                                                                 | see in Li (Comparison A)                                                                 |
| Ochroch2020        | America | 2018.11–2019.07 | 34 (57%)               | 31.9 (6.4)                | Patients with ASA I-III undergoing primary TKA; Age 18–80 years;                                                | Patients were excluded from the study if they had an allergy to any of the study medications; BMI > 45, coagulopathy, chronic kidney disease or recent chronic opioid therapy, defined as the use of regular daily doses of systemic opioids for the past 3 months prior to the surgery. Revision knee replacement procedures were also excluded | IPACK block reduced the incidence of posterior knee pain 6 h postoperatively. Given the relative ease and safety profile, it may have a potential role as part of the multimodal analgesia after knee arthroplasty, particularly as a distinct alternative to sciatic nerve blockade that does not affect motor function. The IPACK block can also be considered as a more consistent and reproducible alternative to surgical PAI of the posterior capsule of the knee, but more studies are needed |

\(^a\)Women\(^a\) \(\geq 50\) years old

\(^b\)BMI \(\geq 30\) kg/m\(^2\)
Table 2 (continued)

| Study                  | Country | Period               | Women\(^a\) (no. [%]) | BMI\(^b\) (kg/m\(^2\)) | Inclusion                                                                                           | Exclusion                                                                                           | Conclusion                                                                                                                                                                                                 |
|------------------------|---------|----------------------|------------------------|--------------------------|-----------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Patterson2020          | America | 2016.11–2018.01     | 21 (60%)               | 31 (1.732)               | Eligible patients with elective unilateral primary TKA; Age > 18 years old; English speaking; ASAI-III | Exclusion criteria were contraindication to regional anesthesia or peripheral nerve blocks, allergy to local anesthetics, nonsteroidal anti-inflammatory drugs (NSAIDs), chronic renal insufficiency (Cr > 1.4 mg/dL or glomerular filtration rate < 60 mL/min), chronic pain not related to the knee joint, chronic opiate consumption (daily or almost daily use for ≥ 3 months), pre-existing peripheral neuropathy involving the operative site, and body mass index > 40 kg/m\(^2\) | IPACK and CACB improved pain scores in the immediate postoperative period but otherwise provided no additional benefit in pain scores, opioid consumption, physical therapy performance, the frequency of opioid-related side effects, and hospital length of stay were not affected by the addition of the IPACK. Therefore, IPACK and CACB may not provide a significant clinical benefit in TKA patients |
| Sankineani2018         | India   | 2016.09–2017.03     | 38 (63.33%)           | 29.36                    | Patients undergoing bilateral or revision total knee replacement, with history of bleeding diathesis or prior vascular surgery on femoral vessels on operated site, severe renal insufficiency, history of arrhythmia or seizures, sepsis, pre-existing lower extremity neurological abnormality and difficulties in comprehending visual analog scale (VAS) pain scores, were excluded from the study | ACB + IPACK is a promising technique that offers improved pain management in the immediate postoperative period without affecting the motor function around the knee joint resulting in better ROM and ambulation compared to ACB alone |
| Tak2020 (Comparison A) | India   | 2019.03–2019.06     | 29 (51.8%)            | 26                       | Unilateral tricompartmental TKA for primary OA; Age 45–80 years; ASA I–III                          | Exclusion criteria included patients who underwent bilateral or revision TKA, knee flexion deformity of ≥ 30°, varus–valgus deformity of ≥ 30°, arthritis due to rheumatoid disease or trauma or septic arthritis, creatinine > 1.2, renal or hepatic dysfunction, known allergy to any study medication, chronic opioid use, BMI > 40, chronic pain unrelated to knee joint, pre-existing neuropathy, arrhythmia, epilepsy, had a history of bleeding diathesis or prior vascular surgery on femoral vessels on operated site and difficulty in comprehending VAS pain scores | CACB provides better pain control, decreased opioid consumption and superior ambulation capacity in the immediate postoperative period compared to SACB + IPACK without any significant adverse side effects |
### Table 2 (continued)

| Study          | Country | Period          | Women* (no. [%]) | BMI† (kg/m²) | Inclusion | Exclusion                                                                 | Conclusion                                                                 |
|----------------|---------|-----------------|------------------|--------------|-----------|---------------------------------------------------------------------------|----------------------------------------------------------------------------|
| Tak2020(Comparison B) | India   | 2019.03–2019.06 | 29 (51.8%)       | 37 (63.8%)   | 26        | 266 See in TAK (comparison A)                                             | This study also concludes that the addition technique of IPACK to SACB may not add any additional benefit in postoperative pain control, ambulation, opioid consumption or rehabilitation compared to SACB alone |
| Vichainarong2020 | Thailand | 2018.07–2019.05 | 29 (87.87%)      | 27 (84.37%)  | 27 (4.4)  | 28.2 (4.2) Adult patients with ASA I–III scheduled for elective primary TKA using standard spinal anesthesia Age < 18 or > 80 years; BMI > 40 kg/m²; inability to provide informed consent; cognitive or psychiatric history that may interfere with assessment; a varus-valgus knee deformity > 20°; knee flexion deformity > 30°; contraindication for spinal anesthesia or peripheral nerve block; allergy or intolerance to local anesthetics or any component of the multimodal analgesic regimen; pre-existing chronic pain or opioid drug use (daily or almost daily use of opioid drugs for ≥ 3 months or morphine use ≥ 60 mg/day for ≥ 1 month); Pre-existing neuropathy or neurological deficit in the lower extremities The addition of an IPACK block to the LIA and CACB does not reduce the postoperative opioid consumption nor improve analgesia. However, it may improve immediate functional performance and reduce the length of hospitalization after TKA |
| Zheng2020      | China   | N/A             | 21 (63.64%)      | 20 (66.66%)  | 27.1 (3.4)  | 267 (2.7) Age between 18 to 65 years; BMI between 18–24 kg/m²; ASA I or II; Infection diseases; Nerve damage on operation side; Coagulation dysfunction; Liver or kidney diseases; Analgesic allergy; mental disfunction IPACK and SACB could help improve the postoperative function recovery |

*IPACK interspace between the popliteal artery and capsule of the knee, SACB single abductor canal block, CACB continues abductor canal block, ASA American Society of Anesthesiologists, OA osteoarthritis, BMI body mass index, TKA total knee arthroplasty, VAS visual analogue scale, mPAI modified periarticular injection, TNB tibial nerve block, LFCNB lateral femoral cutaneous nerve block, LIA local infiltration anesthesia, SNB sciatic nerve block
†The values are presented as the mean and the standard deviation
‡The values are given as the number of patient and the percentage of the group
– 4.63 to – 0.49, \( p = 0.015 \)). Subgroup analysis suggested that IPACK reduced the oral morphine consumption from 24 to 48 h postoperatively (WMD = – 2.97 mg, 95% CI 5.71 to − 0.24, \( p = 0.033 \)). The rate of morphine requirement was reduced with a statistically significant difference in the subgroup of 12 to 24 h (RR = 0.51, 95% CI 0.31 to 0.83, \( p = 0.007 \)). The cumulative z-score failed to cross the benefit’s monitoring boundary or reach the required sample size (Fig. 5). The certainty of the evidence was evaluated as moderate (Table 4).

**Functional recovery**

We found that patients who received an additional IPACK could achieve longer ambulation distances during the hospital stay (WMD = 1.12 feet, 95% CI 0.37 to 1.88, \( p = 0.004 \)). A better result was also observed on POD2 (\( p = 0.015 \)). No difference was found on POD0, POD1, or POD3. The synthesized results found that the level of quadriceps muscle strength favored patients in the IPACK group when measured at 0 degrees (WMD = 0.41, 95% CI 0.04 to 0.77, \( p = 0.029 \)). No statistically significant difference was found when patients flexed at 45 or 90 degrees. Moreover, we found no difference regarding the outcomes of ROM (\( p = 0.66 \)) or TUG (\( p = 0.58 \)).

**Complications**

Four studies reported the rate of postoperative nausea and vomiting (PONV), and we found no difference in the synthesized rate of PONV between patients who received IPACK and not (\( p = 0.60 \)). The incidence of sleep disturbance was reduced following the use of IPACK (RR = 0.50, 95% CI 0.31 to 0.80, \( p = 0.04 \)). Subgroup analysis found a similar benefit on POD 1 for IPACK using (\( p = 0.012 \)).

**Clinical outcomes**

In our study, IPACK was associated with a shorter length of hospital stay while the difference lost significance (\( p = 0.07 \)). No significant difference was found in either operation time (\( p = 0.71 \)) or patient satisfaction (\( p = 0.058 \)).

**Sensitivity analysis**

We conducted a sensitivity analysis on all outcomes with moderate-to-high heterogeneity \( (I^2 > 50\%) \) to validate our results. The conclusions remain unchanged in all outcomes, which suggests the stability of our outcomes.

**Publication bias**

The symmetrical distribution of funnel plots and the \( p \) value of the egger test both showed no publication bias (Fig. 6). Egger’s test revealed no potential publication bias (\( p > 0.01 \)). No publication bias was found in the trials included.

**Post hoc meta-regression**

Meta-regression results found that other nerve blocks can explain 70.08% of heterogeneity, while the others cannot (Additional file 2: Table S1).

**Discussion**

Our meta-analysis suggests that the administration of IPACK significantly reduced pain scores when measured at ambulation and rest, and the differences vanished over 24 h. Similarly, IPACK was associated with lower morphine consumption and reduced rate of morphine requirement without increasing the rate of complications. Moreover, functional metrics such as ambulation distances and quadriceps muscle strengthen also favored IPACK, but these differences were marginal and lacked clinical importance.

Due to the rich supply of sensory innervation around the knee joint, patients after TKA always complained about their knee pain. Postoperative pain will increase opioid consumption, prolonged functional immobility, and diminished patient satisfaction. Therefore, adequate analgesia is of paramount importance. Peripheral nerve blocks are effective for TKA pain management. Femoral nerve block targets the anteromedial aspects of the knee, while the weakness of the quadriceps muscle will delay ambulation and increase the risk of fall [4]. The sciatic nerve block provided posterior knee analgesia, while foot drop often occurred [6]. The adductor canal block is gaining popularity by providing better motor preservation and non-inferior analgesia to a femoral nerve block. However, the posterior knee cannot be covered in an isolated adductor canal block [28]. IPACK is a novel but simple procedure that provides adequate analgesia of the posterior capsule of the knee by anesthetizing the articular branches from the sciatic and obturator nerves [29]. Recent evidence confirmed the effect of IPACK in controlling pain, improving physical performance, and decreasing hospital stay [6].

In our analysis, the addition of IPACK improved pain scores at rest and pain scores at ambulation within 24 h, and our results were consistent with previous studies [1, 6, 28]. There was no difference concerning pain VAS scores after 24 h, and possible reasons are that the duration of anesthetic had worn off by one day due to the simple formulation. A new finding was that subgroup analysis suggested the benefits existed beyond one week, suggesting a long-term analgesic effect of IPACK. The associations between immediate postoperative pain
### Table 3  The confounding factors of included studies

| Study     | Country | ASA | Medications | Multi-modal Pain Management Methods |
|-----------|---------|-----|-------------|--------------------------------------|
|           |         |     |             | Rescue Methods | Anesthesia | Pre-operative | Intra-operative | Post-operative |
|           |         |     |             | IPACK | Non-IPACK | IPACK | Non-IPACK | IPACK | Non-IPACK |
| El-Emam2020 | Egypt | I/II/5/0/6 | (IPACK+SACB) SACB: 10 mL of 0.125 bupivacaine plus 40 mg methylprednisolone IPACK: 10 mL of 0.125 bupivacaine plus 40 mg methylprednisolone; | N/A | N/A | N/A | N/A | N/A |
| Hu2020     | China  | I/II/III: 25/35/16 | (IPACK+SACB) IPACK: 0.2% ropivacaine 15 mL; SACB: 0.2% ropivacaine 20 mL; | VAS >5, 20–40 mg Parecoxib sodium was given via Intravenous injection | General anesthesia | N/A |
| Kim2019    | America | I/II/III: 1/81/4 | IPACK+SACB+mPAI IPACK: 25 mL of 0.25% bupivacaine; SACB: 15 mL of bupivacaine 0.25% with 2 mg of preservative-free dexamethasone; mPAI: bupivacaine 0.25% with 1:300,000 epinephrine at a volume of 30 mL, methylprednisolone 40 mg/mL in 1 mL; cefazolin, 500 mg in 10 mL; and normal saline, 22 mL; note:mPAI: modified PAI PAI: bupivacaine 0.5% with 1:300,000 epinephrine at a volume of 30 mL, methylprednisolone 40 mg/mL in 1 mL, cefazolin, 500 mg in 10 mL; and normal saline, 22 mL, 20 mL of 0.25% bupivacaine, 2 mg IV dexamethasone, and ensure 10 mg dexamethasone via all route | NRS >6 for 2 h, an IV hydromorphone PCA was ordered | spinal epidural anesthetic | Meloxicam: 7.5 mg per os if age ≥ 75 or older 15 mg otherwise; Extended-release oxycodone (10 mg per os) in the holding area | Combined spinal epidural anesthetic with 60 mg mepivacaine spinal IV sedation: 2–5 mg with midazolam and propofol infusion; Ondansetron 4 mg IV Famotidine: 20 mg IV Fentanyl: up to 100 mcg | 1. Acetaminophen: 1000 mg IV every 6 h for 4 doses. Then, 1 g PO every 8 h 2. Ketorolac: 30 mg IV every 6 h for 4 doses. If patient is 75 or older, 15 mg IV every 6 h for 4 doses 3. Oxycodone (IR): 5 mg (for NRS pain 0–4) or 10 mg (for NRS 5–10) every 3 h PRN; 4. Meloxicam: 15 PO to start after ketorolac is finished (7.5 mcg PO if age > 75 years old); 5. Hydromorphone: 0.5 mg IV every 10 min X 4 doses for breakthrough pain (NRS >6, rescue analgesia);
Table 3 (continued)

| Study                  | Country | ASA | Medications | Multi-modal Pain Management Methods | Rescue Methods | Anesthesia | Pre-operative | Intra-operative | Post-operative |
|------------------------|---------|-----|-------------|-------------------------------------|----------------|------------|---------------|----------------|----------------|
|                         |         |     |             |                                     |                |            |               |                |                |
| Kertkiatkachorn2020    | Thailand| I/II/III: 3/58/6 | (IPACK + SACB + CACB) IPACK: 20 mL of 0.25% levobupivacaine with ketorolac (15 mg) and epinephrine (0.1 mg) SACB: 20 mL of 0.25% levobupivacaine with ketorolac (15 mg) and epinephrine (0.1 mg) with intermittent negative aspirations CACB: 0.15% levobupivacaine (5 mL/h for 60 h) | CACB + PAI CACB: 0.15% levobupivacaine (5 mL/h for 60 h) PAI: 20 mL of 0.9% levobupivacaine, 30 mg of ketorolac, 0.3 mg of epinephrine combined with isotonic saline for a total volume of up to 80 mL into the posterior capsule, medialis, and lateral collateral ligament insertions, medial and lateral meniscus remnant, anterior capsule, suprapatellar pouch, fat pad, and soft tissue; | VAS score ≥ 4 during their stay in PACU, 2 mg of IV morphine was administered every 30 min | All patients received oral acetaminophen (2 x 375-g tablets) and oral celecoxib (400-g tablet) 30 min before surgery | Dexamethasone (10 mg) and ondansetron (4 mg) were administered for postoperative nausea and vomiting prophylaxis | Parecoxib (40 mg IV every 12 h, 2 doses) Acetaminophen (orally, 650 mg per dose every 6 h) Pregabalin (orally, 75 mg per dose once a day), and Celecoxib (orally, 400 mg per dose once a day; started after the last dose of parecoxib) |
|                         |         |     |             |                                     |                |            |               |                |                |
| Kampitak2020(Comparison A) | Thailand| I/II/III: 1/62/2 | (Proximal IPACK + CACB) Proximal IPACK: 5 mL 0.25% levobupivacaine with 1:200,000 epinephrine; simultaneously, the needle was slowly withdrawn, and 15 mL of local anesthetic was injected until the tip of the needle reached the end of the medial aspect of the femur CACB: 15 mL of 0.25% levobupivacaine was injected with intermittent negative aspirations, 0.15% levobupivacaine was continuously dripped at 5 mL/hour via a disposable infusion pump LIA: 20 mL of 0.9% levobupivacaine, 0.3 mL of 1:1000 epinephrine, 30 mg of ketorolac, and 40 mL of isotonic sodium chloride solution; | TNB + CACB TNB: 15 ml 0.25% levobupivacaine were injected in divided doses of 5 mL, aspirating frequently to avoid intravascular injection CACB: same with intervention group LIA: same with intervention group | NRS > 4, 2 mg of intravenous morphine was administered every 30 min; Continued NRS > 4 for up to 1 h, PCA was administered using Morphine (no basal rate, PCA dose 2 mg, lockout 10 min); | Spinal anesthesia (3 mL of 0.5% hyperbaric bupivacaine) | Lorazepam (0.5 mg) was administered orally on the night before surgery (mild or worse anxiety), Paracetamol (650 mg orally) 30 min prior to surgery as premedication | Intravenous dexamethasone (10 mg) and ondansetron (4 mg) for postoperative nausea and vomiting prophylaxis | 20 mg of intravenous parecoxib every 12 h on postoperative day (POD) 0–1, 650 mg of acetaminophen orally every 6 h, 75 mg of pregabalin orally once daily; After the last dose of parecoxib, 400 mg of celecoxib and half a tablet of tramadol hydrochloride/acetaminophen were administered, followed by 650 mg of acetaminophen orally every 6 h as needed |
| Study                      | Country | ASA       | Medications                                                                 | Multi-modal Pain Management Methods                                                                 |
|---------------------------|---------|-----------|-----------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------|
| Kampitak2020(Comparison B)| Thailand| I/II/III: 1/52/2 | (Distal IPACK+CACB) Distal IPACK: 20 mL of 0.25% levobupivacaine with 1:200 000 epinephrine was injected while slowly withdrawing the needle until the tip of the needle reached the medial femoral condyle; CACB: same with intervention group |
|                           |         |           | (TNB + CACB) TNB: same with intervention group                                |------------------------------------------------------------------------------------------------------|
|                           |         |           | CACB: same with intervention group                                            |------------------------------------------------------------------------------------------------------|
|                           |         |           | same as Comparison A                                                         |------------------------------------------------------------------------------------------------------|
|                           |         |           | same as Comparison A                                                         |------------------------------------------------------------------------------------------------------|
|                           |         |           | same as Comparison A                                                         |------------------------------------------------------------------------------------------------------|
|                           |         |           | same as Comparison A                                                         |------------------------------------------------------------------------------------------------------|
| Li2019                    | China   | I/III: 6/38/16 | IPACK + SACB IPACK: 0.33% ropivacaine 15 mL SACB: 0.33% ropivacaine 20 mL | NRS > 5, Nalbuphine was injected at 0.08 mg/kg intravenously)                                        |
|                           |         |           | SACB: 0.33% ropivacaine 20 mL                                                |------------------------------------------------------------------------------------------------------|
|                           |         |           | Combined spinal and epidural anesthesia (0.5% bupivacaine 1.6–2 mL, lidocaine was added as needed) |
|                           |         |           | Flurbiprofen 50 mg (intravenous injection)                                    |------------------------------------------------------------------------------------------------------|
|                           |         |           | N/A                                                                          |------------------------------------------------------------------------------------------------------|
|                           |         |           | Celecoxib 200 mg, bid, po                                                     |------------------------------------------------------------------------------------------------------|
| Li2020(Comparison A)      | China   | I/III: 1/7/52/1 | IPACK + SACB + LFCNB IPACK: 20 mL AV SACB: 20 mL AV LFCNB: 10 mL AV LIA: 60 mL AV note: AV, 0.2% ropivacaine and 2.0 ug/mL of epinephrine | N/A                                                                                                    |
|                           |         |           | SACB: 20 mL AV LFCNB: 10 mL AV LIA: 60 mL AV                                 |------------------------------------------------------------------------------------------------------|
|                           |         |           | N/A                                                                          |------------------------------------------------------------------------------------------------------|
|                           |         |           | N/A                                                                          |------------------------------------------------------------------------------------------------------|
|                           |         |           | Tranexamic acid first dose of 20 mg/kg IV used during surgery, another dose used 8 h later; Elastic bandage to reduce the blood loss; Postoperatively, ice compression devices were applied, Loxoprofen (60 mg, 1 tablet, bid) was prescribed to control postoperative pain and alprazolam (0.4 mg, 1 tablet, qn) was given as a sleep aid, Tourniquet was used. After hospital discharge, patients were given rivaroxaban orally (10 mg, qd) to prevent venous thromboembolism for 2 weeks, Loxoprofen orally for pain control (60 mg twice a day) until patients felt no pain, and were introduced to functional recovery methods |
| Study                  | Country  | ASA | Medications                                                                                                           | Multi-modal Pain Management Methods                                                                 |
|-----------------------|----------|-----|-----------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Li2020(Comparison B)  | China    | I/II/III: 2/2/4/3/3.5 | IPACK + SACB; SACB: 20 ml AV; IPACK: 20 ml AV; LFCNB: 10 ml placebo; LIA: 60 ml AV                                           | Rescue Methods: See in Li (comparison A); Pre-operative: See in Li (comparison A); Intra-operative: See in Li (comparison A); Post-operative: See in Li (comparison A) |
| Ochroch2020           | America  | I/II/III: 1/6/5/3   | IPACK + CACB; CACB: ropivacaine 0.2% at a basal rate of 8 mL/hour with a PCA of 5 mL, every 30 min; IPACK: 20 ml of ropivacaine 0.5% | Rescue Methods: CACB: ropivacaine 0.2% at a basal rate of 8 mL/hour with a PCA of 5 mL, every 30 min; Sham IPACK: superficial injection of local anesthetic to create a skin weal of the medial side of the knee; Pre-operative: Ophthalmic block or general anesthesia; Intra-operative: All patients received prophylaxis for postoperative nausea and vomiting; Post-operative: N/A |
| Patterson2020         | America  | I/II/III: 3/4/4/2   | IPACK + CACB; CACB: 20 ml ropivacaine 0.25% with epinephrine 3 mcg/mL; 8 mL/h continuous infusion of ropivacaine 0.2% was initiated through the adductor canal catheter; IPACK: 15 ml ropivacaine 0.25% with epinephrine 3 mcg/mL with an additional 5 ml of local anesthetic, a total of 20 ml of local anesthetic | Rescue Methods: Oxytocin immediate-release tablets; Pre-operative: All patients received prophylaxis for postoperative nausea and vomiting; Intra-operative: IV morphine, and/or IV hydromorphone were available for breakthrough pain not relieved by oral medications; Post-operative: Patients received intravenous (IV) ketamine 0.25 mg/kg (up to 50 mg) and/or IV hydromorphone 8 mg IV; Patients were prescribed 1 g IV acetaminophen followed by 1 g oral acetaminophen every 6 h while in the hospital, 400 mg oral celecoxib followed by 200 mg daily, and 75 mg or 150 mg oral pregabalin daily in the evening |
| Study                        | Country   | ASA   | Medications                                                                 | Multi-modal Pain Management Methods                                                                 |
|------------------------------|-----------|-------|-----------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------|
| Sankineani2018               | India     | N/A   | IPACK + SACB 15 ml of 0.2% ropivacaine SACB 20 ml of 0.2% ropivacaine       | Rescue Methods: If patients have breakthrough pain, intravenous diclofenac 75 mg along with a transdermal buprenorphine patch (5 mcg/h) |
|                             |           |       | IPACK: 15 ml of 0.2% ropivacaine                                            | Anesthesia Pre-operative: Spinal anesthesia (2.5 ml 0.5% hyperbaric bupivacaine)                      |
|                             |           |       | Rescue Methods: If patients have breakthrough pain, Intravenous diclofenac 75 mg along with a transdermal buprenorphine patch (5 mcg/h) | Intra-operative: N/A                                                                               |
|                             |           |       | SACB 20 ml of 0.2% ropivacaine                                              | Post-operative: N/A                                                                                 |
|                             |           |       | Rescue Methods: If patients have breakthrough pain, Intravenous diclofenac 75 mg along with a transdermal buprenorphine patch (5 mcg/h) | Post-operative: N/A                                                                                 |
| Tak2020 (Comparison A)      | India     | II/III| IPACK + SACB 20 ml of 0.2% ropivacaine                                      | Rescue Methods: If patients have breakthrough pain, Intravenous diclofenac 75 mg along with a transdermal buprenorphine patch (5 mcg/h) |
|                             |           |       | Rescue Methods: If patients have breakthrough pain, Intravenous diclofenac 75 mg along with a transdermal buprenorphine patch (5 mcg/h) | Anesthesia Pre-operative: Spinal anesthesia (2.5 ml 0.5% hyperbaric bupivacaine)                      |
|                             |           |       | SACB 20 ml of 0.2% ropivacaine                                              | Intra-operative: N/A                                                                                 |
|                             |           |       | Rescue Methods: If patients have breakthrough pain, Intravenous diclofenac 75 mg along with a transdermal buprenorphine patch (5 mcg/h) | Post-operative: N/A                                                                                 |
|                             |           |       | SACB 20 ml of 0.2% ropivacaine                                              | Post-operative: N/A                                                                                 |
| Tak2020 (Comparison B)      | India     | II/III| IPACK + SACB 20 ml of 0.2% ropivacaine                                      | Rescue Methods: If patients have breakthrough pain, Intravenous diclofenac 75 mg along with a transdermal buprenorphine patch (5 mcg/h) |
|                             |           |       | Rescue Methods: If patients have breakthrough pain, Intravenous diclofenac 75 mg along with a transdermal buprenorphine patch (5 mcg/h) | Anesthesia Pre-operative: Spinal anesthesia (2.5 ml 0.5% hyperbaric bupivacaine)                      |
|                             |           |       | SACB 20 ml of 0.2% ropivacaine                                              | Intra-operative: N/A                                                                                 |
|                             |           |       | Rescue Methods: If patients have breakthrough pain, Intravenous diclofenac 75 mg along with a transdermal buprenorphine patch (5 mcg/h) | Post-operative: N/A                                                                                 |
|                             |           |       | SACB 20 ml of 0.2% ropivacaine                                              | Post-operative: N/A                                                                                 |
| Vichainarong2020            | Thailand  | I/II/III| IPACK + CACB 20 ml of 0.2% ropivacaine                                      | Rescue Methods: If patients presented with persisting pain and NRS ≥ 4, the patient would receive 2 mg of intravenous morphine as rescue therapy |
|                             |           |       | Rescue Methods: If patients presented with persisting pain and NRS ≥ 4, the patient would receive 2 mg of intravenous morphine as rescue therapy | Anesthesia Pre-operative: Spinal anesthesia (15 mg of 0.5% hyperbaric bupivacaine)                      |
|                             |           |       | SACB 20 ml of 0.2% ropivacaine                                              | Intra-operative: All patients received 650 mg of acetaminophen and 400 mg of celecoxib orally 30 min before surgery |
|                             |           |       | Rescue Methods: If patients presented with persisting pain and NRS ≥ 4, the patient would receive 2 mg of intravenous morphine as rescue therapy | Post-operative: All patients received 10 mg of dexamethasone and 4 mg of ondansetron intravenous for postoperative nausea and vomiting prophylaxis |
|                             |           |       | SACB 20 ml of 0.2% ropivacaine                                              | Post-operative: Two consecutive doses of 15 mg ketorolac intravenous, 650 mg oral acetaminophen every 6 h, and 75 mg oral pregabalin (Lyrica) daily. After the last dose of ketorolac intravenous, 400 mg oral celecoxib (Celebre) daily and half a tablet of tramadol hydrochloride/acetaminophen (Ultracet) were administered every 8 h; 40 mg intravenous esomeprazole daily for preventing upper gastrointestinal bleeding and 4 mg intravenous ondansetron every 6 h to prevent nausea and vomiting |

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**Note:** The medications and pain management methods are detailed in the table above. Please refer to the table for specific details on the medications and methods used in each study.
### Table 3 (continued)

| Study           | Country   | ASA     | Medications | Multi-modal Pain Management Methods |
|-----------------|-----------|---------|-------------|-------------------------------------|
|                 |           |         | IPACK + SACB | Pre-operative | Intra-operative | Post-operative |
|                 |           |         | IPACK: 0.375% ropivacaine 15 ml | N/A | N/A | N/A |
|                 |           |         | SACB: 0.375% ropivacaine 25 ml | FNB + SNB FNB: 0.375% ropivacaine 20 ml; SNB: 0.375% ropivacaine 20 ml; | VAS > 3, Intravenous sufentanil was used as 0.1 μg/kg | Intravenous Administration: Midazolam 0.02 mg/kg; Sufentanil 0.2-0.3 g/kg; Etomidate 0.2 mg/kg; Aquarium sulfonate 0.6 mg/kg | N/A |
| Zheng2020       | China     | I/II: 17/33 | | | | |

| Study           | Country   | ASA     | Surgical factors | ITT | Follow-up | Lost (n) |
|-----------------|-----------|---------|-------------------|-----|-----------|----------|
|                 |           |         | Surgeons | Prothesis | Approach | Others | | |
| El-Emam2020     | Egypt     | I/II: 50/6 | N/A | N/A | N/A | Only OA patients included | No | 12w | 0 |
| Hu2020          | China     | I/II: | N/A | N/A | N/A | N/A | No | 2d | 0 |
| Kim2019         | America   | I/II: 1/81/4 | Investigator surgeons | N/A | N/A | Tourniquet was used | Yes | 2d | 0 |
| Kertkijkachorn2020 | Thailand | I/II: 3/58/6 | performed by or under the supervision of two senior surgeons | tricompartmental prostheses; hand-mixed cementing techniques | minimally invasive minimidvastus approach | N/A | Yes | 2 m | 2 |
| Kampitak2020(Comparison A) | Thailand | I/II: 1/62/2 | performed by three orthopedic surgeons | hand-mixed cementing techniques; tricompartmental prostheses | minimally invasive minimidvastus approach | Tourniquet was used | Yes | 6w | 5 |
| Kampitak2020(Comparison B) | Thailand | I/II: 1/62/2 | same as Comparison A senior surgeons | same as Comparison A | same as Comparison A | same as Comparison A | same as Comparison A | 5 same as Comparison A | 2d | 0 |
| Li2019          | China     | I/II: 6/38/16 | same as Comparison A senior surgeons | same as Comparison A | same as Comparison A | same as Comparison A | No | 3 m | 0 |
| Li2020(Comparison A) | China     | I/II: 17/52/31 | performed by 2 senior surgeons | Prostheses: DePuy P.F.C; Stryker Triathlon | standard medial parapatellar approach | LIA was used in every group | No | | |
| Li2020(Comparison B) | China | I/II: 22/43/35 | See in Li (comparison A) | See in Li (comparison A) | See in Li (comparison A) | See in Li (comparison A) | See in Li (comparison A) | See in Li (comparison A) | 0 |
Table 3 (continued)

| Study            | Country | ASA                      | Surgical factors          | ITT | Follow-up | Lost (n) |
|------------------|---------|--------------------------|----------------------------|-----|-----------|----------|
|                  |         |                          | Surgeons                  |     |           |          |
| Ochroch2020      | America | I/II/III: 1/65/53        | N/A                       | No  | 2w        | 1        |
|                  |         |                          | Prothesis                 | N/A |           |          |
|                  |         |                          | Approach                  | N/A |           |          |
|                  |         |                          | Others                    | N/A |           |          |
| Patterson2020    | America | I/II/III: 3/44/22        | Performed by one of three | No  | 2d        | 2        |
|                  |         |                          | fellowship-trained total  |     |           |          |
|                  |         |                          | joint surgeons            |     |           |          |
|                  |         |                          | posterior stabilized      |     |           |          |
|                  |         |                          | approach                  |     |           |          |
|                  |         |                          | tourniquet was used        |     |           |          |
| Sankineani2018   | India   | N/A                      | performed by a single     | No  | 2d        | 0        |
|                  |         |                          | surgeon                   |     |           |          |
|                  |         |                          | (AVGR)                     |     |           |          |
|                  |         |                          | Posterior stabilized      |     |           |          |
|                  |         |                          | knee prosthesis           |     |           |          |
|                  |         |                          | medial parapatellar       |     |           |          |
|                  |         |                          | approach                  |     |           |          |
| Tak2020(Comparison A) | India  | II/III: 106/7           | Two fellowship trained     | No  | 2d        | 0        |
|                  |         |                          | joint replacement          |     |           |          |
|                  |         |                          | surgeons                  |     |           |          |
|                  |         |                          | Posterior stabilized      |     |           |          |
|                  |         |                          | knee prosthesis           |     |           |          |
|                  |         |                          | without patellar          |     |           |          |
|                  |         |                          | resurfacing               |     |           |          |
| Tak2020(Comparison B) | India  | II/III: 106/8           | see in Tak(Comparison A)  | No  | 2d        | 0        |
|                  |         |                          | see in Tak(Comparison A)  |     |           |          |
|                  |         |                          | see in Tak(Comparison A)  |     |           |          |
| Vichainarong2020 | Thailand| I/II/III: 3/59/3        | performed by or under the | Yes | 2m        | 1        |
|                  |         |                          | supervision of two         |     |           |          |
|                  |         |                          | senior surgeons            |     |           |          |
|                  |         |                          | minimally invasive        | N/A |           |          |
|                  |         |                          | minimidvas-tus approach    | N/A |           |          |
| Zheng2020        | China   | I/II: 17/33             | N/A                       | No  | 2d        | 0        |

* represented a significant difference, indicating \( p < 0.05 \)

IPACK interspace between the popliteal artery and capsule of the knee, SACB single abductor canal block, CACB continues abductor canal block, ASA American Society of Anesthesiologists, OA osteoarthritis, BMI body mass index, TKA total knee arthroplasty, VAS visual analogue scale, mPAI modified periarticular injection, TNB tibial nerve block, LFCNB lateral femoral cutaneous nerve block, LIA local infiltration anesthesia, SNB sciatic nerve block
and chronic pain after TKA may explain this difference [30]. Of note, the minimal clinically important difference (MCID) for pain scores in TKA was 1.0. The differences brought by the administration of IPACK did not surpass the pre-designated threshold for the clinical importance of 1.0. Possible reasons are that the efficacy of an isolated IPACK was relatively small since the volume was usually 20 to 30 ml and could not infiltrate the membrane. Moreover, there were differences between the architecture of tissue and the properties of injectate and unavoidable variations (i.e., the position of the patient, muscle contraction, needle orientation, etc.) that affect the efficacy of IPACK. Two studies used questionnaires in postoperative pain measurement. Ochroch et al. found reduced average pain scores with IPACK ($p < 0.01$) by the Revised American Pain Society Patient Outcome Questionnaire (APS-POQ-R). Kim et al. [16] found improved analgesia results in the IPACK group (i.e., worst pain scale, least pain scale, severe pain experience on POD1 and POD2) by the patient self-reported questionnaire (Pain OUT). Most studies classified pain as rest and ambulation pain but did not locate the origin of knee pain (i.e., anterior, posterior, medial, lateral). Only two studies reported posterior knee pain [12, 26]. Adequate analgesia following TKA can reduce pain scores and opioid use to prevent complications and facilitate functional recovery. Our study also found positive results regarding reduced morphine consumption. Our results were consistent with previous studies [31–33]. However, the differences failed to reach MCID since a reduction of 40% in opioid usage were considered clinically relevant differences after TKA.

As for functional recovery, patients receiving an additional IPACK block performed better than those who did not receive regarding ambulation distances and muscle strength, indicating that the IPACK might provide potential additional functional improvement when combined with other regional anesthesia methods but was not associated with any meaningful clinical benefits. Possible reasons are that the improved pain experience can promote early ambulation, and decreased opioid consumption reduces adverse events, thereby improving patients’ functional outcomes. Moreover, several studies used questionnaires in measuring knee recovery. Li et al. [3] reported the Knee Society Score (KSS) at discharge, and in three months, they found similar results with IPACK and without. El-Emam et al. [13] found superior Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) scores in the IPACK group (2–12 weeks),
Fig. 3  Forest plots: a forest plot of pain, at ambulation; b trial sequential analysis of pain, at ambulation (adjusted boundaries). c Trial sequential analysis of pain at ambulation (penalized test).
Fig. 3 continued
**Table 4** GRADE, summary of findings, IPACK versus non-IPACK for patients with primary TKA

| Patient or Population: | | Setting: | | | Intervention: | The interspace between the popliteal artery and capsule of the knee, IPACK | Comparison: Non-IPACK |
|------------------------|-----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
| Outcome indicator      | Importance      | Relative effect (95%CI) | No. of Participants (studies) | Quality of the evidence | Comments |
| Pain at rest (6–12 h)  | Critical        | $-0.960\ (\ -1.467, \ -0.454)$ | 1309 (13) | ⊕⊕⊕ | Moderate $^a$ | inconsistency |
| Pain at ambulation (6–12 h) | Important | $-0.691\ (\ -1.064, \ -0.318)$ | 1223 (13) | ⊕⊕⊕ | Moderate $^b$ | inconsistency |
| Morphine consumption (24–48 h) | Critical | $-2.979\ (\ -5.714, \ -0.244)$ | 812 (10) | ⊕⊕⊕⊕ | High | inconsistency |
| Morphine requirement (12–24 h) | Important | $0.506\ (0.309, 0.829)$ | 281 (4) | ⊕⊕⊕ | Moderate | inconsistency |
| Ambulation distances (POD2) | Important | $1.743\ (0.339, 3.147)$ | 439 (5) | ⊕⊕⊕ | Moderate | inconsistency |
| Sleep disturbance (POD1) | Important | $0.388\ (0.185, 0.812)$ | 264 (4) | ⊕⊕⊕ | Moderate | Small number of participants |

GRADE Working Group grades of evidence. High quality: further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. Very low quality: we are very uncertain about the estimate.

$^a$ Downgraded by two levels due to inconsistency (unexplained high heterogeneity without change results, $I^2 \geq 75\%$)

$^b$ Downgraded by one level due to inconsistency (unexplained high heterogeneity without change results, $I^2 \geq 50\%$)
Fig. 4  Forest plots  

a Forest plot of pain at rest; b trial sequential analysis of pain at rest (adjusted boundaries). c Trial sequential analysis of pain at rest (Penalized Test)
while Li [3] found no difference (at discharge, three months). In general, a marginally better benefit on functional ability was found in our study, which required more data for clarification.

Complications were rare when applying IPACK into the multimodal analgesia pain management, which also proved the safety of IPACK in our study. Possible reasons are that effective pain control reduced opioid consumption and minimized associated side effects further. Some complications cannot be quantitatively synthesized. Li et al. reported two patients with slight numbness on the operative lower extremity with IPACK [3]. Tak et al. found two cases of cardiac events with IPACK, which they believed was not ascribed to IPACK [10]. Kertkitchenakorn et al. used the VAS to assess the severity of PONV and dizziness and found no difference [7]. Moreover, improved sleep quality was found in the IPACK group on POD1 in our study, which improved knee pain and mitigated anxiety [34]. Studies demonstrated that patient satisfaction is not a sole reliable proxy for pain relief and functional recovery outcomes since the factors affecting satisfaction are complex [35, 36]. However, overall patient satisfaction was similar in our study.

New techniques of IPACK have been discussed in several studies. Kampitak et al. [26] compared the effect of proximal IPACK with distal IPACK and found a lower rate of posterior knee pain in the proximal IPACK group. Possible explanations were that the injection point of the proximal IPACK block was closer to the popliteal plexus and promoted the spread of local anesthetic [38–40].

This study has some limitations. First, there was relatively high heterogeneity in several outcomes. However, sensitivity analysis was carried out, and all outcomes’ conclusions remained unchanged. Second, the control groups were not a placebo, and these interventions were various. A network meta-analysis would be of extreme interest. In addition, considering the small sample size and low incidence of the complications, we also designed similar RCTs with a larger sample size to evaluate complications of IPACK (ChiCTR2000032963, ChiCTR2000032964, ChiCTR2000032965, ChiCTR2000032966).

**Conclusions**

Our trial demonstrated significantly better pain scores, opioid consumption, and functional outcomes after using IPACK. However, the differences were small and lacked clinical importance, suggesting that IPACK was a relatively effective perioperative analgesia method. Taken as a whole, the current results support the performance of IPACK as a supplement analgesic method. Further investigation with larger samples would lend further insight and implications on the use of IPACK.

![Fig. 5 Forest plot of morphine consumption. a Forest plot of pain, at rest; b trial sequential analysis of morphine consumption (Adjusted Boundaries). c Trial sequential analysis of morphine consumption (Penalized Test)](image-url)
Abbreviations
TKA: Total knee arthroplasty; ACB: Adductor canal block; IPACK: Interspace between the popliteal artery and posterior capsule of the knee; PAI: Periarticular injection; LIA: Local infiltration anaesthesia; VAS: Visual analog scale; 95% CI: 95% Confidence intervals; FNB: Femoral nerve block; POD: Postoperative day; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT: Randomized controlled trial; R.O.M.: Range of motion; RR: Relative risks; WMD: Weight mean difference; NRS: Numeric rating scale.

Supplementary Information
The online version contains supplementary material available at https://doi.org/10.1186/s13018-022-03266-3.

Additional file 1. The search strategy of our study.
Additional file 2. The results of meta-regression.

Acknowledgements
Not applicable.

Authors’ contributions
TX and LY helped with protocol and search strategy development, selection of studies, risk of bias assessment, data extraction and analyses, interpretation of analyses, article drafting, and final review. SD and NN helped with data analyses, interpretation of analyses, and final review. JC and ZZ helped select studies, risk of bias assessment, interpretation of analyses, article drafting, and final review. All authors read and approved the final manuscript.

Funding
This study was supported by Sichuan Science and Technology Program (No. 2019YJ0031).

Availability of data and materials
The data could be retrieved from the corresponding authors if necessary.

Declarations
Ethics approval and consent to participate
This meta-analysis and all the included studies meet all the ethical standards described in the declaration of Helsinki. No ethical committee approval was required for this study.

Consent for publication
All authors agreed with the publications.
Competing interests
No benefits in any form have been received or will be received relating to this article. The authors declared no financial interests.

Received: 19 May 2021  Accepted: 26 July 2022
Published: 29 September 2022

References
1. Summers S, et al. Analgesia in total knee arthroplasty: current pain control modalities and outcomes. J Bone Joint Surg Am. 2020;102(8):719–27.
2. Chaia PA, Cannesson M, Bui CCM. Opioid free anesthesia: feasible? Curr Opin Anaesthesiol. 2020;33(4):512–7.
3. Li D, et al. Efficacy of adductor canal block combined with additional analgesic methods for postoperative analgesia in total knee arthroplasty: a prospective, double-blind randomized controlled study. J Anesthesiol. 2020;35(12):3554–62.
4. Layera S, et al. Motor-sparing nerve blocks for total knee replacement: A scoping review. J Clin Anesth. 2020;68(1):10076.110076.
5. Sebastian MP, Bykar H, Sell A. Saphenous nerve and IPACK block. Reg Anesth Pain Med. 2020;45(1):89–90.
6. Sinha SK, Clement A, Surette A                                  M. Infiltration between the popliteal artery and capsule of the knee (IPACK): essential anatomy, technique, and literature review. Curr Anesthesiol Rep. 2019;3(4):474–8.
7. Kerkwijkdom W, et al. Adductor canal block combined with IPACK (interspace between the popliteal artery and the capsule of the posterior knee) block vs periacrural injection for analgesia after total knee arthroplasty: a randomized noninferiority trial. J Anesthesiol. 2021;36(1):122–9.
8. Zheng F, et al. Optimized strategy of anesthesia for total knee arthroplasty: IPACK-adductor canal block, combined with general anesthesia. Chin J Anaesthesiol. 2020;40(5):561–4.
9. Vichainorong C, et al. Analgesic efficacy of infiltration between the popliteal artery and capsule of the knee (IPACK) block added to local infiltration analgesia and continuous adductor canal block after total knee arthroplasty: a randomized clinical trial. Reg Anesth Pain Med. 2020;45(11):872–9.
10. Tal R, et al. Continuous adductor canal block is superior to adductor canal block alone or adductor canal block combined with IPACK block (interspace between the popliteal artery and the posterior capsule of knee) in postoperative analgesia and ambulation following total knee arthroplasty: randomized control trial. Musculoskelet Surg. 2020;106:155–62.
11. Patterson ME, et al. The effect of the IPACK block on pain after primary TKA: a double-blinded, prospective, randomized trial. J Anesthesiol. 2020;35(6S):S173–7.
12. Ochroch J, et al. Analgesic efficacy of adding the IPACK block to a multimodal analgesic protocol for primary total knee arthroplasty. Reg Anesth Pain Med. 2020;45(10):799–804.
13. El-Emam EM, Billottt EAA. Ultrasound-guided adductor canal block versus combined adductor canal and infiltration between the popliteal artery and the posterior capsule of the knee block for osteoarthritis knee pain. Anesthesiol Essays Res. 2020;6(1):127–31.
14. Hu L, et al. Application of ultrasound-guided adductor canal block combined with IPACK in total knee arthroplasty for the elderly patients. J Pract Med. 2020;36(7):950–3.
15. Li M, et al. Efficacy of adductor canal block combined with IPACK block for multimodal analgesia after total knee arthroplasty. Chin J Anaesthesiol. 2019;39(5):5154–7.
16. Kim DH, et al. Addition of infiltration between the popliteal artery and the capsule of the posterior knee and adductor canal block to periacrural injection enhances postoperative pain control in total knee arthroplasty: a randomized controlled trial. Anesthesiol Analg. 2019;129(2):526–35.
17. Shamseer L, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.
18. Drahota. “Revman Calculator.” RevMan Calculator | Cochrane Training. https://training.cochrane.org/resource/revmanculator.
19. Sterne JAC, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366:k4898.
20. Guyatt GH, et al. GRADE guidelines 6. Rating the quality of evidence—imprecision. J Clin Epidemiol. 2011;64(12):1283–93.
21. Guyatt GH, et al. GRADE guidelines: 8. Rating the quality of evidence—indirectness. J Clin Epidemiol. 2011;64(12):1303–10.
22. Guyatt GH, et al. GRADE guidelines: 7. Rating the quality of evidence— inconsistency. J Clin Epidemiol. 2011;64(12):1294–302.
23. Guyatt GH, et al. GRADE guidelines: 5. Rating the quality of evidence—publication bias. J Clin Epidemiol. 2011;64(12):1277–82.
24. Guyatt GH, et al. GRADE guidelines: 4. Rating the quality of evidence—study limitations (risk of bias). J Clin Epidemiol. 2011;64(4):407–15.
25. Kampstak W, et al. Motor-sparing effect of IPACK (interspace between the popliteal artery and capsule of the posterior knee) block versus tibial nerve block after total knee arthroplasty: a randomized controlled trial. Reg Anesth Pain Med. 2020;45(4):267–76.
26. Sankineani SR, et al. Comparison of adductor canal block and IPACK block (interspace between the popliteal artery and the capsule of the posterior knee) with adductor canal block alone after total knee arthroplasty: a prospective control trial on pain and knee function in immediate postoperative period. Eur J Orthop Surg Traumatol. 2018;28(7):1391–5.
27. Kandarian BS, et al. Updates on multimodal analgesia and regional anesthesia for total knee arthroplasty patients. Best Pract Res Clin Anaesthesiol. 2019;33(1):111–23.
28. Lindberg MF, et al. Preoperative risk factors associated with chronic pain profiles following total knee arthroplasty. Eur J Pain. 2021;25(3):680–92.
29. Thobhani S, et al. Novel regional techniques for total knee arthroplasty promote reduced hospital length of stay: an analysis of 106 patients. Ochsner J. 2017;17(3):233–8.
30. Eccles CJ, et al. Decreased opioid consumption and length of stay using an IPACK and adductor canal nerve block following total knee arthroplasty. J Knee Surg. 2019;34:705–11.
31. Klement MR, et al. Continuous adductor canal blockade facilitates increased home discharge and decreased opioid consumption after total knee arthroplasty: Knee. 2019;26(3):679–86.
32. Luo ZY, et al. Preoperative sleep quality affects postoperative pain and function after total joint arthroplasty: a prospective cohort study. J Orthop Surg Res. 2019;14(1):378.
33. Munn JS, et al. Can met expectations moderate the relationship between pain/function and satisfaction in total knee arthroplasty? J Arthroplasty. 2021;36:1942–6.
34. Bovonratwet P, et al. Is there an association between negative patient-experience comments and perioperative outcomes after primary total hip arthroplasty? J Arthroplasty. 2021;36:2086–21.
35. Herman J, et al. Adductor canal block duration of analgesia successfully prolonged with perineural dexmedetomidine and dexmethasone in addition to ipack block for total knee arthroplasty. Cureus. 2020;12(9):e10566.
36. Zeylabi A, Shirani F, Heidari F, Farhad AR. Endodontic management of a fused mandibular third molar and distomolar: a case report. Aust Endod J. 2010;36(1):29–31.
37. Zhang Y, et al. Cadmium content of blood area. Dent Hypotheses. 2017;8(3):65.
38. Zeylabi A, Shirani F, Heidari F, Farhad AR. Endodontic management of a fused mandibular third molar and distomolar: a case report. Aust Endod J. 2010;36(1):29–31.
39. Tolou NB, Fathi MH, Monshi A, Mortazavi VS, Shirani F, Mohammadi M. The effect of adding TiO2 nanoparticles on dental amalgam properties. Iran J Mater Sci Eng. 2013;10(2):46–56.
40. Malekpour MR, Shirani F, Taromi Z, Shahnazari S. Comparison of color stability of two resin composites in blood area. Dent Hypotheses. 2017;8(3):65.

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