SYSTEMATIC REVIEW OF PHONOPHORESIS: AN EXTRAORDINARY COMBINATION OF PHYSIOTHERAPY AND PHARMACOLOGY

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Phonophoresis is an effective transdermal drug delivery system. By utilizing ultrasound waves, phonophoresis helps in transmitting a topically applied drug to the deeper layers of the skin. Clinical scope of phonophoresis technique has been proved for a plethora of conditions ranging from skin related disorders to musculoskeletal pain. [1]

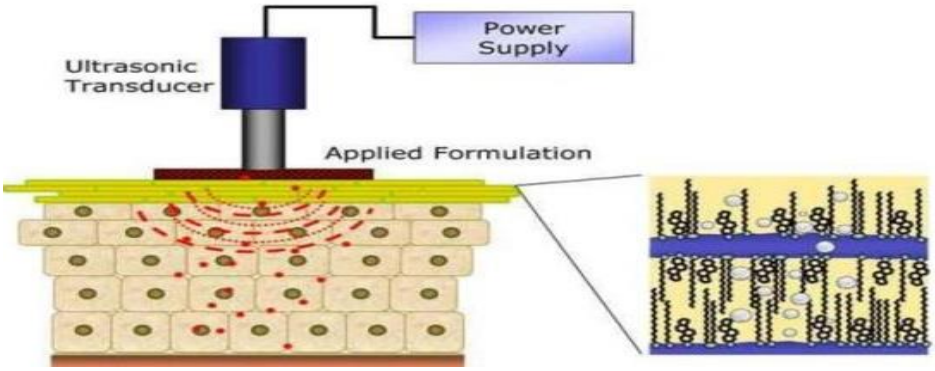

Fig 1. Basic Principle of Phonophoresis (Taken from Kharat R., Bathe R. A Comprehensive Review on: Transdermal drug delivery systems. International Journal of Biomedical and Advance Research 2016; 7(4): 147-159.)

The benefits of Phonophoresis can be attributed to the physical properties of ultrasound waves. Ultrasound waves are longitudinal waves with phases of compressions and rarefactions. When passed through the human tissue, compressions of the wave lead to formation of bubbles inside the tissue. During rarefactions, these bubbles expand in size and during compression, size of the bubble decreases ***(Acoustic cavitation).***[2]

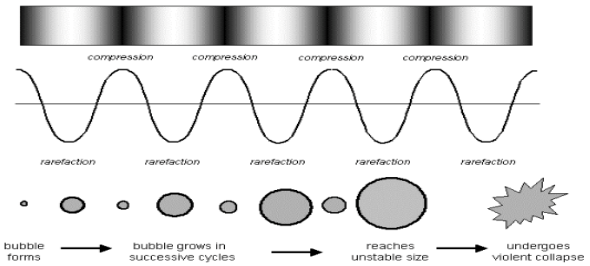

Fig 1. Acoustic Cavitation (Taken from Mason J. (2003) High Powered Ultrasound in Physical and Chemical Processing. New Acoustics – Selected Topics. Biblioteca de Ciecias:95-130)

Continuous oscillations of the ultrasound field will result in cyclic expansion and compression of the bubbles thus, causing to and fro motion in the tissues and body fluids resulting in

Microstreaming.[2]

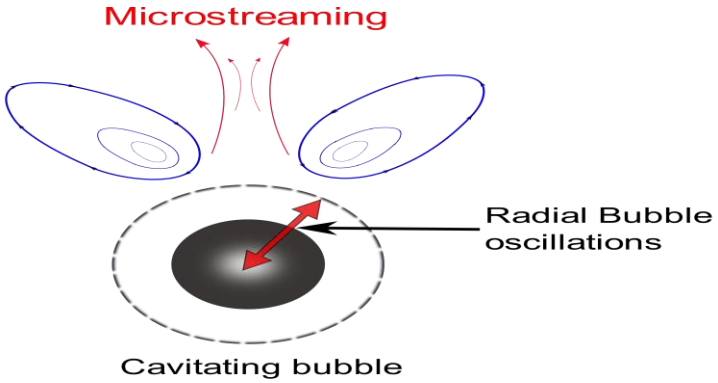

Fig 3. Microstreaming (Taken from : Silhavaid. File:acoustic microstreaming.svg [Internet]. Wikimedia Commons. [cited 2023Apr22]. Available from: https://commons.wikimedia.org/ wiki/ File: Acoustic_ Microstreaming.svg)

Ultrasound can be used to enhance the permeability of the skin via Acoustic cavitation and Microstreaming, thereby ensuring effective delivery of the drug applied topically. The application of ultrasound based transdermal delivery of drugs through the skin is known as 'Phonophoresis'. Utilising the principles mentioned above, Phonophoresis technique with ultrasound modality can help deliver the topically applied drug to the deeper layers of the skin. Microstreaming and Acoustic Cavitation together help the drug molecules to pass through the Stratum Corneum thus paving them towards the underlying structures of skin such as muscles, ligaments, tendons, cartilage, etc.[3] There are numerous systematic reviews providing evidence to the effectiveness of ultrasound on pain but the scope of Phonophoresis in pain management and reduction of inflammation is yet to be explored in a more scientific manner. Therefore, the main aim of this study was to analyse the clinical scope of Phonophoresis in pain management.

The search for the articles was performed following the guidelines for systematic review suggested in Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). The search was carried out between September 2022 and March 2023 on the following databases: Academia, PubMed and Scopus. All clinical trials, systematic review and meta analyses were included in the search which were publishes on these databases in the past 10 years. The keywords used in this search were "phonophoresis", "pain management", "transdermal drug delivery" and "topical application". Inclusion criteria for the study was based on PICO Model. (i) Population: Patients having musculoskeletal pain; (ii) Intervention-Phonophoresis given with therapeutic ultrasound, (iii) Comparison: analysing effectiveness in relation to other treatment techniques from physiotherapy and pharmacology. (iv) Outcomes: pain relief and decrease in other symptoms. Those articles combining phonophoresis with any other treatment technique were excluded.

Yang et al. conducted a review study to analyse the effect of phonophoresis in Knee Osteoarthritis and they noticed significant improvement in pain and functional performance by giving phonophoresis to patients with corcticosteroid and NSAID gel.[4] In a literature review conducted by Ead J et al. with an aim to explore the benefits of phonophoresis in delivering antibiotics to patients with chronic wounds, it was concluded that Ultrasound enhances the delivery of Antibiotics, Anti-Inflammatory Agents, and Nutraceutical. They established effectiveness of Phonophoresis as an adjunct to standard chronic wound management.[5]

In some conditions, it might seem beneficial to combine two or more topical drugs belonging to different classes for the enhanced pain relief outcome. But it is important to rule out any adverse reaction caused to patient by drug combination. Tan et al. conducted an in-vitro kinetic assay and molecular docking study to analyse the impact of glucosamine, chondroitin and diacerein on human hepatic CYP2D6 and concluded that combination of Glucosamine, Chondroitin Sulphate and Diacerein do not cause any adverse drug reactions when administered together.[6]

Some researchers might argument that topically administered drugs take extra time for providing symptomatic relief in comparison with drugs taken orally. Tandon N et al. conducted a comparative study for oral administration v/s topical application of combination of diacerein and glucosamine sulphate and found both the methodologies equally effective in providing symptomatic relief in patients with Grade 2 Knee Osteoarthritis.[7]

It has been proved that Phonophoresis technique helps to enhance the drug delivery to deeper layers under the skin when compared to simple topical application of the drug. Mao L et al. conducted a systematic review to analyse various in-vitro and in-vivo studies related to various drug delivery systems and found topical delivery systems combined with electrical modalities such as ultrasound and transcutaneous electrical nerve stimulation as a safe non-invasive method.[8] Masterson J et al. compared sustained phonophoretic administration of NSAIDs with normal topical application of NSAIDs and their effectiveness in Osteoarthritis patients and concluded that phonophoretic administration produces highly significant results in comparison to standardised topical application. [9]

Phonophoresis is also proved to improve cartilage and tendon strucure in a joint. Wang L et al. analysed the effectiveness of ultrasound delivered nanoparticle medicine on collagen induced arthritis in rat model. They used drug in nanoparticle medium and concluded that ultrasound based delivery with drug in nanoparticle medium is highly effective in improving the collagen structure and cartilage health in an arthritic joint.[10] Leite C. B. et al. conducted a research to study effect of glucosamine and chondroitin sulphate (NANO-CG) when administered phonophoretically in

patients with knee chondropathy. It was concluded that NANO-CG formulation is highly effective in reducing the pain and stiffness in knee chondropathy.[11]

Rigby J et al. conducted a study on 40 healthy men to analyse the depth of penetration of Dexamethasone when given with ultrasound at low frequency (45-kHz) and high frequency (1-MHz). Drug penetration at higher frequency was found to be more deeper in comparison to drug penetration at lower frequency.[12] In various musculoskeletal conditions such as Back pain, Neck pain and Muscular Stiffness, patients are reported to develop trigger points thus stimulating the pain-spasm-pain cycle. Phonophoresis may help to deliver anti-inflammatory drugs to the muscular layers. Tabatabaiee A et al. conducted a longitudinal study on Phonophoresis with Hydrocortisone in patients with Trigger points in Upper Trapezius myofascia. The phonophoretic treatment group showed decrease in pain and increase in range of motion in comparison to the results whoed in the control group. [13]

Not just limited to musculoskeletal disorders, Phonophoresis may prove highly beneficial in patients with skin disorders. Akhalkatsi V et al studied the effects of hydrocortisone injections combined with phonophoresis at 1 MHz in patients with arthrofibrosis. It was concluded that combination of phonophoresis with hydrocortisone injections is more beneficial than the injection alone. [14]

Phonophoresis has proven itself time and again in various clinical conditions to be highly effective in delivering the drug to the deeper layers under the skin and thereby creating a greater impact on the patient's symptoms. This makes it a considerable option for its use as an adjunct to the various treatment protocols. Transdermal drug delivery systems are showing promising results with little to no side effects of the drugs. Drugs when taken orally for a longer duration can produce serious complications in patients ranging from gastrointestinal complications to liver damage. But when given topically, its side effects are reduced drastically. Moreover, phonophoresis helps to deliver the drugs to the deeper layers thereby enhancing the effect of the topical application.

This systematic review has considered articles that provide evidence for Phonophoresis being beneficial for patients suffering from a variety of musculoskeletal conditions. Studies have been included which prove its effectiveness in certain skin disorders. Certain studies in the review give a clear picture of the benefits of Phonophoresis in comparison to oral intake of drugs and simple topical application.[17,18] These benefits can be owed to 'Acoustic Cavitation' and 'Microstreaming' principles which help the drug to penetrate through the Stratum Corneum and reach the deeper layers of the body tissues.

Outcomes extracted from the articles included in systematic review have not been assessed for sensitivity and risk of bias which becomes a limitation of the study. More large scale RCTs are required in this field to give a quantified evidence for the benefits of Phonophoresis.

Phonophoresis has a wide clinical scope not just limited to musculoskeletal ailments, but also pertaining to skin diseases and wound management. This systematic review has been done to provide ample amount of evidence for the effectiveness of Phonophoresis in a plethora of clinical conditions. No adverse reactions due to Phonophoresis were reported in any of the articles included in this review.

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