Effectiveness and weakness of local infiltration analgesia in total knee arthroplasty: a systematic review

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Abstract
Local infiltration analgesia has been widely used for pain relief in patients undergoing total knee arthroplasty. However, the effectiveness and major weakness of this technique have not been clarified; therefore, improvements in the technique have been limited. We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials and conducted a meta-analysis of randomized controlled trials comparing local infiltration analgesia with placebo infiltration in patients undergoing total knee arthroplasty. Fourteen trials involving 1305 knees were eligible. The results showed that local infiltration analgesia significantly reduced early perioperative pain and total narcotic consumption. However, postoperative functional outcomes were not significantly different between local infiltration analgesia and placebo. The pain-relieving effect of local infiltration analgesia was found to be strong but short in duration. In the future, modified delivery methods and formulas with longer durations of action and analgesia may provide a better environment for patients and therefore improve their function outcomes.

Keywords
Local infiltration analgesia, total knee arthroplasty, placebo, perioperative pain, narcotic consumption, randomized controlled trial, meta-analysis

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Introduction
Conventional perioperative opioid-based analgesia techniques for total knee arthroplasty (TKA), such as patient-controlled analgesia and spinal or epidural analgesia, are associated with side effects including respiratory depression, sedation, postoperative

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nausea and vomiting, urinary retention, and constipation.\textsuperscript{1}

A comparatively new technique known as local infiltration analgesia (LIA), popularized by doctors from Sydney, Australia,\textsuperscript{2} has been applied to TKA for more than 5 years. This technique has achieved inspiring goals in reducing the overall narcotic consumption, therefore decreasing the incidence of adverse effects.\textsuperscript{3,4} However, some other researchers found that LIA was not superior to placebo infiltration with respect to outcome indicators such as pain scores and range of motion (ROM).\textsuperscript{5,6} These divergent findings may cause confusion among practitioners. The questions that still remain unanswered are: Is LIA effective for TKA? What is the major weakness of LIA? How can LIA be improved?

We conducted a systematic review and meta-analysis of randomized placebo-controlled trials of LIA in patients undergoing TKA to examine the efficacy and major weakness of this technique.

\textbf{Methods}

\textbf{Search strategy}

A literature search for randomized controlled trials comparing LIA versus saline was performed independently by two authors (Z.H.Z., B.S.) using PubMed (1966 to January 2016), Embase (1984 to 2016), and the Cochrane Central Register of Controlled Trials (issue 1 to January 2016). All relevant English-language articles were retrieved, and the last data search occurred on 10 January 2015. References of the retrieved articles were also reviewed to broaden the database search. The search strategy used is listed in the \textit{Appendix}.

\textbf{Eligibility criteria and data extraction}

We included all published articles describing randomized controlled trials that compared LIA versus saline, regardless of the publication year or country. All selected articles provided adequate data for quantitative analysis, especially the means and standard deviations for continuous variables and the ratio of patients who developed adverse events to the total number of patients for dichotomous variables.

The exclusion criteria were as follows: the study focused on irrelevant procedures, the study did not involve primary clinical research, indispensable data were missing or unavailable, and duplicate publications were present. Two reviewers (Z.H.Z., B.S.) independently screened the titles, abstracts, and full texts of all articles to determine their eligibility for inclusion after consensus. Data were extracted from the included articles based on a preformed sheet.

\textbf{Quality assessment of the included studies}

The methodological assessment of the included trials was based on the modified Jadad score\textsuperscript{7,8} and was completed independently by two reviewers (Z.H.Z., B.S.). Articles with ≥4 points were considered high-quality studies, and divergences were solved by discussion.

\textbf{Statistical analysis}

The meta-analysis was performed using Review Manager Version 5.0 software for Windows (The Nordic Cochrane Centre, The Cochrane Collaboration, Oxford, England). The mean difference (MD) and 95% confidence interval (CI) were calculated for continuous variables, and the odds ratio and 95% CI were calculated for dichotomous variables. Heterogeneity was estimated by the chi-square test. A \( P \)-value of 0.10 was defined as the level of statistical significance in the tests for heterogeneity (\( P \leq 0.10 \) indicated the presence of heterogeneity). A fixed-effects model was employed when
heterogeneity was absent; otherwise, a random-effects model was employed. Data are presented by forest plots.

**Ethics statement**

This study was totally based on online published articles without the direct use of any data from or interventions involving patients or animals. Therefore, the requirement for ethics committee approval was waived.

**Results**

**Screening results**

In total, 297 articles were retrieved on the basis of the predefined search strategy. After screening the titles, abstracts, and full texts, we included 14 articles that met the eligibility criteria. A total of 960 patients with 1305 knees in 14 randomized controlled trials were included in the quantitative analysis. Among the 14 included trials, ropivacaine was used as the infiltration drug in 7 trials, while bupivacaine was used alone in 6 trials and together with levobupivacaine in 1 trial. Epinephrine was used as a supplement in seven trials. A flow chart of the study inclusion process is shown in Figure 1. Table 1 shows the general demographic characteristics of the included trials, and Table 2 shows the surgical and anesthetic data. All included studies used a similar operative anesthetic technique between the LIA and saline groups.

**Methodological quality assessment**

We summarized the modified Jadad score of the included articles in Table 3 for quality assessment. The results showed that all 14 included articles were of high quality, with a minimum modified Jadad score of 4 points. The level of bias in all 14 studies was low according to the modified Jadad score scale.

**Meta-analysis results**

In this meta-analysis, we included eight outcome indicators that were reported by no less than two trials: the visual analogue scale (VAS) score, narcotic dose equivalent, adverse effects, ROM, ambulation distance, straight-leg raise (SLR), Oxford score, and length of stay (LOS). Only two of these eight indicators, the VAS score and narcotic dose equivalent, were significantly different between the LIA group and saline group as described below.

**VAS score**

Five of the included articles reported the VAS score. The VAS score at 24 hours postoperatively was analyzed. There was no evidence of statistical heterogeneity among the studies (I^2 = 6%), and a fixed-effect model was used. The meta-analysis results (see Table 4) showed that patients in the LIA group had significantly lower VAS scores (MD, 0.10; 95% CI, 0.23 to 0.02; P = 0.003).

**Narcotic dose equivalent**

Eight of the included articles reported the narcotic dose equivalent at 24 and/or 48 hours postoperatively. Statistical heterogeneity was found among the studies (P < 0.0001, I^2 = 79%), so a random-effects model was used. The meta-analysis results (see Table 4) showed that patients in the LIA group had significantly lower narcotic dose equivalents (MD, 1.01; 95% CI, 0.90 to 0.11; P = 0.03).

**Adverse effects**

Four trials provided data regarding adverse effects. There was no evidence of statistical heterogeneity among the studies (I^2 = 0%), and a fixed-effects model was used. No significant difference in adverse effects was observed between the LIA
group and saline group (see Table 4) (odds ratio, 0.93; 95% CI, 0.47 to 1.85).

Function indicators

ROM. Four trials provided data regarding ROM. \(^6,10,12,15\) Statistical heterogeneity was found among the studies \((P < 0.00001, I^2 = 93\%)\), so a random-effects model was used. No significant difference in ROM was observed between the LIA group and saline group (see Table 4) (MD, 9.33; 95% CI, −5.02 to 23.69).

Ambulation distance. Two articles reported the ambulation distance. \(^10,12\) There was no evidence of statistical heterogeneity between the two studies \((I^2 = 0\%)\), and a fixed-effects model was used. No significant difference in the ambulation distance was found between the LIA group and saline group (see Table 4) (MD, 13.40; 95% CI, −3.90 to 30.69).

SLR. Data regarding the SLR were available in two articles. \(^3,12\) There was no evidence of statistical heterogeneity between the studies \((I^2 = 0\%)\), and a fixed-effects model was used. No significant difference in the SLR was observed between the LIA group and

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**Figure 1.** Flow chart of study inclusion process.
saline group (see Table 4) (odds ratio, 2.02; 95% CI, 0.88 to 4.62).

Oxford score. Pooled data regarding the Oxford score from two articles were analyzed. There was no evidence of statistical heterogeneity between the studies ($I^2 = 0\%$), and a fixed-effects model was used. The meta-analysis results showed no significant difference in the Oxford score between the LIA group and saline group (see Table 4) (MD, 1.17; 95% CI, 0.40 to 3.71).

LOS. Data regarding the hospital LOS were available in four articles. Statistical heterogeneity was found between the studies ($P = 0.0002$, $I^2 = 85\%$), so a random-effects model was used. No significant difference in the LOS was observed between the LIA group and saline group (see Table 4) (MD, –0.31; 95% CI, –1.20 to 0.58).

Discussion

The efficacy of LIA, which is an emerging and aspiring technique, remains controversial. Considering the uncertain efficacy of LIA,5,6 orthopedic surgeons are not willing to apply this technique without the ability to improve it. Clarification in this field is urgently needed.

The present meta-analysis indicated that patients who underwent TKA who had received LIA treatment had significantly lower VAS scores than those in the placebo groups. Patients in the LIA group also had significantly lower narcotic dose equivalents. No significant differences were found in most of the other outcome indicators, including the ROM, SLR, and Oxford score. The meta-analysis results regarding the VAS score show promise with respect to improvement in the patients’ subjective feeling after undergoing LIA.4,6,9,12 However, the LOS was not significantly different between the two groups, which is

Table 1. General demographic characteristics.

| Study                  | Knees | Sex | Mean age, y | BMI, kg/m² | ASA | Diagnosis | Total follow-up |
|------------------------|-------|-----|------------|------------|-----|-----------|----------------|
| Browne et al.          | 60    | 60  | 30         | 30         | 21  | 39        | 67             |
| Nechleba et al.        | 30    | 30  | 14         | 16         | 11  | 19        | 65             |
| Andersen et al.        | 12    | 24  | 12         | 7          | 5   | 69        | 29             |
| Krenzel et al.         | 66    | 67  | 35         | 32         | 23  | 43        | 66.2           |
| Reeves and Skinner     | 61    | 61  | 31         | 30         | 25  | 36        | 69.5           |
| Andersen et al.        | 16    | 32  | 16         | 16         | 9   | 7         | 63             |
| Essving et al.         | 48    | 48  | 24         | 24         | 22  | 26        | 71             |
| Gómez-Cardero and Rodríguez-Merchán | 50    | 50  | 25         | 25         | 19  | 31        | 71.3           |
| Kazak et al.           | 60    | 60  | 40         | 20         | 11  | 49        | 69.7           |
| Fajardo et al.         | 30    | 60  | 30         | 30         | 7   | 23        | 63.5           |
| Joo et al.             | 286   | 572 | 286        | 286        | 14  | 272       | 79.1           |
| Ikekuchi et al.        | 40    | 40  | 20         | 20         | 12  | 28        | 75.5           |
| Goyal et al.           | 150   | 150 | 75         | 75         | 65  | 85        | 63.9           |
| Williams et al.        | 51    | 51  | 26         | 25         | 21  | 30        | 66.5           |

Pts, patients; LIA, local infiltration analgesia; NS, normal saline; M, male; F, female; BMI, body mass index; ASA, American Society of Anesthesiologists physical status; OA, osteoarthritis; RA, rheumatoid arthritis.
| Study                        | Surgical approach | Infiltration information | Main analgesia schemes                          | Length of surgery, minutes |
|------------------------------|-------------------|--------------------------|-------------------------------------------------|----------------------------|
| Browne et al.                | MP, MV            | Bupivacaine Epinephrine  | Intra-op                                        | 106 100                    |
| Nechleba et al.              | MP                | Bupivacaine None         | Post-op                                         | – –                        |
| Andersen et al.              | MP                | Ropivacaine Epinephrine  | Post-op                                         | 109 109                    |
| Krenzel et al.               | MP                | Ropivacaine None         | Intra to post-op                                | – –                        |
| Reeves and Skinner           | MP                | Ropivacaine None         | Post-op                                         | 114 103                    |
| Andersen et al.              | MP                | Ropivacaine None         | Intra to post-op                                | 100 100                    |
| Essving et al.               | MP                | Ropivacaine Epinephrine, | Intra to post-op                                | 93 87                      |
| Gómez-Cardero and Rodríguez-Merchán | MV          | Ropivacaine None         | Post-op                                         | – –                        |
| Kazak et al.                 | MP                | Bupivacaine, Levobupivacaine Epinephrine | Intra and post-op | 102 85 |
| Fajardo et al.               | MP, SV            | Bupivacaine Epinephrine, | Intra-op                                        | – –                        |
| Joo et al.                   | MP                | Bupivacaine Epinephrine, | Intra-op                                        | 73 73                      |

(continued)
consistent with a previous systematic review.\textsuperscript{19}

The meta-analysis results regarding the function outcome indicators implicate that LIA is not effective for postoperative function improvement, which is in contrast to the results of a former clinical trial.\textsuperscript{20} Application of a pressure bandage and ice pack on the wound area may help to prolong the duration of action of LIA and therefore improve the postoperative function of patients who have undergone TKA.\textsuperscript{2}

Besides the findings regarding the VAS score, the significantly lower narcotic dose equivalent in the LIA group confirms the potential capacity of LIA in replacing some routinely used narcotics, which could be the foundation of further studies comparing LIA with femoral nerve block\textsuperscript{21} or patient-controlled analgesia.\textsuperscript{22}

Compared with a previous non-quantitative systematic review,\textsuperscript{19} the present meta-analysis has higher power. First, more high-quality trials were included in our study, substantially advancing the evidence level of the concerned topic. Second, a comprehensive collection of outcomes was considered in this meta-analysis, broadening the study overview. Finally, and importantly, this meta-analysis is more persuasive because of the use of a quantity analysis technique.

This current study still has several limitations. Heterogeneity in the local analgesic drug combinations, infiltration sites, and volumes was present among the studies. One of the included studies\textsuperscript{5} was conducted in simultaneous bilateral patients, which may have bias because of the systemic effect of LIA. In addition, the periods of use of LIA were not long enough, and the results therefore may not reflect the long-term effects. Finally, the small quantity of included studies may restrict the statistical persuasion.

In summary, the efficacy of LIA in improving short-term postoperative pain
Table 3. Quality assessment using the modified Jadad score.

| Study                                | Randomization | Blinding | Dropouts | Inclusion/exclusion criteria | Adverse effects assessment | Statistical analysis | Modified Jadad score |
|--------------------------------------|---------------|----------|----------|------------------------------|----------------------------|----------------------|----------------------|
| Browne et al.                        | Yes           | Unclear  | Yes      | Not described                | Described                 | Described            | 5                    |
| Nechleba et al.                      | Yes           | Unclear  | Yes      | Not described                | Not described             | Described            | 4                    |
| Andersen et al.                      | Yes           | Yes      | Yes      | Not described                | Described                 | Not described        | 6                    |
| Krenzel et al.                       | Yes           | Unclear  | Yes      | Not described                | Described                 | Not described        | 4                    |
| Reeves and Skinner                  | Yes           | Unclear  | Yes      | Described                    | Not described             | Described            | 6                    |
| Andersen et al.                      | Yes           | Unclear  | Yes      | Not described                | Described                 | Not described        | 5                    |
| Essving et al.                       | Yes           | Yes      | Yes      | Described                    | Described                 | Described            | 8                    |
| Gómez-Cardero and Rodríguez-Merchán | Yes           | Unclear  | Yes      | Not described                | Described                 | Not described        | 4                    |
| Kazak et al.                         | Yes           | Unclear  | Yes      | Not described                | Described                 | Described            | 6                    |
| Fajardo et al.                       | Yes           | Unclear  | Yes      | Not described                | Described                 | Not described        | 4                    |
| Joo et al.                           | Yes           | Yes      | Yes      | Described                    | Described                 | Described            | 8                    |
| Ikeuchi et al.                       | Yes           | Unclear  | Yes      | Not described                | Described                 | Described            | 6                    |
| Goyal et al.                         | Yes           | Yes      | Yes      | Described                    | Described                 | Described            | 8                    |
| Williams et al.                      | Yes           | Yes      | Yes      | Described                    | Described                 | Described            | 8                    |
relief and reducing total narcotic consumption has been confirmed. No consensus has been reached regarding the best infiltration sites, volumes, or timings of LIA, and additives of LIA are variable. For example, the addition of steroids and ketorolac has been questioned because of the potentially increased risk of intra-articular infection and possible renal and gut toxicity, respectively. LIA is still a recommended analgesic option, but it does not have the ability to improve the functional outcomes compared with placebo infiltration in patients undergoing TKA. Additional high-quality prospective randomized controlled trials focusing on different delivery methods (e.g., controlled and slow-release techniques), infiltration sites, volumes, timings, drug combinations, and local bandaging techniques are needed to prolong the action time of LIA and thus improve its effectiveness.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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Table 4. Meta-analysis results of outcome indicators.

| Outcome indicators                  | Studies (n) | Knees | P-value | Mean difference/odds ratio | Heterogeneity | Model |
|-------------------------------------|-------------|-------|---------|----------------------------|---------------|-------|
| Visual analogue scale score         | 5           | 358   | 0.003   | −0.66 (−1.08 to −0.23)     | 0.37 (6%)     | Fixed |
| Narcotic dose equivalent            | 8           | 507   | 0.03    | −1.01 (−1.90 to −0.11)     | <0.0001 (79%) | Random |
| Adverse effects                     | 4           | 301   | 0.84    | 0.93 (0.47 to 1.85)        | 0.67 (0%)     | Fixed |
| Range of motion                     | 4           | 196   | 0.20    | 9.33 (−5.02 to 23.69)      | <0.00001 (93%)| Random |
| Ambulation distance                 | 2           | 97    | 0.13    | 13.40 (−3.90 to 30.69)     | 0.48 (0%)     | Fixed |
| Straight-leg raise                  | 2           | 107   | 0.10    | 2.02 (0.88 to 4.62)        | 0.53 (0%)     | Fixed |
| Oxford score                        | 2           | 99    | 0.37    | 1.17 (−1.38 to 3.71)       | 0.86 (0%)     | Fixed |
| Length of hospital stay             | 4           | 310   | 0.50    | −0.31 (−1.20 to 0.58)      | 0.0002 (85%)  | Random |

CI, confidence interval.

References

1. White PF. The role of non-opioid analgesic techniques in the management of pain after ambulatory surgery. *Anesth Analg* 2002; 94: 577–585.
2. Kerr DR and Kohan L. Local infiltration analgesia: a technique for the control of acute postoperative pain following knee and hip surgery. *Acta Orthopaedica* 2008; 79: 173–183.
3. Ikeuchi M, Kamimoto Y, Izumi M, et al. Local infusion analgesia using intra-articular double lumen catheter after total knee arthroplasty: a double blinded randomized control study. *Knee Surg Sports Traumatol Arthrosc* 2013; 21: 2680–2684.
4. Goyal N, McKenzie J, Sharkey PF, et al. The 2012 Chitranjan Ranawat award: intra-articular analgesia after TKA reduces pain: a randomized, double-blinded, placebo-controlled, prospective study. *Clin Orthop Relat Res* 2013; 471: 64–75.
5. Joo JH, Park JW, Kim JS, et al. Is intra-articular multimodal drug injection effective in pain management after total knee arthroplasty? A randomized, double-blinded, prospective study. *J Arthroplasty* 2011; 26: 1095–1099.
6. Williams D, Petrucelli D, Paul J, et al. Continuous infusion of bupivacaine following total knee arthroplasty: a randomized control trial pilot study. *J Arthroplasty* 2013; 28: 479–484.
1. Oremus M, Wolfson C, Perrault A, et al. Interrater reliability of the modified Jadad quality scale for systematic reviews of Alzheimer’s disease drug trials. *Dement Geriatr Cogn Disord* 2001; 12: 232–236.

2. Huang Z, Ma J, Pei F, et al. Meta-analysis of temporary versus no clamping in TKA. *Orthopedics* 2013; 36: 543–550.

3. Browne C, Copp S, Reden L, et al. Bupivacaine bolus injection versus placebo for pain management following total knee arthroplasty. *J Arthroplasty* 2004; 19: 377–380.

4. Nechleba J, Rogers V, Cortina G, et al. Continuous intra-articular infusion of bupivacaine for postoperative pain following total knee arthroplasty. *J Knee Surg* 2005; 18: 197–202.

5. Andersen LO, Husted H, Otte KS, et al. High-volume infiltration analgesia in total knee arthroplasty: a randomized, double-blind, placebo-controlled trial. *Acta Anaesthesiol Scand* 2008; 52: 1331–1335.

6. Krenzel BA, Cook C, Martin GN, et al. Posterior capsular injections of ropivacaine during total knee arthroplasty: a randomized, double-blind, placebo-controlled study. *J Arthroplasty* 2009; 24(6 Suppl): 138–143.

7. Reeves M and Skinner MW. Continuous intra-articular infusion of ropivacaine after unilateral total knee arthroplasty: a randomized, double-blind, placebo-controlled study. *Anaesth Intensive Care* 2009; 37: 918–922.

8. Andersen LO, Husted H, Kristensen BB, et al. Analgesic efficacy of subcutaneous local anaesthetic wound infiltration in bilateral knee arthroplasty: a randomized, placebo-controlled, double-blind trial. *Acta Anaesthesiol Scand* 2010; 54: 543–548.

9. Essving P, Axelsson K, Kjellberg J, et al. Reduced morphine consumption and pain intensity with local infiltration analgesia (LIA) following total knee arthroplasty: a randomized double-blind study involving 48 patients. *Acta Orthopaedica* 2010; 81: 354–360.

10. Gómez-Cardero P and Rodríguez-Merchán EC. Postoperative analgesia in TKA: ropivacaine continuous intraarticular infusion. *Clin Orthop Relat Res* 2010; 468: 1242–1247.

11. Kazak Bengisun Z, Aysu Salviz E, Darcin K, et al. Intraarticular levobupivacaine or bupivacaine administration decreases pain scores and provides a better recovery after total knee arthroplasty. *J Anesth* 2010; 24: 694–699.

12. Fajardo M, Collins J, Landa J, et al. Effect of a perioperative intra-articular injection on pain control and early range of motion following bilateral TKA. *Orthopedics* 2011; 34: 354.

13. Gibbs DM, Green TP and Esler CN. The local infiltration of analgesia following total knee replacement: a review of current literature. *J Bone Joint Surg Br* 2012; 94: 1154–1159.

14. Labraca NS, Castro-Sánchez AM, Matarán-Peñarrocha GA, et al. Benefits of starting rehabilitation with 24 hours of primary total knee arthroplasty: randomized clinical trial. *Clin Rehabil* 2011; 25: 557–566.

15. Kurosaka K, Tsukada S, Seino D, et al. Local infiltration analgesia versus continuous femoral nerve block in pain relief after total knee arthroplasty: a randomized controlled trial. *J Arthroplasty* 2016; 31: 913–917.

16. Pandazi A, Kanellopoulos I, Kalimeris K, et al. Periarticular infiltration for pain relief after total hip arthroplasty: a comparison with epidural and PCA analgesia. *Arch Orthop Trauma Surg* 2013; 133: 1607–1612.

17. Kehlet H and Andersen LØ. Local infiltration analgesia in joint replacement: the evidence and recommendations for clinical practice. *Acta Anaesthesiol Scand* 2011; 55: 778–784.

18. Hoeft MA, Rathmell JP, Dayton MR, et al. Continuous, intra-articular infusion of bupivacaine after total-knee arthroplasty may lead to potentially toxic serum levels of local anesthetic. *Reg Anesth Pain Med* 2005; 30: 414–415.

19. Desai A, Ramankutty S, Board T, et al. Does intraarticular steroid infiltration increase the rate of infection in subsequent total knee replacements. *Knee* 2009; 16: 262–264.

20. Busch CA, Shore BJ, Bhandari R, et al. Efficacy of periarticular multimodal drug injection in total knee arthroplasty.
A randomized trial. *J Bone Joint Surg Am* 2006; 88: 959–963.

27. Fu P, Wu Y, Wu H, et al. Efficacy of intra-articular cocktail analgesic injection in total knee arthroplasty—a randomized controlled trial. *Knee* 2009; 16: 280–284.

**Appendix**

**Search strategy of PubMed:**

(infiltration[Title/Abstract] OR LIA[Title/Abstract]) AND (((((knee arthroplasty [Title/Abstract] OR total knee arthroplasty[Title/Abstract]) OR TKA[Title/Abstract]) OR knee replacement[Title/Abstract]) OR total knee replacement [Title/Abstract]) OR TKR[Title/Abstract]).

**Search strategy of Embase:**

total AND 'knee'/exp AND 'arthroplasty'/exp OR tka OR (total AND 'knee'/exp AND replacement) OR tkr AND (infiltration OR lia OR ('wound'/exp AND instillation))

**Search strategy of Cochrane Central Register of Controlled Trials (CENTRAL):**

#1 TKA in Trials

#2 total knee arthroplasty in Trials

#3 TKR in Trials

#4 total knee replacement in Trials

#5 #1 or #2 or #3 or #4 in Trials

#6 Local Anesthesia in Trials

#7 Local anesthetics in Trials

#8 Local infiltration analgesia in Trials

#9 LIA in Trials

#10 Tissue infiltration in Trials

#11 wound instillation in Trials

#12 #6 or #7 or #8 or #9 or #10 or #11 in Trials

#13 #5 and #12 in Trials