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

Yeow Leng Tan, MBBS, MRCP, Edmund Jin Rui Neo, MBBS, MMed, and Tze Chao Wee, MBBS

**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 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.

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 inferior medial 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 been 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-guided 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-guided 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.*

<table>
<thead>
<tr>
<th>Database</th>
<th>PubMed</th>
<th>Embase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Search terms</td>
<td>((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)</td>
<td>((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)</td>
</tr>
</tbody>
</table>
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.

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 $\kappa$ 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).
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>
<thead>
<tr>
<th>First author, year of publication, and author's country</th>
<th>Type of study</th>
<th>Pain characteristic and treatment history of patients</th>
<th>Radiological severity</th>
<th>Disease/symptom duration</th>
<th>Nerves targeted and landmarks used</th>
<th>Description of interventions performed</th>
<th>Injectate/intervention type</th>
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<tbody>
<tr>
<td>Ahmed, 2019, India (18)</td>
<td>Case series (n = 4)</td>
<td>NRS-11 pain score 7-9 Failed conservative management and intraarticular injections</td>
<td>K&amp;L grade 3 or 4</td>
<td>Mean 51 months (pain)</td>
<td>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.</td>
<td>22G needle Diagnostic: ULSD-g. Therapeutic: ULSD-g after 2 successive positive diagnostic blocks at 3-week intervals. Confirmation with nerve stimulator (sensory).</td>
<td>Intention: diagnostic + therapeutic. Diagnostic: 1.5-2 mL of 2% lignocaine; Therapeutic: 0.5-1 mL of 50% alcohol + 0.25% bupivacaine.</td>
</tr>
<tr>
<td>Dass, 2019, Korea (17)</td>
<td>Case series (n = 1); there was another described case as well but for a separate condition</td>
<td>NRS-11 8/10 No mention if conservative treatment had been tried and failed</td>
<td>K&amp;L grade 3</td>
<td>10 years (disease)</td>
<td>SMGN: periarterial in the junction of the epicondyle and shaft of the femur. SLGN: periarterial in the junction of the epicondyle and shaft of the femur. IMGN: periarterial in the junction of the epicondyle and shaft of the tibia.</td>
<td>Needle size not mentioned Diagnostic: Dual modalities (ULSD and fluoroscopy with dye).</td>
<td>Intention: diagnostic + therapeutic. Diagnostic: 2 mL of 1% lidocaine; Therapeutic: 1 mL of 99% alcohol + 1 mL of 2% lidocaine.</td>
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<td>Demir, 2017, Turkey (16)</td>
<td>Case report (n = 1)</td>
<td>80 mm on 100 mm VAS Failed conservative, exercise, and intra-articular injections, declined surgery</td>
<td>K&amp;L grade 3</td>
<td>7 years (disease)</td>
<td>SMGN: periarterial to the superior medial genicular artery. SLGN: periarterial to the superior lateral genicular artery. IMGN: periarterial to the inferior medial genicular artery.</td>
<td>23G needle</td>
<td>Intention: therapeutic. 6 mL comprising 1 mL betamethasone, 2 mL of 2% lidocaine, and 3 mL of saline.</td>
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<tr>
<td>Risso, 2021, Brazil (19)</td>
<td>Prospective cohort study (n = 43)</td>
<td>Mean NRS-11 7.21, mean 10.0 on WOMAC pain subscale Failed conservative treatment and on waiting list for TKA</td>
<td>K&amp;L grade 3 or 4</td>
<td>&gt; 6 months (pain)</td>
<td>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.</td>
<td>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.</td>
<td>Intention: diagnostic + therapeutic. Diagnostic: 1.5 mL of 0.25% bupivacaine; Therapeutic: 1.5 mL of 7% glycerinated phenol solution.</td>
</tr>
<tr>
<td>First author, year of publication, and author's country</td>
<td>Type of study</td>
<td>Pain characteristic and treatment history of patients</td>
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<td>Ragab, 2021, Egypt (24)</td>
<td>Intra-articular steroid (n = 20) vs GNB (n = 20)</td>
<td>87.1 mm on 100 mm VAS scale (IACSI), 87.75 mm (GNB)</td>
<td>K&amp;L grade 3 or 4</td>
<td>Mean 12.15 years (IACSI), 12.3 years (GNB)</td>
<td>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</td>
<td>22G needle for both IACS and GNB Location confirmed with US doppler IACSI performed into suprapatellar bursa</td>
<td>Intention: therapeutic IACSI: 6 mL of solution comprising 1 mL (40 mg) triamcinolone and 5 mL lidocaine GNB: 6 mL of solution comprising 20 mg of triamcinolone and 6 mL of lidocaine across three injection sites</td>
</tr>
<tr>
<td>Yilmaz, 2021, Turkey (22)</td>
<td>Intra-articular steroid (n = 20) vs intra-articular steroid and GNB (n = 20)</td>
<td>VAS 6.75 (intraarticular steroid group), 6.65 (steroid and GNB group)</td>
<td>K&amp;L grade 2 to 4</td>
<td>Mean 10.95 years (intraarticular steroid, disease), 9.25 years (steroid and GNB, disease)</td>
<td>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</td>
<td>21G needle for IACSI Needle size unknown for GNB</td>
<td>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</td>
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<tr>
<td>Cankurtaran, 2020, Turkey (21)</td>
<td>US-guided GNB (n = 11) vs blind GNB (n = 12)</td>
<td>100 mm VAS (baseline data not specified)</td>
<td>K&amp;L grade 3 or 4</td>
<td>&gt; 3 months (disease)</td>
<td>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</td>
<td>Needle size not mentioned Blind: based on surface landmarks ULSD-g: based on surface landmarks too though with sonographic evaluation before injection</td>
<td>Intention: therapeutic 6 mL comprising 2% lidocaine and 20 mg triamcinolone, divided among 3 injection sites</td>
</tr>
<tr>
<td>Kim, 2019, Korea (20)</td>
<td>ULSD-g (n = 40) vs fluoroscopic (n = 40)</td>
<td>Mean NRS-11 score 6.3 (ULSD-g), 6.7 (fluoroscopic)</td>
<td>K&amp;L grade 2 to 4</td>
<td>Mean 14 months (ULSD-g, pain), 12 months (fluoroscopic, pain)</td>
<td>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</td>
<td>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</td>
<td>Intention: therapeutic 6 mL comprising 2% lidocaine and 20 mg triamcinolone across 3 injection sites</td>
</tr>
</tbody>
</table>
Table 3 (cont).

<table>
<thead>
<tr>
<th>Study types and intervention details</th>
<th>Description of interventions</th>
<th>Nerves targeted and landmarks used</th>
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<tr>
<td>Type of study</td>
<td>Pathological severity</td>
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<td>Pain characteristic and treatment</td>
<td>Disease/ symptom duration</td>
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<td>patients</td>
<td>Radiological severity</td>
<td>Nerves targeted and landmarks used</td>
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<tr>
<td>History of patients</td>
<td>Pain characteristics</td>
<td>Nerves targeted and landmarks used</td>
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<tr>
<td>patients</td>
<td>Type of study</td>
<td>Nerves targeted and landmarks used</td>
</tr>
</tbody>
</table>
| First author, year of publication, and country | 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. |}(226x726)
<table>
<thead>
<tr>
<th>Publication</th>
<th>Pain outcomes</th>
<th>Other outcomes described</th>
<th>Adverse effects</th>
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</thead>
<tbody>
<tr>
<td><strong>Observational studies - case reports/case series</strong></td>
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<tr>
<td>Ahmed, 2019 (18)</td>
<td>One month: &gt; 50% reduction in NRS-11 in all patients at rest, &gt; 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</td>
<td>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</td>
<td>No major immediate or delayed complications observed; hypoesthesia and numbness in two patients which resolved in six months</td>
</tr>
<tr>
<td>Dass, 2019 (17)</td>
<td>24 hours: &gt; 50% reduction in NRS-11 6 weeks: NRS-11 score of 0/10</td>
<td>Improvement in all 5 domains of KOOS for case 2 but only for symptom, pain, and quality of life domains for case 1</td>
<td>Nil</td>
</tr>
<tr>
<td>Demir, 2017 (16)</td>
<td>4 weeks: reduction from 80 mm to 10 mm on 100 mm VAS 24 weeks: reduction 0 mm on 100 mm VAS</td>
<td>Improvement of WOMAC total score from 96 (preintervention) to 5 at 4 weeks and 4 at 24 weeks</td>
<td>Nil</td>
</tr>
<tr>
<td><strong>Observational studies - cohort studies</strong></td>
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<tr>
<td>Risso, 2021 (19)</td>
<td>6 months: statistically significant NRS-11 improvement from 7.2 at baseline to 4.2 in 43 patients</td>
<td>Statistically significant improvement in WOMAC from 48.7 at baseline to 20.7 at 6 months</td>
<td>Local pain, hypoesthesia, swelling and bruise at 2 weeks with frequency quoted up to 30%; these complications all resolved by 2 months</td>
</tr>
<tr>
<td><strong>Controlled studies</strong></td>
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<tr>
<td>Ragab, 2021 (24)</td>
<td>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</td>
<td>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</td>
<td>None</td>
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<td>Yilmaz, 2021 (22)</td>
<td>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</td>
<td>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</td>
<td>None</td>
</tr>
<tr>
<td>Cankurtaran, 2020 (21)</td>
<td>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</td>
<td>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</td>
<td>None</td>
</tr>
<tr>
<td>Kim, 2019 (20)</td>
<td>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</td>
<td>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</td>
<td>None</td>
</tr>
<tr>
<td>Kim, 2018 (23)</td>
<td>Greater drop in 100 mm VAS at 1 and 2 weeks compared to 4 and 8 weeks for both groups</td>
<td>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 2 weeks Considerably lower MQS but no significant between-group difference</td>
<td>None</td>
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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 pretreatment 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.
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
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.
REFERENCES


