Does the addition of iPACK to adductor canal block in the presence or absence of periarticular local anesthetic infiltration improve analgesic and functional outcomes following total knee arthroplasty? A systematic review and meta-analysis

Nasir Hussain [1], Richard Brull [2], Brendan Sheehy,[1] Michael Dasu,[1] Tristan Weaver,[1] Faraj W Abdallah [3]

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[1]Department of Anesthesiology, Ohio State University Wexner Medical Center, Columbus, Ohio, USA
[2]Department of Anesthesiology, Toronto Western Hospital, Toronto, Ontario, Canada
[3]Faculty of Medicine, Anesthesia, University of Ottawa, Ottawa, Ontario, Canada

Correspondence to
Dr Faraj W Abdallah; mank_abda@yahoo.ca

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ABSTRACT

Background When combined with adductor canal block (ACB), local anesthetic infiltration between popliteal artery and capsule of knee (iPACK) is purported to improve pain following total knee arthroplasty (TKA). However, the analgesic benefits of adding iPACK to ACB in the setting of surgeon-administered periarticular local infiltration analgesia (LIA) are unclear.

Objectives To evaluate the analgesic benefits of adding iPACK to ACB, compared with ACB alone, in the setting of LIA following TKA.

Evidence review We conducted a meta-analysis of randomized trials comparing the effects of adding iPACK block to ACB versus ACB alone on pain severity at 6 hours postoperatively in adult patients undergoing TKA. We a priori planned to stratify analysis for use of LIA. Opioid consumption at 24 hours, functional recovery, and iPACK-related complications were secondary outcomes.

Findings Fourteen trials (1044 patients) were analyzed. For the primary outcome comparison in the *presence* of LIA (four trials, 273 patients), adding iPACK to ACB did not improve postoperative pain at 6 hours. However, in the *absence* of LIA (eight trials, 631 patients), adding iPACK to ACB reduced pain by a weighted mean difference (WMD) (95% CI) of −1.33 cm (−1.57 to −1.09) (p<0.00001). For the secondary outcome comparisons in the *presence* of LIA, adding iPACK to ACB did not improve postoperative pain at all other time points, opioid consumption or functional recovery. In contrast, in the *absence* of LIA, adding iPACK to ACB reduced pain at 12 hours, and 24 hours by a WMD (95% CI) of −0.98 (−1.79 to −0.17) (p=0.02) and −0.69 (−1.18 to −0.20) (p=0.006), respectively, when compared with ACB alone, but did not reduce opioid consumption. Functional recovery was also improved by a log(odds ratio) (95% CI) of 1.28 (0.45 to 2.11) (p=0.003). No iPACK-related complications were reported.

Conclusion Adding iPACK to ACB in the setting of periarticular LIA does not improve analgesic outcomes following TKA. In the absence of LIA, adding iPACK to ACB reduces pain up to 24 hours and enhances functional recovery. Our findings do not support the addition of iPACK to ACB when LIA is routinely administered.

BACKGROUND

Managing postoperative pain following total knee arthroplasty (TKA) continues to be challenging. Despite the relatively recent advent of the adductor canal block (ACB) and surgeon-administered periarticular local infiltration analgesia (LIA) for TKA, moderate-to-severe pain[1] localized to the posterior knee remains commonplace during the first 24 hours postoperatively.[2] Such pain interferes with early functional recovery,[3] particularly within the context of clinical pathways[4] featuring outpatient models of care.[5] The infiltration between popliteal artery and capsule of knee (iPACK) block, an acronym for local anesthetic infiltration between the popliteal artery and capsule of the knee, is a relatively novel ultrasound (US)-guided technique purported to improve posterior knee pain post-TKA.[6] However, US-guided iPACK may be redundant, and its incremental benefit limited, when local anesthetic is routinely administered intraoperatively by surgeons as part of periarticular LIA. Furthermore, the potential for foot-drop associated with iPACK, stemming from local anesthetic spread to the peroneal branch of the sciatic nerve, can impede early physiotherapy.[7] Importantly, evidence on the topic is conflicting, with some trials suggesting that adding iPACK to ACB improves patient outcomes,[8 9] while others failed to detect any benefit.[10–12]

This systematic review and meta-analysis seeks to evaluate the analgesic benefits of adding iPACK block to ACB, compared with ACB alone, in the setting of LIA for patients undergoing TKA. The primary outcome of this review was rest pain at 6 hours. Analgesic consumption, rest pain scores at other time points, functional recovery and iPACK-related complications were set as secondary outcomes.

METHODS

This manuscript was written in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement guidelines.[13] We sought randomized controlled trials that evaluated the benefits of adding iPACK to ACB compared with ACB alone in the setting of LIA for postoperative

pain management following TKA. The study protocol was registered with the international prospective register of systematic reviews (PROSPERO): CRD42020210773.

Eligibility criteria

Randomized trials of adult patients undergoing unilateral or bilateral knee arthroplasty allocated to receive either iPACK in combination with ACB compared with ACB alone in the setting of LIA were considered for inclusion. Studies were eligible if ACB was performed in both groups. Surgeries completed under neuraxial or general anesthesia were accepted. No restrictions were imposed on language, and non-English studies were translated using the assistance of online translation.

Search methods

A search strategy was developed by an evidence-based medicine librarian (T.S.) for the US Library of Medicine (MEDLINE) database, the Cochrane Database of Systematic Reviews, and the Excerpta Medica (EMBASE) database. The databases were searched from July 2012 (first description of iPACK block) to March 1, 2021. The full search strategy for the MEDLINE database can be viewed in online supplemental appendix A. We also electronically searched the following clinical trial registries for additional citations: www.clinicaltrials.gov (US Clinical Trials Registry); https://apps.who.int (International Clinical Trials Registry Platform); https://dkrs.de (DRKS-German Clinical Trials Register); www.ctri.nic.in (Indian Clinical Trials Registry); https://www.irct.ir (Iranian Clinical Trials Registry); http://www.chictr.org.cn (Chinese Clinical Trials Registry); and http://www.clinicaltrials.in.th (Thai Clinical Trials Registry). Published abstracts of the following international conferences were also searched: American Society of Anesthesiologist (ASA) 2013–2020, American Society of Regional Anesthesia and Pain Medicine (ASRA) 2013–2020, International Anesthesia Research Society (IARS) 2013–2020, and the European Society of Anesthesiology (ESA) 2015–2020. Finally, the citation lists of all included studies were closely examined to identify any other potentially relevant trials.

Selection of included studies

The title and abstracts obtained from the search strategy were reviewed independently by two reviewers (NH and BS). All potentially eligible citations had their full-text versions retrieved for additional consideration by the same two reviewers. In the case of disagreement on full-text inclusion, a discussion was initiated until a consensus was reached. If a final decision could not be reached by discussion, a third reviewer assessed the article in question (FWA) and made the final decision.

Although LIA is currently the care standard in many centers, a preliminary search of the literature revealed that many trials[8 10 11 14–20] excluded this analgesic component when evaluating the benefits of adding iPACK to ACB. We therefore decided to dichotomize (subdivide) the patient population and evaluation of outcomes based on presence or absence of LIA.

Data extraction

A reviewer (NH) created a standardized data extraction form. Data extraction was then carried out in duplicate independently by two reviewers (NH and BS). Any disagreements in data extraction between the two reviewers was discussed until a consensus was reached. If a final decision could not be reached by discussion, a third reviewer assessed the article in question (FWA) and made the final decision. The data extraction form collected information regarding: publication year; type of surgery; primary outcome of study; iPACK technique (including dose and volume of local anesthetic); ACB technique (including dose, volume, and use of catheter); LIA technique; preoperative, intraoperative and postoperative analgesic regimen; rest pain scores at all time points; analgesic consumption at all reported time intervals; postoperative function and the tool used for measurement; opioid related side effects; and iPACK-related complications. Data presented in graphical format was extracted using a graph digitizing software (GraphClick, Arizona Software, USA). When needed, authors of included studies were contacted for additional methodological trial information and outcome data.

Assessment of methodological quality

The methodological quality of each included trial was assessed using the Cochrane Collaboration Risk of Bias tool. Specifically, each study was evaluated for random sequence generation; allocation concealment; level of blinding of study personnel and outcome assessors; loss to follow-up and selective outcome reporting.[21] The overall methodological quality of evidence across statistically pooled outcomes was assessed using the guidelines created by the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) working group.[22 23] Pooled outcomes were classified as being of high quality (⊕⊕⊕⊕), moderate quality (⊕⊕⊕⊖), low quality (⊕⊕⊖⊖), or very low quality (⊕⊖⊖⊖) evidence.

Primary and secondary outcomes

We designated knee pain at rest reported at 6 hours postoperatively, as measured on a numerical rating scale (NRS), as the primary outcome. The 6-hour time point enables assessment of the analgesic effectiveness of iPACK during its peak effect, based on the duration of local anesthetics used.

Secondary outcomes of this review included postoperative opioid consumption in milligrams of oral morphine equivalents at postanesthesia care unit (PACU) and 24 hours; acute postoperative rest pain severity in the PACU (1 hour), and at 12 and 24 hours; opioid related side effects (postoperative nausea and vomiting, excessive sedation, respiratory depression, pruritus, urinary retention, or constipation); functional recovery; and iPACK-related complications (foot drop (sciatic nerve block), hematoma, nerve injury or local anesthetic systemic toxicity).

Measurement of outcome data

All postoperative pain scores were converted to an equivalent score on the 0–10 cm NRS pain score, with 0 corresponding to no pain and 10 corresponding to worst pain imaginable. All analgesic consumption data were converted to milligrams of oral morphine equivalents.

Statistical analysis

The mean and SD were extracted for all continuous outcome data. If not available, approximations were made using reported data. Specifically, the median and IQR, median and range, or mean and 95% CI were used to approximate these values, based on whichever was available.[24] If needed, dichotomous outcome data were converted to continuous form represented by a mean and SD.[25] Finally, the median was used to approximate the mean in situations when statistical conversions could not be made.[26] Dichotomous outcome data related to adverse events was converted to overall incidence numbers.

Table 1 Study characteristics and outcomes of interest assessed in included studies

Author (year)	Surgery	N	Groups (n)	Surgical anesthesia	Primary outcome	Rest pain scores		Dynamic pain scores		Opioid consumption		Postoperative function	Opioid-related adverse effects	Block-related complications
						Early	Late	Early	Late	Early	Late			
iPACK + ACB vs ACB in the presence of LIA														
Okunlola 2020[41]*	Unilateral TKA	92	1. cACB + iPACK + LIA (46) 2. cACB + LIA (46)	Spinal	Opioid consumption	•				•		•		
Li *et al* (2020)[9]	Unilateral TKA	200	1. sACB + iPACK + Lateral femoral cutaneous + LIA (50) 2. sACB + iPACK + LIA (50) 3. sACB + Lateral femoral cutaneous + LIA (50) 4. sACB + LIA (50)	GA	Pain scores	•	•	•	•	•	•	•	•	•
Vichainarong *et al* (2020)[12*]	Unilateral TKA	72	1. cACB + iPACK + LIA (36) 2. cACB + LIA (36)	Spinal	Opioid consumption	•	•	•	•	•	•	•	•	•
Singtana (2020)[40*]	Unilateral TKA	16	1. sACB + iPACK + LIA (8) 2. sACB + LIA (8)	Spinal	Pain scores	•	•	•	•	•	•		•	
iPACK +ACB vs ACB in the absence of LIA														
Ochroch *et al* (2019)[8]	Unilateral TKA	120	1. cACB + iPACK (60) 2. cACB (60)	Spinal	Pain scores	•				•		•		•
Chia *et al* (2020)[18]	Unilateral TKA	57	1. cACB + iPACK (29) 2. cACB (28)	N/S	Opioid consumption	•				•		•		
Ling *et al* (2020)[14]	Unilateral TKA	80	1. sACB + iPACK (40) 2. sACB (40)	GA	N/S	•	•	•	•		•	•	•	•
Patterson *et al* (2020)[10]	Unilateral TKA	69	1. cACB + iPACK (35) 2. cACB (34)	Spinal or GA	Opioid consumption	•		•		•	•	•	•	•
Tak *et al* (2020)[11]	Unilateral TKA	180	1. sACB + iPACK (60) 2. sACB (60) 3. cACB (60)	Spinal	Pain scores	•	•		•		•	•		•
Vijay (2020)[19]	Unilateral TKA	100	1. cACB + iPACK (50) 2. cACB (50)	Spinal	N/S	•				•			•	•
Wang *et al* (2020)[16]	Unilateral TKA	120	1. sACB + iPACK (40) 2. sACB (40) 3. Periarticular infiltration (40)	GA	Pain scores	•	•	•	•		•	•	•	•
Zadoroznoijs 2020[15]	Unilateral TKA	18	1. sACB + iPACK (10) 2. sACB (8)	Spinal	Pain scores	•	•	•	•	•		•	•	
Zhou and Cheng (2020)[17]	Unilateral TKA	60	1. sACB + iPACK (30) 2. sACB (30)	GA	N/S	•	•	•	•			•	•	

Continued

Table 1 Continued

Author (year)	Surgery	N	Groups (n)	Surgical anesthesia	Primary outcome	Rest pain scores		Dynamic pain scores		Opioid consumption		Postoperative function	Opioid-related adverse effects	Block-related complications
						Early	Late	Early	Late	Early	Late			
Amin and Abotaleb (2021)[20]	Unilateral TKA	60	1. sACB + iPACK (30) 2. sACB (30)	Spinal	Pain scores	•	•				•		•	•

Early: ≤24 hours; Late: >24 hours.
*Data provided from author on clinical trials registry.
cACB, continuous adductor canal block; GA, general anesthesia; iPACK, infiltration between popliteal artery and capsule of knee; LIA, local infiltration analgesia; N/S, not specified; PACU, postanesthesia care unit; sACB, single shot adductor canal block; TKA, total knee arthroplasty.

For postoperative functional recovery, we anticipated that authors may use various tools and scales. Therefore, we a priori planned to report the (1) weighted mean difference (WMD) of all studies if the same continuous scale was used; (2) standardized mean difference (SMD) and corresponding log(OR) if different scales that measured the same theme were used; and (3) OR if all functional recovery was reported in a binary format. Conversion from SMD to log(OR) was done using the formula log(OR)=SMD ($\pi/\sqrt{3}$).[27 28]

Meta-analysis

Statistical pooling was performed for all outcomes when data were available from at least three studies. For continuous outcome data, we used the inverse variance method with random-effects modeling in anticipation of the presence of clinical difference among trials. For dichotomous outcome data, we used the Mantel-Haenszel random-effects method.[29] For the primary outcome of this review, rest knee pain at 6 hours, a WMD with a 95% CI was calculated. A two tailed p value of <0.05 was designated as the threshold of statistical significance.

A WMD with a 95% CI and a OR with 95% CI were calculated for continuous and dichotomous secondary outcomes, respectively. We a priori adjusted the threshold of statistical significance for the pooled secondary outcomes in each comparison using the Bonferroni-Holm correction (P_c, corrected threshold of statistical significance) to account for the secondary outcomes analyzed.[30] A 95% CI was also used for all secondary outcomes.

Interpretation

The minimal clinically important difference (MCID) was used for interpretation of all pain scores presented in this review.[31] For a single time-point, the MCID of NRS acute postoperative pain has been reported to be 1.0 cm.[32]

Exploring heterogeneity

The degree of heterogeneity was evaluated for all statistically pooled outcomes by calculation of an I^2 statistic. Significant heterogeneity was considered to be present with I^2 values >50%.[24] When significant heterogeneity was present in the primary outcome of this review, sensitivity analysis was performed based on preidentified clinical factors that may affect this outcome, namely, (1) ACB technique (single shot vs catheter based) and (2) postoperative analgesic regimen (unimodal opioid-based vs multimodal analgesia).

Assessment of publication bias

The risk of publication bias assessed using the Egger's Regression test[33] for all outcomes examined, and a funnel plot for risk of bias was constructed for the primary outcome.

Data management

Sensitivity analysis was performed using Comprehensive Meta-Analysis V.3.0 (Engelwood, USA). Review Manager Software (RevMan V.5.2; Nordic Cochrane Centre, Cochrane Collaboration) was used to create forest and funnel plots.

RESULTS

Study characteristics

The initial search strategy identified 30 unique citations; 19 were excluded due to being an ineligible study design (n=16) or ineligible comparator (n=3). Of the remaining 11 citations, 6[34–39] were excluded (ineligible study design (n=2)[37 38] ; ineligible comparator (n=3)[34–36] ; and ineligible study population

Table 2 Local anesthetic techniques for iPACK and analgesic regiments of included studies

Author (year)	Preincisional analgesia	Surgical analgesia	Supplemental postoperative analgesia	iPACK characteristics	
				Block timing	LA bolus
iPACK +ACB vs ACB in the presence of LIA					
Okunlola (2020)[41]*	PO acetaminophen 975 mg once; PO celecoxib 400 mg once; PO oxycodone 10 mg once	Intravenous ketamine 0.5 mg/kg; Spinal anesthesia	PO acetaminophen 975 q6 hours; PO celecoxib 200 mg q12 hours; PO pregabalin 50 mg q12 hours; PO oxycodone 2.5–10 mg q3 hours prn; intravenous hydromorphone 0.4 mg q3 hours prn; LIA mixture (ropivicaine 300 mg, morphine 10 mg, ketorolac 30 mg, epinephrine 600 mcg)	Post-Op	20 mL 0.25% ropivacaine
Li *et al* (2020)[9]	N/S	N/S	PO loxoprofen 60 mg q12 hours; intramuscular morphine 10 mg prn	Pre-Op	20 mL 0.2% ropivacaine + Epi
Vichainarong *et al* (2020)[12*]	PO acetaminophen 650 mg once; PO celecoxib 400 mg once	Spinal anesthesia	Intravenous ketorolac 15 mg for two doses then PO celecoxib 400 mg daily; PO acetaminophen 650 mg q6 hours; PO pregabalin 75 mg daily; PO tramadol q8 hours; intravenous morphine 2 mg prn; LIA mixture (levobupivicaine 100 mg, ketorolac 30 mg, epinephrine. 3 mg diluted in 80 mL isotonic saline solution)	Pre-Op	20 mL 0.25% levobupivacaine + Epi
Singtana (2020)[40*]	N/S	Spinal anesthesia	PO nimesulide 100 mg q12 hours; PO norgesic 450–35 mg daily; PO tramadol 50 mg daily; PO paracetamol 500 mg prn; intravenous morphine 3–4 mg prn	Pre-Op	15 mL 0.25% bupivacaine + Epi + Dex
iPACK +ACB vs ACB in the absence of LIA					
Ochroch *et al* (2019)[8]	PO acetaminophen 1000 mg once; PO gabapentin 300 mg once; PO celecoxib 200 mg once	Spinal anesthesia (per discretion); intravenous ketamine 0.3–0.5 mg/kg; intravenous ketorolac 15 mg	PO acetaminophen 1000 mg three times a day for 3 days; PO 200 mg celecoxib two times per day for 3 days; PO gabapentin 300 mg two times per day for 7 days; PO oxycodone 5–10 mg q4 hours prn	Pre-Op	20 mL 0.5% ropivacaine
Chia *et al* (2020)[18]	N/S	N/S	N/S	N/S	N/S
Ling et al (2020)[14]	N/S	Intravenous sufentanil 0.2–0.4 mcg/kg once; intravenous sufentanil 0.10–0.15 mcg/kg prn; intravenous remifentanil 10–15 mcg/kg/hour	Intravenous parecoxib 20–40 mg prn; PCA sufentanil	Pre-Op	15 mL 0.2% ropivacaine
Patterson *et al* (2020)[10]	PO pregabalin 150 mg once	Intravenous ketamine 0.25 mg/kg; spinal anesthesia (per discretion)	Intravenous acetaminophen 1 g once; PO acetaminophen 1 g q6 hours; PO celecoxib 400 mg once; PO celecoxib 200 mg daily; PO pregabalin 75 mg or 150 mg daily; PO oxycodone prn; intravenous morphine prn; intravenous hydromorphone prn	Pre-Op	20 mL 0.25% ropivacaine + Epi
Tak *et al* (2020)[11]	PO celecoxib 200 mg once; PO gabapentin 300 mg once	Spinal anesthesia	Intravenous paracetamol 1 g q8 hours for 3 days; PO paracetamol 1 g q8 hours for 4 weeks; PO gabapentin 300 mg once daily for 4 weeks; PO oxycodone prn; intravenous morphine prn	Pre-Op	20 mL 0.2% ropivacaine
Vijay (2020)[19]	N/S	Spinal anesthesia	Intramuscular diclofenac sodium 75 mg two times per day; intravenous paracetamol 1 g q6 hours	Intra-Op	10 mL 0.25% bupivacaine
Wang et al (2020)[16]	PO celecoxib 200 mg q12 hours	N/S	PO celecoxib 200 mg q12 hours; PO oxycodone 10 mg q12 hours; intravenous morphine 10 mg prn	Pre-Op	20 mL 0.2% ropivacaine + Epi
Zadoroznijs 2020[15]	PO etoricoxib 90 mg once	Spinal anesthesia	Intravenous acetaminophen 1 g q8 hours for 1 day; PO acetaminophen 500 mg q6 hours for 5 days; SQ morphine 5 mg–10 mg prn	Pre-Op	20 mL 0.375% ropivacaine
Zhou and Cheng (2020)[17]	N/S	Intravenous remifentanil infusion	PCA sufentanil	Pre-Op	30 mL 0.25% ropivacaine
Amin and Abotaleb (2021)[20]	N/S	Spinal anesthesia	Intravenous morphine 3 mg prn	Pre-Op	15 mL 0.5% bupivacaine

**Data provided from author on clinical trials registry.
cACB, continuous adductor canal block; Dex, dexamethasone; Epi, epinephrine; iPACK, infiltration between popliteal artery and capsule of knee; LA, local anesthesia; LIA, local infiltration analgesia; N/S, not specified; PCA, patient-controlled analgesia; PO, oral; prn, as needed; q, every; sACB, single shot adductor canal block; USG, ultrasound guidance.

(n=1)[39]) and 5 trials[8–12] were included. Hand searching of conference proceedings, trial registries, and Gray literature identified an additional nine[14–20 40 41] trials that satisfied the eligibility criteria. Thus, a total of 14 trials[8–12 14–20 40 41] were included in this review; 10[8–12 15 16 18 40 41] of these were prospectively registered with clinical trial registries, 1[20] was started prior to 2019, and we could not ascertain the registration status for the remaining 3 due to language barriers[14 17] or inability to communicate with the authors.[14 17 19] The authors of four[12 15 40 41] trials provided supplementary methodological details facilitating this review. A full flow diagram of study inclusion can be viewed in online supplemental appendix B.

The clinically relevant outcomes and trial characteristics are summarized in table 1. The 14 trials[8–12 14–20 40 41] encompassed a total of 1044 patients. The comparisons included 4[9 12 40 41] conducted in the presence of periarticular LIA, and another 10[8 10 11 14–20] conducted in the absence of LIA. Unilateral TKA was performed in all studies under spinal anesthesia in eight trials[8 11 12 15 19 20 40 41] or general anesthesia in four trials.[9 14 16 17] One study[10] permitted both spinal and general anesthesia, and another[18] did not specify the nature of surgical anesthetic used. All included trials assessed postoperative pain severity scores at rest[8–12 14–20 40 41] in the first 24 hours, and eight studies assessed postoperative opioid consumption in the same time frame.[8–10 12 15 18 19 40 41] Finally, it was noted that the results reported in one study[11] were conflicting, with results reported in text and conclusions being different from those reported in the accompanying tables.

The iPACK and ACB techniques and analgesic regimens are presented in table 2. The iPACK blocks were performed preoperatively in 11 studies,[8–12 14–17 20 40] postoperatively in 1,[41] and intraoperatively in 1[19]; 1 study did not specify the timing of iPACK block performance.[18]

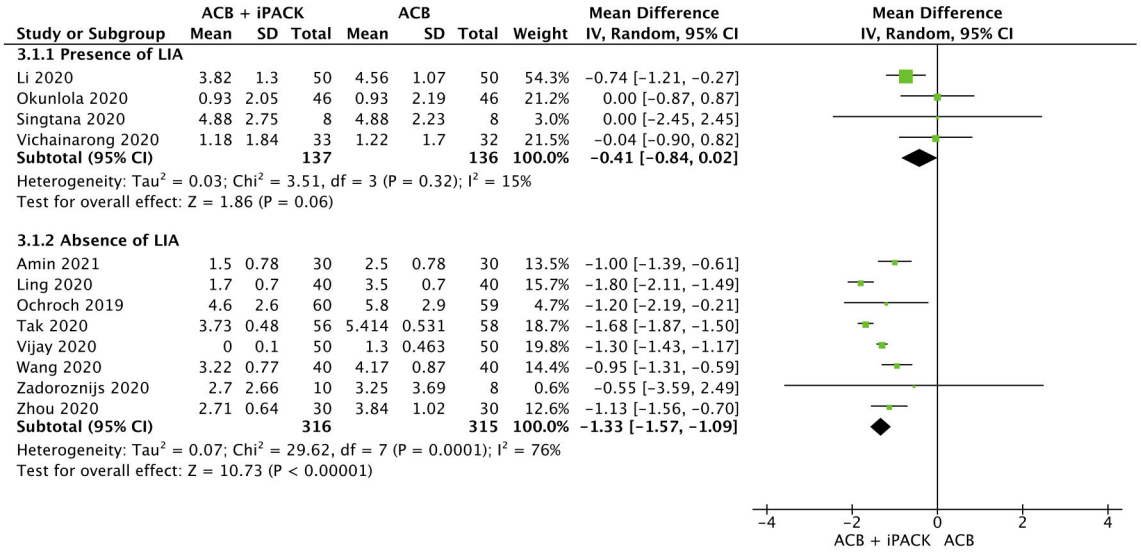

Figure 1 Forest plot of rest pain scores at 6 hours postoperatively for (A) ACB versus ACB with infiltration in the iPACK in the *presence* of LIA) and (B) ACB versus ACB with iPACK in the *absence* of LIA. Pooled estimates of the weighted mean difference are shown with 95% CIs. Pooled estimates are represented as diamonds and lines represent the 95% CIs. ACB, adductor canal block; iPACK, interspace between the popliteal artery and capsule of the knee; LIA, local infiltration analgesia.

The risk of bias assessment for all included studies can be viewed in online supplemental appendix C.

Primary outcome

Rest pain at 6 hours

A total of four studies[9 12 40 41] (273 patients; ACB + iPACK: 137, ACB: 136) evaluated the benefits of adding iPACK block to ACB in the presence of periarticular LIA. Adding iPACK block did not improve postoperative pain severity at 6 hours, with a WMD (95% CI) of −0.41 cm (−0.84 to 0.02) (p=0.06, I^2=15%) (figure 1A). This analysis was characterized by a low heterogeneity (I^2=15%). Although visual inspection of the funnel plot suggested that smaller studies reported greater treatment effects, Egger's test indicated the absence of publication bias (p=0.27) (online supplemental appendix D). The GRADE of evidence was rated as moderate due to imprecision in the pooled estimate.

In contrast, eight studies[8 11 14–17 19 20] (631 patients; ACB + iPACK: 316, ACB: 315) evaluated the effect of adding iPACK to ACB on postoperative rest pain at 6 hours in the absence of periarticular LIA. Adding iPACK reduced rest pain at 6 hours by a WMD (95% CI) of −1.33 cm (−1.57 to −1.09) (p<0.00001, I^2=76%) (figure 1B). This difference surpassed the predesignated threshold for clinical importance of 1.0 cm. Results for this outcome were characterized by high heterogeneity (I^2=77%). Sensitivity analysis by excluding studies that used continuous (catheter based) ACB[8 19] did not decrease heterogeneity. However, the heterogeneity was resolved (I^2=2%) by excluding studies that used unimodal opioid-based analgesic regimens[14 17 20] and the one study[11] with conflicting results. Although visual inspection of the funnel plot suggested that smaller studies reported greater treatment effects, Egger's test indicated the absence of publication bias (p=0.56) (online supplemental appendix D). The GRADE of evidence was rated as moderate due to significant heterogeneity in the overall pooled estimate.

To ensure adherence to the journal's policy[42] regarding prospective trial registration, we also conducted an additional post-hoc sensitivity analysis on the primary outcome by excluding all four trials[14 17 19 20] for which we could not confirm prospective registration. The new WMD (95% CI) was −1.29 (−1.85 to −0.72), indicating that the results were robust to this sensitivity analysis.

Secondary outcomes

Rest pain in PACU, 12 hours and 24 hours

A total of four studies[9 12 40 41] (n=273; ACB + iPACK: 137, ACB: 136) evaluated the effect of adding iPACK block to ACB in the presence of periarticular LIA on postoperative pain in the PACU and at the 12-hour and 24-hour time points. Adding iPACK did not improve pain severity at any of these time points (table 3). All p values were robust in directionality to the Bonferroni-Holm correction (PACU, $p>P_c$=0.05; 12 hours, $p>P_c$=0.01; and 24 hours, $p>P_c$=0.017). The GRADE of evidence was rated as moderate for the measurements in PACU and 12 hours, and high for 24 hours (online supplemental appendix E).

In contrast, adding iPACK block to ACB in the absence of periarticular LIA was evaluated by 5[10 14 16 18 20] (n=345; ACB + iPACK: 173, ACB: 172), 6[8 14 16 17 19 20] (n=499; ACB + iPACK: 250, ACB: 249), and 10[8 10 11 14–20] (n=757; ACB+iPACK: 380, ACB: 377) trials at the PACU, 12-hour, and 24-hour time points, respectively. In the absence of LIA, the addition of iPACK to ACB reduced rest pain at 12 and 24 hours by a WMD (95% CI) of −0.98 (−1.79 to −0.17) (p=0.02, I^2=97%) and −0.69 (−1.18 to −0.20) (p=0.006, I^2=94%), respectively; however, these differences did not surpass predesignated threshold for clinical importance of 1.0 cm on a NRS. No differences in rest pain scores were observed between the two groups in the PACU (table 3). The p values were robust in directionality to Bonferroni-Holm correction at PACU ($p>P_c$=0.025) and 24 hours ($p<P_c$=0.01); however non-significance was obtained at 12 hours ($p>P_c$=0.012). The GRADE of evidence was rated as low at PACU and moderate for all other time points (online supplemental appendix E).

Postoperative opioid consumption in PACU

No trials assessed PACU opioid consumption in the presence of periarticular LIA.

Table 3 Secondary endpoint results

Outcome	Studies included	ACB (SD) or n/N	ACB + iPACK (SD) or n/N	Mean difference or OR (95% CI)	P value for statistical significance	P value for heterogeneity	I^2 test for heterogeneity	Quality of evidence (GRADE)
iPACK +ACB vs ACB in the presence of LIA*								
Rest pain at 0 hours (PACU) (cm)	4	1.53 (1.83)	1.28 (1.68)	−0.02 (−0.12 to 0.07)	0.62	0.42	0%	⊕⊕⊕⊖
Rest pain at 12 hours (cm)	4	2.56 (2.43)	2.09 (2.11)	−0.41 (−0.90 to 0.08)	0.10	0.10	53%	⊕⊕⊕⊖
Rest pain at 24 hours (cm)	4	2.63 (2.00)	2.29 (2.21)	−0.19 (−0.52 to 0.13)	0.24	0.57	0%	⊕⊕⊕⊕
Morphine consumption at 24 hours (mg)	4	26.19 (24.06)	18.18 (23.05)	−4.17 (−9.85 to 1.51)	0.15	0.04	65%	⊕⊕⊖⊖
Postoperative function	3	N/A	N/A	−0.90 (−2.65 to 0.84)†	0.31	<0.00001	92%	⊕⊕⊖⊖
iPACK + ACB vs ACB in the absence of LIA‡								
Rest pain at 0 hours (PACU) (cm)	5	2.82 (2.55)	1.89 (1.81)	−0.87 (−1.76 to 0.02)	0.06	<0.00001	94%	⊕⊕⊖⊖
Rest pain at 12 hours (cm)	6	3.46 (2.45)	2.53 (2.17)	−0.98 (−1.79 to −0.17)	0.02	<0.00001	97%	⊕⊕⊕⊖
Rest pain at 24 hours (cm)	10	3.45 (2.38)	2.74 (2.21)	−0.69 (−1.18 to − 0.20)	0.006	<0.00001	94%	⊕⊕⊕⊖
Morphine consumption at 24 hours (mg)	3	52.65 (45.53)	50.08 (41.45)	−1.21 (−9.71 to 7.29)	0.78	0.82	0%	⊕⊕⊕⊖
Postoperative function	9	N/A	N/A	1.28 (0.45 to 2.11)†	0.003	<0.0001	87%	⊕⊕⊕⊖
Opioid-related side effects	6	32/198	17/200	0.43 (0.21 to 0.91)	0.03	0.36	7%	⊕⊕⊕⊕
Block-related complications	6	0/266	0/268	N/A	N/A	N/A	N/A	⊕⊕⊕⊕

⊕⊕⊕⊕, high quality evidence; ⊕⊕⊕⊖, moderate quality evidence; ⊕⊕⊖⊖, low quality evidence, ⊕⊖⊖⊖, very low-quality evidence.
*The outcomes of morphine consumption in PACU, opioid-related side effects, and block-related complications were assessed by less than two studies and are not shown since no statistical pooling was performed.
†Log(OR) reported.
‡The outcome of morphine consumption in PACU was assessed by less than two studies and is not shown since no statistical pooling was performed.
ACB, adductor canal block; GRADE, Grades of Recommendation, Assessment, Development and Evaluation; iPACK, infiltration between popliteal artery and capsule of knee; LIA, local infiltration analgesia; N/A, not applicable; PACU, postanesthesia care unit.

Two studies[10 18] wherein iPACK was added to ACB in the absence of periarticular LIA evaluated opioid consumption in the PACU. Results for this outcome were not pooled; but qualitatively, both studies[10 18] failed to detect a benefit when iPACK was added.

Cumulative 24-hour postoperative opioid consumption

The effect of adding iPACK block to ACB in the presence of periarticular LIA on cumulative 24-hour postoperative opioid consumption was evaluated by four[9 12 40 41] studies (n=273; ACB + iPACK: 137, ACB: 136). The addition of iPACK failed to reduce 24-hour postoperative opioid requirements. (table 3) The p value remained robust in directionality to Bonferroni-Holm correction ($p>P_c=0.012$) and the GRADE of evidence was rated low (online supplemental appendix E).

Similarly, the effect of adding iPACK block to ACB in the absence of periarticular LIA on cumulative 24-hour postoperative opioid consumption was assessed by three studies[8 10 18] (n=246; ACB + iPACK: 124, ACB: 122). The addition of iPACK did not improve this outcome (table 3). The p value remained robust in directionality to Bonferroni-Holm correction ($p>P_c=0.05$) and the GRADE of evidence was rated as moderate (online supplemental appendix E).

Functional recovery

The effect of adding iPACK block to ACB in the presence of periarticular LIA on functional recovery was evaluated by three[9 12 41] studies (n=257; ACB + iPACK: 129, ACB: 128). The addition of iPACK did not improve functional recovery (table 3). The p value remained robust in directionality to Bonferroni-Holm correction ($p>P_c=0.025$) and the GRADE of evidence was rated low (online supplemental appendix E).

In contrast, the effect of adding iPACK block to ACB on postoperative function in the absence of periarticular LIA was evaluated by nine studies[8 10 11 14–19] (n=696; ACB + iPACK: 349, ACB: 347). Adding iPACK improved the log(OR) (95% CI) of functional recovery by 1.28 (0.45 to 2.11) (p=0.003, $I^2=87\%$) (table 3); The p value remained robust in directionality to Bonferroni-Holm correction ($p<P_c=0.008$) and the GRADE of evidence was rated moderate (online supplemental appendix E).

Opioid-related side effects

Evaluating the effect of adding iPACK block to ACB on opioid-related side effects in the presence of periarticular LIA was performed in two studies[9 40] (n=116; ACB + iPACK: 58, ACB:

58). Data were not pooled for this outcome; but qualitatively, both studies did not detect a difference between the two groups.

Evaluating the effect of adding iPACK block to ACB on opioid-related side effects in the absence of periarticular LIA was performed in six studies[14–17 19 20] (n=398; ACB + iPACK: 200, ACB: 198). Adding iPACK seemed to reduce the OR (95% CI) of opioid related side effects by 0.43 (0.21 to 0.91) (p=0.03, I^2=7%) (table 3); however, correction for multiple testing using the Bonferroni-Holm correction rendered this difference non-significant ($p>P_c$=0.017). The GRADE of evidence was rated as high (online supplemental appendix E).

iPACK complications

No block-related complications were reported in any of the studies included in this review.[8–12 14 16 20] The quality of evidence for this outcome was rated as high.

DISCUSSION

This systematic review and meta-analysis indicates that the addition of iPACK to ACB in the setting of periarticular LIA for postoperative pain management following TKA does not confer any clinically important analgesic benefits. However, in the absence of periarticular LIA, moderate quality evidence suggests improvement in pain severity between 6 and 24 hours postoperatively and enhanced functional recovery when iPACK is added to ACB. These improvements in pain severity appear to be clinically meaningful at 6 hours but not at the remaining time points.

First described by Sinha *et al*,[6] the theoretical benefits of iPACK stem from anesthetizing the articular branches originating from main trunks of tibial and obturator nerves, which contribute to posterior knee pain following TKA.[6 43] Unlike the sciatic nerve block, the US-guided iPACK block is arguably easier to perform and aims to spare the main trunks of the tibial and common peroneal nerves and maintains sensorimotor function below the knee,[6] which is paramount to promoting early functional recovery and participation in physical therapy.[38 44] The results of our review are largely consistent with these proposed benefits as iPACK was found to improve pain scores after surgery when LIA is not used. However, our review found no important benefits when iPACK was added to ACB in the presence of LIA, which is most likely explained by redundancy in local anesthetic coverage and effect between iPACK and LIA. While the trials included in this review did not describe the LIA technique in full detail, the benefits observed herein suggest that the posterior knee capsule was among the tissues routinely targeted by LIA.

Our systematic review and meta-analysis has multiple strengths. First our literature search was comprehensive enabling us to generate meaningful estimates of effects for clinically important outcomes. Second, we successfully resolved heterogeneity in our primary outcome using sensitivity analysis according to prespecified clinically relevant covariates (use of multimodal analgesia). This generated an estimate of effect that was more generalizable to modern clinical practice, where a multimodal postoperative analgesia is routinely used. Third, we were able to highlight the relative effectiveness of iPACK by stratifying our analysis by the use of LIA, reflecting contemporary multimodal practices. Fourth, results for analgesic and functional outcomes were consistent across the stratified analysis, which corroborates our findings. Fifth, our use of conservative thresholds for statistical significance in our secondary outcomes by using the Bonferroni-Holm correction limited the risk of multiple testing bias.

However, limitations of this systematic review exist. This review included a limited number of relatively small clinical trials, which may predispose to bias and limit external validity. This was most notable for the comparison conducted in the presence of periarticular LIA, which was limited to four studies.[9 12 40 41] Furthermore, because of lack of systematic assessment, we were unable to provide estimates of effect for important outcomes, such as postoperative pain localized to the posterior knee. Finally, some outcomes[8 10 18 20] required using the median to approximate the mean; this approximation is true only if the distribution of data is symmetrical. This assumption may not necessarily be true, in which case the validity of the estimate becomes questionable.

CONCLUSIONS

The addition iPACK to ACB in the setting of periarticular LIA does not improve post-TKA analgesic outcomes. In contrast, moderate-quality evidence suggests that adding iPACK to ACB in the absence of LIA reduces pain severity up to 24 hours and enhances functional recovery, but without a corresponding reduction in opioid consumption. This appears to be most pronounced at 6 hours, where the improvement in pain is clinically meaningful (based on a MCID of 1 cm on a NRS). Our findings do not support the addition of iPACK to ACB when periarticular LIA is routinely administered as part of a multimodal analgesic pain management strategy.

Twitter Faraj W Abdallah @Faraj_RegAnesth

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ORCID iDs
Nasir Hussain http://orcid.org/0000-0003-0353-1002
Richard Brull http://orcid.org/0000-0002-7708-8843
Faraj W Abdallah http://orcid.org/0000-0003-2435-6186

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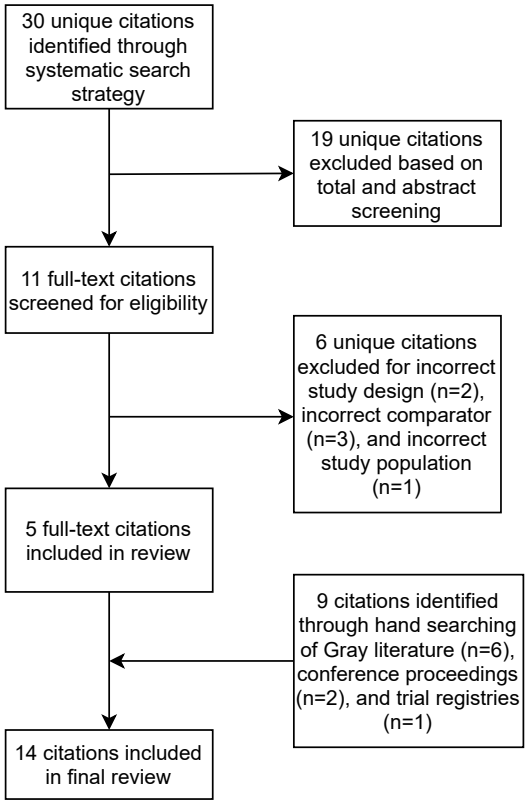
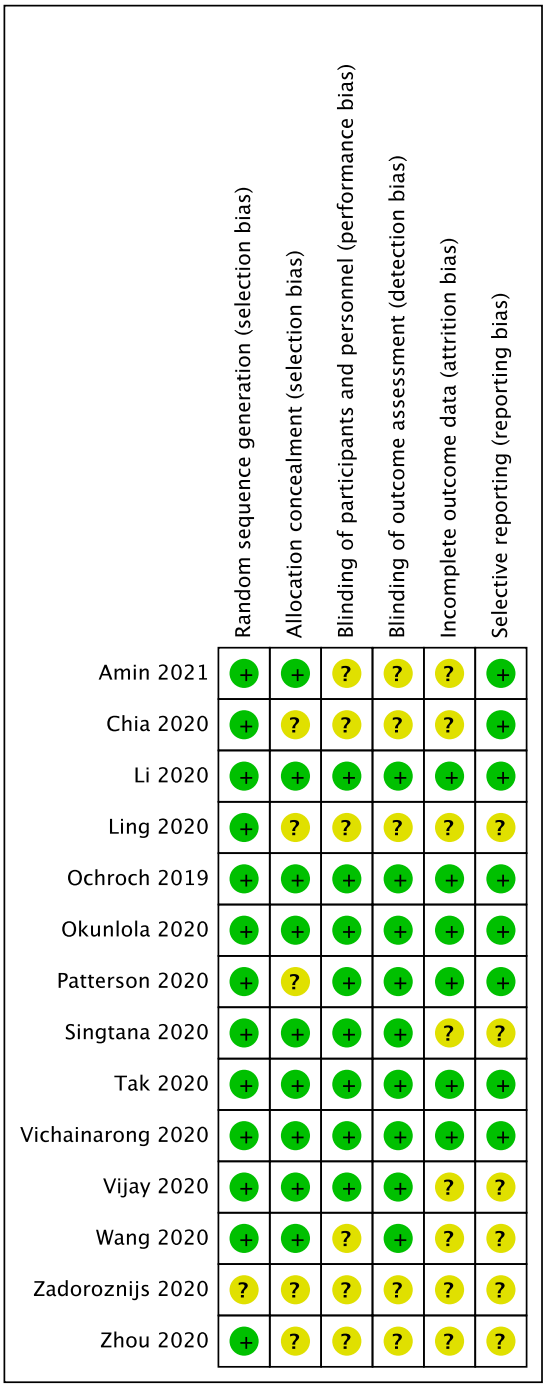
Appendix A – Search strategy for MEDLINE database.

1 IPack.kw. (7)
2 IPack.mp. (27)
3 (IPack adj10 block).mp. (20)
4 (interspace between the popliteal artery adj10 capsule of the posterior knee).mp. (4)
5 or/1-4 (27)
6 Adductor canal block.kw. (81)
7 (Adductor adj10 canal block).mp. (277)
8 adductor canal block.ti. (209)
9 or/6-8 (277)
10 5 and 9 (11)
11 exp Nerve Block/ (22237)
12 5 and 11 (8)
13 10 or 12 (17)
14 exp Arthroplasty, Replacement, Knee/ (23611)
15 Total knee.mp. (25263)
16 Knee*.kw. (14552)
17 Total knee*.kw. (4690)
18 exp Knee Joint/ (60116)
19 exp Knee Injuries/su [Surgery] (10973)
20 Knee arthroplasty.ab. /freq=2 (5205)
21 Joint Capsule/ (2062)
22 or/14-21 (99148)
23 13 and 22 (31)
24 limit 23 to english language (30)
25 remove duplicates from 24 (30)

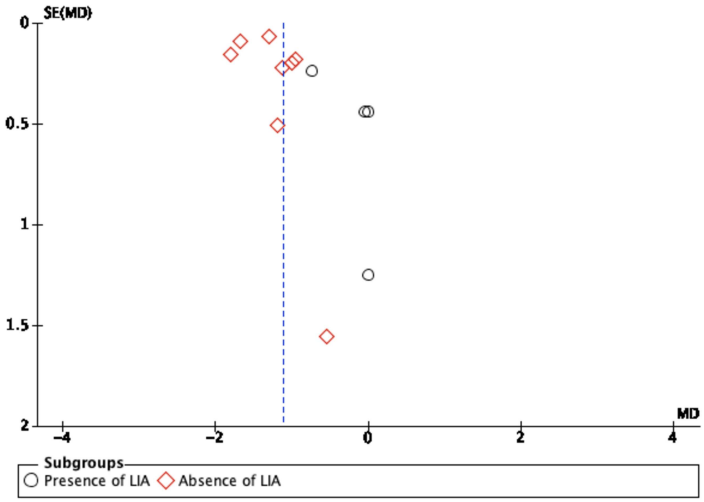
Appendix B - Study Flow Diagram



Appendix C – Risk of Bias Summary



Appendix D – Publication bias funnel Plots for rest pain scores at 6 hours post-operatively for a) Adductor canal block (ACB) versus ACB with Infiltration in the interspace between the popliteal artery and capsule of the knee (iPACK) in the *presence* of local infiltration analgesia (LIA) (circle dots) and b) ACB versus ACB with iPACK in the *absence* of LIA (diamond dots).



Appendix E – Evidence Profile for all outcomes assessed.

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	IPACK + sACB	sACB	Relative (95% CI)	Absolute (95% CI)		
iPACK + ACB versus ACB in presence of LIA												
Rest pain at 0 hours (PACU) (cm)												
4	randomised trials	not serious	not serious	not serious	serious [b]	none	137	136	Not Applicable	MD **0.02 lower** (0.12 lower to 0.07 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Rest pain at 6 hours (cm)												
4	randomised trials	not serious	not serious	not serious	serious [b]	none	137	136	Not Applicable	MD **0.41 lower** (0.84 lower to 0.02 higher)	⨁⨁⨁◯ MODERATE	CRITICAL
Rest pain at 12 hours (cm)												
4	randomised trials	not serious	not serious	not serious	serious [b]	none	137	136	Not Applicable	MD **0.41 lower** (0.90 lower to 0.08 higher)	⨁⨁⨁◯ MODERATE	IMPORTANT
Rest pain at 24 hours (cm)												
4	randomised trials	not serious	not serious	not serious	not serious	none	137	136	Not Applicable	MD **0.19 lower** (0.52 lower to 0.13 higher)	⨁⨁⨁⨁ HIGH	IMPORTANT
Post-operative function												
3	randomised trials	not serious	serious [a]	not serious	serious [b]	none	129	128	Not Applicable	Log(OR) **0.90 lower** (-2.65 lower to 0.84 higher)	⨁⨁◯◯ LOW	IMPORTANT
Morphine consumption at 24 hours (mg)												
4	randomised trials	not serious	serious [a]	not serious	serious [b]	none	137	136	Not Applicable	MD **4.17 lower** (9.85 lower to 1.51 higher)	⨁⨁◯◯ LOW	IMPORTANT
iPACK + ACB versus ACB in absence of LIA												
Rest pain at 0 hours (PACU) (cm)												
5	randomized trials	not serious	serious [a]	not serious	serious [b]	none	173	172	Not Applicable	MD **0.87 lower** (1.76 lower to 0.02 higher)	⨁⨁◯◯ LOW	IMPORTANT

Rest pain at 6 hours (cm)

8	randomized trials	not serious	serious [a]	not serious	not serious	none	316	315	Not Applicable	MD **1.33 lower** (1.58 lower to 1.08 lower)	⊕⊕⊕◯ MODERATE	CRITICAL

Rest pain at 12 hours (cm)

6	randomized trials	not serious	serious [a]	not serious	not serious	none	250	249	Not Applicable	MD **0.98 lower** (1.79 lower to 0.17 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT

Rest pain at 24 hours (cm)

10	randomized trials	not serious	serious [a]	not serious	not serious	none	234	234	Not Applicable	MD **0.69 lower** (1.18 lower to 0.20 lower)	⊕⊕⊕◯ MODERATE	IMPORTANT

Morphine consumption at 24 hours (mg)

3	randomized trials	not serious	not serious	not serious	serious [b]	none	124	122	Not Applicable	MD **1.21 lower** (-9.71 lower to 7.29 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT

Post-operative function

9	randomized trials	not serious	serious [a]	not serious	not serious	none	349	347	Not Applicable	Log(OR) **1.88 higher** (0.45 higher to 2.11 higher)	⊕⊕⊕◯ MODERATE	IMPORTANT

Opioid related side effects

6	randomised trials	not serious	not serious	not serious	not serious	none	17/200 (8.5%)	32/198 (16.2%)	**OR 0.43** (0.26 to 1.02)	**72 fewer per 1,000** (from 114 fewer to 3 more)	⊕⊕⊕⊕ HIGH	CRITICAL

Block-related complications

6	randomised trials	not serious	not serious	not serious	not serious	none	0/190 (0.0%)	0/190 (0.0%)	Not applicable	Not Applicable	⊕⊕⊕⊕ HIGH	CRITICAL

CI: Confidence interval; **MD:** Mean difference; **OR:** Odds ratio; **ACB**: adductor canal block; **iPACK:** infiltration between popliteal artery and posterior capsule of knee; **CM:** centimeter.

Explanations

a. Heterogeneity > 50%.
b. Lower and upper bound of confidence interval change direction of benefit.