Is sciatic nerve block advantageous when combined with femoral nerve block for postoperative analgesia following total knee arthroplasty? a meta-analysis

Le bloc du nerf sciatique est-il bénéfique lorsqu'il est combiné à un bloc du nerf fémoral pour l'analgésie postopératoire après une arthroplastie totale du genou? Une méta-analyse

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Abstract

Background Total knee arthroplasty (TKA) is associated with moderate-to-severe postoperative pain despite the use of femoral nerve block (FNB). The analgesic benefits of adding sciatic nerve block (SNB) to FNB following TKA are unclear. The aim of this meta-analysis was to quantify the analgesic effects of adding SNB to FNB following TKA. **Methods** We searched the US National Library of Medicine (MEDLINE), Excerpta Medica (Embase), and Cochrane Central Controlled Trials Register databases in March 2015 for randomized and quasi-randomized controlled trials (RCTs) that evaluated the analgesic advantages of adding SNB to FNB compared to FNB alone after TKA. The designated primary outcome was intravenous morphine consumption during the 24-hr postoperative interval. The severity of pain was evaluated at rest and with movement two, four, eight, 12, 24, 36, and 48 hr postoperatively. Morphine consumption during the postoperative 24–48 hr interval, time to first analgesic request, opioid-related side effects, block-related complications, patient satisfaction, functional recovery, and time to hospital discharge were also evaluated. Trials were stratified based on whether a single-shot SNB (SSNB)

or continuous SNB (CSNB) was used. Data were combined using random effects modelling.

Results Eight RCTs, including 379 patients, were analyzed. Five trials examined SSNB, and three assessed CSNB. Together, SSNB and CSNB reduced the 0–24 hr weighted mean difference [95% confidence interval] of morphine consumption by 10.6 [−20.9 to −0.3] mg ($P = 0.042$; $I^2 = 97\%$) and 20.5 [−28.6 to −12.4] mg ($P < 0.001$, $I^2 = 86\%$), respectively. SSNB reduced pain at rest and during movement up to 8 hr postoperatively ($P = 0.023$ and $P < 0.001$, respectively), whereas CSNB reduced pain at rest up to 36 hr ($P = 0.004$) and pain with movement up to 48 hr ($P = 0.031$). CSNB also decreased the odds of postoperative nausea and vomiting by 91% ($P = 0.011$).

Conclusion The available evidence supporting the analgesic benefits of adding SNB to FNB following TKA is marked by significant heterogeneity. With this challenge in mind, our meta-analysis suggests that SNB can significantly reduce postoperative opioid consumption and diminish knee pain following TKA compared to no SNB in the setting of FNB.

Résumé

Contexte L'arthroplastie totale du genou (ATG) est associée à une douleur postopératoire modérée à grave malgré le recours au bloc du nerf fémoral (BNF). Les avantages analgésiques de l'ajout d'un bloc du nerf sciatique (BNS) au FNB après une ATG sont mal connus. L'objectif de cette méta-analyse était de quantifier les effets analgésiques de l'ajout d'un BNS au BNF après une ATG.

Méthode Nous avons lancé une recherche dans les bases de données de la Bibliothèque nationale de médecine américaine (MEDLINE), Excerpta Medica (Embase), et du Registre central des études contrôlées Cochrane en mars

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2015 pour en tirer les études randomisées et quasi-randomisées contrôlées (ERC) évaluant les avantages analgésiques de l'ajout d'un BNS au BNF par rapport à un BNF seul après une ATG. Le critère d'évaluation principal désigné était la consommation de morphine intraveineuse pendant un intervalle postopératoire de 24 h. La gravité de la douleur a été évaluée au repos et en mouvement à deux, quatre, huit, 12, 24, 36 et 48 h postopératoires. La consommation de morphine pendant l'intervalle postopératoire de 24-48 h, le temps jusqu'à la première demande d'analgésique, les effets secondaires liés aux opioïdes, les complications liées au bloc, la satisfaction des patients, la récupération fonctionnelle et le temps jusqu'au congé de l'hôpital ont également été évalués. Les études ont été stratifiées selon leur recours à une injection unique pour le BNS (BNS-U) ou à une perfusion continue (BNS-C). Les données ont été combinées à l'aide d'un modèle à effets aléatoires.

Résultats Huit ERC, incluant 379 patients, ont été analysées. Cinq études examinaient le BNS-U, et trois évaluaient le BNS-C. Ensemble, le BNS-U et le BNS-C ont réduit la différence moyenne pondérée pour la période 0-24 h [intervalle de confiance 95 %] de consommation de morphine de 10,6 [−20,9 à −0,3] mg ($P = 0,042$; $I^2 = 97\%$) et de 20,5 [−28,6 à −12,4] mg ($P < 0,001$, $I^2 = 86\%$), respectivement. Le BNS-U a réduit la douleur au repos et en mouvement jusqu'à 8 h après l'opération ($P = 0,023$ et $P < 0,001$, respectivement), alors que le BNS-C a réduit la douleur au repos jusqu'à 36 h ($P = 0,004$) et la douleur en mouvement jusqu'à 48 h ($P = 0,031$). Le BNS-C a également réduit le risque de nausées et vomissements postopératoires de 91 % ($P = 0,011$).

Conclusion Les données probantes à disposition appuyant les avantages analgésiques de l'ajout d'un BNS au BNF après une ATG sont sujettes à une importante hétérogénéité. Tout en gardant cette difficulté à l'esprit, notre méta-analyse laisse à penser que le BNS pourrait réduire de façon significative la consommation postopératoire d'opioïdes et diminuer la douleur au genou après une ATG par rapport à l'absence de BNS dans le cadre d'un BNF.

The number of total knee arthroplasties (TKAs) performed annually in the United States has doubled during the last decade.¹ Although the potential for local infiltration analgesia (LIA)² and adductor canal block³ techniques await to be fully elucidated,⁴ in many centres femoral nerve block (FNB) remains a mainstay of multi-modal analgesic management following TKA.⁵⁻⁹ Despite a functioning FNB, however, TKA continues to be

associated with moderate-to-severe postoperative pain in the majority of patients.¹⁰ To improve pain control, it has been suggested that proximal sciatic nerve block (SNB) performed between the parascacral and mid-thigh regions should be added to FNB in patients undergoing TKA.¹¹⁻¹³ Unfortunately, the relevant evidence examining the role of SNB had been limited to observational studies and low-quality randomized controlled trials (RCTs), thus precluding a valid and reliable estimation of effect.¹⁴ Recently, however, nine RCTs have been separately published, with seemingly mixed results.¹⁵⁻²³ In this updated meta-analysis, we aimed to quantify the analgesic effects of adding proximal single-shot or continuous SNB to single-shot or continuous FNB in the absence of LIA on analgesic consumption and pain scores during the first 48 hr postoperatively in adult patients undergoing unilateral TKA.

Methods

The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines²⁴ were followed while preparing this systematic quantitative review. Randomized and quasi-randomized controlled trials examining the analgesic effects of adding SNB to FNB following TKA were retrieved and reviewed with an *a priori* designed but unregistered systematic review protocol.

Literature search

Two authors (F.W.A., R.B.) separately searched the US National Library of Medicine database (MEDLINE), Excerpta Medica database (Embase), Medline In Process, Cochrane Central Controlled Trials Database Register, Cochrane Systematic Reviews Database, and other non-indexed databases of citations. The search was conducted for medical subject headings (MeSH), controlled terms, and text words relevant to the components of the study question of this review. They encompassed sciatic nerve block, knee arthroplasty or replacement, postoperative pain, and analgesia. The terms were used individually and in combinations (Appendix). We also hand-searched the bibliography sections of the manuscripts retrieved to identify any additional studies that met our eligibility criteria. Trials involving human adults (18 yr or older) published from January 1950^{25,26} to March 2015 were considered. We also sought and reviewed related abstracts of meetings of the following medical professional societies: American Society of Regional Anesthesia (2005-2014), American Society of Anesthesiologists

Fig. 1 Flowchart summarizes the study selection process and depicts retrieved, included, and excluded randomized controlled trials

(2000–2014), and the European Society of Regional Anesthesia (2006–2014). In addition, the Internet-based registries of clinical trials including www.clinicaltrials.gov, www.ISRCTN.org, <https://www.clinicaltrialsregister.eu>, and <http://www.anzctr.org.au> were examined for ongoing relevant trials.

Eligibility criteria

We retrieved complete manuscripts and published abstracts of trials that evaluated the impact of single-shot or catheter-based infusion proximal SNB (i.e., parasacral, Labat, infraglueteal, anterior, and mid-femoral approaches)

(SNB group) compared to placebo or systemic intravenous analgesia (Control group) on postoperative analgesic outcomes in patients undergoing unilateral TKA. Only RCTs in which single-shot or continuous FNB was administered to both groups were included. RCTs examining blocks performed for surgical anesthesia and/or postoperative analgesia were also eligible. We excluded trials that (1) did not assess analgesic outcome measures (i.e., pain severity scores or postoperative analgesic consumption); (2) were performed only as distal (i.e., popliteal) SNB; (3) made it impossible to evaluate the analgesic impact of SNB separately from other co-analgesic interventions that were simultaneously

Table 1 Summary of trial outcomes

Author/ Year	Jadad score	N	Groups (n)	Surgical anesthesia	Primary outcome	Rest pain	Dynamic pain	Time to first analgesic request	Opioid consumption	Opioid- related side effects	SNB-related complications	Patient satisfaction	Chronic pain	Functional recovery	Length hospital stay
Single shot sciatic nerve block															
Allen 1998 ³⁸	4	36	1. SFNB + Sham SSNB (12) 2. SFNB + SSNB (12) 3. Sham FNB + sham SSNB (12) *	Spinal	Postoperative opioid consumption	•	•	•	•	•	•	•			
Hunt 2009 ³⁹	3	88	1. SFNB (33) GA 2. SFNB + SSNB (31) 3. Sham SFNB (24) *	GA	Postoperative opioid consumption	•			•		•				
Carvalho 2012 ¹⁹	5	50	1. CFNB (23) GA 2. CFNB + SSNB (25)	GA	Postoperative pain score	•	•		•	•	•	•			
Safa 2014 ²¹	5	100	1. SFNB (35) Spinal 2. SFNB + SSNB (33) 3. SFNB + infiltration (32) *	Spinal	Postoperative pain score	•	•		•	•			•	•	•
Abdallah 2014 ²⁸	5	60	1. CFNB + Sham SSNB (18) 2. CFNB + SSNB (17) 3. CFNB + Popliteal block (18) *	Spinal	Proportion of patients experiencing moderate- to-severe posterior knee pain	•	•	•	•	•	•				
Continuous sciatic nerve block															
Pham Dang 2005 ⁴⁰	3	28	1. CFNB (14) GA 2. CFNB + CSNB (14)	GA	Postoperative pain score	•	•		•	•				•	

Table 1 continued

Author/ Year	Jadad score	N	Groups (n)	Surgical anesthesia	Primary outcome	Rest pain	Dynamic pain	Time to first analgesic request	Opioid consumption	Opioid- related side effects	SNB-related complications	Patient satisfaction	Chronic pain	Functional recovery	Length hospital stay
Morin 2005 ⁴¹	3	90	1. CFNB (30) 2. CFNB + CSNB (30) 3. Psoas block (29) *	GA	Postoperative opioid consumption	•	•	•	•				•	•	
Wegener 2011 ⁴⁶	3	90	1. CFNB (29) 2. CFNB + CSNB (30) 3. CFNB + SSNB (30) *	GA	Hospital discharge readiness	•	•	•	•	•					•

(*) Study group not included in the analysis

CFNB = continuous femoral nerve block; CSNB = continuous sciatic nerve block; GA = general anesthesia; N = original sample size; n = number analyzed; SFNB = single-shot femoral nerve block; SSNB = single-shot sciatic nerve block

administered (e.g., intra-articular injection, epidural anesthesia, wound infiltration); (4) performed additional surgery on areas other than the knee joint (e.g., the ankle); (5) undertook knee procedures that did not include arthroplasty (e.g., cruciate ligament repair); (6) used local anesthetic adjuvants, except epinephrine, to prolong postoperative analgesia; and (7) included fewer than 10 study subjects to limit the possibility of detecting a treatment effect. In the absence of resources to support the translation of RCTs published in foreign languages, inclusion was limited to RCTs published in English, although English abstracts published in foreign-language journals were reviewed for potential relevance. Two authors (F.W.A., R.B.) separately evaluated the search results. Decisions on inclusion of qualifying studies were made by consensus between the two authors. The opinion of a third author (C.M.) was obtained when agreement could not be reached.

Evaluation of methodological quality

The Jadad score²⁷ was used to evaluate the methodological quality of the retrieved trials. A score was separately assigned for the overall quality by two of the authors. The final quality score for each RCT was determined by consensus, although the opinion of a third author was obtained whenever agreement could not be reached. Quality scores were not used to exclude trials.

Definition of relevant outcome data

A standardized data collection form was developed and used to extract outcome results. When consensus could not be reached, discrepancies were resolved by re-examining the source data and asking the opinion of a third author. The authors also agreed *pre hoc* to refrain from extracting data from any RCTs that they had previously co-authored,²⁸ leaving this task to the third co-author. Extracted data included the name of the first author, publication year, the type of surgical anesthetic received, sample size and number of patients per study group, the nature of comparative groups, and the designated primary outcome. The analgesic outcomes extracted were the opioid consumption for two postoperative intervals: 0-24 hr and 24-48 hr. Pain severity scores were obtained at rest and with motion at two, four, eight, 12, 24, 36, and 48 hr postoperatively. Also obtained were the time-to-first analgesic request (minutes); risk of opioid-related side effects (postoperative nausea and vomiting, pruritus, undesirable sedation); occurrence of block-related complications; patient satisfaction with analgesia received; extent of functional recovery (knee flexion, in degrees) four days following TKA; and time to hospital

Table 2 Characteristics of the SNB and analgesic regimen

Author/ Year	Type of SNB	SNB approach	Premedication	Block timing	Localization	Block solution	Assessment of block success	Surgical anesthesia and analgesia	Supplementary postoperative analgesia	
									PACU	Ward
Allen 1998 ³⁸	Single-shot	Labat	IV midazolam, IV fentanyl	Postoperative	Nerve- stimulator	30 mL of bupivacaine 0.25% with 1:400,000 epinephrine	Yes	Spinal, no IT opioids	IV morphine, IV ketorolac	IV PCA morphine, IV ketorolac
Hunt 2009 ³⁹	Single-shot	Labat	None	Preoperative, under general anesthesia	Nerve- stimulator	10-15 mL of bupivacaine 0.5%	No	General	IV PCA morphine	Same as PACU
Carvalho 2012 ¹⁹	Single-shot	Anterior	None	Preoperative	Nerve- stimulator	25 mL of ropivacaine 0.375%	Yes	General, IV fentanyl, IV ketorolac, IV paracetamol	Oral diclofenac, oral paracetamol, oral tramadol	Same as PACU
Safa 2014 ²¹	Single-shot	Infragluteal	Oral acetaminophen, oral celecoxib, oral gabapentin	Preoperative	Nerve- stimulator + ultrasound	20 mL of ropivacaine 0.5%	No	Spinal, with 0.015 mg IT fentanyl	IV PCA hydromorphone	IV PCA hydromorphone, oral acetaminophen, oral celecoxib, oral gabapentin, oral oxycodone
Abdallah 2014 ²⁸	Single-shot	Infragluteal	None	Preoperative	Nerve- stimulator + ultrasound	30 mL of 2:1 mixture of bupivacaine 0.5%:lidocaine 2% with 1:200,000 epinephrine	Yes	Spinal, with 0.1mg IT morphine	IV fentanyl	Oral celecoxib, oral acetaminophen, short- and long- acting oral oxycodone, IV PCA as backup
Pham Dang 2005 ⁴⁰	Continuous for 72 hr	Mid- femoral	None	Preoperative	Nerve- stimulator	15 mL of ropivacaine 0.5%	No	General, IV remifentanyl,	10 mL bolus of ropivacaine 0.2% every 12 hr via catheter, IV paracetamol, IV ketoprofen	Same as PACU
Morin 2005 ⁴¹	Continuous for 48 hr	Anterior	Oral clorazepate	Preoperative	Nerve- stimulator	30 mL of 2:1 mixture of prilocaine 1%:ropivacaine 0.75%	Yes	General, IV fentanyl, IV metamizole, diclofenac supp	7 mL·hr ⁻¹ of ropivacaine 0.2% via catheter, oral diclofenac, IV PCA piritramide	Same as PACU
Wegner 2011 ¹⁶	Continuous for 36 hr	Parasacral	Oral lorazepam, oral acetaminophen	Preoperative	Nerve- stimulator + ultrasound	20 mL of levobupivacaine 0.375%	Yes	General, IV remifentanyl	10 mL·hr ⁻¹ of levobupivacaine 0.125% via catheter, IV morphine	Same as PACU + oral acetaminophen, oral diclofenac

discharge (days). The cumulative opioid medications consumed during the first interval (0–24 hr) postoperatively, converted into equi-analgesic doses of intravenous morphine, was selected as a primary outcome. All of the other analgesic outcomes were designated secondary outcomes. This choice of the primary outcome reflects the subjective nature of the pain severity scores and the influence of anxiety, catastrophisation, use of patient-controlled analgesia, and aggressiveness of postoperative physiotherapy.^{29–31}

For this review, verbal rating scale scores and pain numerical rating scale (NRS) scores were converted³² to 0–10 visual analogue scale (VAS) scores, where 10 = worst pain imaginable, and 0 = no pain. The amounts of all postoperative opioid analgesics consumed during the first 48 hr were converted to equianalgesic doses of morphine.³³ The degree of patient satisfaction with the pain relief at 24 hr postoperatively was reported as a VAS score (10 = most satisfied, 0 = least satisfied).

A priori identified sources of heterogeneity

To explore the possible heterogeneity sources in our review, we *a priori* determined the clinical and design characteristics of RCTs that could potentially produce clinically important variations in the outcomes assessed. We subsequently evaluated the contribution of these characteristics to the heterogeneity of the results using subgroup analysis. Because evidence suggests that continuous SNB (i.e., catheter-based infusion via a pump) prolongs the duration of SNB analgesia,¹⁶ we hypothesized that catheter use would introduce significant heterogeneity into our results. Consequently, we planned to analyze the outcome data separately according to whether single-shot sciatic nerve block (SSNB) or continuous sciatic nerve block (CSNB) had been used. Other sources of clinical heterogeneity that were explored via subgroup analysis included (1) surgical anesthetic (general vs spinal); (2) nature of the local anesthetic used for SNB (intermediate vs long acting); (3) SNB guidance technique (nerve stimulator vs nerve stimulator and ultrasonography); (4) type of FNB (single-shot vs continuous); and (5) postoperative analgesic regimens used (multimodal vs unimodal).

Statistical analysis

The data analyzed were primarily gathered from the tables in each of the source manuscripts. When data were not available in tables, we contacted the corresponding authors of the respective studies. If the authors did not reply or supply the outcome results needed, we resorted to

abstracting results from the figures published in the source manuscripts as a secondary source of data. We also contacted the authors of published abstracts that met the eligibility criteria for further explanation regarding any missing details deemed relevant.

Dichotomous outcome results describing opioid-related side effects during a specified time interval were converted to frequencies (n/N). The single highest frequency was used to estimate the number of subjects who experienced a certain side effect at least once. Continuous outcome results were reported as the mean and standard deviation (SD). The median and interquartile range [IQR] was used as an estimate whenever the mean value was not explicitly reported.³⁴ In studies where the SD values were not provided in tables or graphs, the SD value was estimated as the value of the range/4³⁴ or the IQR/1.35, as appropriate.³⁵ Where applicable, the 95% confidence interval (CI) was used as an estimate of the range, and the most extreme values were used to estimate the SD. When a specific outcome measure was reported more than once during a prespecified interval, we selected the most conservative available value.

Meta-analysis

The extracted results were separately entered into the systematic review statistical package (Revman 5.3, Cochrane Library, Oxford, England) and were cross-examined by two of the authors (F.W.A., R.B.). We employed meta-analytic statistics to pool and analyze the outcome results. Because clinically heterogeneous anesthetic techniques were used (e.g., general vs spinal anesthesia, varying doses of local anesthetics in SNB, different postoperative analgesic regimens), random effect modelling was selected. The weighted mean difference and 95% CI were calculated for continuous outcomes, and the odds ratio (OR) and 95% CI were calculated for dichotomous outcomes. Differences from the Control group were considered statistically significant when $P < 0.05$ (two-sided), and when 0 and 1 were not included in the 95% CI for continuous and dichotomous outcomes, respectively.

We used the I^2 statistic to evaluate the degree of heterogeneity among the RCTs reviewed.³⁶ When heterogeneity was significant ($I^2 > 50\%$), we explored the heterogeneity sources using subgroup analysis as per the preidentified potential sources of heterogeneity.³⁷ An additional post-hoc sensitivity analysis was planned to examine the effects of any of the preidentified factors where a meaningful subgroup analysis was not feasible as well as the effects of any additional factors identified during the data analysis.

Fig. 2 Forest plots of intravenous morphine equivalent consumption during the first 24 hr postoperatively (0–24 hr interval). The sample sizes, means, standard deviations, and pooled estimates of the mean difference are shown. The 95% confidence intervals (CI) are shown as

lines for individual studies and as diamonds for pooled estimates. CSNB = continuous sciatic nerve block; SSNB = single-shot sciatic nerve block

Results

Our literature search yielded 54 studies (Fig. 1), eight of which were published between January 1998 and March 2015 and met the eligibility criteria.^{16,19,21,28,38–41} One published abstract¹⁷ was excluded for lack of outcome results after contacting its authors. Five trials that compared SNB with various analgesic modalities, but lacked an appropriate FNB control group, were also excluded.^{15,18,20,22,23} A single relevant RCT comparing single-shot FNB to single-shot FNB + SNB was identified in the trial registries (clinical trials registry NCT02135120, relevant sample size = 30), but it was still in the recruitment phase with no available outcome results. One other RCT published in a foreign language was excluded.

All reviewed trials were randomized, but only three reported appropriate randomization techniques.^{19,21,28} Five of the trials were double-blinded,^{19,21,28,38,39} but only four of them^{19,21,28,38} reported appropriate blinding techniques. Three^{19,21,28} of the eight trials achieved a quality score of 5 out of 5 (i.e., they were randomized, double-blinded, reported appropriate blinding and randomization techniques, and described complete patient disposition. The median [IQR] and range of the methodological quality score for the eight trials included in this review was 3.5 (3–5). None of the RCTs was excluded based on its methodological quality scores or because the number of patients was fewer than ten. Table 1 describes the methodological quality and the risk of bias of the trials that were included.

The data from 386 patients were used in our meta-analysis, which included 192 patients in the SNB group and 194 in the Control group. The characteristics and outcomes sought in each trial are presented in Table 1. Each of the eight RCTs included analgesic outcomes, including analgesic consumption and pain severity scores. An SSNB was used in five trials^{19,21,28,38,39} and a CSNB in two.^{40,41} Although both techniques were used in a single trial,¹⁶ only the CSNB group was included in the analysis. The local anesthetic solution, volume, localization technique, and delivery method for all SNBs performed are summarized in Table 2. One trial included two patient groups that underwent SNB,²⁸ but only one group met the eligibility criteria.

Analgesic consumption for the 0–24 hr interval

Data relating to postoperative analgesic consumption during the 0–24 hr interval were available from seven RCTs,^{16,21,28,38–41} which included a total of 338 patients (167 patients in the SNB group and 171 in the Control group). Compared to no Controls, both the SSNB and CSNB reduced the weighted mean difference [95% CI] postoperative intravenous morphine equivalent consumption by 10.6 [–20.9 to –0.3] mg ($P = 0.042$) and 20.5 [–28.6 to –12.4] mg ($P < 0.001$), respectively, during the 0–24 hr interval postoperatively (Fig. 2).

The primary outcome results were characterized by high heterogeneity for the SSNB and CSNB subgroups, with $I^2 = 97\%$ ($P < 0.001$) and $I^2 = 86\%$ ($P < 0.001$),

Table 3 Summary of outcomes results

Outcome	Subgroup	Studies included	SNB Mean or n/N	Control Mean or n/N	OR or WMD [95% Confidence Interval]	P-value for statistical significance	P-value for heterogeneity	I ² Test for heterogeneity
Cumulative morphine consumption for 0-24 hr (mg)	SSNB	21,28,38,39	11.8	23.7	-10.59 [-20.88 to -0.30]	0.04	<0.00001	97%
	CSNB	16,40,41	4.9	25.5	-20.54 [-28.64 to -12.43]	<0.00001	0.0008	86%
Cumulative morphine consumption for 24-48 hr (mg)	SSNB	38	13.9	9.8	4.10 [2.17 to 6.03]	<0.0001	N/A	N/A
	CSNB	16,41	3.5	4.07	-0.82 [-2.69 to 1.04]	0.39	0.69	0%
Rest pain at 2 hr (cm)	SSNB	19,28,38,39	2.6	4.4	-1.94 [-3.83 to -0.04]	0.04	<0.00001	94%
	CSNB	16,40,41	0.13	4.8	-4.29 [-6.45 to -2.14]	<0.0001	<0.00001	94%
Rest pain at 4 hr (cm)	SSNB	21,28,38,39	2.7	3.7	-1.15 [-2.28 to -0.03]	0.04	<0.00001	94%
	CSNB	40,41	0.3	3.1	-2.84 [-3.36 to -2.33]	<0.00001	0.82	0%
Rest pain at 8 hr (cm)	SSNB	21,28,38,39	3.0	3.8	-0.68 [-1.25 to -0.10]	0.02	<0.001	82%
	CSNB	16,40,41	0.2	3.5	-3.18 [-4.09 to -2.28]	<0.00001	0.02	74%
Rest pain at 12 hr (cm)	SSNB	19,21,28	1.96	2.61	-0.64 [-1.52 to 0.31]	0.19	0.05	66%
	CSNB	40,41	0.24	3.18	-2.95 [-3.50 to -2.40]	<0.00001	0.96	0%
Rest pain at 24 hr (cm)	SSNB	19,21,28,38,39	3.0	2.9	-0.05 [-0.88 to 0.79]	0.91	<0.00001	90%
	CSNB	16,40,41	0.2	2.3	-2.02 [-2.89 to -1.15]	<0.00001	0.05	65%
Rest pain at 36 hr (cm)	SSNB	21,38,39	2.7	2.7	0.36 [-0.69 to 1.41]	0.5	<0.00001	95%
	CSNB	16	0	1.3	-1.28 [-2.15 to -0.41]	0.004	N/A	N/A
Rest pain at 48 hr (cm)	SSNB	21,38,39	2.0	1.9	0.13 [-0.02 to 0.29]	0.1	0.31	14%
	CSNB	16,40,41	1.0	1.5	-0.24 [-0.61 to 0.14]	0.22	0.36	2%
Dynamic pain at 2 hr (cm)	SSNB	28	2.2	3.7	-1.45 [-2.70 to -0.20]	0.02	N/A	N/A
	CSNB	41	2.5	5.1	-2.56 [-3.44 to -1.68]	<0.00001	N/A	N/A
Dynamic pain at 4 hr (cm)	SSNB	21,28	2.2	5.0	-3.24 [-6.20 to -0.29]	0.03	<0.00001	95%
	CSNB	41	2.5	5.1	-2.56 [-3.44 to -1.68]	<0.00001	N/A	N/A
Dynamic pain at 8 hr (cm)	SSNB	21,28	4.2	4.6	-0.52 [-0.78 to -0.26]	<0.0001	0.7	0%
	CSNB	41	2.5	5.1	-2.56 [-3.44 to -1.68]	<0.00001	N/A	N/A
Dynamic pain at 12 hr (cm)	SSNB	19,21,28	3.33	4.2	-0.7 [-1.49 to 0.08]	0.08	0.21	35%

Table 3 continued

Outcome	Subgroup	Studies included	SNB Mean or n/N	Control Mean or n/N	OR or WMD [95% Confidence Interval]	P-value for statistical significance	P-value for heterogeneity	I ² Test for heterogeneity
Dynamic pain at 24 hr (cm)	CSNB	⁴¹	2.54	5.1	−2.56 [−3.44 to −1.68]	<0.00001	N/A	N/A
	SSNB	^{19,21,28,38}	4.9	4.8	0.29 [0.04 to 0.55]	0.02	0.59	0%
Dynamic pain at 36 hr (cm)	CSNB	^{16,41}	1.3	4.1	−2.74 [−3.43 to −2.05]	<0.00001	0.52	0%
	SSNB	^{21,38}	3.8	3.8	0.03 [−0.19 to 0.25]	0.79	0.63	0%
Dynamic pain at 48 hr (cm)	CSNB	¹⁶	2	3.3	−1.29 [−2.28 to −0.30]	0.01	N/A	N/A
	SSNB	^{21,38}	3.8	3.2	0.70 [0.09 to 1.30]	0.02	0.01	84%
Incidence of PONV at 24 hr (n/N)	CSNB	^{16,40,41}	2.6	3.8	−1.07 [−2.06 to −0.08]	0.03	0.12	53%
	SSNB	^{28,38}	5/12	3/12	0.56 [0.04 to 7.12]	0.66	0.03	80%
Incidence of pruritus at 24 hr (n/N)	CSNB	⁴⁰	2/14	9/14	0.09 [0.01 to 0.59]	0.01	N/A	N/A
	SSNB	³⁸	2/12	2/12	1.00 [0.12 to 8.56]	1.0	N/A	N/A
Incidence of sedation at 24 hr (n/N)	CSNB	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	SSNB	³⁸	2/12	0/12	0.17 [0.01 to 3.90]	0.27	N/A	N/A
Block-related complications	CSNB	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	SSNB	^{19,28,39}	2/69	0/71	5.97 [0.27 to 133.87]	0.26	N/A	N/A
Functional recovery at 4 days (flexion in degrees)	CSNB	N/A	N/A	N/A	N/A	N/A	N/A	N/A
	SSNB	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Time-to-hospital discharge (days)	CSNB	^{16,40,41}	77.7	64.8	11.74 [−2.64 to 26.12]	0.11	<0.00001	93%
	SSNB	²¹	4.3	4.3	0.00 [−0.39 to 0.39]	1	N/A	N/A
	CSNB	¹⁶	4	4	0.00 [−1.59 to 1.59]	1	N/A	N/A

CSNB = continuous sciatic nerve block; N/A = not applicable; OR = odds ratio; PONV = postoperative nausea and vomiting; SSNB = single-shot sciatic nerve block; WMD = weighted mean difference

respectively. Alternative subgroup analysis showed that the patients undergoing SNB continued to have reduced opioid consumption during the 0–24 hr interval compared with that of the Control group. Specifically, the reduction in cumulative postoperative morphine equivalent consumption was 22.1 [−27.8 to −16.3] mg ($P < 0.001$), $I^2 = 82\%$ and 6.5 [−12.0 to −1.1] mg ($P < 0.001$), $I^2 = 92\%$ for the general anesthesia vs spinal anesthesia subgroups, respectively; 17.9 [−32.7 to −3.1] mg ($P = 0.022$), $I^2 = 98\%$ and 10.9 [−20.7 to −1.1] mg ($P = 0.011$), $I^2 = 96\%$ for the nerve stimulator vs nerve stimulator and ultrasonography, respectively; 12.7 [−22.2, to −3.2] mg (P

< 0.001), $I^2 = 98\%$ and 18.8 [−25.5 to −12.0] mg ($P < 0.001$), $I^2 = 87\%$ for the single-shot FNB vs continuous FNB, respectively. No trials used intermediate-acting local anesthetics, and only one^{38,39} used unimodal postoperative analgesic regimens, precluding a meaningful subgroup analysis for the respective *a priori* identified sources of heterogeneity. The test for subgroup differences was statistically significant for the general anesthesia vs spinal anesthesia subgroup analysis ($P < 0.001$) but not for the nerve stimulator vs nerve stimulator and ultrasonography analysis ($P = 0.421$) or for the single-shot FNB vs continuous FNB analysis ($P = 0.212$). This subgroup

Fig. 3 Forest plots of pain severity at rest using visual analogue scale (VAS) pain scores at 2 hr. The sample sizes, means, standard deviations, and pooled estimates of the mean difference are shown. The 95% confidence intervals (CI) are shown as lines for individual

studies and as diamonds for pooled estimates. CSNB = continuous sciatic nerve block; SNB = sciatic nerve block; SSNB = single-shot sciatic nerve block

difference suggests that patients who undergo TKA under general anesthesia may benefit more from SNB than those who receive a spinal anesthetic.

Analgesic consumption during the 24-48 hr interval

Only three studies reported analgesic consumption during the 24-48 hr interval. Whereas one study³⁸ suggested that the cumulative postoperative opioid analgesic (intravenous morphine equivalent) consumption during the 24-48 hr interval was greater by 4.1 [2.2 to 6.0] mg ($P < 0.001$) in the SSNB subgroup compared to that of the Controls (Table 3), the remaining two studies^{16,41} indicated that the difference was not significant for the CSNB subgroup.

Pain at rest

Compared with the Controls, SSNB decreased the pain severity at rest at the two-, four-, and eight-hour checkpoints postoperatively by 1.9 [-3.8 to 0.0] cm ($P = 0.041$), 1.2 [-2.3 to 0] cm ($P = 0.04$), and 0.7 [-1.3 to -0.1] cm ($P = 0.023$), respectively (Table 3). The eight-hour assessment of pain severity at rest was the last point at which we observed a significant reduction in pain attributed to SSNB. Figures 3 and 4 show forest plots of the weighted mean difference in pain at rest (VAS scores) at 2 and 8 hr, respectively.

Compared with the Controls, CSNB decreased pain severity at rest two, four, eight, 12, 24, and 36 hr postoperatively by 4.3 [-6.4 to -2.1] cm ($P < 0.001$), 2.8 [-3.4 to -2.3] cm ($P < 0.001$), 3.2 [-4.1 to -2.3] cm

($P < 0.001$), 3.0 [-3.5 to -2.4] cm ($P < 0.001$), 2.0 [-2.9 to -1.2] cm ($P < 0.001$), and 1.3 [-2.2 to -0.4] cm ($P = 0.004$), respectively (Table 3). The 36-hr assessment of pain severity at rest was the last point at which we observed a significant reduction in pain attributed to CSNB. The changes in pain at rest (VAS scores, weighted mean difference) for the Controls and the CSNB subgroup over time are shown in Fig. 4.

Pain with movement

Compared with the Controls, SSNB decreased pain severity with movement at two, four, and eight hours postoperatively by 1.5 [-2.7 to -0.2] cm ($P = 0.023$), 3.2 [-6.2 to -0.3] cm ($P = 0.034$), and 0.5 [-0.8 to -0.3] cm ($P < 0.001$), respectively (Table 3). We observed no benefit attributable to SSNB beyond eight hours. In contrast, CSNB reduced pain with movement at all measured time points, including 48 hr, compared with that in the Control group (Table 3).

Opioid-related side effects

The frequency of opioid-related side effects was selected as an outcome by a limited number of trials. Three RCTs - two in the SNB subgroup^{28,38} and one in the CSNB subgroup⁴⁰ - reported the incidence of postoperative nausea and vomiting, and only one RCT in the SNB subgroup³⁸ reported the incidence of pruritus and sedation. The frequency of opioid-related side effects in the SNB subgroup did not differ from that in the Controls.

Fig. 4 Forest plots of the pain severity at rest using visual analogue scale (VAS) pain scores at 8 hr. The sample sizes, means, standard deviations, and pooled estimates of the mean difference are shown. The 95% confidence intervals (CI) are shown as lines for individual

studies and as diamonds for pooled estimates. CSNB = continuous sciatic nerve block; SNB = sciatic nerve block; SSNB = single-shot sciatic nerve block

However, CSNB reduced the odds of postoperative nausea and vomiting at 24 hr by 93% (OR [95% CI], 0.09 [0.01 to 0.59], $P = 0.011$) compared with the Controls (Table 3). Inconsistent reporting precluded evaluating the effect of CSNB on pruritus and sedation.

Other outcomes

The frequency of block-related complications was reported only in trials with an SSNB subgroup (Table 3). Two patients were reported to experience transient paresthesias lasting one week,²⁸ but we found no difference in block-related complications when the SSNB group was compared with the Controls. Functional recovery was reported only in trials with a CSNB subgroup (Table 3). We found no difference in functional recovery when the CSNB group was compared with the Controls (Fig. 5). In addition, we found no differences in the discharge time when SNB - whether SSNB or CSNB - were compared with the Controls (Table 3). We were unable to examine quantitatively the remaining secondary outcomes (time to first analgesic request, patient satisfaction with pain relief) because of inconsistent reporting and the heterogeneous assessment procedures in the source trials.

We performed a *post hoc* alternative subgrouping and sensitivity analysis to explore the potential sources of the heterogeneity of the results. Alternative subgrouping by incorporating the SSNB arm of the study by Wegener *et al.*¹⁶ (a three-arm RCT that included SSNB, CSNB, and Control groups) in the analysis, instead of the CSNB arm, maintained the significance of results but reduced the heterogeneity of the CSNB subgroup, with opioid

consumption reduced by 11.2 [−19.9 to −2.6] mg ($P = 0.013$), $I^2 = 97\%$ and 25.0 [−30.0 to −20.0] mg ($P < 0.001$), $I^2 = 16\%$ in the SSNB and CSNB subgroups, respectively.

Post-hoc sensitivity analysis was used to examine the impact of several factors on the results' heterogeneity, including the methodological quality scores (i.e., inappropriate blinding), mixing epinephrine with local anesthetics, timing of SNB, not assessing block success, and using unimodal *vs* multimodal postoperative analgesia. Eliminating the results of the four RCTs^{16,39-41} that achieved a Jadad score of 3 rendered the SSNB subgroup results insignificant, with a weighted mean difference in opioid consumption of 5.4 [−12.0 to 1.1] mg ($P = 0.142$). Also, all of the RCTs in the CSNB subgroup were eliminated. Furthermore, removing the data of the two RCTs^{28,38} that mixed their local anesthetic solution with epinephrine rendered the SSNB subgroup results insignificant, with a weighted mean difference in opioid consumption of 13.4 [−37.3 to 10.5] mg ($P = 0.274$) and 20.5 [−28.6 to −12.4] mg ($P < 0.001$), $I^2 = 86\%$ for the SSNB and CSNB subgroups, respectively. Additionally, removing the results of the single RCT³⁸ that performed SNB postoperatively rendered the SSNB subgroup results insignificant, with a weighted mean difference in opioid consumption of 13.6 [−28.6 to 1.4] mg ($P = 0.082$) and 20.5 [−28.6 to −12.4] mg ($P < 0.001$), $I^2 = 86\%$ for the SSNB and CSNB subgroups, respectively. Moreover, excluding the data of the three RCTs^{21,39,40} that did not perform block assessment to confirm SNB success rendered the SSNB subgroup results insignificant, with a weighted mean difference in opioid consumption of 7.8

Fig. 5 Forest plots of postoperative functional recovery (range of motion in degrees). The sample sizes, means, standard deviations, and pooled estimates of the mean difference are shown. The 95% confidence intervals (CI) are shown as lines for individual studies

[-19.9 to 4.2] mg ($P = 0.232$) and 21.1 [-30.9 to -11.3] ($P < 0.001$), $I^2 = 93\%$ for the SSNB and CSNB subgroups, respectively. Finally, eliminating the data of the two RCTs^{38,39} that used unimodal postoperative analgesia rendered the SSNB subgroup results insignificant, with a weighted mean difference in opioid consumption of 7.6 [-20.1 to 5.0] mg ($P = 0.244$) and 20.5 [-28.6 to -12.4] mg ($P < 0.001$), $I^2 = 86\%$ for the SSNB and CSNB subgroups, respectively. As such, our *post hoc* analysis failed to reduce the extent of heterogeneity in the source data.

Discussion

This meta-analysis suggests that adding SNB to FNB can improve analgesia following TKA by reducing postoperative opioid consumption up to 24 hr, with a larger reduction associated with CSNB than SSNB. The magnitude of this improvement may be greater in patients who undergo TKA under a general anesthetic compared with spinal anesthesia. Unfortunately, the heterogeneity and intrinsic limitations of the source data reviewed limit the strength of our findings. The present quantitative review nonetheless points to level 1a– (minus) evidence⁴² (i.e., representing a systematic review with significant heterogeneity) in support of the SNB, a notable improvement from the level 2a– evidence supporting SNB that we observed in our earlier qualitative review of the literature.¹⁴

Our results also suggest that SSNB can reduce pain at rest and during movement up to eight hours postoperatively, whereas CSNB can reduce pain at rest up to 36 hr and pain with movement up to 48 hr. The relative superior analgesia associated with CSNB

and as diamonds for pooled estimates. CSNB = continuous sciatic nerve block; SNB = sciatic nerve block; SSNB = single-shot sciatic nerve block

compared with SSNB during the first eight hours postoperatively may well be attributable to the extensive multi-modal analgesic regimen used in CSNB trials. Also, the increase in opioid consumption and opioid-related side effects during the 24–48 hr interval associated with SSNB compared with CSNB may be at least partially explained by the “rebound pain” phenomenon that has been described in TKA patients when the effect of the nerve block dissipates.⁴³ Additional SNB benefits may include a reduction in the frequency of postoperative nausea and vomiting in patients who underwent CSNB. Importantly, our results also signal no delay in functional recovery or hospital discharge associated with SNB for TKA. Finally, the relatively small number of patients reviewed herein ($n = 338$), coupled with the inconsistent assessment of block-related complications, preclude any meaningful conclusions regarding SNB safety. Consequently, concerns regarding SNB-related nerve injury, masking of surgical injury to the peroneal nerve, and delayed mobilization still apply.^{44,45}

Clinically, the present results support the idea that the sciatic nerve contributes to the postoperative pain following TKA. Anatomically, however, our understanding of the innervation of the posterior knee is relatively incomplete as it is based primarily on anatomical descriptions dating back to more than six decades ago.⁴⁶ Hence, designing trials to quantify the effect of SNB accurately when its distribution is not clearly delineated is difficult at best. Additionally, the combined innervation of the knee joint by both the femoral and sciatic nerves, and the overlap in their innervation of the anterolateral aspect of the knee,⁴⁶ further complicate accurate assessment. In fact, few studies¹² have conceived designs capable of reliably isolating pain transmitted by the femoral and sciatic nerves, which would permit accurate quantification

of a block's analgesic effects on the individual nerves.⁴⁴ Furthermore, the human capacity to distinguish between pain arising from two adjacent sources as separate is subject to the interplay between spatial summation⁴⁷ and discrimination.⁴⁸ Summation may account for a lack of difference in perceived pain arising from the anterior knee vs that arising from both the anterior and posterior knee.⁴⁹ Also, discrimination enables distinguishing pain from two sources only if they are ≥ 10 cm apart.⁵⁰ Realistically, overall knee pain may be the best available surrogate measure of the analgesic effects of SNB. Finally, LIA is an emerging analgesic modality²; but whether its ultimate role in a post-TKA analgesic regimen is to complement nerve blocks⁵¹ or replace them altogether⁵²⁻⁵⁵ is to be determined by future research.

Our systematic review has several areas of strength. The literature search we conducted was exhaustive and included all of the relevant electronic databases. Our eligibility criteria restricted the evidence sought to that in RCTs and excluded several observational studies¹¹⁻¹³ that had been included in earlier reviews.¹⁴ Additionally, all of the trials we included were of high quality (Jadad score ≥ 3). These factors thus reinforce the validity of our findings.

Our systematic review, however, also has some limitations. First, the outcome data originated from varying RCT settings with diverse anesthetic and analgesic practices. For example, the nerve localization techniques employed and the analgesic regimens used varied among the trials, leading to considerable heterogeneity. We also did not use a specific type of TKA surgery to stratify our results. Variations among TKA techniques could result in differences in the duration and severity of postoperative pain as well as the dose of postoperative morphine needed to treat the pain. Second, the majority of the trials we reviewed were characterized by their small sample size, with a maximum of 33 patients per group. Such small RCTs could increase the likelihood of detecting a treatment effect and/or misestimating its magnitude because of a combination of mere chance and publication bias. Third, analgesic techniques other than SNB (e.g., intra-articular local anesthetic infiltration,^{18,23} posterior knee capsule injection⁵⁶ have achieved effective pain relief following TKA, whether in combination with or as substitutes for SNB. The influence of the aforementioned analgesic options on SNB analgesia is not within the scope of our systematic review. Fourth, it is not possible to exclude reporting bias because publishing the study protocols on trial registration sites has not been common practice. Fifth, the reviewed RCTs used varying and sometimes unclear definitions to describe reported outcomes, which questions the validity of combining these outcome results. Sixth, this review was limited to RCTs published in English, and we did not translate any foreign

trials. Seventh, although the absolute difference in pain scores may seem modest at certain time points, including at four and eight hours for SSNB, differences in pain severity scores as small as 0.9 and 1.1 units on the VAS have been proven to be clinically important.^{57,58} Finally, none of the RCTs described any preexisting (i.e., preoperative) knee pain, which precluded analysis of the association between this postoperative pain predictor⁵⁹ and the duration of post-TKA analgesia supplied by the SNB.

In conclusion, the available evidence supporting an analgesic benefit of adding SNB to FNB following TKA is marked by significant heterogeneity. Keeping this heterogeneity limitation in mind, our meta-analysis suggests that SNB can significantly reduce postoperative opioid consumption and diminish the knee pain following TKA compared to no SNB in the setting of FNB. Although analgesic strategies vary greatly across institutions,^{45,60} our results support a role for SNB in acute pain management following TKA.

Author contributions: *Faraj W. Abdallah* conceived the idea, helped in designing and conducting the study, collecting and analyzing the data, and preparing the final manuscript. *Caveh Madjdpour* helped in conducting the study, collecting and analyzing the data, and preparing the final manuscript. *Richard Brull* helped in designing and conducting the study, collecting and analyzing the data, and preparing the final manuscript. All authors attest to the integrity of the original data and the analysis reported in this manuscript. All authors approved of the final manuscript.

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Competing interests No competing interests declared.

Appendix: Medline search strategy as: 2015-03-27

Ovid MEDLINE(R) 1950 to March Week 4 2015

#	Searches	Results	Search Type
1	Arthroplasty, Replacement, Knee/	12424	Advanced
2	Knee Prosthesis/	8524	Advanced
3	((knee or knees) adj3 replac*).mp.	15099	Advanced
4	((knee or knees) adj3 arthroplast*).mp.	15809	Advanced
5	((knee or knees) adj3 prosth*).mp.	9624	Advanced
6	(total adj2 knee?).mp.	12273	Advanced
7	tka.tw. [Total Knee Arthroplasty]	3413	Advanced

Appendix continued

Ovid MEDLINE(R) 1950 to March Week 4 2015

#	Searches	Results	Search Type
8	tkr.tw. [Total Knee Replacement]	1030	Advanced
9	tkas.tw.	790	Advanced
10	tkrs.tw.	175	Advanced
11	or/1-10	21320	Advanced
12	Knee/	10263	Advanced
13	exp Knee Joint/	42355	Advanced
14	exp Knee Injuries/	15682	Advanced
15	Osteoarthritis, Knee/	10346	Advanced
16	Patella/in [Injuries]	1934	Advanced
17	Patella/su [Surgery]	2229	Advanced
18	knee.tw.	80573	Advanced
19	knees.tw.	14927	Advanced
20	or/12-19	105201	Advanced
21	exp Arthroplasty/	39132	Advanced
22	exp Joint Prosthesis/	34450	Advanced
23	"Prostheses and Implants"/	36086	Advanced
24	arthroplast*.tw.	32856	Advanced
25	proste*.tw.	87061	Advanced
26	replac*.tw.	282245	Advanced
27	implant*.tw.	252903	Advanced
28	endoprosthe*.tw.	5601	Advanced
29	exp Prosthesis Failure/	21219	Advanced
30	or/21-29	614708	Advanced
31	20 and 30	27250	Advanced
32	11 or 31 [Knee Replacement & Related Terms]	29228	Advanced
33	exp Sciatic Nerve/ and exp Nerve Block/	1032	Advanced
34	exp Sciatic Nerve/ and exp Anesthesia, Conduction/	1139	Advanced
35	(sciatic nerve* adj3 block*).mp.	728	Advanced
36	(sciatic adj3 block*).mp.	830	Advanced
37	snb.tw. [Sciatic Nerve Block]	1127	Advanced
38	or/33-37	2491	Advanced
39	32 and 38	97	Advanced
40	limit 39 to english language	81	Advanced

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