Original Article

Efficacy of Novel Application of Succinylcholine Nanoformulation Administered by Phonophoresis for Myofascial Pain Syndrome: Single-arm Phase Zero Clinical Trial

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Abstract

Background: Succinylcholine is a depolarizing neuromuscular blocker characterized by quick onset and brief duration, conventionally utilized in anesthesia but never for the treatment of myofascial pain syndrome (MFPS). Phonophoresis-based drug delivery enhances skin absorption and localized therapeutic effects, introducing a novel therapy modality. **Objective:** To develop and evaluate the efficacy of a novel application of the nanoformulated succinylcholine gel administered through phonophoresis for reducing pain in patients with MFPS. **Methods:** The gel was formulated and optimized using carbopol 934. The physicochemical characterization encompassed pH, viscosity, extrudability, and stability. A pilot single-arm phase 0 clinical trial was then conducted on 35 enrolled patients with upper trapezius MFPS with active myofascial trigger points. One gram of topical gel-containing 25 mg of succinylcholine was administered to trigger pointfor a single session, subsequently followed by ultrasound treatment for the duration of 5 min. Pain was evaluated by the Visual Analog Scale (VAS) at baseline, 15 min, 30 min, 2 h, second, and 3rd day. **Results:** The gel was stable, viscous, penetrated well, and had no side effects. Out of 35 enrolled patients, 29 completed the study. Upon phonophoresis, pain intensity markedly decreased from 7.82 ± 0.92 at baseline to 0.46 ± 0.98 on day 3 ($P < 0.05$). **Conclusion:** The optimized succinylcholine nano-gel demonstrated safety, stability, and significant efficacy in alleviating MFPS when utilized in conjunction with phonophoresis. This noninvasive therapy has the potential to enhance the patient outcomes and decrease the manual labor of physiotherapists, warranting validation in larger trials.

Keywords: Myofascial pain syndrome, nanoformulation, novel application, phonophoresis, succinylcholine, topical drug delivery

Introduction

Succinylcholine is a quaternary skeletal muscle relaxant typically found in bromide, chloride, or iodide salt forms. It is commonly utilized as a supplementary agent to general anesthesia to aid in tracheal intubation, provide skeletal muscle relaxation during surgical interventions, and support mechanical breathing. Succinylcholine is a depolarizing neuromuscular blocker that functions at the motor end plate,[1] exhibiting an onset of action within 30 s and a duration of effect lasting 3–5 min. Notwithstanding its clinical efficacy in anesthesia, succinylcholine has not been utilized in the treatment of myofascial pain syndrome (MFPS) attributable to its transitory effects and systemic application.

MFPS is a common musculoskeletal condition marked by hyperirritable loci, referred to as myofascial trigger points (MTrPs), within skeletal muscle. These trigger points are linked to tense muscle fiber bands and elicit pain upon palpation or mechanical stimulation. MFPS is a predominant source of chronic musculoskeletal discomfort, frequently localized to the neck, shoulder, and upper back, and it substantially impacts disability, diminishes quality of life, and exacerbates the global healthcare burden.[2-4]

Topical preparations provide numerous benefits for musculoskeletal problems, such as enhanced patient adherence,

Access this article online

Quick Response Code:

Website: https://journals.lww.com/BVMJ/

DOI: 10.4103/BVMJ.BVMJ_107_25

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Submitted: 27-09-2025 **Revised:** 12-11-2025
Accepted: 02-12-2025 **Published:** 31-12-2025

How to cite this article: Jain S, Goyal RK, Aggarwal G, Ajmera P. Efficacy of novel application of succinylcholine nanoformulation administered by phonophoresis for myofascial pain syndrome: Single-arm phase zero clinical trial. Bhar Vid Med J 2025;5:212-6.

decreased systemic adverse effects, evasion of first-pass hepatic metabolism, and direct administration to the target location.[5-7]

Conventional management strategies include pharmacological agents (nonsteroidal anti-inflammatory drugs, muscle relaxants, and antidepressants), local injections (anesthetics, corticosteroids, and botulinum toxin), physiotherapy, and dry needling. Nonetheless, each method possesses limitations: Systemic medications include risks of unwanted systemic effects and dependency; injections are intrusive and may not be well-received; and physical therapy frequently necessitates numerous sessions with inconsistent results.[2,8]

In light of these deficiencies, there is an expanding demand in noninvasive, locally acting medicines that deliver good pain relief while reducing systemic exposure. Topical medication administration, particularly when integrated with methods such as phonophoresis, signifies a promising approach for augmenting therapeutic success in MFPS.[9,10]

Topical administration techniques, including creams, ointments, gels, and sprays, have demonstrated efficacy in numerous dermatological and inflammatory disorders.[11-13] Gels offer faster medication release and skin penetration relative to creams (Azagury *et al*., 2014). Moreover, the integration of topical medication delivery with ultrasound (phonophoresis) augments skin penetration.[14,15]

Carbopol, a synthetic high-molecular-weight polymer of acrylic acid, is one of the most widely used gelling agents in pharmaceutical formulations. When neutralized, it forms a clear, stable hydrogel with favorable rheological properties, including high viscosity at low concentrations and excellent spreadability. These characteristics make it an ideal vehicle for topical and transdermal drug delivery. Carbopol-based gels not only provide patient compliance due to their smooth, nongreasy texture but also facilitate enhanced drug permeation through the skin. Importantly, Carbopol gels are highly suitable for phonophoresis, as they serve both as an ultrasound coupling medium and a controlled drug delivery system. This dual functionality makes them particularly valuable in physiotherapy, where they can reduce the need for intensive manual techniques such as myofascial release and stretching, thereby supporting both patient care and therapist well-being.[11,16]

Considering these benefits, we posited that a nanoformulation of succinylcholine in a gel matrix, tailored for phonophoresis, would deliver effective analgesia in individuals with MFPS. The primary objective of the study is to develop and optimize a stable nanoformulation of succinylcholine gel for a novelphonophoretic drug administration and secondarily, to assess its initial clinical effectiveness in alleviating pain in patients with MFPS impacting the upper trapezius muscle, caused due to active MTrPs.

Methods

Formulation development

A gel-based nanoformulation of succinylcholine was developed utilizing varying concentrations of carbopol 934 and carbopol 940. The formulation comprised antioxidants, polyols, chelating agents, nonvolatile solvents, preservatives, penetration enhancers, pH-adjusting agents, and pharmaceutically acceptable excipients.[11]

Preparation of optimized gel base

Carbopol 934 was hydrated in demineralized water with continuous stirring. Disodium edetate and triethanolamine were prepared separately and added to adjust the pH to ~7. Preservatives (methyl and propyl parabens) were dissolved and incorporated with propylene glycol as a moistening agent.

Six formulations of succinylcholine gel (F1–F6) were developed utilizing different amounts of Carbopol 934 and Carbopol 940 as gelling agents, with each formulation comprising 2.5% succinylcholine. Formulations F1 to F3 utilized Carbopol 934 at the concentrations of 0.75%, 1%, and 1.5%, respectively, whereas F4 to F6 employed Carbopol 940 at the same corresponding concentrations. Each formulation included triethanolamine (1.5 g) as a neutralizing agent, disodium ethylenediaminetetraacetic acid (0.005 g) as a chelating agent, propylene glycol (3 g) as a humectant, and the preservatives methyl paraben (0.4 g) and propyl paraben (0.1 g), with demineralized water added to achieve a total weight of 100 g of gel. Formulation F2, containing 2.5% succinylcholine and 1% Carbopol 934, demonstrated superior viscosity, homogeneity, pH stability, and extrudability, leading to its selection for further physicochemical, safety, and clinical assessments.[17]

Physicochemical evaluation

The formulations were evaluated for extrudability, pH, viscosity (using a Brookfield viscometer), and homogeneity.

In vitro permeability

Permeation was tested using Franz diffusion cells with a cellophane membrane and Phosphate-Buffered Saline (PBS) (pH 7.4) as the receptor fluid at 32°C ± 0.5°C. The drug concentration in the receptor fluid was measured at the intervals of up to 5 h.

Safety evaluation

Skin irritation testing was performed on six healthy volunteers. A 1 g sample of gel was applied to a 2-cm^2 area of the hand and observed for 24 h for erythema, itching, edema, or irritation.

Study design

A single-arm, phase 0 pilot clinical trial was conducted, commenced after obtaining ethical approval from the Institutional Ethics Committee of Delhi Pharmaceutical Sciences and Research University (Ref. DPSRU-BREC/2021/A/025). A convenience sample of 35 patients was recruited from the Outpatient Physiotherapy Department of Delhi Pharmaceutical Sciences and Research University from the last week of January 2021 to March 2021. No formal sample size calculation was performed given the exploratory nature of this pilot study.

Participants aged 18–45 years with MFPS resulting from active MTrPs in the upper trapezius muscle, diagnosed according to Travell and Simons' criteria, including the existence of a

palpable taut band within the muscle, a hypersensitive tender nodule within that taut band, an occurrence of the patient's referred pain pattern upon manual compression, and a local twitch response induced by snapping palpation.[10] Furthermore, experiencing nonspecific neck discomfort for over 3 weeks, a VAS pain level >4, and a Neck Disability Index exceeding 25, were eligible to participate upon providing informed consent.

The exclusion criteria comprised congenital spinal abnormalities, spinal stenosis, radiculopathy, previous spinal surgery within the past year, or invasive spinal operations conducted in the preceding 4–6 months. Individuals with active malignancies, inflammatory rheumatic diseases, uncontrolled diabetes, severe cardiovascular, neurological, or renal illnesses, hemophilia, pregnancy, corticosteroid or anticoagulant use, dermatological issues at the treatment site, or psychological disorders were excluded.[18,19]

Intervention was the application of 1 g of succinylcholine gel (equal to 25 mg of the medication) at the site of the trigger point, succeeded by ultrasonic treatment (1.2 W/cm^2, 1 MHz, pulsed mode, 5 min), with pain intensity assessed using the Visual Analogue Scale (VAS). The optimized formulation (F2) demonstrated favorable physicochemical characteristics, excellent permeation, and dermatological safety.

Procedure

Upon enrolling the participants, preliminary information was collected, including demographic details and preintervention VAS scores for pain, after the identification and validation of the active trigger site. The participants were explained about all the procedures and asked to sit in the comfortable position.[18]

The MTrP was identified, exposed, and sanitized with an alcohol swab 1 g of succinylcholine gel was administered topically to the targeted trigger point of the participant and was gently rubbed with gloved hand for approximately 8–10 s to facilitate absorption before initiating the ultrasound application, ensuring that the medication was not disseminated beyond the MTrP.[4,8]

Therapeutic ultrasound was delivered at an intensity of 1.2 W/cm^2 with a 1 MHz frequency in pulsed mode for 5 min per session.[20] Outcome assessments of pain intensity were conducted at baseline, 15 min, 30 min, 2 h, day 2, and day 3.

Data were analyzed using the SPSS software (version 20.0; IBM Corp., Armonk, NY, USA). Descriptive statistics were used to summarize the outcome variable – pain intensity (VAS scores), measured at multiple time points and were expressed as mean ± standard deviation. Normality of the data was assessed using the Shapiro–Wilk test. Pre- and postintervention Visual Analog Scale (VAS) scores were compared using paired *t*-tests. A two-tailed $P < 0.05$ was considered statistically significant.

Results

Formulation development and optimization

Among the six formulations prepared, F2 (carbopol 934) demonstrated the most favorable physicochemical profile. It exhibited smooth texture, translucency, excellent extrudability, viscosity of 4.123 poise, a pH range of 7.1–7.3, and stability under the varied storage conditions. These properties made F2 the optimized formulation for further testing.

In vitro permeability

The optimized formulation demonstrated effective permeation across the cellophane membrane [Table 1], confirming its potential for transdermal delivery.

Dermatological safety evaluation

Topical application of the optimized formulation in volunteers revealed no signs of erythema, edema, itching, or irritation, confirming its dermatological safety.

Pilot clinical evaluation and effect of the formulated gel on pain intensity

Succinylcholine gel administered via phonophoresis produced a marked, time-dependent reduction in pain intensity. Of 35 participants recruited, 29 completed the study (6 lost to follow-up). All reductions in VAS scores were statistically significant ($P < 0.05$). No adverse events or serious adverse effects were observed. Mean VAS scores decreased significantly from baseline (7.82 ± 0.92) to day 3 (0.46 ± 0.98). Notable reductions were observed at 15 min (5.92 ± 1.51), 30 min (4.07 ± 2.68), 2 h (2.25 ± 2.62), and day 2 (0.96 ± 1.20) [Table 2]. Findings were not adjusted for any confounding factors, as no additional data on confounding factors was collected.

Discussion

Succinylcholine is a depolarizing neuromuscular blocking drug that binds to nicotinic acetylcholine receptors at the

Table 1: *In vitro* permeation of succinylcholine gel (F2) through cellophane membrane

Time (h)	Cumulative drug permeated (μg/cm^2)
0.25	66.19±14.10
0.5	102.34±18.28
0.75	102.54±8.08
1	132.43±5.46
2	148.79±16.55
3	143.26±20.87
4	194.55±25.59
5	196.86±31.07

Table 2: Effect of phonophoresis with succinylcholine on pain (n=29)

Time point	VAS score, mean±SD
Baseline	7.82±0.92
After 15 min	5.92±1.51
After 30 min	4.07±2.68
After 2 h	2.25±2.62
Day 2	0.96±1.20
Day 3	0.46±0.98

SD: Standard deviation, VAS: Visual Analogue Scale

neuromuscular junction, resulting in temporary depolarization and subsequent flaccid paralysis. Traditionally employed in anesthesia for fast muscle relaxation, localized transdermal administration in small doses facilitates precise regulation of excessive muscle activity without inducing systemic neuromuscular blockade limited systemic use due to its rapid hydrolysis and short half-life.[19,21,22] Phonophoretic augmentation, by sonic cavitation and microstreaming, promotes drug infiltration into superficial and deeper muscle tissues, allowing for localized receptor engagement and a short alleviation of muscle hypertonicity.[20,23] The brief plasma half-life of succinylcholine for 1–2 min, resulting from swift breakdown by plasma cholinesterase, reduces systemic exposure and deleterious effects while facilitating targeted local action.[19] This localized neuromuscular modulation may disrupt the pain–spasm–pain loop typical of myofascial trigger sites, offering effective pain relief without sedation or systemic adverse effects. In this study, succinylcholine was reformulated into a nano-gel designed for topical administration to address muscle hypertonicity associated with MFPS caused by the presence of MTrPs.

The optimized formulation (F2) presented favorable physicochemical characteristics, effective membrane permeation, and dermatological safety, indicating its suitability for phonophoresis. Clinically, its application resulted in a significant, sustained reduction in pain intensity, with improvements evident within 15 min and persisting through day 3. This rapid and lasting analgesic effect supports its potential role in targeting both pain and underlying muscle tension.

These findings are consistent with prior studies demonstrating enhanced transdermal penetration and therapeutic efficacy of phonophoresis.[14,15] Carbopol-based gels, as used here, are recognized for their stability and acoustic coupling efficiency in ultrasound-mediated delivery.[16] Importantly, this is probably the first report to explore succinylcholine for musculoskeletal pain via this modality (patent no. 463571, dated October 30, 2023).[24] This study successfully repurposed succinylcholine into a nanoformulated gel designed for topical administration specifically for the tightened structures, specifically the soft tissues resulted by MFPS.[25-27]

For physiotherapists, this approach offers particular value. Manual myofascial release techniques demand considerable physical exertion, potentially leading to therapist fatigue or soft-tissue strain. A pharmacologically assisted modality such as succinylcholine phonophoresis can reduce therapist workload while providing superior patient outcomes.

The results, however, must be interpreted with caution. The feasibility of application is hampered by the study's pilot design, small sample size, no data on confounding factors and brief follow-up. In order to confirm effectiveness, identify the best treatment parameters, and evaluate long-term safety, larger randomized controlled trials and mechanistic research are required.

Conclusion

The succinylcholine nanoformulated gel delivered through phonophoresis demonstrated excellent physicochemical properties, safety, and significant clinical efficacy in reducing MFPS-related pain specifically aggravated by the presence of active MTrPs. This innovative strategy represents a physiotherapy-oriented, noninvasive, and patient-compliant therapeutic option that could reduce reliance on systemic pharmacological treatments while alleviating therapist fatigue. Phonophoresis with this formulation enables physiotherapists to provide pain relief without exerting significant manual effort, thereby sustaining their own musculoskeletal health while enhancing the patient outcomes.

Ethical consideration

The study received ethical approval from the Institutional Ethics Committee of DPSRU (Ref. DPSRU-BREC/2021/A/025). Written informed consent was obtained from all participants, and ethical standards outlined in the Declaration of Helsinki were followed.

Author's contribution statement

RKG conceived the study, GA developed the formulation, RKG and SJ designed the methodology, conducted the clinical evaluation, PA analyzed the data, SJ and GA prepared the manuscript and proof read by RKG.

Data availability statement

Data would be made available from the corresponding author upon reasonable request.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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