Orthopaedic Surgery

REVIEW ARTICLE OPEN ACCESS

Targeting the Infrapatellar Branch of the Saphenous Nerve for Pain Relief in Patients With Acute or Chronic Knee Pain: A Systematic Review of Randomized Controlled Trials and Cohort Studies

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Received: 1 August 2024 | **Revised:** 26 October 2024 | **Accepted:** 10 December 2024

Funding: This work was supported by Young Scientists Fund of the Natural Science Foundation of China, 82202755. Young Scientists Fund of the Natural Science Foundation of Jiangsu Province, BK20220183.

Keywords: arthroplasty | arthroscopy | knee pain | systematic review | the infrapatellar branch of the saphenous nerve

ABSTRACT

Blocking the infrapatellar branch of the saphenous nerve (IPBSN) can provide analgesic benefits for patients with postoperative acute pain or chronic pain, with minimal adverse effects. To evaluate the analgesic efficacy and potential adverse events associated with IPBSN block in patients suffering from acute or chronic knee pain. We conducted a systematic review across PubMed, Cochrane, Web of Science, and Embase to identify all relevant randomized controlled trials (RCTs) and cohort studies according to predefined selection criteria. The study quality of the RCTs was evaluated using the Cochrane risk of bias assessment tool, while cohort studies were assessed using the ROBINS-I risk of bias tool. The primary outcomes measured were pain intensity and opioid consumption following the nerve block. A total of eight studies were included in this systematic review, encompassing 613 subjects with 276 participants in the control group and 337 participants in the IPBSN block group. The level of evidence was rated high for the RCTs and moderate for the cohort studies. The nerve block was administrated either through the injection of local anesthetic or percutaneous cryoneurolysis targeting the IPBSN. The results indicated that the IPBSN block significantly improved pain relief and reduced opioid consumption in patients with acute postoperative or chronic pain, with no significant difference in the rate of adverse events relating to the procedures or device. The IPBSN block holds promise for improving pain relief and reducing opioid consumption. However, further well-designed randomized controlled trials are needed to confirm these results.

1 | Background

Anterior knee pain is a common complaint among patients of all ages, arising from conditions such as osteoarthritis or post-surgical pain. Knee surgeries, including knee arthroplasty and arthroscopic knee surgery, are widely performed globally, with many patients experiencing moderate to severe acute postoperative pain [1]. Sufficient postoperative pain relief is crucial for facilitating early physical rehabilitation, enabling patients to regain their physical capacity and be discharged early from the hospital [2]. However, pain may become chronic if inadequately controlled [3]. Recent data have shown that the rate of chronic pain following total knee arthroplasty (TKA) ranges from 10% to 34%, persisting even 3 months to 5 years after surgery [4]. Additionally, persistent knee pain is often observed in patients undergoing tibial nailing and can significantly restrict daily and leisure activities [5–7]. Osteoarthritis can also induce chronic knee pain, which requires multimodal and individualized treatment, as many current interventions fail to provide sufficient long-term pain relief and may have associated side effects [8, 9]. Recent advances in sensory peripheral nerve blocks have enabled targeted anesthesia of superficial sensory nerves without causing motor blockades. This technique offers advantages such as faster rehabilitation, early recovery, and a lower risk of postoperative accidental falls compared to femoral nerve blocks [10, 11].

Saphenous nerve exits from the adductor hiatus and give off an infrapatellar branch named the infrapatellar branch of the saphenous nerve (IPBSN), which then pierces the fascia lata to become subcutaneous in the knee [12]. The IPBSN is a purely sensory nerve that innervates the skin on the anterior and medial aspect of the knee [13, 14]. Blocking this nerve provides sensory analgesia to the knee without the concomitant quadriceps weakness associated with femoral nerve blockades, making it an effective alternative target for nerve blocks aimed to reducing knee pain [15]. Typically, IPBSN block is performed under ultrasound guidance to accurately locate the needle and observe the spread of the local anesthetic [16]. Recently, cryoneurolysis has emerged as a temporal yet effect analgesic modality by targeting the peripheral nerves through causing Wallerian degeneration of the nerve axons [17], leading to a long-term nerve block. Within the past few years, there is growing evidence supporting its use in both nonsurgical and surgical orthopedic patients for pain relief.

Several recently published randomized controlled trials (RCTs) have reported that blocking the IPBSN with local anesthetics or cryoneurolysis provides significant analgesic benefits without notable adverse effects or disadvantages in patients undergoing knee surgeries [18–20]. Moreover, IPBSN blocks can decrease chronic pain in patients with osteoarthritis [21] or knee pain after tibial nailing [22]. However, no systematic review has yet summarized these results to evaluate the overall analgesic efficacy of IPBSN blocks for knee pain relief. Therefore, we conducted a systematic review to assess the analgesic efficacy and potential adverse events associated with IPBSN blocks in patients with knee pain.

2 | Method

For this review, we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement [23]. The protocol for this study was registered on PROSPERO (registration number: 42023437429).

2.1 | Search Methods for Identification of Studies

We searched PubMed, Cochrane Library, Web of Science, and Embase with time range from inception until July 2023. The search strategy consisted of both Medical Subject Headings (MeSh) and text words, following a PICOS methodology. The detailed search strategy is provided in Table S1. Additionally, we manually searched the reference lists of relevant studies to identify additional papers for potential inclusions. Two independent investigators (QQL and A.Akram) conducted the selection process, and a third investigator (DYC) resolved any disagreements. Figure 1 depicts the search strategy.

2.2 | Literature Inclusion and Exclusion Criteria

Two reviewers (QQL and A.Akram) individually identified and evaluated potentially eligible trials based on predefined inclusion criteria. Inclusion and exclusion criteria were as follows: [1] Participants: adult participants (≥ 18 years old) without restriction on their sex, excluding pregnant, or lactating females [2]. Interventions: We included RCTs and comparative (prospective or retrospective) studies comparing IPBSN block versus sham treatment without restrictions on the technique used (regional anesthetic technique, cryoneurolysis, etc.) [3]. Outcomes: Primary outcomes included the mean density of pain and opioid consumption following the nerve block. Secondary outcomes included functional outcomes and rates of block-related adverse events [4]. Study design: We included all RCTs and comparative cohort studies (prospective or retrospective) in humans. A third investigator (DYC) was invited to solve the disagreements regarding the selection process.

2.3 | Data Extraction

Data were extracted from each eligible trial according to a prepared data extraction form (Tables 1 and 2). Basic information of each study included author, publication date, country, study design, and intervention. Demographic characteristics retrieved included the patient age, sex, body mass index (BMI), country, sample size, type of pain (acute or chronic), type and duration of surgery, and type of anesthesia. For the IPBSN block procedure, we recorded the timing, method of intervention, control intervention, target nerve and adverse events. Another investigator (A.Akram) double-checked the extracted data to minimize reviewer errors. Discrepancies were resolved and group consensus was reached by consulting a third reviewer (DYC) to ensure accuracy of the data.

2.4 | Quality Assessment

Two review authors (QQL and A.Akram) independently assessed the risk of bias of the eligible RCT studies using the Cochrane risk assessment tool, which includes seven criteria [24]. Risk of bias was classified as low, high, or unknown following Cochrane

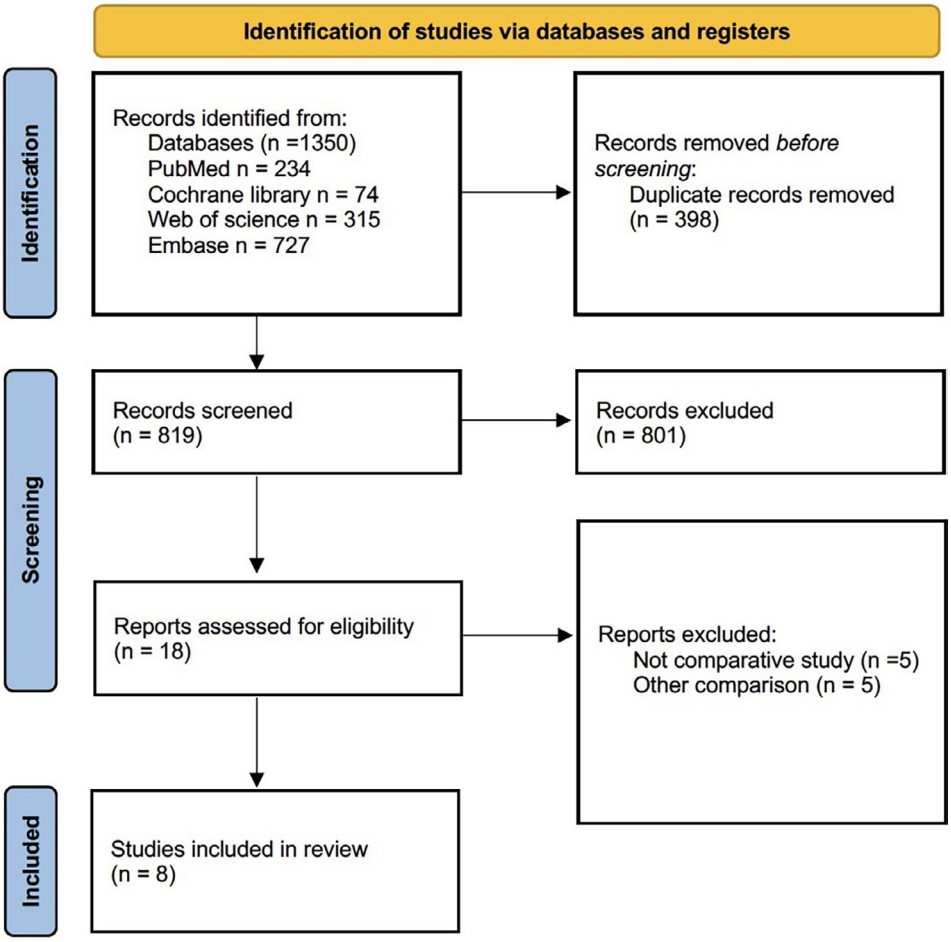

FIGURE 1 | Study flow diagram.

Handbook recommendations. The quality of cohort studies was evaluated using the ROBINS-I risk of bias tool, a risk of bias assessment tool for nonrandomized studies [25]. The quality was assessed by two review authors independently.

3 | Results

3.1 | Selection and Identification of Studies

The flow diagram of paper inclusion and selection process was shown in Figure 1. In summary, a total of 1350 publications were identified from the databases searched, including PubMed (234), Cochrane library (74), Web of Science (315), and Embase (727), which yielded 819 papers after removing duplicates (398 articles). We retrieved 18 full texts for further screening based on titles and abstracts [18–22, 26–38]; 10 were excluded and eight were finally included in the review according to inclusion and exclusion criteria [18–22, 26, 27, 29]. Trials were excluded for the following reasons: not a comparative study ($n = 5$) [28, 30, 36–38], and other comparisons ($n = 5$) [31–35].

3.2 | Study Characteristics

The study characteristics of the included trials are shown in Table 1. Overall, 16 treatment arms were extracted from six RCTs and two cohort studies that included a total of 613 participants, of which 276 participants were in the control group and 337 patients were in the IPBSN block group. The studies were published between 2011 and 2022, with six conducted in the United States [18, 19, 21, 26, 27, 29], one in Sweden [20], and one in the Netherlands [22]. The number of participants ranged from 8 to 121, with a predominance of female adults. Four studies included patients undergoing TKA [19, 26, 27, 29], two included patients receiving knee arthroscopies [18, 20], one study recruited patients with mild to moderate knee osteoarthritis [21], and one reported on chronic anterior knee pain following tibial nailing surgery [22]. Patients received general anesthesia prior to surgery in three studies on surgical patients [18–20], and spinal anesthesia in two studies [26, 27], while the other studies did not report relevant information [29] or include nonsurgical patients [21, 22].

The included studies employed different methods for administering nerve blocks (Table 2). Five studies utilized percutaneous cryoneurolysis with a probe containing nitrous oxide gas connected to a cryoneurolysis machine [19, 21, 26, 27, 29]. Three studies used local anesthetic to block the IPBSN [18, 20, 22] and the anesthetics included bupivacaine (0.25% and 5%) and lidocaine (2%). For nerve targeting, three studies employed ultrasound guidance [18–20], while five relied on visualization and palpation of anatomical landmarks [21, 22, 26, 27, 29]. Control group patients received either sham surgery or placebo treatment.

TABLE 1 | Characteristics of the included studies.

Author	Country	Patients	Sample size (F/M)	Age	BMI	Duration of surgery (min)	Type of anesthesia	Primary outcome	Significant findings
Swisher 2022	USA	TKA	8 (7/1) vs. 8 (3/5)	67 (63–77) vs. 68 (64–72)	28 (27–30) vs. 26 (25–28)	NR	General or neuraxial anesthesia	Worst and average pain, opioid consumption	Lower average and worst pain scores of POD [4–21] after cryoneurolysis
Hsu 2013	USA	Arthroscopy	34 (16/18) vs. 34 (19/15)	49.6 ± 14.1 vs. 51.7 ± 12.1	29.9 ± 7.5 vs. 30.6 ± 9.4	34.1 ± 10.4 vs. 36.4 ± 12.3	General anesthesia	NRS score, opioid consumption	Improved early NRS score and 12-week Lysholm knee scores after the nerve block
Lundblad 2011	Sweden	ACLR	32 (16/16) vs. 30 (15/15)	30.8 (16–50.4) vs. 25.9 (15.0–53.3)	NR	65 (25–115) vs. 56 (30–95)	General anesthesia	Pain intensity, numbers of hours spent sleeping	Improved pain relief after the nerve block
Radnovich 2017	USA	Mild to moderate knee OA	59 (40/19) vs. 121 (79/42)	61.3 ± 8.17 60.6 ± 8.98	30.0 ± 3.54 vs. 29.1 ± 3.97	NR	NA	VAS, WOMAC, SF-36	Improved pain relief after receiving the treatment
Leliveld 2018	Netherlands	Chronic anterior knee pain after tibial nailing	17 (8/9) vs. 17 (7/10)	38 (18–60) vs. 40 (22–62)	NR	NR	NA	Pain intensity during activities	IPBSN block reduces pain during kneeling
Mihalko2020	USA	TKA	48 (26/22) vs. 48 (25/23)	66.5 ± 6.8 vs. 66.1 ± 7.7	31.5 ± 4.7 vs. 30.1 ± 4.3	NR	Spinal anesthesia	Functional scores and pain scores	Preoperative cryoneurolysis reduces opioid consumption and improve functional outcomes
Dasa 2016	USA	TKA	50 (36/14) vs. 50 (34/16)	66.4 ± 9.4 vs. 68.5 ± 8.2	30.9 ± 5.7 vs. 32.1 ± 5.3	NR	Spinal anesthesia	Opioid consumption, pain intensity	Perioperative cryoneurolysis significantly improves outcomes in patients undergoing TKA
Lung 2022	USA	TKA	28 (18/10) vs. 29 (19/10)	67 ± 7 vs. 68 ± 7	31 ± 6 vs. 33 ± 5	86 ± 24 vs. 75 ± 11	NR	MME requirement, ROM, KOOS JR, SF-12	Cryoneurolysis reduces opioid consumption, improves knee ROM, and improves patient satisfaction

Note: Data were expressed as mean ± SD or mean/median (range).
Abbreviations: ACLR, anterior cruciate ligament reconstruction; BMI, body mass index; KOOS, the knee injury and osteoarthritis outcome score; NA, not applicable; NR, not reported; POD, post-op day; TKA, total knee arthroplasty; SF-12, the 12-item Short Form Survey (SF-12); WOMAC, Western Ontario and McMaster Universities Arthritis Index.

3.3 | Risk of Bias Assessment

The risk of bias assessment, presented in Figures S1 and S2 and Table S2, indicated that the overall quality of the included RCTs was high. All RCTs were considered to have a low risk of bias for random sequence generation and allocation concealment. Additionally, all included RCT studies were double blinded with the participant and the provider of the intervention blinded to therapy. Two trials were rated as having a low risk of bias for blinding of outcome assessment (detection bias), two had unclear risk, and one had a high risk due to nonblinding of the outcome assessor. All included RCTs included in the analysis were rated as having a low risk of bias for incomplete outcome data. However, due to insufficient data sources, all RCTs were rated as having an unclear risk of bias for selective reporting and other potential sources of bias. The results of the methodologic quality assessment for the included nonRCTs, evaluated using the ROBINS-I risk of bias tool, are presented in Table S2. Both studies exhibited a moderate risk of bias related to confounding factors, as there were no prognostic variables predicting baseline intervention and no instances of patients switching between interventions during the study period. One study was rated as having a serious risk of bias due to patient selection [27]. Both studies clearly classified treatment type (low risk of bias). Both studies used nonblinded, yet identical postoperative protocols (moderate risk of bias). No studies showed bias due to missing data (low risk of bias). Both studies involved physicians not blinded to treatment group or used self-reported outcomes (serious risk of bias). Lastly, there was no evidence of bias due to selective reporting in any of the studies (low risk of bias).

3.4 | Primary Outcomes: Pain Intensity and Opioid Consumption Following Nerve Block

All studies compared the mean difference in pain intensity before and after the intervention. Key findings from each study are listed in Table S3. Six of the eight studies reported a significant reduction in pain intensity in patients experiencing acute pain following knee surgeries [18, 20, 26, 27] and chronic pain from severe osteoarthritis [21, 22]. Patients in the nerve block group also consumed significantly fewer cumulative opioids compared to those in the sham or control group [18, 26, 27]. In the two studies that did not show a significant difference in pain intensity post-intervention, there was still an overall decrease in visual analogue score (VAS) pain score and opioid consumption [19, 29]. These findings collectively suggest that IPBSN block is associated with improved pain relief and decreased opioid consumption, both for acute post-surgical pain and chronic pain.

3.5 | Secondary Outcomes: Physical Function and Adverse Events

Hsu et al. found that IPBSN blocks in knee arthroscopy were associated with improved 12-week Lysholm knee scores [18]. Similarly, Radnovich et al. reported that patients with knee osteoarthritis in the cryoneurolysis group experienced significantly better physical function, as measured by the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) physical function at Day 30 [21]. Dasa et al. showed that perioperative cryoneurolysis led to greater reductions in the Knee Injury and Osteoarthritis Outcome Score (KOOS) symptoms subscale from baseline to six and 12 weeks post-operation compared to the control group [27]. Lung et al.'s cohort study reported a significantly better improvement in mental score and KOOS score from pre-operation to a 12-month follow up [29]. Regarding the adverse events, Swisher et al. reported no treatment-related adverse events [18, 19, 29]. Lundblad et al. mentioned a case of altered sensation at the administration site in a patient after sham treatment [20]. Leliveld, Kamphuis, and Verhofstad did not report any block-related adverse events [22]. Hsu et al. reported the successful rate of 85% in their study, while no other trials provided such data [18].

4 | Discussion

4.1 | Summary of Main Findings

This systematic review evaluates the efficacy of IPBSN block for pain relief in adults with acute or chronic knee pain. The review encompasses 6 RCTs and two cohort studies, involving a total of 613 participants. The findings indicate that IPBSN block is associated with improved pain relief and reduced opioid consumption compared to sham treatment, suggesting potential benefits as an adjunct in knee surgery or for chronic knee pain management.

4.2 | Quality of Evidence

Most RCTs had a low risk of bias, although concerns were raised regarding the blinding process in one study, where assessors were not masked. The small sample sizes across studies contribute to potential heterogeneity and limit the generalizability of the findings. Despite employing a comprehensive and systematic search strategy, the possibility of publication bias remains, as some unpublished studies may not have been captured. The quality of the included cohort studies was relatively low, underscoring the necessity for more rigorous RCTs with adequate follow-up and larger sample sizes to better assess the causal role of IPBSN blocks in pain relief.

4.3 | Agreements and Disagreements With Other Studies

To date, no systematic review has focused on this topic. Previous studies have indicated that IPBSN was encountered in all knees during TKA using a standard midline approach [39]. Iatrogenic injury to the IPBSN is a common complication of both open and arthroscopic surgeries, leading to neuropathic pain symptoms in the anterior and medial aspect of the knee [40]. This may be due to the highly variable location of the IPBSN (Figure 2). Neuroma formation in the IPBSN is an often-overlooked cause of persistent anterior pain following TKA. Selective neuroma denervation provides improvements in the quality of life of patients with neuroma in the IPBSN [41]. Despite these findings, there is no consensus on how to manage the IPBSN during knee surgery. Recent studies have explored various approaches to block the IPBSN, such as local anesthetics and cryoneurolysis,

TABLE 2 | Comparison of IPBSN intervention among included studies.

Author	Patients	Timing of intervention	Control group	Intervention group	Target nerve	Adverse events
Swisher 2022	TKA	Immediately before surgery	Sham surgery with the sham probe vented the nitrous oxide at its proximal end and no freezing occurred at the distal tip	Ultrasound-guided percutaneous cryoneurolysis with a 14-gauge cryoneurolysis probe connected to a cryoneurolysis machine with settings of three cycles of 2 min on and 1 min of defrost.	IPBSN	No treatment-related adverse events
Hsu 2013	Arthroscopy	Immediately before surgery	10 mL saline	Ultrasound-guided block with 10 mL 0.25% bupivacaine block	IPBSN	No major adverse reactions. Less subjective nausea in block group
Lundblad 2011	ACLR	Immediately before surgery	10 mL saline	Ultrasound-guided block with10 ml of levobupivacaine (5 mg/mL)	IPBSN	Higher percentage of patients were asleep in IPBSN group compared to sham block
Radnovich 2017	Mild to moderate knee OA	Not applicable	Sham smart tip identical with the block group without freezing zone	Iovera device with a functioning Smart Tip	IPBSN	Administration site altered sensation in a sham treatment group
Leliveld 2018	Chronic anterior knee pain after tibial nailing	Not applicable	5 mL saline	Depositing 5 mL of lidocaine in a fan-like manner between the medial surface of the medial femoral condyle	IPBSN	Not reported
Mihalko 2020	TKA	3–7 days pre-op	Preoperative standard of care treatment	Iovera device delivering nitrous oxide	IPBSN	No device-related or procedure-related adverse events
Dasa, 2016	TKA	5 days pre-op	Without intervention	Iovera device containing liquid nitrous oxide	IPBSN	No complications related to cryoneurolysis treatment
Lung, 2022	TKA	7 days pre-op	No intervention	Iovera device containing liquid nitrous oxide	IPBSN	No device or procedure related adverse event

Abbreviations: AE, adverse event; IPBSN, infrapatellar branch of the saphenous nerve; NR, not reported; OA, osteoarthritis; Pre-op, preoperative; TKA, total knee arthroplasty.

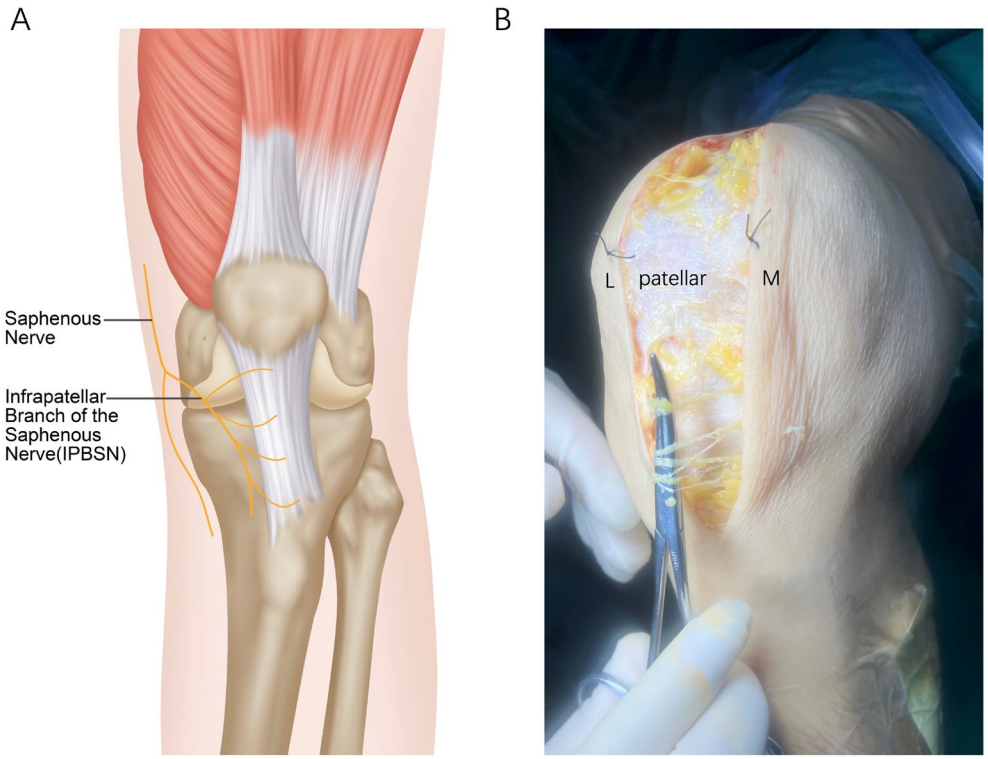

FIGURE 2 | (A) Infrapatellar branch of the saphenous nerve. (B) Intraoperative view of the infrapatellar branch of the saphenous nerve. L, lateral; M, medial.

reporting significant analgesic, and opioid-sparing benefits. Our systematic review combined these results and showed substantial analgesic and opioid-sparing benefits of IPBSN block. However, we were unable to perform a meta-analysis due to the relatively small number of included studies and the lack of standardized outcome measures. Therefore, this review highlights the need for well-designed RCTs with adequate follow up and large sample sizes with consistent and comprehensive outcome reporting, including opioid- and block-related adverse events, as well as knee function. Additionally, we could not perform subgroup analyses (e.g., knee arthroscopy vs. knee joint replacement) because of limited data. Emerging evidence suggests using preoperative cryoneurolysis to treat pain and symptoms of knee osteoarthritis; therefore, future studies are warranted to investigate the efficacy of preoperative cryoneurolysis for pain relief in patients with knee osteoarthritis.

4.4 | Implications for Research

The most important limitation was the small number of trials reporting each outcome, which impeded planned meta-analysis and subgroup analyses. Variability in self-reported pain intensity and the timing of assessments made it challenging to synthesize results. For example, the included studies used self-report surveys reporting pain intensity at diverse time points, making it difficult to merge the results and conduct a meta-analysis. Three of eight trials did not report all relevant procedure-related adverse events, which are clinically more relevant for the patient than cumulative opioid consumption. Additionally, our review revealed some clinical heterogeneities of the included studies, such as the method of intervention (block vs. cryoneurolysis), the indication for the intervention (acute vs. chronic pain), and the anesthetics used for the block (bupivacaine or lidocaine). As such, our confidence in the current conclusion is limited, and there is a high risk that future studies will reach different conclusions.

5 | Conclusions

IPBSN block appears to be a promising approach for managing knee pain, offering pain relief and reducing opioid consumption. Further well-designed trials are warranted to confirm the efficacy and safety of IPBSN block for knee pain relief. Future research should prioritize patient-relevant outcomes, including adverse events related to opioid and nerve blocks, rather than focusing solely on opioid consumption.

Author Contributions

Conceptualization: Qiangqiang Li and Dongyang Chen. Data curation: Qiangqiang Li and Aikeremu Aierken. Formal analysis: Qiangqiang Li. Investigation: Qiangqiang Li, Aikeremu Aierken, and Jianghui Qin. Methodology: Qiangqiang Li and Dongyang Chen. Software: Qiangqiang Li. Supervision: Dongyang Chen and Qing Jiang. Writing – original draft: Qiangqiang Li. Writing – review and editing: Qing Jiang and Dongyang Chen. All authors have read and agreed to the published version of the manuscript. Qiangqiang Li and Aikeremu Aierken contributed equally to this manuscript.

Acknowledgments

This systematic review was funded by Young Scientists Fund of the Natural Science Foundation of China (Ref No. 82202755 to QQL) and

Young Scientists Fund of the Natural Science Foundation of Jiangsu Province, China (Ref No. BK20220183 to QQL). The funder had no role in study design, data collection and analysis, interpretation of data, preparation of the manuscript or decision to publish.

Ethics Statement

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data relevant to the study are included in the article or uploaded as supplementary information.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.