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Intradermal Glucose 5% Injections for Mild Localized Neuropathic Pain- A New Approach to Reduce Pain Medication

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Abstract- As localized neuropathic pain can seriously decrease quality of life, physicians are challenged to look for treatment modalities which are easy to apply, safe and effective. Over the last decade, isotonic glucose (or dextrose) injections have received more attention among clinicians worldwide. In this article, the focus is on the application of intradermal injections of glucose 5%. Glucopuncture is especially interesting for doctors and patients who live in remote areas where pain medications are not available, or too expensive.

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Abstract- As localized neuropathic pain can seriously decrease quality of life, physicians are challenged to look for treatment modalities which are easy to apply, safe and effective. Over the last decade, isotonic glucose (or dextrose) injections have received more attention among clinicians worldwide. In this article, the focus is on the application of intradermal injections of glucose 5%. Glucopuncture is especially interesting for doctors and patients who live in remote areas where pain medications are not available, or too expensive.

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I. Neuropathic pain

Nerves are usually viewed as simple conduits of electrical signals to make muscles move and enable sensation of pain, temperature and pressure. However, axons within nerves, also known as nervi nervorum, are also capable of reacting to their immediate environment, such as to mechanical pressure or to direct injury from trauma.

Nociceptors are sensory neurons that detect harmful stimuli, and can become sensitized after infection (e.g., herpes), direct injury, surgery [i,ii] or repetitive overstimulation. When nociceptors are sensitized, they often exhibit spontaneous activity in the absence of stimulation, called “ongoing activity” [iii]. Because of their very specialized anatomy and physiology, nerves are capable of creating or mediating certain types of (chronic) pain [iv]. It has been made clear that nociceptor neurons also release neuropeptides and neurotransmitters from nerve terminals which can regulate adaptive immune cell responses [v]. Macrophages can activate nociceptors and nociceptors can secrete neuropeptides and chemokines which act on macrophages; in chronic pain these bilateral macrophage-nociceptor interactions are mediated by microRNAs and microRNA-containing exosomes [vi].

Neuropathic pain (NP) is described as a (superficial) pain arising as a direct consequence of a lesion or disease affecting the somatosensory system at the peripheral or central level [vii]. It affects about 10% of the world population [viii, ix]. Despite the progress in pain management methods made over the last decades, neuropathic pain significantly impacts patients’ quality of life. Both pharmacological and non-pharmacological methods often fail to reduce the pain or may induce serious side effects. Neuropathic pain resulting from diabetes or chemotherapy are not considered as a subject of this article.

Diverse causes of neuropathic pain are associated with excessive inflammation in both the peripheral and central nervous system which may contribute to the initiation and even maintenance of persistent pain [x]. Chemical mediators, such as cytokines, released during an inflammatory response have the undesired side effect of sensitizing or stimulating nociceptors. These changes can promote long-term persistent neuropathic pain. Transient receptor potential vanilloid channel 1 (TRPV1), a nonselective cation channel, has been shown to play an important role in neuropathic pain (xi). It has been found that IL-6 and IL-1beta also play a role in pain induced by perineural inflammation [xii]. All this may explain why sometimes a minor trauma can lead to extreme sensitivity to touch (allodynia) and severe chronic neuropathic pain.

II. Localized Neuropathic Pain

In more than half of cases of NP, the pain is localized and affects a certain area of the body [xiii]. This article focusses on this peripheral or localized type of neuropathic pain. Localized neuropathic pain (LNP) is characterized by circumscribed areas of pain with abnormal skin sensitivity or spontaneous burning pain with no obvious cause.

It is hypothesized that even a minor peripheral nerve injury can induce functional and structural changes in neuronal cells. These functional and structural changes release numerous signaling molecules in response to the nerve damage. As these mediators modulate corresponding receptors on cell membranes, such interactions can create vicious circles of complaints such as burning pain and allodynia. These maladaptive mechanisms contribute to further sensitization of peripheral nerve endings [xiv]. It is hypothesized that noxious stimuli stimulate peripheral nerves to release calcitonin gene-related peptide

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(CGRP) and prostaglandin E2 (PGE2) [xv]. Interleukin-1beta also seems to play a role in neuropathic pain [xvi, xvii].

III. Differential Diagnosis

LNP needs to be differentiated from complex regional pain syndrome (CRPS) which is a difficult-to-treat chronic pain condition [xviii]. CRPS often involves hyperalgesia and allodynia of the extremities and on top of that there is autonomic nervous system involvement. CRPS is not an indication for Glucopuncture. Neither can neuropathic pain resulting from nerve compression, autoimmune disease, diabetes [xix] or chemotherapy be treated with Glucopuncture.

IV. Regional Treatments for Localized Neuropathic Pain

The standard treatment of LNP is antidepressants and anticonvulsants [xx]. Regional treatments such as patches and injections are gaining popularity in the local management of peripheral neuropathic pain. A major advantage of transdermal treatments is that they may reduce the risk of adverse events that are often associated with systemic medication. Topical modalities may be used in combination with oral drugs resulting in less drug-drug interactions.

Topical treatments such as 5 % lidocaine patches and 8 % capsaicin patches have been used in several LNP models [xxi, xxii, xxiii]. In this article, the focus will solely be on local intradermal injections with glucose 5%. Typically, 1 mL of solution is injected per cm (half inch) of the symptomatic area. Positive feedback of patients treated with this new technique has encouraged certain clinicians to present it as a new approach to treat mild forms of LNP. The new term Glucopuncture is introduced to raise awareness about these injections among both doctors and patients. However, no randomized clinical trials have illustrated its safety or efficacy yet. This technique is especially interesting for physicians who work in remote areas where modern diagnostic and therapeutic modalities are not available, or too expensive for their patients.

V. Glucopuncture for Mild Localized Neuropathic Pain

As pointed out earlier, first-line pharmacological treatments for LNP include pain medication, antidepressants and anticonvulsants such as gabapentin and pregabalin [xxiv]. However, some patients complain about side effects of such medication. Others obviously overuse pain medication. One of the goals of Glucopuncture is to reduce the use of systemic medication by giving a series of glucose 5% injections intradermally. Best results are achieved when the injections are started in the beginning of the disease before the somatosensory system is affected at central level. Instead of giving intradermal injections, one can also give the glucose perineurally [xxv, xxvi, xxvii] but this technique is not a topic of this article. Clinical randomized studies are required to see which dose, frequency and injection technique works best for mild LNP.

VI. Definition of Glucopuncture

Glucopuncture (GP) is an easy-to-learn procedure which can be done in a small private practice without ultrasound guidance. GP is defined as an injection-based therapy for the management of a variety of musculoskeletal conditions [xxviii]. In general, glucose 5% in water (G5W) injections are given in dermis, muscles, fascia, tendons and ligaments. No local anesthetics nor corticosteroids are added. When treating localized neuropathic pain, multiple intracutaneous injections with G5W in the zone of pain referral are advised. The treatment is repeated once a week to once every two weeks. After a series of sessions, the pain modulation can last up to several months. If no major improvement is noticed after five sessions, the treatment is stopped.

VII. Glucose Metabolism in Brain Cortex

The human brain depends upon glucose as its main source of energy, and glucose metabolism is critical for brain physiology [xxix, xxx]. The brain accounts for about 2% of the body weight, yet it consumes about 20% of glucose-derived energy [xxxi]. Glucose metabolism provides the fuel for physiological brain function through the generation of ATP, the foundation for neuronal and non-neuronal cellular maintenance [xxxii]. Therefore, regulation of glucose metabolism is critical for cortex physiology [xxxiii]. The largest proportion of energy in the brain is consumed for neuronal computation and information processing [xxxiv], e.g., the generation of action potentials and postsynaptic potentials generated after synaptic events, and the maintenance of ion gradients and neuronal resting potential [xxxv]. Additionally, glucose metabolism provides the energy and precursors for the biosynthesis of neurotransmitters [xxxvi]. The question is whether glucose is equally important for the peripheral nervous system as it is for the brain. This question has not been answered yet, but further exploration of this issue might explain the clinical effects which are noticed when injecting isotonic glucose perineurally (e.g., carpal tunnel) or intradermally. It is clear that when glucose is applied to a patient systemically, for example, as an IV infusion, there are no pain modulating effects at all. This means that in the search for the exact mode of action of Glucopuncture, the scientific community needs to focus

on what exactly is happening when the glucose arrives directly in the extracellular matrix (ECM). In other words, the mechanisms of action of glucose as found in lab tests (*in vitro*) or hypotheses from diabetic research provide only limited value.

VIII. Working Hypothesis of Glucopuncture

Glucose is a crucial energy source for cellular health. The goal of Glucopuncture is to deliver additional glucose in the extracellular space to support directly cellular ATP production. Hypertonic solutions are not advised because they lead to osmotic destruction of the cells. When glucose is injected into the body, it arrives in the extracellular matrix (ECM). Then, the glucose is transported across the cell membrane [xxxvii].

a) *The Effect of Glucose on Dermal Sensory Nociceptors*

Nociceptors are sensory neurons that detect harmful stimuli, and can become sensitized following injury or repetitive stimulation. When sensitized, nociceptors often exhibit spontaneous activity in the absence of apparent stimulation [xxxviii]. Sensory receptors are found in dermis, muscles, fascia, tendons and ligaments [xxxix]. These receptors include mechanoreceptors, nociceptors, and thermoreceptors [xl, xli]. Especially dermal nociceptors [xlii, xliii, xliv] are important to explain the pain modulating effects of intradermal glucose injections. And this is very likely the most important mechanism when treating regional neuralgia [xlv]. The transient receptor potential ankyrin1 (TRPA1), a member of the TRP channels, acts as 'polymodal cellular sensor' on primary sensory neurons where it mediates the peripheral and central processing of pain [xlvi].

b) *ATP as a Pain Modulator*

ATP may play a direct role in pain modulation, especially when dealing with peripheral nerves. It has been illustrated that ATP injection increases expression of several markers for regenerative activity in sensory neurons, including phospho-STAT3 and GAP43 [xlvii]. It has been found that ATP infusion improves spontaneous pain and tactile allodynia [xlviii, xlix] in patients with (postherpetic) neuralgia. It also became clear that it works for neuropathic orofacial pain, but not for other types of orofacial pain, indicating that the neuropathic element seems to be an important factor in the effects of ATP [l]. These studies might indicate that glucose may have its pain modulating effects on neuropathic pain via ATP [li]. More research in this field may confirm the anecdotal information available so far.

IX. History of Glucopuncture

Subcutaneous injections with glucose 5% were first described in the treatment of Achilles tendinopathy [lii]. Later on, glucose 5% injections were used to treat other forms of musculoskeletal pain [liii, liv, lv]. Some physicians also used glucose 5% injections for tennis elbow [lvi], tension headache, postherpetic neuralgia, and Dupuytren's stage 1. As the total amount of glucose is very small (similar to eating a few strawberries once a week), glucopuncture can be applied for patients who are diabetic or those who are on a strict calorie diet.

X. Difference Between Glucopuncture and Prolotherapy

Glucose and dextrose injections have been used for several decades in prolotherapy [lvii, lviii, lix, lx, lxi, lxii, lxiii, lxiv]. Prolotherapy injects hypertonic dextrose (10% net concentration or more) into, for example, entheses of ligaments, bands and tendons. Injections into periost and into joint cavities are also given. Hyperosmolar solutions lead to localized cell shrinking and subsequent cell destruction. This phenomenon creates release of arachidonic acid (from the cell membrane) which creates a local inflammatory reaction. The latter may lead to local tissue proliferation – hence the description prolotherapy - and even formation of scar tissue [lxv]. Local anesthetics are always added to make the injections less painful.

Glucopuncture also injects glucose (or dextrose) but only in an isotonic concentration (5%). As a result, there is no local osmotic shock, no cell death, no subsequent inflammatory reaction. That is why the ATP hypothesis was required to explain the pain modulating effects of glucopuncture, as well as the positive effect of glucose 5% injections on tissue repair (as in Dupuytren's stage 1). The injection techniques are also different. Glucopuncture typically uses more shallow injections than prolotherapy. Most of the injections are given in the dermis, and also in trigger points of muscles and ligaments. In contrast to prolotherapy, local anesthetics are never added to the solution (Table 1).

XI. Intradermal Glucose 5% Injections for Localized Neuropathic Pain

During questioning, the patient is asked to point out the zone of pain referral. Sometimes the physician can localize pain points within the pain region which are extra sore. Such points may receive an extra dose of injectate. The treatment itself is remarkably simple and straightforward. The injection procedure itself typically takes less than a minute to perform. After identifying the tender zone, one gives multiple intradermal injections (intracutaneous wheals) with glucose 5% in the pain region, as indicated by the patient. Intracutaneous injections usually feel like sharp stings for a few seconds. Intracutaneous injections (IC) are more painful than subcutaneous injections (SC) but IC injections seem to be more effective regarding modulation of

neuropathic pain. Some patients have a very thin epidermis, which makes IC injections impossible, so one has to rely on SC injections instead. The injections are usually given 1 cm apart. About 0.5 to 1 mL is given in each spot with a 30 G or 27 G needle. The total volume per session is usually between 2 and 20 mL, depending on the size of the tender region. It often happens that the patient experiences immediate pain relief a few seconds or minutes after the glucose 5% injections. This is rather surprising, as no local anesthetics are added to the glucose. Unfortunately, this pain modulating effect of glucose 5% lasts only for a few hours to a few days. In some patients, the symptomatic improvement only becomes apparent after the second or third session. To obtain long term results, repetition is required until lasting pain relief has been achieved.

XII. Conclusion

In the search for treatment modalities which are safe, affordable and effective, several clinicians worldwide have experienced that glucose 5% injections are an inexpensive treatment to reduce their patient's intake of pain medication. This is especially true for mild forms of regional neuropathic pain. More research in this field may confirm their clinical findings.

Table-1

Difference PT and GP	Prolotherapy	Glucopuncture
What?		
Hypertonic Glucose	x	
Local Anesthetics	x	
Glucose 5% in Water		x
Where?		
ID		x
IM		x
IL	x	x
IA	x	
How?		
Osmotic Shock	x	
Proliferation	x	
ATP Production	x	x
TRPV1 (Needle Effect)	x	x

Table: Difference between PT (Prolotherapy) and GP (Glucopuncture). ID: Intradermal. IM: intramuscular, IL: intraligamentous, IA: intraarticular

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