Meta-Analysis

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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.[1]

A comparatively new technique known as local infiltration analgesia (LIA), popularized by doctors from Sydney, Australia,[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.[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).[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.

Methods

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 *Appendix*.

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.

Quality assessment of the included studies

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

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[3–6,9–18] 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.[4,6,9,10,12] 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, −0.66; 95% CI, −1.08 to −0.23; $P = 0.003$).

Narcotic dose equivalent

Eight of the included articles reported the narcotic dose equivalent at 24 and/or 48 hours postoperatively.[3,4,6,9,10,12,13,15] 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, −1.90 to −0.11; $P = 0.03$).

Adverse effects

Four trials provided data regarding adverse effects.[4,9,10,13] 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

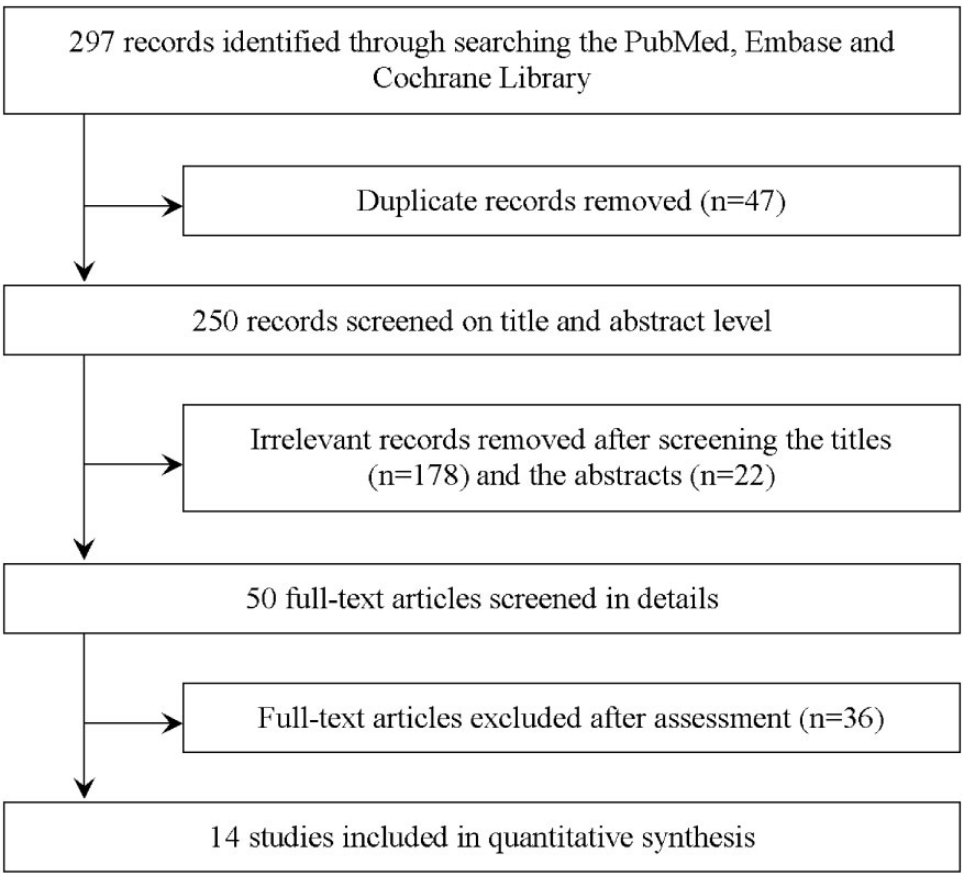

Figure 1. Flow chart of study inclusion process.

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

Table 1. General demographic characteristics.

Study	Pts	Knees			Sex		Mean age, y	BMI, kg/m^2	ASA		Diagnosis	Total follow-up
		Total	LIA	NS	M	F			I/II	III		
Browne et al.	60	60	30	30	21	39	67	–	–		OA (57)	1 d
Nechleba et al.	30	30	14	16	11	19	65	–	–		OA (60)	3 d
Andersen et al.	12	24	12	12	7	5	69	29	11	1	–	2 d
Krenzel et al.	66	67	35	32	23	43	66.2	–	–		OA (63), RA (3)	1 d
Reeves and Skinner	61	61	31	30	25	36	69.5	–	48	12	–	3 d
Andersen et al.	16	32	16	16	9	7	63	31	16	0	–	1 d
Essving et al.	48	48	24	24	22	26	71	–	47	1	OA (48)	3 m
Gómez-Cardero and Rodríguez-Merchán	50	50	25	25	19	31	71.3	–	–		OA (48)	1 m
Kazak et al.	60	60	40	20	11	49	69.7	–	45	15	–	2 d
Fajardo et al.	30	60	30	30	7	23	63.5	–	–		OA (30)	3 d
Joo et al.	286	572	286	286	14	272	79.1	27.4	–		OA (286)	14 d
Ikeuchi et al.	40	40	20	20	12	28	75.5	–	–		OA (40)	3 m
Goyal et al.	150	150	75	75	65	85	63.9	30	–		OA (150)	3 d
Williams et al.	51	51	26	25	21	30	66.5	29.4	16	35	OA (51)	1 y

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.

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[6,15] 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, −1.38 to 3.71).

LOS. Data regarding the hospital LOS were available in four articles.[4,6,13,15] 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 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 2. Anesthetic and surgical information.

Study	Surgical approach	Infiltration information			Main analgesia schemes	Length of surgery, minutes	
		Main drug	Supplements	Timing		LIA	NS
Browne et al.	MP, MV	Bupivacaine	Epinephrine	Intra-op	PCA morphine, IM narcotics, Oral narcotics	106	100
Nechleba et al.	MP	Bupivacaine	None	Post-op	PCA morphine, Oral narcotics	–	–
Andersen et al.	MP	Ropivacaine	Epinephrine	Post-op	PCA morphine, Oral narcotics	109	109
Krenzel et al.	MP	Ropivacaine	None	Intra to post-op	PCA morphine, FNB, Oral narcotics	–	–
Reeves and Skinner	MP	Ropivacaine	None	Post-op	SQ morphine, FNB, Oral narcotics	114	103
Andersen et al.	MP	Ropivacaine	None	Intra to post-op	PCA morphine, Oral narcotics	100	100
Essving et al.	MP	Ropivacaine	Epinephrine, Ketorolac	Intra to post-op	PCA morphine, Oral narcotics	93	87
Gómez-Cardero and Rodríguez-Merchán	MV	Ropivacaine	None	Post-op	SQ and IV pethidine, Oral narcotics	–	–
Kazak et al.	MP	Bupivacaine, Levobupivacaine	Epinephrine	Intra and post-op	PCA tramadol, Oral narcotics	102	85
Fajardo et al.	MP, SV	Bupivacaine	Epinephrine, Ketorolac, Morphine	Intra-op	Oral narcotics	–	–
Joo et al.	MP	Bupivacaine	Epinephrine, Methylprednisolone, Morphine	Intra-op	PCA morphine, Oral narcotics, Fentanyl patch	73	73

(continued)

Table 2. Continued.

Study	Surgical approach	Infiltration information			Main analgesia schemes	Length of surgery, minutes	
		Main drug	Supplements	Timing		LIA	NS
Ikeuchi et al.	MP	Ropivacaine	Epinephrine, Dexamethasone, Isepamicin	Intra to post-op	PCA fentanyl, Oral narcotics	115	119
Goyal et al.	MP	Bupivacaine	None	Post-op	Oral narcotics	–	–
Williams et al.	MP	Bupivacaine	None	Post-op	PCA morphine, Oral narcotics	–	–

MP, medial parapatellar approach; MV, midvastus approach; SV, subvastus approach; PCA, patient-controlled analgesia; IM, intramuscular; FNB, femoral nerve block; SQ, subcutaneous; IV, intravenous; LIA, local infiltration analgesia; NS, normal saline infiltration.

consistent with a previous systematic review.[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.[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.[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[21] or patient-controlled analgesia.[22]

Compared with a previous non-quantitative systematic review,[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[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
	Described	Appropriate	Described	Appropriate					
Browne et al.	Yes	Unclear	Yes	Unclear	Not described	Described	Described	Described	5
Nechleba et al.	Yes	Unclear	Yes	Unclear	Not described	Not described	Described	Described	4
Andersen et al.	Yes	Yes	Yes	Yes	Not described	Described	Not described	Described	6
Krenzel et al.	Yes	Unclear	Yes	Unclear	Not described	Described	Not described	Described	4
Reeves and Skinner	Yes	Unclear	Yes	Yes	Described	Not described	Described	Described	6
Andersen et al.	Yes	Unclear	Yes	Yes	Not described	Described	Not described	Described	5
Essving et al.	Yes	Yes	Yes	Yes	Described	Described	Described	Described	8
Gómez-Cardero and Rodríguez-Merchán	Yes	Unclear	Yes	Unclear	Not described	Described	Not described	Described	4
Kazak et al.	Yes	Unclear	Yes	Yes	Not described	Described	Described	Described	6
Fajardo et al.	Yes	Unclear	Yes	Unclear	Not described	Described	Not described	Described	4
Joo et al.	Yes	Yes	Yes	Yes	Described	Described	Described	Described	8
Ikeuchi et al.	Yes	Unclear	Yes	Yes	Not described	Described	Described	Described	6
Goyal et al.	Yes	Yes	Yes	Yes	Described	Described	Described	Described	8
Williams et al.	Yes	Yes	Yes	Yes	Described	Described	Described	Described	8

Table 4. Meta-analysis results of outcome indicators.

Outcome indicators	Studies (n)	Knees	*P*-value	Mean difference/odds ratio Value (95% CI)	Heterogeneity *P*-value (I^2)	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.

relief and reducing total narcotic consumption has been confirmed. No consensus has been reached regarding the best infiltration sites, volumes, or timings of LIA,[23,24] 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[25] and possible renal and gut toxicity,[2] 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,[26,27] 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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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