Systematic Review

Ultrasound-guided Genicular Nerve Blockade With Pharmacological Agents for Chronic Knee Osteoarthritis: A Systematic Review

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Background: Ultrasound-guided (ULSD-g) genicular nerve blocks (GNB) using pharmacological agents for pain control in chronic knee osteoarthritis (OA) are gaining in popularity. There lacks a systematic review to evaluate the ULSD techniques and pharmacological agents used during the intervention, and to assess the knee's function postintervention.

Objectives: Our study aimed to determine the clinical characteristics of patients with chronic knee OA selected for ULSD-g GNB, describe the various ULSD-g techniques and pharmacological agents used to target the genicular nerves, and evaluate the primary outcomes of pain and function.

Study Design: Systematic review.

Methods: We looked at patients with chronic knee OA with symptoms or disease features of at least 3 months and the use of ULSD guidance for GNB using either local anesthetic agents and/or corticosteroids or alcohol. Two major electronic databases (Medline/PubMed and EMBASE) were searched from their inception through August 2021, without language restriction.

After removing duplicates, 2 reviewers independently reviewed the abstracts of 340 records. Nine of the 10 full texts that were reviewed were selected for inclusion. A third reviewer was involved in resolving disagreements.

Two reviewers extracted relevant information pertaining to study types, patient characteristics, intervention details, outcome measures, and adverse effects. This was followed by independent verification for accuracy.

Results: Data synthesis: Nine studies were included with a total of 280 patients who had symptoms or disease features of at least 3 months. The National Institute of Health's Study Quality Assessment Tools were used for quality appraisal, of which 8 studies were at least of fair quality. All studies involved targeted at least the superior medial, superior lateral, and inferior medial genicular nerves. ULSD techniques relied on bony, soft tissue, or periarterial landmarks; either local anesthetic agents and/or corticosteroids or alcohol were used in the injections. Follow-up intervals for pain and functional assessments were heterogeneous, ranging from one week to 6 months postprocedure. Sustained improvements in both pain and knee function were observed for up to 6 months regardless of the choice of pharmacological agents. Minimal adverse effects were reported.

Limitations: Meta-analysis was not performed due to heterogeneity of study designs, ULSD techniques, pharmacological agents used, and dosages administered. Only one study targeted additional genicular nerves; conclusions regarding the therapeutic blockade of these nerves could not be made.

Conclusions: There is fair evidence to at least target the superior medial genicular nerve, inferior medial genicular nerve, and superior lateral genicular nerve using local anesthetics, corticosteroids, or alcohol to reduce pain and to improve knee function in patients with chronic knee OA under ULSD guidance. The procedure is safe but more research is needed to determine the optimal interventional approach.

Key words: Ultrasonography, genicular nerve block, neurolysis, knee osteoarthritis

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Knee osteoarthritis (OA) causes significant pain and disability in the aging population (1,2). Although total knee arthroplasty is an effective surgical option as the condition progresses, some patients are excluded due to preexisting comorbidities or their reluctance to surgical interventions. These patients can only seek nonsurgical treatment strategies to help cope with their pain and disability (3,4). Amidst a plethora of such nonsurgical interventions, the genicular nerve block (GNB) has gained in popularity over the past decade (4-6). GNB has also seen usage in postoperative analgesia for patients who underwent knee arthroplasty, with reported success (7,8).

Earlier studies evaluating the use of GNB in knee OA often utilize fluoroscopy for procedural guidance (9). However, in recent years, procedures done under ultrasound (ULSD) guidance have been gaining traction within the field of pain medicine (10,11). ULSD confers distinct advantages over fluoroscopic guidance as it is portable and radiation-free, facilitating use in clinical and bedside settings. A recent systematic review (11) demonstrated that use of ultrasound guidance in radiofrequency ablation was both safe and effective for pain relief and functional improvement in patients with knee OA. However, there has not yet been a systematic analysis of ULSD-g GNB with pharmacological agents such as local anesthetics, corticosteroids, and alcohol. These injectables are commonly used in pain-related procedures, and when combined with ULSD-g GNB, could present another possible treatment option in the armamentarium of physiatrists and pain management specialists. Consequently, we sought to conduct a systematic review to investigate the role of this intervention in reducing pain and improving functional outcomes for patients with chronic knee OA.

Methods

Search Strategy

This review is reported using the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) checklist and registered on the International Prospective Register of Systematic Reviews database (PROSPERO) (CRD42021274596) (12).

A structured computer search strategy was applied to Medline/PubMed and EMBASE from their inception through August 2021 using a combination of search terms. Search terms included "genicular nerve block," "ablation techniques," "chemical neurolysis," and "knee osteoarthritis." Search terms were tailored to each database and are described in Table 1. We performed manual searches on the reference lists of our included studies, as well as associated systematic reviews and meta-analyses to identify relevant studies. There was no restriction on the language used.

Inclusion Criteria

Studies were included in this systematic review if they:

1. Involved primary research (randomized and nonrandomized experimental trials, cohort and case-control studies, as well as case series and case reports)
2. Studied the intervention of GNB or neurolysis (either diagnostic or therapeutic) specifically referring to only the genicular branches of the femoral and sciatic nerves
3. Involved the use of ULSD guidance
4. Had a primary diagnosis of chronic knee OA (> 6 months) without any diagnostic uncertainty
5. Described the severity of the knee OA using classification by any radiological, arthroscopic, or clinical scales
6. Consisted of patients who received either unilateral or bilateral interventions
7. Involved adult participants aged 18 years and older.

We also considered studies that involved surgical procedures (such as knee arthroplasty) alongside

Table 1. *Search terms*.

Database	PubMed	Embase
Search terms	((genicular nerve block) OR (genicular nerve ablation) OR (genicular nerve neurolysis) OR (ablation techniques[MeSH Terms]) OR (neurolysis, chemical[MeSH Terms]) OR (ablation techniques[MeSH Terms]) OR (chemical neurolysis[MeSH Terms])) AND ((knee osteoarthritis) OR (knee osteoarthritides[MeSH Terms]) OR (knee osteoarthritis[MeSH Terms])) AND (human)	((genicular nerve block) OR (genicular nerve ablation) OR (genicular nerve neurolysis) OR (ablation techniques) OR (neurolysis, chemical) OR (ablation techniques) OR (chemical neurolysis)) AND ((knee osteoarthritis) OR (knee osteoarthritides)) AND (human)

the intervention of interest to be suitable for inclusion. Non-English language articles were deemed acceptable if the authors were able to assist with translation.

Exclusion Criteria

Studies were excluded if they:

1. Involved cadaveric or dissection work
2. Were presented as conference proceedings or poster abstracts
3. Were duplicate works carried by multiple publications
4. Incorporated multiple interventions that limited attributability of the results to GNB
5. Involved radiofrequency, thermal, or cryoablation of the genicular nerves.

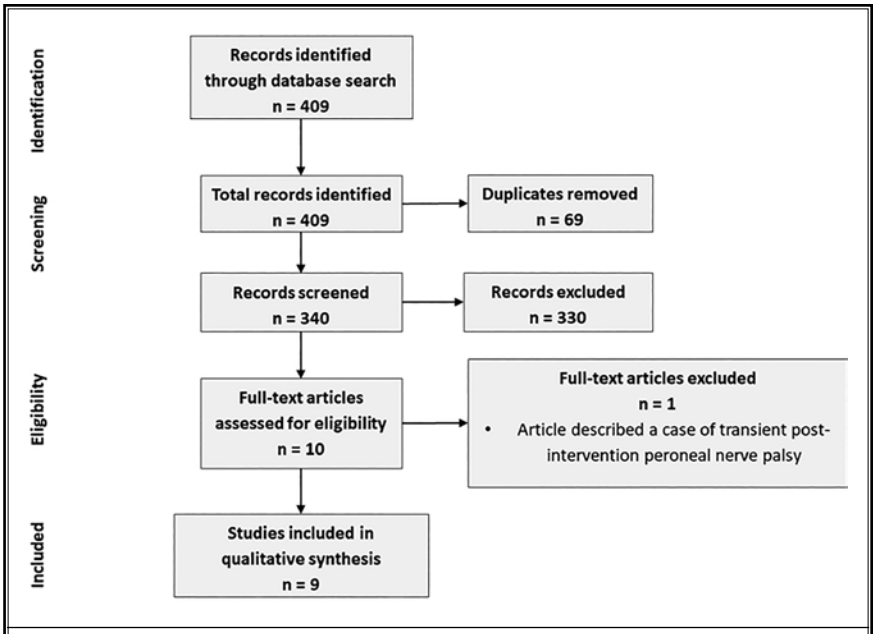

Fig. 1. *PRISMA Flowchart.*

Screening and Selection

Two authors (YLT, EN) independently reviewed all search results for appropriate studies, followed by extraction of data into spreadsheets and quality appraisal. Where there were disagreements in assessment, this was resolved through discussion. The casting vote was held by a third author (TCW) if consensus could not be achieved.

Risk of Bias Assessment

We used the National Institute of Health's (NIH) Study Quality Assessment Tools for determining study quality (13,14). Disagreements regarding the methodological quality of the studies were discussed between the 2 reviewers (YLT, EN). If consensus was not reached, a third reviewer (TCW) arbitrated.

Results

A total of 409 references were obtained through the search. The PRISMA flow diagram is depicted in Fig. 1. After removing 69 duplicates, 340 records were screened using their titles and abstracts to identify 10 potential articles. One case report was excluded as it discussed a patient who had developed transient peroneal nerve palsy following the intervention without addressing pain and efficacy outcomes (15). There were a total of 9 articles that cleared the full-text review and were included in the qualitative synthesis. These 9 articles consisted of one case report (16), 2 case series (17,18), one observational cohort study (19), and 5 randomized controlled trials (20-24).

Methodological quality across all studies was deemed fair-to-good for the case report and case series studies, fair for the observational cohort study, and poor-to-fair for the controlled intervention studies (Table 2). Cohen's κ for interrater reliability was 0.51, which corresponds to moderate agreement between the reviewers. A meta-analysis was not performed due to the heterogeneity of the study types, interventions, outcomes, and adverse events.

Characteristics of the Included Studies

Clinical Characteristics of the Patients With Chronic Knee OA

A total of 280 patients were involved in the 9 included studies. Patients had a confirmed diagnosis of symptomatic knee OA with mean durations ranging from 3 months to 12 years, and of severity ranging from grade 2 to grade 4 on the Kellgren and Lawrence classification system (25).

Table 2. *Quality assessment*.

Domain	Case reports/case series			Cohort study	Controlled studies				
	Ahmed 2019 (18)	Dass 2019 (17)	Demir 2017 (16)	Risso 2021 (19)	Cankurtaran 2020 (21)	Kim 2018 (23)	Kim 2019 (20)	Ragab 2021 (24)	Yilmaz 2021 (22)
1	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
2	Yes	Yes	Yes	Yes	Yes	Yes	Yes	CD	CD
3	CD	NA	NA	Yes	Yes	Yes	Yes	Yes	CD
4	Yes	NA	NA	Yes	NA	Yes	NA	Yes	NA
5	Yes	Yes	Yes	Yes	Yes	Yes	CD	Yes	CD
6	Yes	Yes	Yes	Yes	CD	Yes	Yes	Yes	Yes
7	Yes	Yes	Yes	Yes	CD	Yes	Yes	Yes	CD
8	Yes	No	NA	NA	Yes	Yes	Yes	Yes	CD
9	Yes	No	Yes	Yes	NR	Yes	Yes	Yes	CD
10				Yes	Yes	Yes	Yes	Yes	CD
11				Yes	Yes	Yes	Yes	Yes	Yes
12				NA	Yes	Yes	Yes	NR	CD
13				No	Yes	Yes	Yes	Yes	Yes
14				Yes	NR	Yes	Yes	Yes	CD
Overall	Good	Fair	Fair	Fair	Fair	Good	Good	Good	Poor

CD: cannot determine, NA: Not applicable

Intervention Specifics

Description of the Comparison of Various Modalities Used to Guide the Intervention

Among the randomized controlled trials, one study compared the effect of ULSD guidance versus surface landmarks techniques while another compared ULSD guidance versus fluoroscopic guidance (20,21). The remaining 7 studies used only ULSD guidance.

Nerves Targeted

All 9 studies described the targeting of 3 nerves - the superior medial genicular nerve (SMGN), the superior lateral genicular nerve (SLGN), and the inferior medial genicular nerve (IMGN). In addition to these nerves, only one study, by Ahmed, et al (18), included the inferior lateral genicular nerve (ILGN), the middle genicular nerve, and the recurrent peroneal nerve.

Anatomical Landmarks Used

There were 4 main guidance techniques described for performing the intervention. The first and most common technique was through periarterial injection at the levels of the superior medial, superior lateral, and inferior medial genicular arteries (16,20,22,23). The second technique involved other ULSD landmarks, either at the bony junctions of the epicondyle and shafts of the femur and tibia (17,24), or deep into soft tissue structures such as the vastus medialis, intermedius, and lateralis muscles, as well as the medial collateral ligament (19). The third method was through dynamic maneuvers combined with sonographic landmarks, such as with the hip in internal or external rotation and with proximal or medial movement from bony prominences such as the medial femoral condyle (18). The final method was through static surface landmarks, using the intersections of lines drawn between the fibular head and 4 cm superior to the tip of the lateral femoral epicondyle, between the femoral epicondyles, and from the medial femoral epicondyle to the medial tibial epicondyle (21).

Description of the Intervention Performed to Verify Needle Placement

Where this was described, the needle sizes ranged from 21G-23G. Intervention intent was both diagnostic and therapeutic in 3 studies (17-19), and therapeutic in the rest. The study by Ahmed, et al (18) used sensory nerve stimulation to support placement confirmation before injection, while Risso, et al (19) used hydro location with 0.2 mL of saline injection. Two studies used fluoroscopic imaging though in one case this was to support ULSD confirmation (17), whereas

in the other this served as the alternative intervention (20). Another 2 studies (Kim, et al [23] and Ragab, et al [24]) described the use of doppler ULSD for placement confirmation.

Choice of Injectate and Comparison Between Injectates

In terms of the type of injectates, Yilmaz, et al (22) and Ragab, et al (24) compared GNB with intraarticular corticosteroid injection (IACSI) (IACSI vs GNB and IACSI vs IACSI + GNB) (22,24) while Kim, et al (23) compared injectate types (lidocaine vs lidocaine + triamcinolone). Characteristics of the studies, patients, and specifics of the interventions are summarized in Table 3 and a network diagram illustrating the relationships among the different randomized trials is found in Fig. 2.

For diagnostic GNB, studies used either lidocaine or bupivacaine (17-19), with one to 2 successful blocks achieved before progression to therapeutic GNB. For therapeutic GNB, this was performed with either betamethasone and lidocaine, 50% alcohol and bupivacaine, or 99% alcohol and lidocaine for the case reports and case series (16-18). Glycerinated phenol 7% was used in the prospective cohort study by Risso, et al (19). In the randomized controlled trials, therapeutic GNB was always performed with a mix of corticosteroids (triamcinolone or betamethasone) and lidocaine of varying dosage (20-24).

Outcome Measures Described

Pain Outcomes

All studies described pain outcomes in the form of the Visual Analog Scale (VAS) or Numeric Rating Scale (NRS-11), with one study also using the Leeds Assessment of Neuropathic Symptoms and Signs (LANSS) (22), another using the Nottingham Health Profile (NHP) (21), and 2 studies reporting the pain subscale of the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) (20,21).

In the observational studies (case report, case series, cohort study), patients experienced a reduction in pain following GNB. This was as early as within one day (> 50% reduction) and maintained for up to 6 months (30-50% reduction depending on activity) (Table 4).

Cankurtaran, et al (21) compared ULSD-g GNB to "blind" (landmark-based) GNB (21). There were significant intragroup improvements in VAS and WOMAC total scores at 3 months though the between-group difference was not significant ($P = 0.43$ and 0.81 respectively). However, there was significant intergroup difference on the pain subscale of the NHP favoring blind injection ($P = 0.03$).

Kim, et al (20) compared ULSD-g GNB to fluoroscopic GNB (20). There were significant intragroup improvements at all timepoints compared to baseline on the NRS-11 for both interventions ($P < 0.05$ throughout), however between-group differences were not significant. Similar results were reported for the WOMAC pain subscale, although the fluoroscopic GNB group's mean score at 3 months was not significant ($P > 0.05$) (20).

Ragab et al (24) compared IACSI to GNB. Although both groups demonstrated significant improvements in VAS compared to baseline, the GNB group had comparatively greater improvements ($P = < 0.001$, < 0.001, and 0.006 at the 2-week, 4-week, and 8-week timepoints respectively).

Yilmaz et al (22) compared IACSI to IACSI with GNB. Although both groups demonstrated significant improvements in VAS and LANSS compared to baseline, the IACSI group had greater improvements at all timepoints on both scores ($P = 0.001$ and 0.001 at one month and 3 months respectively for VAS, and $P = 0.033$ and 0.044 respectively at the same timepoints for LANSS).

Kim et al (23) compared GNB with lidocaine to GNB with lidocaine and triamcinolone. Both groups exhibited significant improvements in VAS at the one-week, 2-week, and 4-week marks, though scores returned to baseline by 8 weeks. The between-group difference in change from baseline was significant at 2 weeks and 4 weeks in favor of the lidocaine and triamcinolone group ($P < 0.001$ and < 0.001 respectively).

Outcomes Other Than Pain

The Knee Osteoarthritis and Outcome Score, Oxford Knee Scale (OKS), and total WOMAC for stiffness, function, and disability, as well as the Global Perceived Effect Scale, and the 36-item Short-form Survey (SF-36) for quality of life were used.

In the observational studies (case report, case series, cohort study), patients were also reported to have statistically significant improvement in OKS, WOMAC, and the SF-36 (physical and mental health domains) (Table 4).

Of the controlled studies included in this review, Cankurtaran et al (21) reported improvements in stiffness and function, but with no clear superiority of either technique (21). The same finding was observed in Kim et al (20) who reported significant improve-

Table 3. *Study types and intervention details*

First author, year of publication, and author's country	Type of study	Pain characteristic and treatment history of patients	Radiological severity	Disease/ symptom duration	Nerves targeted and landmarks used	Description of interventions performed	Injectate/ intervention type
Observational studies - case reports/case series							
Ahmed, 2019, India (18)	Case series (n = 4)	NRS-11 pain score 7-9 Failed conservative management and intraarticular injections	K&L grade 3 or 4	Mean 51 months (pain)	SMGN: move proximally from medial femoral condyle to level of adductor tubercle and insertion of adductor tendon with hip in external rotation SLGN: over junction of lateral epicondyle and femoral shaft with hip in internal rotation IMGN: aligned along short axis of tibia and MCL with hip in external rotation ILGN: over anterolateral aspect of tibial condyle with hip in internal rotation Also: middle genicular nerve, and recurrent peroneal nerve	22G needle Diagnostic: ULSD-g Therapeutic: ULSD-g after 2 successive positive diagnostic blocks at 3-week intervals Confirmation with nerve stimulator (sensory)	Intention: diagnostic + therapeutic Diagnostic: 1.5-2 mL of 2% lignocaine; Therapeutic: 0.5-1 mL of 50% alcohol + 0.25% bupivacaine
Dass, 2019, Korea (17)	Case series (n = 1); there was another described case as well but for a separate condition	NRS-11 8/10 No mention if conservative treatment had been tried and failed	K&L grade 3	10 years (disease)	SMGN: peri-arterial in the junction of the epicondyle and shaft of the femur SLGN: peri-arterial in the junction of the epicondyle and shaft of the femur IMGN: peri-arterial in the junction of the epicondyle and shaft of the tibia	Needle size not mentioned Diagnostic: Dual modalities (ULSD and fluoroscopy with dye)	Intention: diagnostic + therapeutic Diagnostic: 2 mL of 1% lidocaine Therapeutic: 1 mL of 99% alcohol + 1 mL of 2% lidocaine
Demir, 2017, Turkey (16)	Case report (n = 1)	80 mm on 100 mm VAS Failed conservative, exercise, and intra-articular injections, declined surgery	K&L grade 3	7 years (disease)	SMGN: peri-arterial to the superior medial genicular artery SLGN: peri-arterial to the superior lateral genicular artery IMGN: peri-arterial to the inferior medial genicular artery	23G needle	Intention: therapeutic 6 mL comprising 1 mL betamethasone, 2 mL of 2% lidocaine, and 3 mL of saline
Observational studies - cohort studies							
Risso, 2021, Brazil (19)	Prospective cohort study (n = 43)	Mean NRS-11 7.21, mean 10.0 on WOMAC pain subscale Failed conservative treatment and on waiting list for TKA	K&L grade 3 or 4	> 6 months (pain)	SMGN: within the fascial expansion deep to the vastus medialis muscle, at the junction of the epiphysis and diaphysis of the femur and next to the genicular artery SLGN: within the fascial expansion deep to the vastus intermedius/lateralis muscles, at the junction of the epiphysis and diaphysis of the femur and next to the genicular artery IMGN: neurovascular bundle deep to the MCL at the junction of the epiphysis and diaphysis	22G needle (for both procedures) Hydrolocation with 0.2 mL of saline prior to each injection, following anterior-to-posterior in-plane introduction Therapeutic block done one week after successful diagnostic block	Intention: diagnostic + therapeutic Diagnostic: 1.5 mL of 0.25% bupivacaine Therapeutic: 1.5 mL of 7% glycerinated phenol solution

Table 3 (cont). *Study types and intervention details*

First author, year of publication, and author's country	Type of study	Pain characteristic and treatment history of patients	Radiological severity	Disease/ symptom duration	Nerves targeted and landmarks used	Description of interventions performed	Injectate/ intervention type
Controlled studies							
Ragab, 2021, Egypt (24)	Intra-articular steroid (n = 20) vs GNB (n = 20)	87.1 mm on 100 mm VAS scale (IACSI), 87.75 mm (GNB)	K&L grade 3 or 4	Mean 12.15 years (IACSI), 12.3 years (GNB)	SMGN/SLGN/IMGN: close to the arteries identified near the periosteal areas at the junctions of the epicondyle and the shafts of the femur and tibia	22G needle for both IACS and GNB Location confirmed with ULSD doppler IACSI performed into suprapatellar bursa	Intention: therapeutic IACSI: 6 mL of solution comprising 1 mL (40 mg) triamcinolone and 5mL lidocaine GNB: 6 mL of solution comprising 20 mg of triamcinolone and 6 mL of lidocaine across three injection sites
Yilmaz, 2021, Turkey (22)	Intra-articular steroid (n = 20) vs intra-articular steroid and GNB (n = 20)	VAS 6.75 (intraarticular steroid group), 6.65 (steroid and GNB group)	K&L grade 2 to 4	Mean 10.95 years (intraarticular steroid, disease), 9.25 years (steroid and GNB, disease)	SMGN: peri-arterial to the superior medial genicular artery SLGN: peri-arterial to the superior lateral genicular artery IMGN: peri-arterial to the inferior medial genicular artery	21G needle for IACSI Needle size unknown for GNB	Intention: therapeutic IACSI: 3 mL of solution comprising 1 mL betamethasone and 2 mL lidocaine IACSI+GNB: 3 mL of solution comprising 1 mL betamethasone and 2 mL lidocaine + 6 mL of lidocaine across 3 injection sites
Cankurtaran, 2020, Turkey (21)	US-guided GNB (n = 11) vs blind GNB (n = 12)	100 mm VAS (baseline data not specified)	K&L grade 3 or 4	> 3 months (disease)	SMGN/SLGN/IMGN: intersections of lines drawn from fibular head to 4 cm superior to the tip of the lateral femoral epicondyle, horizontally between the femoral epicondyles, and from the medial femoral epicondyle to the medial tibial epicondyle	Needle size not mentioned Blind: based on surface landmarks ULSD-g: based on surface landmarks too though with sonographic evaluation before injection	Intention: therapeutic 6 mL comprising 2% lidocaine and 20 mg triamcinolone, divided among 3 injection sites
Kim, 2019, Korea (20)	ULSD-g (n = 40) vs fluoroscopic (n = 40)	Mean NRS-11 score 6.3 (ULSD-g), 6.7 (fluoroscopic)	K&L grade 2 to 4	Mean 14 months (ULSD-g, pain), 12 months (fluoroscopic, pain)	SMGN: peri-arterial to the superior medial genicular artery SLGN: peri-arterial to the superior lateral genicular artery IMGN: peri-arterial to the inferior medial genicular artery	Needle size not mentioned Fluoroscopic: true anteroposterior view with equal-width interspaces on both sides of the knee joint, with target points at medial (SMGN) and lateral (SLGN) areas connecting the shaft to the femoral epicondyle and medial area (IMGN) connecting the shaft to the tibial epicondyle	Intention: therapeutic 6 mL comprising 2% lidocaine and 20 mg triamcinolone across 3 injection sites

Table 3 (cont). *Study types and intervention details*

First author, year of publication, and author's country	Type of study	Pain characteristic and treatment history of patients	Radiological severity	Disease/ symptom duration	Nerves targeted and landmarks used	Description of interventions performed	Injectate/ intervention type
Kim, 2018, Korea (23)	Lidocaine (n = 24) vs lidocaine and triamcinolone (n = 24)	60.8 mm on 100 mm VAS scale (lidocaine group), 62.1 mm (lidocaine and triamcinolone group)	K&L grade 2 to 4	Mean 5.5 years (lidocaine, pain), 4.5 years (lidocaine and triamcinolone, pain)	SMGN: peri-arterial to the superior medial genicular artery SLGN: peri-arterial to the superior lateral genicular artery IMGN: peri-arterial to the inferior medial genicular artery	Needle size not mentioned Location confirmed with colour Doppler	Intention: therapeutic Steroid group: 6mL of lidocaine + 20mg of triamcinolone LA group: 6mL of lidocaine

Abbreviations: GNB, genicular nerve block; IACSI, intraarticular corticosteroid injections; ILGN, inferior lateral genicular nerve; IMGN, inferior medial genicular nerve; K&L, Kellgren and Lawrence system for classification of osteoarthritis; LA, local anesthetic; MCL, medial collateral ligament; NRS-11, numeric rating scale; OA, osteoarthritis; PT, physiotherapy; SLGN, superior lateral genicular nerve; SMGN, superior medial genicular nerve; TKA, total knee arthroplasty; ULSD, ultrasound; ULSD-g, ultrasound-guided; VAS, visual analog scale

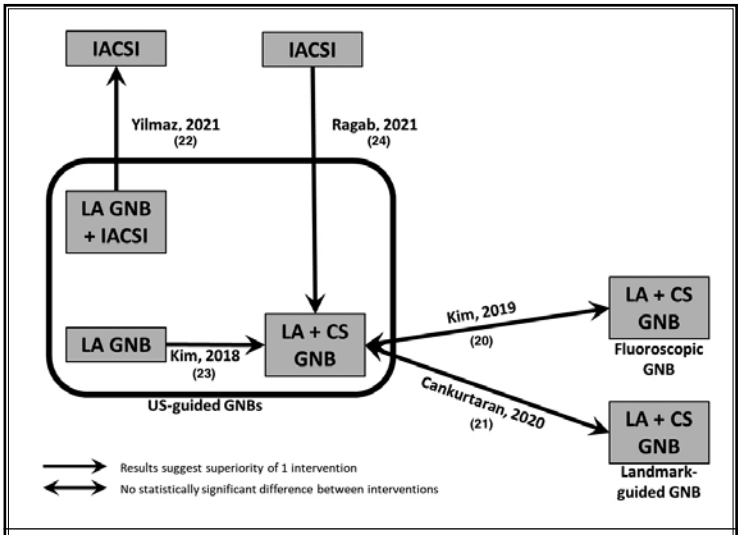

Fig. 2. *Network diagram.*

ments from baseline in both ULSD-g and fluoroscopic groups on the WOMAC stiffness and function subscales at nearly all timepoints (with the exception of the stiffness subscale at 3 months in the fluoroscopic group). Ragab et al (24) reported significant improvements for both groups on the OKS with the GNB group outperforming IACSI. Yilmaz et al (22) reported significant improvements in WOMAC total score and NHP for IACSI compared to IACSI plus GNB. Kim et al (23) found statistically significant improvements for both the lidocaine and lidocaine plus triamcinolone groups on the OKS with greater changes in the latter, though these were not sustained at 2 months.

Adverse Effects From GNB

A majority of the studies reported no adverse effects from GNB. Overall, there were no significant safety concerns highlighted by any of the studies. Further adverse effect details are depicted in Table 4.

Overall Assessment of Quality

For the case series, a cumulative score of 5-7 "yes" answers in the individual quality domains denoted a study overall of fair quality, whereas a score of 8-9 denoted good quality. Likewise, for both observational and controlled interventional studies, a score of 8-11 and 12-14 denoted fair and good individual quality respectively.

Four out of 9 studies, consisting of one case report and 3 controlled studies, were deemed to have good overall quality using the NIH assessment tools (11,13,16,17). Four other studies had fair overall quality (9,10,12,14). Only one study was rated as poor (15).

Discussion

The focus of this systematic review was to establish the use

Table 4. *Outcome measures and adverse effects.*

Publication	Pain outcomes	Other outcomes described	Adverse effects
Observational studies - case reports/case series			
Ahmed, 2019 (18)	One month: > 50% reduction in NRS-11 in all patients at rest, > 50% reduction in NRS-11 in 50% of patients during walking 6 months: 50% reduction in NRS-11 in 50% of patients at rest, 30% reduction in NRS-11 reduction in all patients on walking	Statistically significant improvement in OKS at 1 and 6 months Statistically significant improvement in the physical and mental health domains of SF-36 for quality of life in all patients	No major immediate or delayed complications observed; hypoesthesia and numbness in two patients which resolved in six months
Dass, 2019 (17)	24 hours: > 50% reduction in NRS-11 6 weeks: NRS-11 score of 0/10	Improvement in all 5 domains of KOOS for case 2 but only for symptom, pain, and quality of life domains for case 1	Nil
Demir, 2017 (16)	4 weeks: reduction from 80 mm to 10 mm on 100 mm VAS 24 weeks: reduction 0 mm on 100 mm VAS	Improvement of WOMAC total score from 96 (preintervention) to 5 at 4 weeks and 4 at 24 weeks	Nil
Observational studies - cohort studies			
Risso, 2021 (19)	6 months: statistically significant NRS-11 improvement from 7.2 at baseline to 4.2 in 43 patients	Statistically significant improvement in WOMAC from 48.7 at baseline to 20.7 at 6 months	Local pain, hypoesthesia, swelling and bruise at 2 weeks with frequency quoted up to 30%; these complications all resolved by 2 months
Controlled studies			
Ragab, 2021 (24)	2 weeks: statistically significant drop in VAS in both groups 4 and 8 weeks: recurrence of pain though still statistically significant drop compared to baseline GNB group had statistically greater improvement in VAS	Statistically significant drops in both groups for OKS, most marked at 2 weeks but also at 4 and 8 weeks GNB group had more significant drop in OKS as compared to IACSI	None
Yilmaz, 2021 (22)	One month: statistically significant drops in both VAS and LANSS in both groups 3 months: statistically significant drops in both VAS and LANSS in both groups IACSI group had statistically greater improvements in VAS and LANSS	Statistically significant drops in both WOMAC and NHP for IACSI group but only WOMAC for the IACSI and GNB group Other morphological measures such as cartilage thickness, patellar tendon thickness were consistently better in the IACSI group	None
Cankurtaran, 2020 (21)	One month: both groups revealed drops in VAS and the WOMAC total compared to baseline 3 months: both groups revealed drops in VAS and the WOMAC total compared to baseline No statistically significant intergroup difference for either outcome	Both ULSD-g and blind injection groups revealed improvements in the WOMAC stiffness and physical function subscales as well as total score at one and 3 months compared to baseline No statistically significant inter-group difference for the 3 mentioned outcomes NHP pain and social isolation subscales favoured blind GNB group 30 second chair stand test and 6 minute walk test favoured US-guided group	None
Kim, 2019 (20)	Both ULSD-g and fluoroscopic groups revealed improvements in NRS-11 and the WOMAC pain subscale No statistical significance was observed between the 2 groups at 1 and 3 months for both outcome measures	Both groups revealed improvements in the WOMAC stiffness and function subscales However, no statistical significance was observed for both stiffness and function between the 2 groups at one and 3 months	None
Kim, 2018 (23)	Greater drop in 100 mm VAS at 1 and 2 weeks compared to 4 and 8 weeks for both groups	Decline in OKS in both groups across all weeks with lidocaine + triamcinolone group significantly better but only at 4 weeks Greater improvement in GPES at 4 and 8 weeks in both groups than at 1 and 2weeks Considerably lower MQS but no significant between-group difference	None

of ULSD-g in GNB using pharmacological agents in relieving pain and improving functional outcomes of patients with chronic knee OA.

Presently, the role of GNB in the nonsurgical management of knee OA has yet to be discussed in major international guidelines (26,27). Results from the 9 included studies point toward the feasibility of considering ULSD-g GNB in patients with at least 3 months of symptomatic knee OA, and with a radiological classification of at least grade 2 on the Kellgren-Lawrence system. The described protocols and approaches would be valuable for physicians who are contemplating ULSD-g GNB as an alternative option in patients who had previously failed more common conventional interventions such as IACSI or viscosupplementation.

Innervation of the knee is complex and variable, with its supply arising from intraarticular branches of the sciatic, femoral, common peroneal, saphenous, and tibial nerves. Four sensory branches are commonly described: the SMGN, the SLGN, the IMGN, and the ILGN. The SMGN is a terminal branch of the femoral nerve while the SLGN arises from either the sciatic or common peroneal nerves. The IMGN arises from the tibial nerve and the ILGN arises from the common peroneal nerve. These sensory nerves follow a periosteal course and are common targets for interventions (17,28).

However, the knee exhibits anatomical variation in its multiple sensory innervations (29). Consequently, there is no consensus on the ideal number or combination of nerves to be targeted. From this review, however, we note that all studies included the SMGN, SLGN, and IMGN, with positive outcomes in function and pain. Although cadaveric studies have identified other tributaries such as the nerve to the vastus medialis, saphenous nerve, recurrent peroneal nerve (RPN), and the middle genicular nerve (MGN), we posit that, at the very least, targeting 3 nerves, namely the SMGN, SLGN, and IMGN, may be necessary for reducing pain and improving function of patients with knee OA. Despite the ILGN, MGN, and RPN being discussed in our included studies, we lack sufficient data to comment on their feasibility. The avoidance of the ILGN in GNB has been previously justified as a greater need to avoid damaging the common peroneal nerve which can result in a disabling iatrogenic foot drop (28).

To our knowledge, there is a lack of evaluation of the various ULSD approaches for delivery of pharmacological agents in GNB. The genicular nerves are small in size and cannot be visualized with the resolution offered by conventional ULSD technology, resulting in the identification of anatomical landmarks to guide GNB. The 4 guidance techniques that used periarterial, bony and soft tissue landmarks, dynamic maneuvers, and static surface landmarks serve as important guidance for clinical and bedside practice. Clinicians performing the procedure should conduct a preintervention scan on the knees and combine these approaches before proceeding with the intervention. We were unable to rank the relative superiority of the described injection techniques due to the lack of available comparisons. Additionally, there was insufficient data to determine if sensory and motor nerve stimulation should be used to confirm accuracy of needle placement, although it follows that a documented lack of motor response can help to support procedural safety. We believe these to be important technical questions that future randomized studies should seek to investigate. Figures 3 to 6 illustrate the ULSD images targeting the SLGN, SMGN, IMGN, and the schematic diagram of the knee.

Despite some of the included studies only utilizing steroid and local anesthetic agents such as lidocaine for the GNB, there was sustained pain reduction observed up to 6 months post-GNB. Evidently this long-lasting effect cannot be explained purely by the pharmacological action of the injected agents. Three possible explanations could be offered for this observation. First, it may be contributed by the contextual effect. Contextual effects consist of various physical, psychological, and social factors experienced by the patient within the trial or clinical environment (30). A systematic review estimated that about 61% and 69% of the total treatment effect experienced by patients receiving acupuncture and topical energy modalities respectively for knee OA might be explained by contextual effects (31). Secondly, these local anesthetics may have resulted in interruption of the chronic pain cycle. This may be mediated through the downregulation of peripheral and central sensitization (32). Thirdly, a higher volume of injectate used may cause wider tissue diffusion, leading to blockade of multiple nerve targets and nonneural pain generators (33). The evidence for adding steroids for prolongation of nerve blockade remains weak and is less likely to be a contributing factor toward long-term pain control.

Four studies, consisting of one case report and 3 controlled studies, were deemed to have good overall quality using the NIH assessment tools (11,13,16,17). These ratings corresponded to a low risk of bias. Four other studies received a fair grading, indicating their vulnerability to some bias but not to a sufficient degree

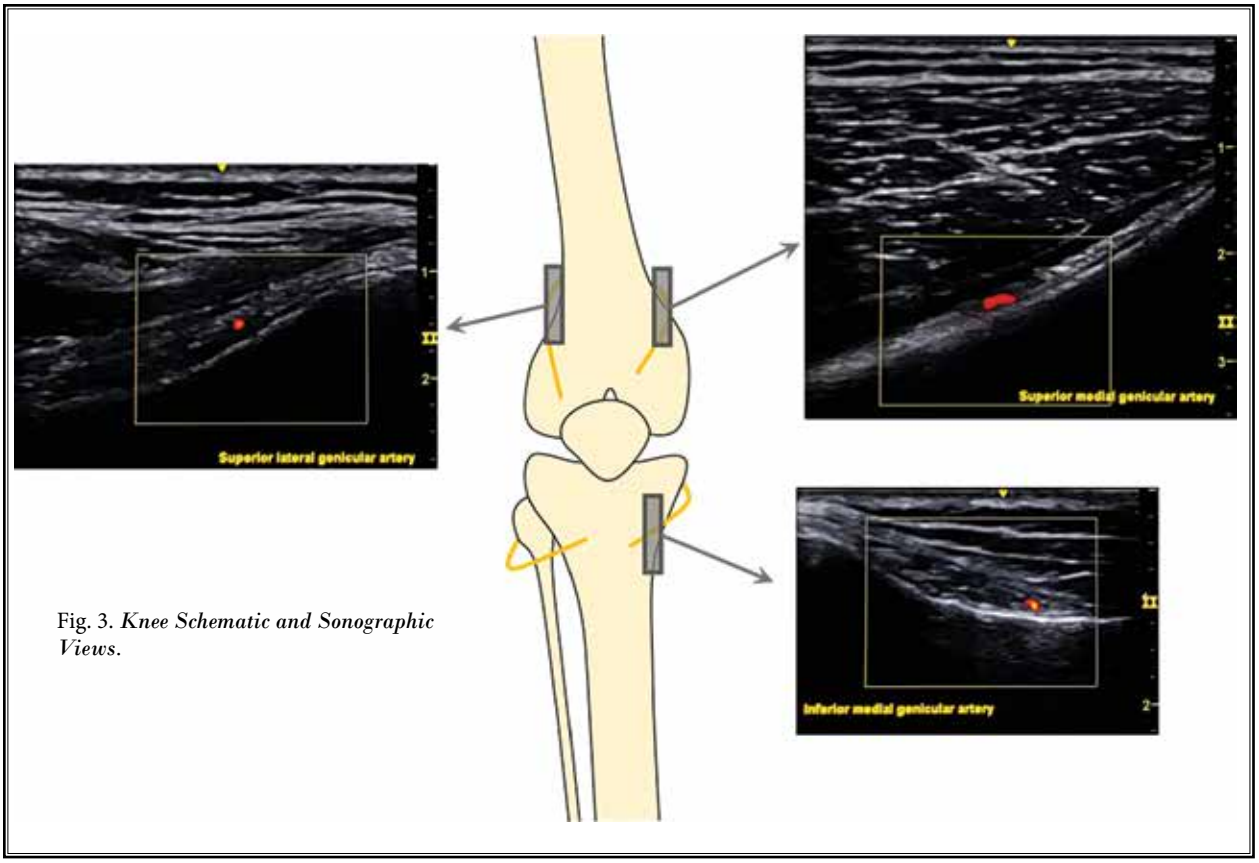

Fig. 3. *Knee Schematic and Sonographic Views.*

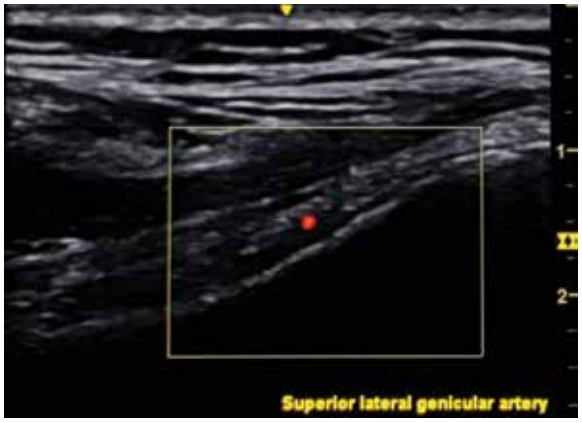

Fig. 4. *Enlarged sonographic view of the superior lateral genicular artery.*

Fig. 5. *Enlarged sonographic view of the superior medial genicular artery.*

for their results to be invalidated (9,10,12,14). Only one controlled study received an overall poor rating due to our inability to determine its method of randomization, treatment allocation, dropout rates, adherence to protocol, and blinding of assessors to the treatment outcomes (15).

Limitations

Several limitations constrain the conclusions we can draw. First, despite allowing for heterogeneity in

Fig. 6. *Enlarged sonographic view of the inferior medial genicular artery.*

study design, the number of studies that met our inclusion criteria remained low. Second, the use of different pharmacological agents with varying doses, diverse descriptions of ULSD technique, and different time intervals for the documentation of outcomes rendered meta-analysis impossible, resulting in the qualitative nature of this review. Third, there was only one included study that described other nerves targeted (MGNs and RPNs) and robust conclusions regarding pain and function outcomes beyond the 3 targeted nerves (SMGN, IMGN, and SLGN) could not be made. Fourth, despite the comprehensive coverage of anatomical and sonographic landmarks, there was a general lack of other technical descriptors such as experience level of the interventionist, needling approach, and accuracy of needle placement. Fifth, the exclusion of all cadaveric studies could have cost us insights into the accuracy of the various guidance techniques. Finally, the volumes of the pharmacological agents used were different. Larger volumes of injectates invariably spread to a wider area, similarly affecting our ability to evaluate the accuracy of the various guidance techniques.

Strengths

This is the first systematic review which focuses on ULSD-g GNB with injectable pharmacological agents for patients with chronic knee OA. Findings from this review provide insight into an additional nonsurgical treatment modality for clinicians who manage patients with advanced knee OA. This intervention requires sonographic skills with the ability to identify landmarks; the selection of suitable patients using clinical, radiological, and surgical criteria; and an awareness of the current state of evidence surrounding the available pharmacological options.

In terms of quality appraisal, although the NIH Study Quality Assessment Tools do not provide a formula for deriving overall study quality, they demonstrate their utility in allowing for the assessment of various study types. Eight out of our 9 studies had at least fair quality, suggesting an overall medium-to-low risk of bias influencing the conclusions we drew regarding pain and functional outcomes.

In this systematic review, both case reports and case series were included which may be considered both a strength and a limitation. We acknowledge that case reports and case series rank low on the hierarchy of evidence and hence are not usually included in systematic reviews. However, these publications represent crucial information with regards to ULSD-g injection techniques, injectates used, and outcomes. In the context of insufficient observational cohort studies or controlled studies on the topic at present, we opine that including case reports and case series provides a more comprehensive coverage of the subject.

Recommendations

ULSD-g GNB targeting the SMGN, SLGN, and IMGN using a combination of local anesthetics, corticosteroids, or neurolytic agents can be considered in patients with chronic knee OA of at least 3 months' duration and at least a Kellgren-Lawrence grade two to provide pain relief and improve function. However, given the heterogeneity of follow-up intervals and injection landmarks, we lowered the strength of our recommendation (Strength of recommendation B, by the Strength of Recommendation Taxonomy) (34).

ULSD-g GNB using local anesthetics, corticosteroids, and alcohol are safe, with minimal or no adverse effects. (Strength of recommendation A).

Conclusions

This systematic review suggests that ULSD-g GNB using pharmacological agents consisting of local anesthetic agents with corticosteroids or alcohol for treating chronic knee OA provides effective pain relief and functional knee improvement by targeting the SMGN, SLGN, and IMGN, for a duration of up to 6 months. There was heterogeneity in the interventional approaches and we are unable to make specific recommendations for the optimal approach. This intervention is safe with minimal adverse effects.

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