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Ultrasound-Guided Genicular Nerve Pulsed Radiofrequency, Local Anesthetic with Steroid Genicular Nerve Block and Intra-Articular Botulinum Toxin Injection in The Management of Osteoarthritis Knee Pain

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ABSTRACT

Knee pain due to osteoarthritis (OA) is a common issue, affecting many elderly individuals. The knee joint receives sensory innervation from four genicular nerves (GN): the superior medial (SMGN), inferior medial (IMGN), superior lateral (SLGN), and inferior lateral (ILGN) genicular nerves. Various procedures target these nerves for pain relief, including corticosteroid and local anesthetic (LA) injections, pulsed radiofrequency (PRF), and intra-articular botulinum neurotoxin (IABoNTA). Genicular nerve block (GNB) and radiofrequency ablation (RFA) have gained popularity, even in patients post-total knee replacement (TKR). These techniques alleviate pain by inhibiting nerve fibers supplying the knee joint. The use of ultrasonography (US) has expanded in nerve block procedures due to its superior visualization of neurovascular structures compared to fluoroscopy. PRF applies alternating current to generate heat through molecular friction, creating a thermal lesion that disrupts pain transmission. RF neurotomy of the genicular nerves is a minimally invasive and safe approach for chronic knee OA. Botulinum neurotoxin has been well studied for its muscle-paralyzing effects via proteolysis of membrane-associated proteins, preventing acetylcholine release. However, emerging research indicates that intra-articular BoNT-A injections can reduce pain and improve joint function through anti-nociceptive mechanisms, offering an alternative for knee OA management.

1. INTRODUCTION

Roughly 250 million people across the globe suffer from osteoarthritis (OA), making it the most prevalent kind of arthritis and a major contributor to disability and over 27 million in the U.S. High-risk groups include the elderly (35% of those over 65), females, obese individuals, and African Americans. With increasing life expectancy and obesity rates, OA prevalence is expected to rise, exacerbating its social and economic impact (Alkady et al., 2023).

Knee osteoarthritis, or degenerative joint disease of the knee, results from progressive cartilage loss, commonly affecting the elderly. It is classified as primary (idiopathic) or secondary (due to trauma or underlying conditions like rheumatoid arthritis) (El Said et al., 2022). OA is progressive, leading to worsening pain, stiffness, swelling, and potential disability. Treatment begins with conservative methods and may progress to surgery when necessary, though no disease-modifying agents currently exist (Komarraju et al., 2020).

Once considered solely a cartilage-degenerative condition, OA is now recognized as a multifactorial disease involving trauma, mechanical forces, inflammation, and metabolic factors. Pain arises primarily from non-cartilaginous connective

tissues, like the synovium, subchondral bone, ligaments, and periarticular muscles (Said et al., 2023). As OA advances, structural changes like osteophyte formation, bone remodelling, ligament laxity, and muscle weakening contribute to its progression and symptoms. The Kellgren–Lawrence (KL) grading system is commonly used to assess disease severity via radiographic findings (Tariq et al., 2024).

2. KNEE OSTEOARTHRITIS

Epidemiology

Knee OA is the most diagnosed form of arthritis, with its prevalence expected to rise alongside increasing life expectancy and obesity rates. Approximately 13% of women and 10% of men aged 60 and older have symptomatic knee OA, with prevalence increasing to 40% in those over 70. The condition is more common in females than males. Notably, radiographic evidence of There is no guarantee that symptoms will accompany knee OA —one study found that only 15% of individuals with radiographic findings experienced symptoms. Approximately 240 instances per 100,000 people experience symptomatic knee OA each year (Hsu & Siwiec, 2018).

Etiology

Knee OA is classified as primary or secondary. Primary OA results from age-related cartilage degeneration without a known cause, while secondary OA stems from identifiable factors such as trauma, surgery, congenital deformities, and conditions like rheumatoid arthritis, gout, or hemophilia (Primorac et al., 2020; Williams et al., 2023).

Some of the risk factors for osteoarthritis of the knee can be changed, while others cannot. Changeable elements comprise trauma, occupations with repetitive knee stress, muscle imbalance, obesity, and metabolic syndrome. Non-modifiable factors include age, gender (higher prevalence in females), genetics, and race (de Brito Fontana et al., 2021).

Pathogenesis

Osteoarthritis (OA) is driven by progressive articular cartilage degradation and disrupted cartilage homeostasis. Chondrocyte alterations, such as age-related or oxidative stress-induced hypertrophy triggers the production of catabolic factors, such as heat-shock proteins (HSPA1A), metalloproteinases (MMP1, MMP3), IL-6, IL-8, RANTES and IP-10, which serve as indicators for the onset and development of OA (Berteau et al., 2022).

Cartilage degradation leads to joint structural changes, including subchondral bone (SB) sclerosis, bone cysts, and osteophyte formation, narrowing the joint space and accelerating OA progression. Ultimately, synovial inflammation and joint capsule fibrosis contribute to stiffness, tenderness, and pain, creating a self-perpetuating cycle (Zaki et al., 2020; Asofsky et al., 2020).

OA pain arises from complex peripheral and central mechanisms. Since hyaline cartilage lacks innervation, pain originates from nociceptive neurons in the periosteum, subchondral bone, and synovial membrane. Bone marrow lesions, synovitis, and knee effusion are examples of structural changes that worsen pain by releasing inflammatory mediators (Hu et al., 2021).

Recent evidence suggests SB plays a central role in OA by failing to absorb joint forces, leading to cartilage damage. SB remodeling increases stiffness, alters gene expression, and disrupts cartilage homeostasis, triggering a vicious cycle of joint degeneration (Fang et al., 2018).

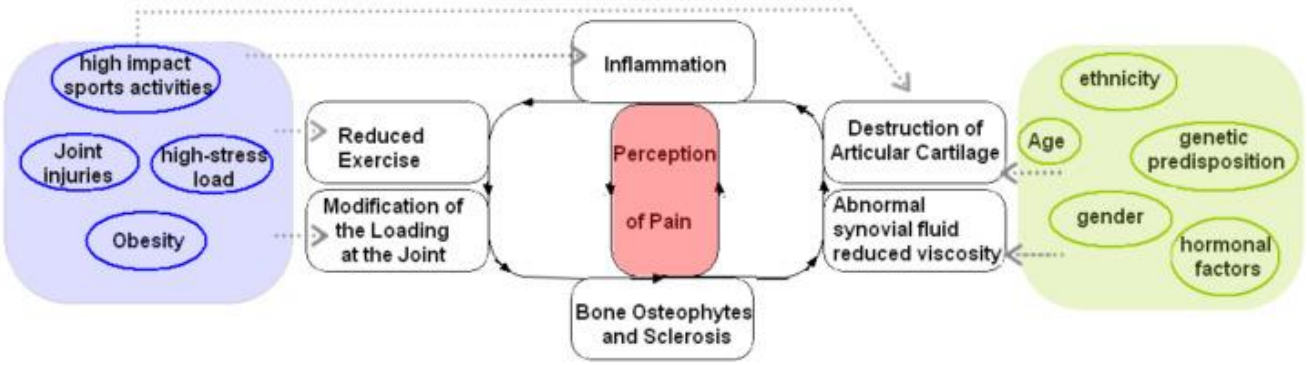

Fig (1): Pain perception plays a crucial role in the debilitating cycle of osteoarthritis progression and related risk factors (Berteau et al., 2022).

Risk Factors

Age

Osteoarthritis (OA) increases exponentially in adults over 50 due to aging-related chondrocyte dysfunction, which reduces proteoglycan production, weakens cartilage, and disrupts homeostasis. This impairs tissue repair, leading to degeneration and OA. However, OA is not solely an age-related wear-and-tear disease, as some joints are more affected than others, and OA can occur without aging. Notably, while rare in youth, individuals under 30 with sports injuries face an increased risk (Cerqueni et al., 2021).

Obesity

Obese people had a 66% chance of developing symptomatic osteoarthritis in their knees, compared to 45% for people of normal weight. Women who lost about 5 kg (2 BMI units) had a halved risk of developing osteoarthritis in their knees, according to the Framingham OA research (Felson et al., 1990).

Obesity contributes to OA through both systemic and biomechanical factors. Systemically, obesity-driven metabolic changes and joint inflammation affect even non-joints that bear no weight like the hands. Biomechanically, excess weight increases the force exerted on weight-bearing joints, such as the hip and knee, by three to six times body weight during walking, heightening tissue damage risk (Sobieh et al., 2023). While moderate knee misalignment (2–7 degrees) may limit weight's impact on OA progression, severe misalignment leads to OA regardless of weight. Additionally, obesity-related adipose tissue secretes adipokines, promoting joint inflammation and disrupting cartilage homeostasis, further increasing OA susceptibility (Mochoge et al., 2022).

Biomechanical Load

Biomechanical overload from repetitive or increased joint stress, such as knee flexion is linked to knee OA. Degradation of cartilage occurs in high-stress areas where cytokines, chemokines, and proteolytic enzymes are overexpressed due to fluid shear stress. High-impact sports like hockey, football, and soccer increase knee OA risk, while deep squatting exerts significant knee forces (7x body weight compressively, 5x posteriorly), though its direct link to OA is unproven (Gherghel et al., 2021).

Joint malalignment alters biomechanics, increasing cartilage and bone damage. Varus knee alignment stresses the medial knee compartment, while valgus alignment stresses the lateral. Leg length discrepancies also disrupt joint mechanics, contributing to OA development. Sports injuries, such as ACL or meniscus damage, alter knee loading and accelerate OA progression. Among Swedish soccer players, 41% of ACL-injured knees showed OA after 14 years, compared to 4% of knees that are not damaged, regardless of surgery. Following meniscus surgery, more than half of young athletes experience osteoarthritis, which is associated by pain and functional impairment, according to longitudinal studies (Russell et al., 2022). The idea that OA is more of a failure of the joints caused by aberrant loading than a separate disease is gaining traction, with biomechanical factors playing a central role in its progression (Cheung et al., 2020).

Diagnosis

Acquiring a comprehensive medical and surgical history is crucial for identifying risk factors linked to secondary knee osteoarthritis. The clinical symptoms of knee osteoarthritis primarily encompass knee pain, which normally manifests gradually and exacerbates with extended activity, repetitive bending, or stair climbing. Lack of activity may exacerbate the pain. Discomfort is typically alleviated with rest, cryotherapy, or anti-inflammatory pharmaceuticals. Patients experience knee rigidity, edema, or diminished mobility (Sharma et al, 2021).

When the patient is standing up straight, the physical examination of the knee begins with a visual evaluation. Check for abnormalities in varus or valgus, quadriceps atrophy, edema, and periarticular erythema. Examine the skin for soft tissue lesions, scars, or injuries, and assess gait for discomfort or instability. Flexion and extension require ROM testing, which includes both active and passive modalities. The medial, middle, and lateral parts of the knee must all be palpated (Epskamp et al., 2020).

A comprehensive neurovascular exam is essential. Assess quadriceps and hamstring strength, as muscle atrophy is common with knee pain. Conduct a sensory exam of the femoral, peroneal, and tibial nerves for neurogenic symptoms. Palpate the popliteal, dorsalis pedis, and posterior tibial pulses to identify potential vascular issues (de Brito Fontana et al., 2021).

Radiographic imaging is essential for diagnosing knee osteoarthritis (OA) alongside a thorough history and physical exam. A skyline view of the patella, standing lateral in extension, and standing AP are all recommended views. For a more accurate evaluation of the bearing surface, a 45-degree PA view is useful. Long-leg standing films may also be used to evaluate deformity and overall alignment. Importantly, all radiographs should be taken with the patient standing to accurately assess joint space narrowing, as supine images can misrepresent joint alignment and space. The radiographic manifestations of OA include subchondral sclerosis, subchondral cysts, osteophyte formation, and narrowing of the joint space (Lee et al., 2021, Zaid & Barry, 2022).

Management of Knee Pain in OA

Knee OA requires a comprehensive management approach, categorized into non-surgical and surgical options, to alleviate

pain and improve joint function (Martel-Pelletier et al., 2019).

Non-surgical treatments serve as the first-line approach, focusing on symptom relief and improving quality of life without modifying disease progression. Patient education about OA, treatment options, and adherence to management plans is crucial. Lifestyle modifications, such as reducing high-impact activities and engaging in supervised exercise programs, help maintain joint mobility and muscle strength. Weight reduction is recommended for individuals with a BMI over 25, with dietary control and low-impact aerobic exercises being effective. Unloader-type braces may be beneficial for patients with valgus or varus deformities by redistributing knee joint load (Huffman et al., 2024).

Pharmacological Treatments includes: 1) Acetaminophen: Commonly used for pain relief due to its favourable safety profile. 2) NSAIDs: Effective for managing pain and inflammation, with selection based on patient history and potential side effects. 3) COX-2 Inhibitors: Provide pain relief with fewer gastrointestinal side effects compared to traditional NSAIDs. 4) Glucosamine and Chondroitin Sulphate: Despite widespread use, strong evidence suggests a lack of efficacy, with any benefit likely placebo driven. 5) Corticosteroid Injections: Effective for short-term inflammation and pain relief, especially in cases with significant inflammation. 6) Hyaluronic Acid (HA) Injections: Intended to improve joint lubrication, though AAOS guidelines strongly discourage its use due to insufficient evidence (Fernández-Martín et al., 2021; Machado et al., 2021).

Interventional Pain Management for Knee Osteoarthritis (OA)

3. GENICULAR NERVE BLOCK (GNB) WITH LOCAL ANESTHETIC AND CORTICOSTEROID

GNB involves injecting a combination of local anesthetic and corticosteroid to block pain signals and reduce inflammation around the genicular nerves. Ultrasonography is used to visualize neurovascular structures for precise injection placement (Hassan et al., 2022). This technique provides both immediate and extended pain relief by numbing the nerves and decreasing local inflammation (Ragab et al., 2021).

Indications

GNB is a feasible choice for individuals with chronic knee discomfort despite conservative treatments. It is particularly beneficial for (ARICAN et al., 2020):

- Individuals experiencing refractory knee pain unresponsive to non-surgical treatments.
- Individuals seeking to avoid surgery or those deemed unsuitable for surgical intervention due to comorbidities.
- Patients with failed knee replacement who experience pain despite no structural abnormalities in the prosthesis.
- Those who previously benefited from GNB or radiofrequency ablation (RFA) but have experienced recurrent pain

Contraindications

GNB is generally a safe procedure with minimal contraindications, primarily (ARICAN et al., 2020):

- Active infection at the injection site.
- Severe joint instability or unsuitable knee anatomy that may affect treatment efficacy.

Equipment and Supplies

Genicular nerve blocks are readily executed in the fluoroscopy suite or at the patient's bedside under ultrasound supervision. 22 or 25 G needles that are 2 or 3.5 inches in length may be used, depending on the patient's body habitus. When using 22 G needles, local skin anesthetic is administered with a small, 1–1.5 inch, 25–27 gauge needle. A total of 1.5 mL of injectate is used for the plane block across the three sites after a three of needles for procedures are placed next to the three targeted sites and 0.5 mL of local anesthetic is given at each site. For a therapeutic block, provide 2 mL of injectate at each site (Ghosh & Kohan, 2022).

Technique

To increase comfort, the patient is in a supine position with a pillow under the popliteal fossa. Sterilized and appropriately wrapped is the treatment area. To locate the long bone's epicondyle, a 12 MHz linear transducer is used, initially oriented perpendicular to the shaft of the long bone and then adjusted superiorly or inferiorly (Fig. 2) (Yilmaz et al., 2021).

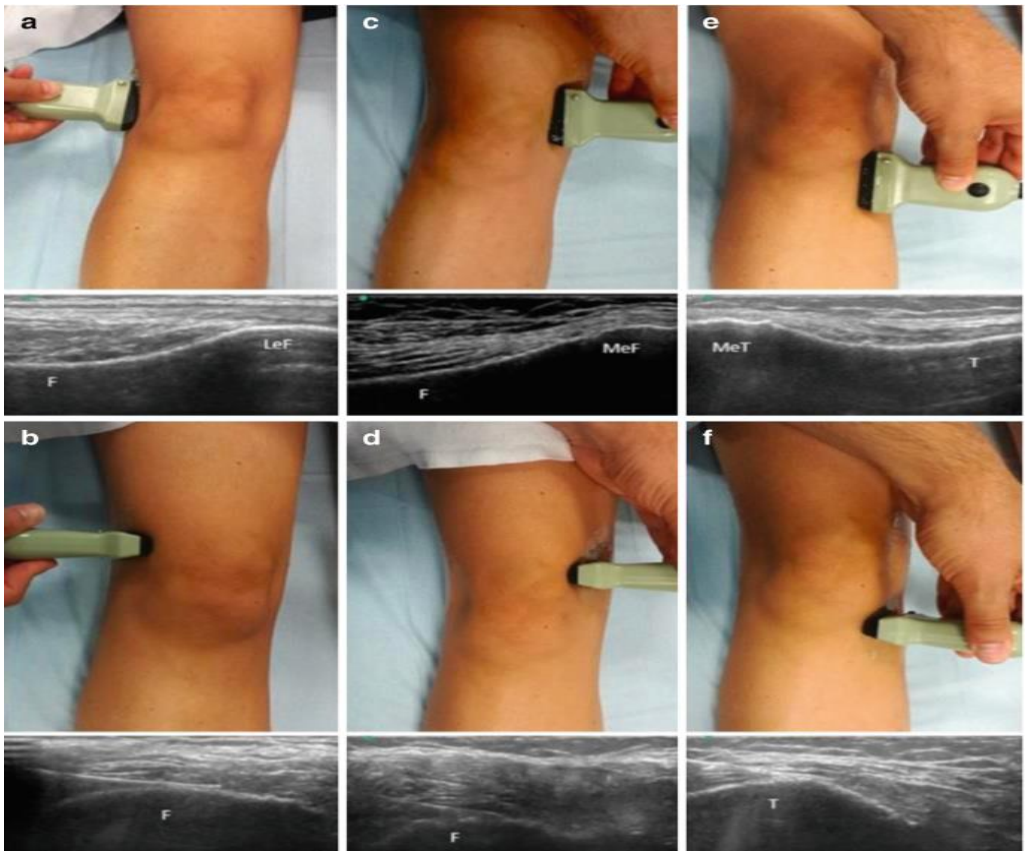

Fig (2): (a–c) putting the probe into a healthy volunteer and using the RF cannula to take precise ultrasound pictures of a cadaver. (a) The target position of the SLGN in the coronal plane. (b) The transverse plane is the ultimate location of the RF cannula for the SLGN.. (c) The SMGN's is located in the coronal plane. (d) The SMGN's RF cannula is finally positioned in the transverse plane. (e) The IMGN's target location in the coronal plane. (f) The transverse plane is the ultimate location for the RF cannula of the IMGN.. Right is distal (a, c, e), whereas left is proximal (a, c, e); Left means anterior, right means posterior (b, d, e). (Ghosh & Kohan, 2022).

To identify the SL genicular nerve, position the transducer in a coronal plane on the lateral portion of the femoral shaft.. Then, move it distally to concentrate on the point where the lateral femoral condyle and shaft meet. About the genicular nerve of the SM, position the transducer on the medial side of the femoral shaft and move it distally to the junction of the medial femoral condyle and shaft. Place the transducer in a coronal plane on the medial aspect of the tibial shaft for the intramuscular genicular nerve, then advance it proximally to the junction of the medial epicondyle and the shaft. Confirm the genicular arteries using Doppler flow, then identify the SM, SL, and IM genicular nerves adjacent to the arteries. Place the needle next to each artery in a long-axis, planar configuration, aspirate to make sure there isn't a vascular puncture, and then provide 0.5 mL of injectate at each site. Remove the needles and apply a bandage if required (Vanneste et al., 2019).

Potential Complications and Adverse Effects

Before doing the genicular nerve blockade, the clinician should be aware of the rare unpleasant reactions and issues that may occur, even though most patients handle it well. Unpleasant effects are rare, save from the discomfort brought on by pain or muscular spasms. They include increased discomfort, decreased movement, and increased stiffness, as well as vascular injection of local anesthetics given close to the genicular arteries (Kose et al., 2022).

Ultrasound-Guided Genicular Nerve Pulsed Radiofrequency (PRF):

PRF utilizes an alternating current to generate molecular friction heat, creating a controlled thermal lesion at the target nerve fibers. This minimally invasive procedure aims to provide long-term pain relief by disrupting pain transmission from the knee joint. Ultrasound guidance ensures accurate targeting of the genicular nerves, enhancing precision and efficacy (Rodríguez-Merchán et al., 2023).

Indications

Failure of conservative treatment (e.g., medications, physical therapy, injections)

Non-surgical candidates due to comorbidities or patient preference

Persistent knee pain following surgery (e.g., total knee replacement)

Chronic knee pain due to osteoarthritis (OA)

Temporary pain relief before considering genicular nerve RFA

Patients who experienced prior pain relief from genicular nerve blocks or RFA

Contraindications

Active infection at the injection site

Severe knee joint deformities making the procedure technically difficult

Bleeding disorders or anticoagulant use (relative contraindication)

Severe neuropathy or nerve damage that may complicate outcomes

Equipment and Supplies

Genicular nerve block can be done using fluoroscopic or ultrasound guidance, both providing comparable pain relief and functional improvement. RFA of the genicular nerves, typically performed under fluoroscopy, is an emerging treatment for osteoarthritis-related knee pain, targeting nerve fibers to reduce pain (Mahmoud et al., 2021). Fluoroscopic guidance ensures accurate needle placement using bony landmarks, while ultrasound offers advantages such as cost-effectiveness, repeatability, and the absence of ionizing radiation. Recent studies confirm the accuracy of ultrasound-guided genicular nerve injections (Karm et al., 2024).

Radiofrequency ablation (RF-Ablation) is a medical procedure that utilizes high-frequency alternating current (approximately 350–500 kHz) to generate an electromagnetic field. This field induces oscillating movements of ions within the target tissue. The oscillation of ions converts electromagnetic energy into heat through frictional or resistive energy loss. This process raises the temperature of the target tissue to between 60 and 100 °C, effectively "lesioning" the nerve to interrupt pain signals (Kok et al., 2020).

Types of Radiofrequency Systems (Vahedifard et al., 2021):

Monopolar System

***Configuration*:** The probe's electrode has a single active tip placed near the nerve.

Circuit: A substantial conductive pad, symbolizing the neutral electrode, is affixed to the patient's skin, typically on the leg, to complete the circuit.

Bipolar System

- ***Configuration:*** To create the circuit, the probe uses two electrodes at the tip.
- ***Variations:*** The electrodes can be within the same probe or utilize two separate probes to form the circuit.

Technique

Ultrasound Examination Procedure (Lash et al., 2020):

The patient lies on the lateral side with the knee in full extension.

- To examine the adductor tubercle and the tendon of the adductor magnus insertion, the transducer is positioned sagittally over the femoral medial epicondyle.

The target for the SMGN injection is the osseous cortex 1 cm anterior to the apex of the adductor tubercle (Fig. 3).

To evaluate the medial collateral ligament, the transducer is positioned sagittally over the tibial medial epicondyle.

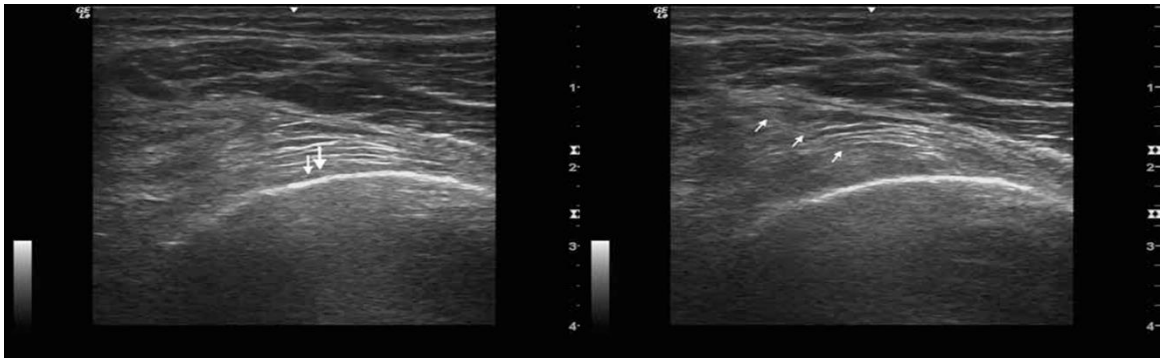

Fig. (3): (a) Transverse ultrasound image of the knee at the level of the femoral medial epicondyle. Superior medial genicular nerve (thick arrow) and the corresponding artery (thin arrow) were visualized. (b) The needle (arrows) was placed to the bony cortex 1 cm anterior to the peak of the adductor tubercle for the superior medial genicular nerve (Kesikburun et al., 2016).

The transducer is thereafter positioned distally at the tibial insertion site of the medial collateral ligament, targeting the bony cortex situated midway between the initial fibers of the medial collateral ligament affixed to the tibia and the apex of the tibial medial epicondyle. (Fig. 4).

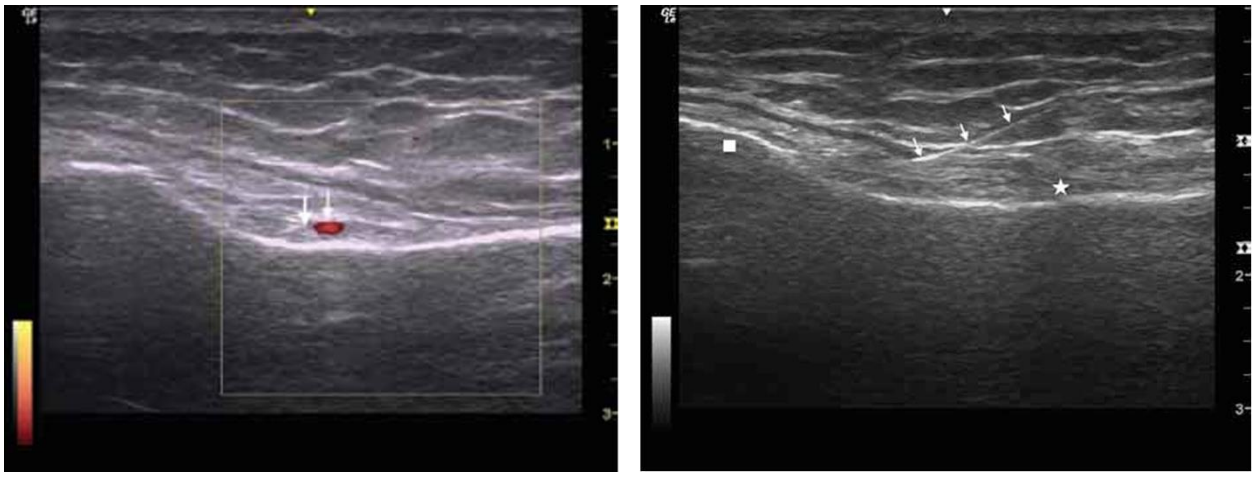

Fig. (4): (a) knee ultrasound image taken longitudinally at the tibial medial epicondyle level. Power Doppler was used to visualize the inferior medial genicular nerve (thick arrow) and the artery that is connected to it (thin arrow). (b) For the inferior medial genicular nerve, The needle (arrows) was positioned at the bony cortex midway between the apex of the tibial medial epicondyle (square) and the initial fibers of the medial collateral ligament (star) that attach to the tibia. (Kesikburun et al., 2016).

Pulsed Radiofrequency (RF) Procedure

A 22-gauge, 10-cm-long RF cannula (NeuroTherm) is introduced into predetermined target sites until the bone is touched by the needle..

The RF probe is oriented perpendicular to the nerve's expected length.

Stimulation and Sensory Testing:

- ***Sensorial Stimulation*:** A stimulation frequency of 50 Hz is utilized, with a threshold set at less than 0.6 V. Patients are encouraged to communicate any sensations of tingling, pain, or discomfort within the knee area. (Abo Elfadl et al., 2024).
- ***Motor Stimulation*:** To make sure there is no fasciculation, a 2.0 V motor stimulation is administered at a frequency of 2 Hz.

(Khaskheli et al.).

Two milliliters of 1% lidocaine are given before the RF generator is started, and then the SMG and IMG nerves receive two 120-second pulsed radiofrequency treatments at 42°C. It takes eight minutes to complete the entire procedure for a single knee (Heskamp et al., 2024).

Outcomes

This preliminary report examines the effectiveness of Gingular nerve pulsed radiofrequency guided by ultrasound in managing Knee discomfort associated with osteoarthritis. Significant pain relief and improved function were observed over three months. RF generates heat-induced lesions in target nerves and has been widely used for chronic pain conditions, including knee osteoarthritis (Choi et al., 2011).

Studies have demonstrated pain reduction with RF genicular neurotomy, particularly for end-stage osteoarthritis patients. While conventional RF typically targets the superomedial, superolateral, and inferomedial genicular nerves, this study focuses on the superomedial and inferomedial nerves, which are strongly associated with medial compartment osteoarthritis (Egeler et al., 2013).

Research supports RF's effectiveness in knee pain management, including post-total knee replacement cases. Ultrasound guidance enhances accuracy by visualizing neurovascular structures, with studies confirming its utility in identifying

genicular nerves and guiding RF procedures (Vas et al., 2014; Protzman et al., 2014).

1. ***Intra-Articular Botulinum Toxin Injection (IABoNTA)*:**

Botulinum neurotoxin (BoNT), a naturally occurring bacterial toxin, can cause severe illness when ingested in large amounts through contaminated food. However, in medical applications, it is precisely measured in units, with therapeutic doses typically below 400 units, compared to the millions of units found in contaminated food (Corsalini et al., 2021).

Among the nine BoNT subtypes, only types A and B are utilized in medicine because of their extended effects. Type A formulations is approved by FDA- include Botox, Xeomin, Dysport, Jeuveau (cosmetic use only), and Daxxify, while Myobloc is the only FDA-approved type B toxin. Unit conversion varies across formulations, with approximations such as 1 unit of Botox is approximately equivalent to 1 unit of Xeomin, 2.5 to 3 units of Dysport, and 40 to 50 units of Myobloc. (Jabbari et al., 2024).

BoNT is administered via injection into muscles or skin, where it reaches nerve endings at neuromuscular junctions. The toxin's light chain inhibits neurotransmitter release, preventing nerve signals from activating muscles. Additionally, it blocks sensory transmitters involved in pain perception, making it a valuable treatment for pain-related conditions, including joint and bone disorders (Jabbari et al., 2024).

A 450,000 Dalton protein with an inactive excipient tail is the therapeutic botulinum toxin component. Once the tail is removed, it separates into botulinum neurotoxin and nontoxic proteins. Upon injection, the toxin binds to cholinergic nerve terminals, where its light chain enters the cell membrane and inhibits acetylcholine release by preventing vesicular transport. This binding is temporary, allowing receptors to regain function once the toxin dissociates. In skeletal muscle, peak effects occur around two and half weeks, whereas in glandular or autonomic tissues, effects may last up to 9 months (Goitom et al., 2024).

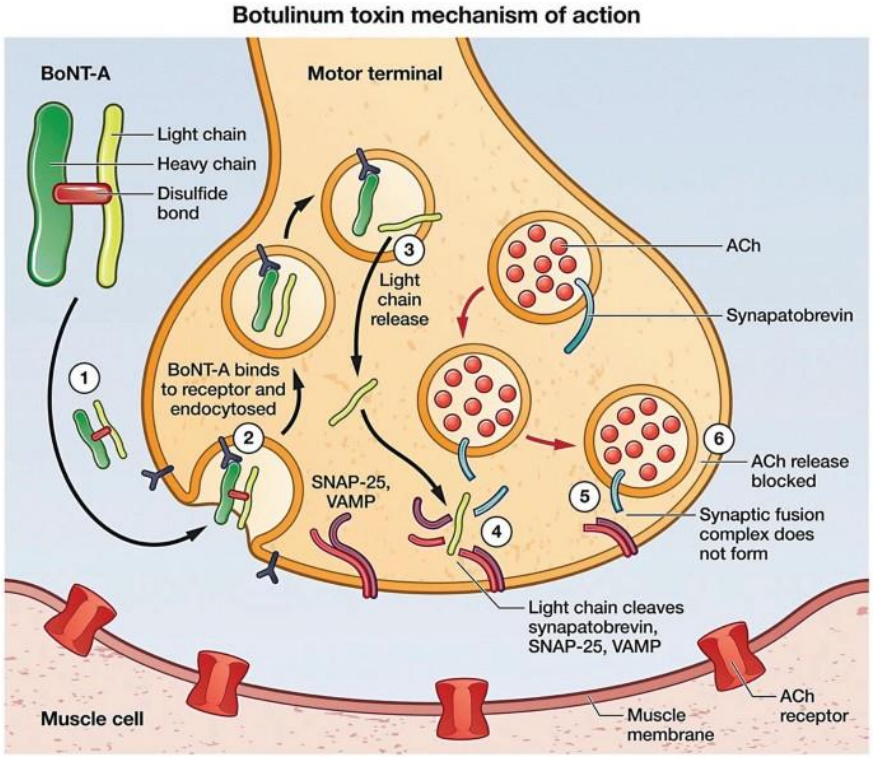

Fig (5): BoNT-A's mechanism of action. The BoNT-A light chain, which is joined by a disulfide bond, is shown in yellow, and the heavy chain is shown in green. Red dots within represent acetylcholine, the neurotransmitter that BoNT-A inhibits.. (Goitom et al., 2024)

Potential mechanisms of botulinum toxin as an analgesic

BoNT/A is a promising option for pain management with minimal adverse effects, except for antigenic responses. It affects the PNS directly and the CNS indirectly. In the PNS, BoNT/A disrupts sensory neuron function by inhibiting receptor expression and neurotransmitter release, including SP, glutamate, and CGRP. This prevents neurogenic inflammation and nociceptive transmission (Luvisetto et al., 2022). In the CNS, BoNT/A deactivates signaling molecules and modulates purinergic transmission, reducing pain signaling (Reyes-Long et al., 2021).

One mechanism of pain modulation is blocking neurotransmitter release. By impairing SNARE-mediated exocytosis, BoNT/A prevents SP and CGRP release, reducing neurogenic inflammation. It also inhibits NK1r internalization in the dorsal horn, mitigating central pain transmission. Another mechanism involves disruption of receptor transfer, particularly TRPV1 and TRPA1, which play roles in pain sensitization. BoNT/A also blocks receptor expression in primary afferent neurons and attenuates the increase in the mRNA levels of NOS1, prodynorphin, and prepronociceptin , highlighting its role in chemical transduction (Moreau et al., 2022).

BoNT/A indirectly desensitizes nociceptors by inhibiting acetylcholine release at neuromuscular junctions, reducing myofascial trigger point formation and ischemia-induced sensitization. It may also exert effects on the CNS through retrograde transport, altering c-fos expression and purinergic signaling. Immunodetection studies confirm BoNT/A's presence in the spinal cord after peripheral administration, indicating its dual action at peripheral and central levels (Antonucci & Bozzi, 2023).

Additionally, BoNT/A interacts with glial cells, which influence pain processing. By cleaving SNAP-25 and SNAP-23 in satellite glial cells (SGCs), it inhibits glutamate release, modulating sensory ganglia activity. BoNT/A also exerts anti-inflammatory effects by inhibiting NF-kB, P38, and ERK1/2 activation in microglia and interacting with TLR2, reducing neuroinflammation (Luvisetto, 2022).

Treatment of Osteoarthritis (OA) with Botulinum Toxin

Botulinum Toxin is considered a novel therapy which is still under investigation to be implied as treatment modality in OA. Botulinum toxin (BoNT) injections have been explored as a management of osteoarthritis (OA) pain owing to the limited effectiveness of standard medical treatment and patients' hesitance to pursue surgical interventions. BoNT inhibits pain transmitter release, and early studies demonstrated its analgesic effects in animal models. Mahowald et al. (2006) first reported its efficacy in humans, showing pain relief after intra-articular (IA) injection in shoulder and limb joints. A 2010 study found Botox superior to placebo in knee OA patients. In a larger, blinded, placebo-controlled study of 121 patients, Botox significantly improved pain, quality of life, and disability, with no major side effects (Arendt-Nielsen et al., 2017). A review confirmed BoNT’s safety in OA treatment (Jabbari et al., 2024).

However, a more recent placebo-controlled study of 158 patients found no difference between BoNT and saline injections. This study's validity is questionable due to the use of an unvalidated pain scale and a strong placebo response (McAlindon et al., 2018). Comparative studies have also been conducted: BoNT combined with triamcinolone provided superior pain relief compared to steroids alone (Shukla et al., 2018); BoNT plus exercise was more effective than hyaluronate (Xiao et al., 2018); and BoNT alone was comparable to steroids in knee OA, though steroids provided faster relief (Mendes et al., 2019). Unlike steroids, BoNT does not cause cartilage degeneration or metabolic side effects. A meta-analysis of seven studies with 548 patients concluded BoNT effectively relieves knee OA pain and called for more high-quality research (C. Wang et al., 2023).

Research on IA BoNT for other joints remains limited. A study indicated that nine shoulder joints experienced functional enhancement and reduced pain. A systematic review on ankle OA found insufficient evidence for clinical benefit from BoNT, hyaluronate, or plasma-rich protein (Paget et al., 2023). Preliminary data suggest Dysport (400 units) may alleviate hip OA pain, but placebo-controlled trials are needed (Eleopra et al., 2018).

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