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(Case Report)

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Ultrasound-guided Glucopuncture in the management of saphenous nerve entrapment in ultra-trail runner: A clinical case

Fischhoff C * and Vincent K

Chiropractic Department, Wellkin Hospital, Moka, Mauritius.

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Abstract

Saphenous nerve entrapment is a painful condition of the thigh. It is commonly managed conservatively, but there is a lack of consensus on the application of new treatment options such as injections with platelet rich plasma (PRP) or sugar water 5% (S5W). Over the last decade, regional PRP and S5W injections have become more recognized for the treatment of orthopedic complaints, sports injuries and peripheral neuropathies because of easy application and interesting safety profile. Sugar water injections also come with a low cost. This article describes a 44-year-old runner suffering from bilateral pain in the inner thighs, knees and inner calves for two years. He was treated successfully with three weekly ultrasound-guided S5W injections. This case report is an invitation to design more research to confirm whether this novel approach may become one of the new tools for athletes suffering from saphenous nerve entrapment.

Keywords: Saphenous Nerve Entrapment; Ultrasound; Glucopuncture; Sports Injury; Hydrodissection; Prolotherapy

1. Introduction

Saphenous nerve entrapment (SNE) is a painful condition of the thigh. It occurs in professional, as well as recreational, athletes. It is described as a noncontact injury, typically characterized by gradually increasing pain in the inner thigh. There is a wide variety of treatment and rehabilitation options available for SNE, the majority of which are non-operative, such as anti-inflammatory medication, physical therapy, and injecting biologics such as PRP or S5W . Both PRP injections [1, 2] and S5W injections [1] hold promise in promoting tissue repair. PRP is more expensive than S5W injections because PRP requires special equipment (centrifuge and special kits)[4]. S5W injections are inexpensive and can be interesting for low-income patients [5]. In this article, the application of palpation-guided and subsequent ultrasound-guided S5W injections is discussed for the treatment of bilateral SNE.

1.1. Saphenous Nerve Entrapment

The saphenous nerve (L3, L4) is the largest terminal cutaneous branch of the femoral nerve, and the longest nerve in the body [6]. It arises in the thigh and descends through the adductor canal [7, 8]. Along its course, the saphenous nerve provides the infrapatellar branch and several cutaneous branches. It continues its course inferiorly as far as the ankle joint and foot. It has several branches which innervate the skin of the lower and anterior part of the knee and the medial part of the knee, leg, and ankle. The main function of this nerve is to provide sensory supply to the medial side of the thigh, knee and foot. The saphenous nerve is a satellite of the femoral artery at the femoral triangle. It diverges from the artery at the adductor canal by perforating the vastoadductor membrane [9], approximately 10 cm (4 in) above the adductor tubercle. This membrane effectively creates a subcompartment within the subsartorial canal. At this level, the vastoadductor membrane becomes a thick fibrous band, which may explain the risk of saphenous nerve neuropathy due to lock-in [10].

* Corresponding author: Fischhoff C.

The saphenous nerve is highly susceptible to mechanical shear forces at its particular location by activities inducing either nerve elongation or friction during its penetration through the vastoadductor membrane [11]. Endurance events, notably ultra-trails, make athletes more prone to saphenous nerve entrapment due to localized muscular fatigue in the external hip rotators. This fatigue contributes to an augmented valgus knee loading [12], thereby inducing tension on the nerve within the adductor canal.

Most saphenous nerve injuries occur in the setting of trauma, overuse or as a complication of lower limb surgery. In most cases, the diagnosis of saphenous neuropathy can be established on the basis of clinical symptoms and electrodiagnostic studies. When the saphenous nerve is compressed in the thigh, pain can travel to the groin, thigh, medial knee, and up to the big toe [13, 14] Besides neuropathic pain in its territory [15], there may be allodynia in some cases. From a clinical point of view, when the compression is at the level of the canal of the adductors, Romanoff et al determined the presence of the following criteria [16] pain in the distribution of the saphenous nerve, normal motor function, pain on palpation with respect to the adductor canal. In their series, 90% of patients had only knee pain, the remaining 10% had calf and ankle pain. The patient may also complain about heaviness or weakness in the leg, or symptoms of vascular claudication. Symptoms can be aggravated by standing, walking or running [17].

The differential diagnosis encompasses femoral neuropathy or radiculopathy. However, pathology affecting diverse structures within the medial knee region may manifest with comparable signs and symptoms. This encompasses degenerative X-ray alterations, distal adductor magnus tendinopathy, myofascial trigger points in the adductor magnus muscle, distal sartorius tendonitis, pes anserine bursitis, medial collateral ligament pathology, and medial joint pathology, all of which can induce medial knee pain. Notably, individuals experiencing saphenous neuropathy often find it hard to accurately point out their medial knee pain. Sensory nerve conduction studies of the saphenous nerve have been described [18].

2. Clinical Examination

The diagnosis of SNE in its proximal portion is often the result of a diagnosis of exclusion. Looking for painful points during palpation is crucial. Compression of the proximal portion of the saphenous nerve can occur at different levels. From the proximal to the most distal point, the compression points can be located at the level of the inguinal ligament, the proximal thigh, the adductor canal or at the level of its infrapatellar branch [19]. The pathophysiology of proximal saphenous nerve neuropathy may involve mechanisms of high-pressure compression, or intermittent compression, but may also be related to post-traumatic or post-surgical adhesion or scarring. Symptoms may be exacerbated during hyperextension and external rotation of the hip [20].

2.1. Anesthetic Block of Saphenous Nerve

Romanoff et al described an anesthetic block based on anatomical landmarks [21]. Their technique consists of palpating the intermuscular sulcus located between the vastus medialis and the sartorius, then advancing a short needle perpendicular to the surface of the skin until a "pop" is felt while the needle tip penetrates the fascia of the vastus medialis. A study found 80% improvement under ultrasound guidance vs. 50% for the landmark-based technique [22]. More and more papers are published concerning S5W injections for nerve entrapment and hydrodissection [23, 24, 25]. Some doctors are still using steroids, but the potential side effects and lack of added value is making steroid injections less popular among young practitioners [26, 27, 28, 29, 30]. On top of that, steroids may slow down tissue healing [31, 32]. For more than a decade, sugar water 5% injections become more popular.

2.2. Clinical Application of Glucopuncture

Glucopuncture is a new term to describe regional S5W injections into dermis, fascia, muscle, ligament and joints with D5W (dextrose 5%) or G5W (glucose 5%). In US and Asia, dextrose (d-glucose) is more common, while in Europe, glucose is applied. Glucopuncture is a nonsteroidal injection therapy for the management of a variety of nonrheumatic musculoskeletal conditions [33, 34, 35, 36, 37]. Especially in the last decade, several clinical studies have confirmed the excellent safety - efficacy ratio of S5W injections [38, 39, 40, 41, 42]. Clinical experience shows that regional S5W injections hold promise in promoting pain modulation and tissue repair [43].

Superficial injections are patient-guided or palpation-guided, which means that the patient points out the pain region and the clinician then looks for pain points in that region. These pain points are then injected with S5W. In most hospitals these days, injections are given under ultrasound-guidance [44, 45, 46, 47].

Local anesthetics are not required because the injections are not painful [48]. Steroids are never added to the injectate because these might undermine tissue repair [49, 50, 51, 52, 53]. As the total dose of sugar is small, these injections can be applied for patients with diabetes [54]. In addition, most of the sugar water is metabolized at the injection site and does not even enter blood flow. When injecting into a joint cavity, one can use S5W or even S10W (10%) to enhance the biochemical effect of sugar water molecules on cartilage [55]. In the past, all joint injections were landmark-based injections, but for more accuracy during injection, one prefers ultrasound-guided intraarticular injections.

2.3. Off-label Use

It is worth noting that regional D5W or G5W injections are off-label use in most countries because the injectate is designed for IV use. However, other injection techniques with a less interesting safety profile such as transforaminal steroid injections are also applied off-label worldwide [56].

2.4. History of Glucopuncture

The use of S5W injections was first described in Korea in 1997 for treatment of myofascial pain [57]. Later it was also used for Achilles tendinopathy [58], carpal tunnel syndrome [59, 60], failed back surgery syndrome [61], epidural injections [62, 63], nerve hydrodissection [64], ankle pain [65], hamstring injury [66] and joint pain [67]. S5W can also be injected into fascia to enhance biotensegrity [68, 69, 70]. Over the last decade, S5W injections have become more popular worldwide, although research in this field is limited [71, 72]. Standardized protocols for S5W administration, such as optimal dosage and number of injections, require further investigation. The lack of funding for large clinical studies so far could be related to lack of interest from pharmaceutical companies because the injectate is inexpensive and cannot be patented. However, over the last two decades, PRP injections [73, 74, 75, 76, 77] receive more support from the medical companies who produce the centrifuge devices and the injection kits for PRP. It is expected that both S5W and PRP injections will slowly replace steroid injections.

2.5. Glucopuncture versus Steroid Injections

Most physicians agree immediately that S5W injections are much safer than steroid injections [78], but most colleagues are surprised to realize that the efficacy of sugar water injections has been illustrated in a few clinical trials. D5W or G5W injections have been found as effective as steroids when treating chronic rotator cuff tendinopathy [79] and ulnar neuropathy [80, 81]. Typically, steroid injections are better in suppressing inflammation in the short term but seem to be less effective in the long term [82]. In a carpal tunnel study, D5W showed to be more effective than triamcinolone at 4 to 6 months [83]. Recently, clinical researchers illustrated that ultrasound-guided D5W injections for carpal tunnel have similar efficacy as steroids for improving pain intensity, functional limitation in daily life, electrophysiologic parameters and ultrasonographic outcomes [84, 85].

2.6. Goal of Glucopuncture

The goal of regional S5W injections is to modulate pain and support tissue repair [86]. Such effects are not observed when giving S5W intravenously. This means that the mode of action of regional sugar water injections is peripheral and not central. Pain modulation is mainly achieved by intradermal [87] and US-guided perineural injections [88, 89, 90, 91], functional improvement is achieved by giving injections into dysfunctional tissues such as muscles, fascia, tendons and ligaments [92, 93, 94]. Physicians who have no access to US, typically use landmark-guided or palpation-guided D5W or G5W injections. It is obvious that S5W can also be injected into joint cavities or into the epidural space, but these techniques are not a topic of this article.

2.7. The Importance of Adenosine Triphosphate Hydrolysis

When glucose 5% is injected into the extracellular matrix (ECM), glucose molecules can be transported across the cell membrane by a specific saturable transport system [95, 96, 97, 98]. This transport system includes two major types of glucose transporters: 1) sodium dependent glucose transporters (SGLTs) which transport glucose against its concentration gradient and 2) sodium independent glucose transporters (GLUTs), which transport glucose by facilitative diffusion in its concentration gradient [99, 100, 101]. Inside the cell, glucose supports adenosine triphosphate (ATP) metabolism. This may explain the positive effect on tissue repair. ATP has been well established as an important extracellular ligand of autocrine signaling, intercellular communication, and neurotransmission with numerous physiological and pathophysiological roles [102]. ATP is abundantly present in cytosol and used to support energy-consuming reactions because hydrolysis of ATP releases energy. As a result, ATP is often described as the energy currency of cells. ATP has also been established as an important extracellular ligand of autocrine signaling, intercellular communication, and neurotransmission in numerous physiological and pathophysiological phenomena [103]. It has also been illustrated that ATP injection increases expression of several markers for regenerative activity in sensory neurons, including phospho-STAT3 and GAP43 [104]. Researchers have found that ATP infusion improves spontaneous pain and tactile allodynia in patients with postherpetic neuralgia [105, 106].

2.7.1. Mechanisms of Action of Glucopuncture

Most researchers confirm that the pharmacological effects of sugar water injections include stabilization effects on neural activity, normalization of regional glucose metabolism, and a decrease in neurogenic inflammation, reducing neuropathic pain via multifactorial mechanisms [107]. Dextrose and glucose have been speculated to indirectly inhibit capsaicin-sensitive receptors (e.g., transient receptor potential vanilloid receptor-1 aka TRPV1) and block the secretion of substance P and calcitonin gene-related peptides, which are pro-nociceptive substances involved in neurogenic inflammation [108]. A recent investigation illustrated that dextrose or glucose exposure restores function in apoptotic nerves after TNF-α exposure via ROS scavenging, enhancement of MAPK family and Akt pathways [109]. These findings suggest that glucose injection about entrapped peripheral nerves may have several favorable biochemical actions that enhance neuronal cell function. This may explain why sugar water injections near peripheral nerves may have such interesting pain modulating effects. This pain modulating effect is typically observed when giving ultrasound-guided perineural injections, but these beneficial clinical benefits are also observed when giving multiple injections near tiny peripheral nerve endings in or near tendons, fascia, dermis, muscles and ligaments.

2.8. Patient-guided, Palpation-guided vs US-guided Glucopuncture

Doctor in remote areas with no access to US, apply glucopuncture using patient-guided and palpation-guided regional S5W injections (Table 1). Patient-guided means that the patient shows the pain region and the clinician simply injects in that particular pain region. This method can be surprisingly efficient and easy to apply. Typically, a high number of injections is applied (5 – 25 injections in the region of complaint). For example, patients with postherpetic neuralgia receive weekly sessions of multiple intradermal (SC or IC) injections in the pain region [110]. Patients with pain in the left deltoid region receive multiple intradermal and intramuscular injections in the left deltoid region.

When applying palpation-guided injections, the clinician looks for pain points in the pain region and gives S5W injections in those points. Most of these pain points (PPs) are found in muscle (MPPs), fascia (FPPs) or ligaments (LPPs). The depth of injection may vary. Sometimes, injections are given at several depths (IM, IF, SC) while withdrawing the needle.

When no regional pain points are found in the pain region, one should look for trigger points in muscles, fascia or ligaments. This means that injections are applied outside the pain region because one is dealing with referred pain. For example, pain in the lateral anterior knee can be referred from muscular trigger points (MTPs) in the lateral head of the quadriceps muscle. If such MTPs are identified, the patient receives injections above the knee instead of in the knee. The advantage of those palpation-guided injections is that clinicians who apply this method on a daily basis become experts in retrieving a lot of information from the patient to decide where exactly to give the injections [111]. While looking for such PPs or TPs, the clinician is looking at the patient's body and not at the screen of the US.

However, US-guidance can enhance safety and accuracy of Glucopuncture. US-guidance is a great tool when the lesion is lying deeper, when the injection is performed close to important vessels or nerves, or when accuracy is crucial. The latter is obviously the case when giving a S5W injection into the hip joint [112] or while applying nerve hydrodissection, such as in carpal tunnel syndrome [113, 114]

Table 1 Different Types of Glucopuncture

Patient-guided GP	Injections into Pain Region	At Random
Palpation-guided GP	Injections into Pain Region	In Pain Point(s)
Palpation-guided GP	Injections outside Pain Region	In Trigger Point(s)
US-guided GP	Injections into Pain Region	Into the Lesion

Palpation-guided glucopuncture is more popular with family physician with no ultrasound. Ultrasound-guided glucopuncture is more popular in hospitals. One can also combine both approaches. This dual approach means that the practitioner first identifies the pain points in the treatment zone during clinical examination, and subsequently uses US to guide the needle exactly in a specific spot in the target tissue. This dual approach produces optimal clinical outcome, and was applied in this clinical case.

2.9. Difference between Glucopuncture and Prolotherapy

Table 2 Differences between Glucopuncture and Prolotherapy

	Glucopuncture	**Prolotherapy**
SW5	X	-
SW15 – SW25	-	X
Local Anesthetics	-	X
Steroids	-	-
ID (IC, SC)	X	-
IM, IF	X	-
IL, IA	X	X
Glucose Effect	X	X
Proliferation Effect	-	X

It is worth noting that S5W injections are totally different from Hackett-Hemwall prolotherapy [115, 116, 117, 118, 119, 120, 121, 122, 123, 124, 125, 126, 127, 128, 129, 130, 131, 132], which injects irritants (such as phenol) or hyperosmolar solutions (such as dextrose 15% or NaCL 3%) to evoke a local reaction phase. Hyperosmolar injections into the ECM lead to immediate water flux out of cells [133, 134]. Hyperosmolar solutions place a lot of mechanical stress on cell membrane, cytoskeleton and cell nucleus [135, 136]. An increase in extracellular osmolarity has many damaging effects on cells by promoting water flux out of the cell, triggering cell shrinkage, and intracellular dehydration [137, 138]. This leads to protein carbonylation, mitochondrial depolarization, DNA damage, and cell cycle arrest [139]. It is hypothesized that such cell damage is not supporting tissue repair but rather creating very small scars inside the injected tissue [140]. Fortunately, many adaptive mechanisms exist to counter all these deleterious effects of hyperosmotic stress, including cytoskeletal rearrangement and up-regulation of antioxidant enzymes, transporters, and heat shock proteins [141]. Osmolyte synthesis is also up-regulated and many of these compounds reduce inflammation [142]. These reactionary mechanisms may explain partly the positive clinical effects of prolotherapy [143, 144, 145]. In other words, intracellular material (cytoplasm, organelles) and substances of the cell membrane (e.g., phospholipids) flow into the ECM, evoking an immediate local inflammatory reaction, which is typical for Prolotherapy. This reaction can lead to subsequent connective tissue proliferation – hence the term "prolo" [146]. This proliferation can lead to thickening and strengthening of, for example, ligaments and bands. As a result, prolotherapy is the best choice when treating weak ligaments, but it is not recommended for Dupyutren's [147] nor for the treatment of nerve entrapments. For pain modulation when dealing with nerve entrapment, ultrasound-guided Glucopuncture is the better option.

2.10. Nerve Hydrodissection

Nerve hydrodissection (HD) is a technique employed in the treatment of nerve entrapments. It involves injecting S5W into the surrounding tissue, fascia, or adjacent structures in order to separate the nerve from the surrounding tissue [148]. Animal models suggest that even minimal compression has the potential to initiate and sustain neuropathic pain. Bennett et al. [149] demonstrated the vulnerability of mixed sensory/motor nerves to circumferential compression using a rat model. They applied self-dissolving ligatures around the sciatic nerve with light constriction, avoiding visible restriction of blood flow or significant indentation of the nerve surface. This led to rapid morphological changes, the development of allodynia and hyperesthesia, suggesting that in humans, tiny peripheral nerves may be susceptible to light compression and entrapment effects [150]. The use of fluid to separate nerves from surrounding soft tissue in treating neuropathic pain may offer a potential benefit by relieving pressure on nervi nervorum (small nerves supplying the main nerves) and on vasa nervorum (small blood vessels located outside the epineurium). Therefore, one has to hydrodissect the soft tissues surrounding the nerve layer by layer until the epineurium has no further layers of fascia surrounding it. Administration of SW5 alongside the nerve thus regulates pain through the mechanical mechanisms described earlier. In other words, when performing nerve hydrodissection, there is a mechanical release and a biochemical effect of the sugar water (Table 2). This may explain the effectiveness of US-guided glucopuncture by releasing the nerve, enhancing vascular supply and venous drainage of peripheral nerves and the effect of S5W on the peripheral nerve. It is obvious that HD requires ultrasound-guidance. Prof Lam from Hong Kong comprehensively described the ultrasound-guided hydrodissection technique, covering theoretical foundations to practical application [151]

1/ Mechanical Release of the Nerve 2/ Biochemical Effect of S5W

Table 3. Dual Effect of Nerve Hydrodissection with Sugar Water 5%

3. Clinical Case

A 44-year-old athlete who practices high-level trail running suffers from bilateral pain in the inner thighs, inner knees and inner calves for two years. He describes it as a "cramp" which starts while running for about 20 minutes. When pain occurs while running, he has to slow down or even stop running. He desperately wants a solution because this condition prevents him from preparing the next Ultra-Trail (80 km) competition. Both medical interventions to suppress the pain as well as physical therapy (massage and stretching) were not successful.

The patient has no particular medical or surgical history. There are no signs of paresthesia, edema or venous stasis. The patient does not complain about low back pain or pseudosciatic pain. Palpation of femoral, popliteal or pedal arteries is normal on both sides. Static and dynamic lumbar examination, looking for spontaneous or induced segmental pain, is normal. Orthopedic examination of hips and knees is normal. Palpation of inner thighs reveals the presence of a painful area approximately 10 cm above the femoral epicondyle, resulting in a withdrawal reflex by flexion and internal rotation of the hip on both sides. During ultrasound examination (Samsung EVH HM70) of both legs with a high-frequency linear probe (16 Mhz), no abnormalities could be identified in regional tendons or muscles (quadriceps, adductors and hamstrings), nor in the femoral arteries or veins. At the above mentioned painful point, there is a significant isoechoic thickening of the vasto-adductor membrane. There is also a hypoechoic thickening of the saphenous nerve at the crossing of the vasto-adductor membrane (Fig. 1). The diagnosis was an entrapment of the saphenous nerve at the level of the vasto-adductor membrane.

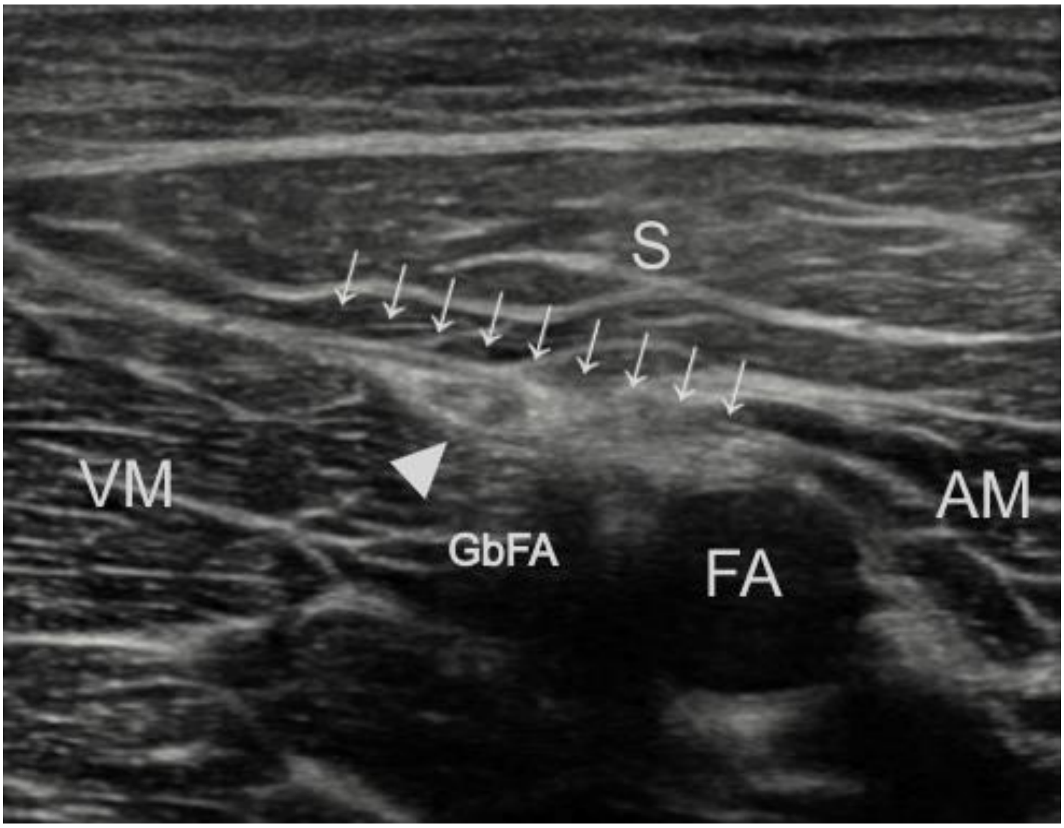

Figure 1 Ultrasound Investigation Inner Thigh

S : Sartorius Muscle; AM : Adductor Magnus Muscle; FA : Femoral Artery; GbFA : Genicular branch of Femoral artery; VM : Vastus Medialis Muscle ; Arrows : Vasto-Adductor Membrane; Large arrow head : Enlarged and hypoechoic saphenous nerve.

3.1. Treatment with Palpation-guided and US-guided Glucopuncture

After obtaining informed consent, the patient received an injection of 10 mL of glucose 5% in water (G5W) into the left and right vasto-adductor membranes. The injections were given in the pain regions as found during clinical examination. US-guidance was used to obtain optimal accuracy of the needle tip (Fig. 2).

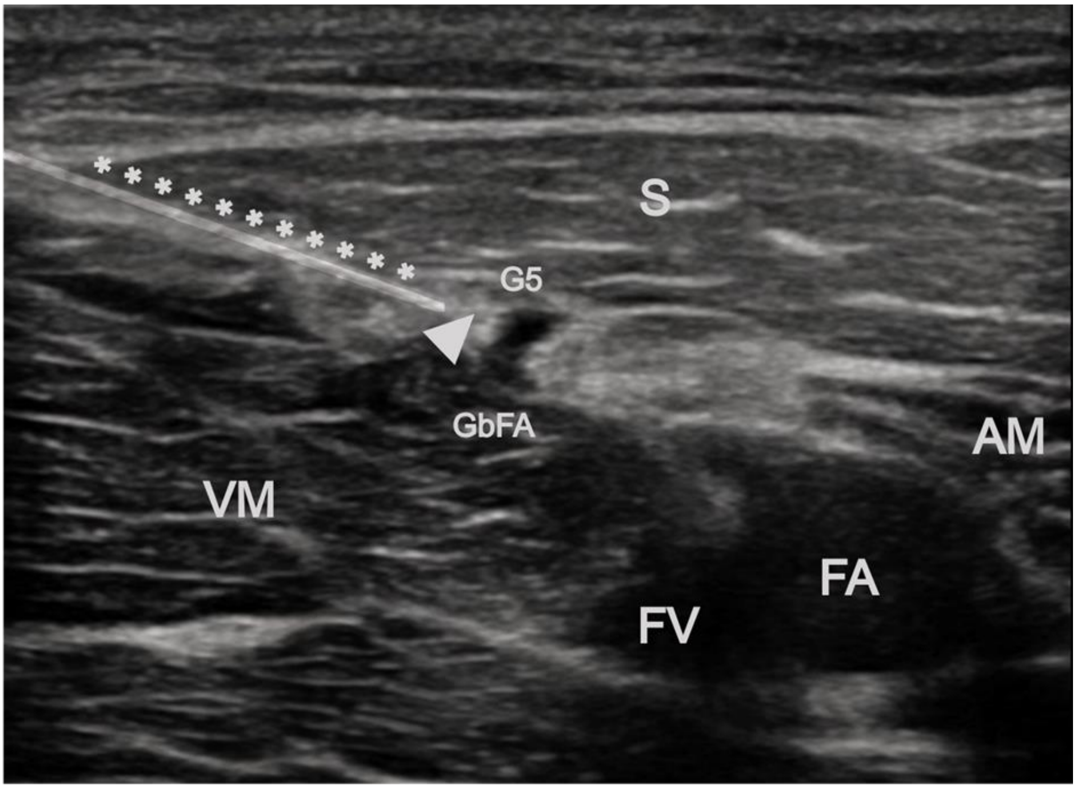

Figure 2 US-guided Glucopuncture

S : Sartorius Muscle; AM : Adductor Magnus Muscle; FA: Femoral Artery; GbFA: Genicular branch of Femoral artery; FV: Femoral Vein; VM: Vastus Medialis Muscle; Arrows: Vasto-adductor Membrane; Large arrow head: Enlarged and hypoechoic saphenous nerve. G5: hypoechoic appearance of glucose solution *** : Position of the needle (Long Axis approach)

The patient is placed in the supine position with the hip in external rotation. After disinfecting the area with Alcoholic Chlorhexidine 2% solution, the probe is covered with a sterile cover, and sterile ultrasound gel is used. The technique described by Lecigne et al [152] was used. A 25G needle (5 cm / 2 in) enters the interaponeurotic space between Sartorius and Vastus Medialis, "threading" the vasto-adductor membrane to the level of the saphenous nerve. The injection of G5W is first applied rather deeply near the saphenous nerve in order to limit the risk of air bubbles which can create an ultrasound refractive effect and make the nerve invisible. In other words, the superficial injection is applied after injecting the deeper layer.

The patient is advised to remain active, but to resume running only the day before the next appointment. During the 2nd visit, one week later, the patient described a decrease of more than 50% in his pain after 30 minutes of running, without requiring to stop running. The pain region was now more at the level of the thighs and less in the knees and calves. After three weekly sessions of ultrasound-guided Glucopuncture, the patient is asymptomatic and was able to run an 80 km race without experiencing those pains. There was no recurrence of pain 4 weeks after the last hydrodissection session.

4. Conclusion

Hydrodissection by ultrasound-guided glucopuncture can be an interesting option in the treatment of saphenous nerve compression at the vasto-adductor membrane. This article is an invitation to the medical community to design controlled studies to compare S5W injections with other injectates such as PRP, and to establish a standardized protocol for its application in SNE.

Compliance with ethical standards

Disclosure of conflict of interest

All authors disclose all financial relationships (including employment, grants, patent ownership, and other interests) with any commercial entities that have an interest in the subject matter or materials discussed in the manuscript.

Statement of informed consent

Informed consent was obtained from the individual participant included in this case study.

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