



Efficacy of diclofenac & thicolchioside gel phonophoresis comparison with ultrasound therapy on acute low back pain; a prospective, double-blind, randomized clinical study

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ABSTRACT

Purpose: To investigate the effect of Phonophoresis (PP) with the combination of nonsteroidal anti-inflammatory drugs (NSAID's) and myorelaxant versus routine Ultrasound (US) treatment with non-therapeutic gel on the patients with acute low back pain (ABP).

Methods: Sixty patients with ABP were randomly assigned into 2 groups. In Group 1 (n = 30) US was applied using diclofenac + Thicolchioside gel for 10 min and for a total of 10 sessions. In Group 2 (n = 30) the same US protocol was applied with the same setting and timing with Group 1 using US gel that does not contain any pharmaceutical ingredient. Evaluation parameters were Visual numeric scale (VNS), Oswestry Disability Index (ODI), and Shober test.

Results: Comparison of the results obtained from the two groups before treatment and at second (W2) and sixth weeks (W6) posttreatment showed significant improvement in all parameters in both groups (p < 0.05). Comparison of the groups showed significantly superior improvement in Group 1 for ODI while there was no difference in other parameters at W2. At W6, there was significantly superior improvement in all parameters (p < 0.05) except for Shober test in Group1.

Conclusion: Our results showed that PP treatment is superior than conventional US therapy at short term in ABP patients.

1. Introduction

Low back pain is a frequent form of painful musculoskeletal conditions and it is also a cause of substantial health expense. The prevalence of low back pain has been reported to vary between 49 and 90% and it is expected to increase considerably in the near future as the population becomes more aged globally [33,16]. The clinical presentation of low back pain can be acute, subacute, transient, recurrent, or chronic [8]. Although most cases of acute low back pain (ABP) may resolve spontaneously, recurrent symptoms or persistent functional limitations are not infrequent. When the high prevalence of recurrent and chronic low back pain and the associated treatment costs and the socioeconomic burden are taken into account, it becomes obvious that timely and proper interventions for acute back pain are crucial to prevent recurrences and development of chronic low back pain [8]. While nonsteroidal anti-inflammatory drugs (NSAID's) and

myorelaxants are known to be far more superior than simple analgesics [21,2] in acute back pain treatment, systemic use of the former agents may cause substantial side-effects that may restrict oral intake in some patients [27]. Topical application of NSAID's and myorelaxants have been shown to be as effective as the oral forms but without the gastrointestinal side-effects [9]. Combination of NSAID's and myorelaxants are frequently used in acute back pain treatment. In a study performed in the patients with acute low back pain, aceclofenac-tizanidine combination was found to be safe and more effective than aceclofenac alone [25].

Clinical effectiveness of a topical agent obviously depends on its penetration through the epidermis into the deeper layers [6]. The skin has been used as a route for administration of pharmacological agents for a long time and many drug delivery techniques that use some form of energy to enhance absorption and penetration of these agents through the skin have been explored [22,26]. Phonophoresis (PP)

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depends on the use of ultrasound (US) to help introduce such agents with a wide range of molecular weight drugs through the skin and into the soft tissue below. PP, is a method of increasing the penetration of drugs from the skin that usually poor transcutaneous absorption/permeation profiles with conventional methods [29]. The technique has been widely used in sports medicine for the last six decades [22]. Two recent studies have shown positive effect of PP with capsaicin on pain, functional status, and quality of life of the patients with chronic neck and back pain [13,12].

Besides pharmacological treatment, several physical therapy agents such as electrotherapy and US are also routinely used in back pain. Therapeutic US is known to generate both thermal and non-thermal effects which have been shown in a number of randomized controlled studies to be effective in reducing pain and improving function in chronic back pain [14,3,11]. However, a recent Cochrane review has failed to show superiority of US for improving pain or quality of life in patients with non-specific chronic LBP [15]. There is even less published research on assessment of US in acute back pain, thus there is also a lack of consensus as to the efficacy of US in ABP [36,34].

The purpose of this study is to investigate the effect of PP with the combination of NSAID and myorelaxant versus routine US with non-therapeutic gel in the patients with acute back pain not accompanied by radiculopathy.

2. Patients and methods

2.1. Study design

This prospective, double-blind randomized controlled study was performed in the Physical Therapy and Rehabilitation Outpatient department of our Hospital, Bursa, Turkey.

The patients who were admitted to our outpatient department with the complaint of ABP for a maximum of 12 weeks but without radiculopathy were assessed during a period of 6 months. Sixty patients who met the criteria described below were included in the study.

The inclusion criteria were: (1) Being 20–50 years old, (2) Having had low back pain for a maximum of 12 weeks, (3) Not to have had any physical therapy in the past 12 weeks, (4) Not to have any another etiological factor (rheumatologic disease, infection, etc.) which may cause low back pain.

The exclusion criteria were: (1) Pain due to established radiculopathy, (2) Compression fracture of the spine, (3) NSAID or myorelaxant use during the past 10 days (4) Previous surgical operation for low back pain (3) Any systemic condition contraindicating the use of ultrasound (unstable hypertension, heart failure, pregnancy, etc.)

The informed consent from the patients and local ethic committee approval were obtained.

2.2. Randomization and study protocol

The patients were randomly assigned into 2 groups using random number table. Group 1 ($n = 30$) was the PP group. In this group, first Diclofenac + Thiocolchicoside gel was applied circularly with a thickness of 2–3 mm. Then US was applied to lumbar paravertebral area on both sides (1 W/cm^2 , 1 MHz) while patients were in the prone position for 10 min and for a total of 10 sessions for 2 wk using a BTL-4000 Premium US device (BTL Industries, Stevenage, Hertfordshire, UK) with a 5-cm^2 1-MHz probe continuously in a circular movement, any other USG gel was not used in group 1. Group 2 ($n = 30$) was the conventional US group. The same US protocol was applied in exactly the same setting and timing with Group 1 using US gel. BTL as a company & SWT Ultrasound Gel connecting medium US gel was used that does not contain any pharmaceutical ingredient.

In both groups, evaluation of the patients before treatment and 2 (W2) and 6 (W6) weeks after treatment was performed by the same investigator who was unaware of which group the patients belonged to.

Patients were also unaware which gel was used during US application.

2.3. Evaluation parameters

2.3.1. Pain severity

The patients were asked to evaluate their pain at rest and during movement on the Visual Numeric Pain Scale (VNS) with 0 representing no pain and 10 representing the worst pain imaginable [31].

2.3.2. Oswestry Disability Index

Oswestry Disability Index (ODI) is a questionnaire consisting of 10 items that inquire daily life activities. These items are intensity of pain, ability to self-care, lifting, ability to walk, ability to sit, sexual function, ability to stand, social life, sleep quality, and ability to travel. Each item is scored on a scale of 0–5. A score of 0–14 means minimal, between 15 and 29 moderate, and between 30 and 50 severe disabilities. Turkish form of the questionnaire was previously found reliable and valid [41].

2.3.3. Schober test

The patient is examined in the standing position. The point of lumbosacral junction is marked with a horizontal line and a second line parallel and 10 cm above to the first line is drawn. Next, the patient is instructed to bend forward with the knees fixed and the resulting change in the distance between these two parallel lines is measured [30].

2.4. Statistical analysis

An IBM SPSS 22.0 Statistics software was used to analyze the data obtained in the study. For categorical variables, Fisher's exact test was used to assess differences in the comparison of gender. Descriptive statistics were expressed as mean \pm standard deviation for normal distribution and as median (minimum-maximum) for non-normal distribution of the variables. The normality of the variables was tested with Shapiro-Wilk test. For intragroup analysis, paired t test or Wilcoxon test was used. For intergroup analysis, Mann-Whitney U test was used after calculating the percentage changes for measured values and the difference scores for overall score values. Data were investigated within 95% confidence interval and p lower than 0.05 was considered significant.

3. Results

Two patients from group 1 and 4 patients from group 2 lost to follow up. Evaluations were completed with 28 patients in group 1 and 26 patients in group 2. There was no statistically significant difference between the two groups in demographic data, symptom duration, baseline VNS at rest, VNS during motion, ODI scores and Schober test ($p > 0.05$) (Table 1).

In the Group 1 and in the group 2, statistically significant improvements were observed in all parameters assessed at week 2 and week 6 ($p < 0.05$) (Table 2).

Intergroup comparisons revealed statistically significant differences in favor of the Group 1 in ODI at week 2. At week 6, there was significantly superior improvement in all parameters except for Schober test in group 1 ($p < 0.05$) (Table 3).

We did not observe any side effects due to treatment.

4. Discussion

The results of our study showed that significant improvement was obtained for all parameters in both groups compared to pretreatment measurements. However, W6 evaluation was found to be in favor of the PP group.

US application is regarded as one of the most important physical therapy modalities in musculoskeletal pain treatment. US is known to

Table 1
Comparison of the demographic characteristics of the patients and pre-treatment evaluation parameters.

	Group 1 (n = 28)	Group 2 (n = 26)	p value
Age (years)	44.25 ± 13.52	41.42 ± 11.81	0.384
Gender	Female	17 (%64)	1
	Male	9 (%35)	
BMI (kg/m ²)	26.80 ± 4.53	25.70 ± 4.08	0.343
Symptom duration (day)	20 (1–60)	15 (3–90)	0.752
VNS at rest	5 (0–9)	3 (0–9)	0.112
VNS during motion	8 (4–10)	8 (3–10)	0.717
ODI	24 (12–36)	23 (12–47)	0.142
SCHOBER test	4.75 (3–6)	5 (0–6)	0.396

VNS: Visual numeric pain scale; BMI: Body Mass Index; ODI: Oswestry Disability Index.

The values were presented as mean ± standard deviation or median (maximum–minimum).

accelerate the rate of local metabolism, increase circulation, and support regeneration via its thermal and mechanical effects. We used thermal stimuli parameters for USG application in this study.

Significant pain reduction obtained in our study may be attributed to the analgesic effect of US via both thermal and non-thermal mechanisms [5]. Mardiman et al. [23] have shown the increase in the pain threshold using dolorimeter in the pain-free subjects who received real US compared to sham US. US treatment may also reduce pain by modulating nociceptive neurons. It has been shown in an experimental study performed on the rats with peripheral inflammatory arthritis that US treatment has caused substantial suppression of NO synthetase-like neurons in the spinal cord [17]. US-induced pain relief has been attributed to the increase in capillary permeability, tissue metabolism, and fibrous tissue extensibility [5]. Deep heating provided by US can increase extensibility of tendons, ligaments and joint capsules [5,19]. The role of gate-control pain relief mechanism has also been implicated in the explanation of US therapeutic effect on Aδ and C-fiber pathways through activation of Aα and Aβ mechanoreceptors [40].

While the accumulation of such results has popularized therapeutic US treatment for various musculoskeletal disorders in the daily practice, its efficacy is still being debated based on several contradictory reviews. Rutjes et al. [32] pointed out in a review of a large number of studies on knee OA to the low quality of the evidence presented which made it difficult to be certain about the magnitude of the effects of US. They thought US could indeed be beneficial in knee OA treatment but suggested appropriately designed trials of adequate power to have a definitive opinion.

We observed significantly superior improvement in the PP group particularly in the long-term. Pain and muscle spasm frequently co-exist in acute back pain and the clinical picture is dominated by a vicious cycle of pain-spasm-more pain-more spasm in most patients. Thus, myorelaxants should be used besides analgesics in treatment [1]. However, serious side-effects of NSAID's particularly on the gastrointestinal system have been observed not infrequently and oral intake of

Table 2
Intra-group comparison of post-treatment (2nd and 6th weeks) values.

		Week 2 (W2)	Week 6 (W6)	p value (W2-W0)	p value (W6-W0)
VNS at rest	Group 1 (n = 28)	2 (0–6)	1 (0–6)	< 0.001	< 0.001
	Group 2 (n = 26)	2 (0–8)	1 (0–4)	0.004	0.002
VNS during motion	Group 1 (n = 28)	3.5 (1–10)	3.0 (0–8)	< 0.001	< 0.001
	Group2 (n = 26)	5 (0–10)	4 (0–7)	< 0.001	< 0.001
ODI	Group 1 (n = 28)	9.0 (0–38)	2 (0–33)	< 0.001	< 0.001
	Group 2 (n = 26)	11 (0–29)	10 (0–25)	< 0.001	< 0.001
SCHOBER test	Group 1 (n = 28)	5 (4–6)	5 (4–6)	< 0.001	< 0.001
	Group 2 (n = 26)	5 (3–6)	5 (4–6)	0.028	0.004

VNS: Visual numeric pain scale; ODI: Oswestry Disability Index, bold values indicate that p < 0.05 statistically significant. The values were presented as median (maximum–minimum).

Table 3
Comparison of the difference scores between the groups.

	Week 2		p value	Week 6		p value
	Group 1	Group 2		Group1	Group 2	
VNS at rest	−1.0 (−5 to 8)	−2.5 (−6 to 2)	0.056	−3.0 (−7 to 0)	−1.0 (−6 to 3)	0.041
VNS during motion	−3.0 (−8 to 5)	−4.0 (−8 to 0)	0.139	−5.0 (−19 to −2)	−3.5 (-9 to 1)	0.023
ODi	−11.0 (−29 to −1)	−15.0 (−26 to 2)	0.023	−22.0 (−31 to −2)	−13.0 (−29 to −2)	0.007
SCHOBER test	0.0 (-2 to 5)	0.50 (0 to 2)	0.143	0.50 (0 to 2)	0.0 (0–5)	0.158

VNS: Visual numeric pain scale; ODI: Oswestry Disability Index, bold values indicate that p < 0.05 statistically significant.

The values were presented as median (maximum–minimum).

myorelaxants may cause sedation and diarrhea to a varying extent in some patients [1,39]. In a recent review, topical NSAID's were found to have a much less incidence of side-effects compared to the oral forms [9]. Obviously, the efficacy of a topical agent is dependent first on its effective absorption through the skin surface and then its ability to reach the target tissue via both the systemic circulation and direct penetration. While the skin provides an essential barrier for limiting exchanges with the external environment and penetration of exogenous compounds, it nevertheless may allow for administration of several drugs such as estradiol, nitroglycerin, and fentanyl, which are effective in much deeper tissue planes [22].

Percutaneous administration is known to provide stable plasma levels without passage through the liver and gastrointestinal tract [22]. All topical drugs are transported through the stratum corneum to the deeper layers of the epidermis and finally into the dermis, where they are presented to the systemic circulation. Un-ionised drugs easily pass through the lipophilic stratum corneum whereas aqueous agents penetrate through deeper epidermal layers. Consequently, both hydrophilic and hydrophobic properties are necessary for optimal penetration of a particular topical agent through all layers of the skin [38].

A number of substances have previously been investigated for enhancement of drug absorption through the skin [38]. Phonophoresis (PP) is the method of employing US as a physical agent to enhance penetration of the topical agents transdermally to the subcutaneous tissues by increasing the cell permeability via thermal effects and induction of local vasodilatation [22,29,28].

The effects of PP have been summarized as enhancement of skin permeability resulting from increased fluidity of intercellular lipids by heating or mechanical stress, enlargement of the intercellular space, cavitation through corneocytes and keratinocytes, and movement of the drug and the vehicle through the permeabilized skin by convection. However, this increase in skin permeability to drugs may not persist beyond the period of PP application [22].

Several authors have investigated the optimal rise in surface temperature of the skin necessary for enhancement of absorption of the drugs. Miyazaki et al. [24] showed a rise of 6 °C with 1 MHz for a fairly low intensity of 0.25 W/cm² and 12 °C for an intensity of 0.75 W/cm², suggesting the rise in skin temperature as a major factor to explain the increase in percutaneous absorption in the frequency range of 1–3 MHz and in the continuous mode. On the other hand, in a number of in vitro studies using 1-MHz continuous US at spatial peak doses equal to or higher than 1 W/cm², cell damage due to cavitation was observed. High-intensity US application is also known to generate a feeling of warmth and cause pain. We made our choice of US dose in our study in accordance with the above suggestions in order to optimize beneficial thermal effects and avoid tissue damage. A study on human muscle by Draper et al. [10] has shown that the temperature in the gastrocnemius muscle at a depth of 3 cm was increased by 5 °C. Following 10 min of 1-MHz continuous US at an intensity of 1.5 W/cm² with a 20-cm² transducer applied to a skin area of 80 cm². These researchers suggested confining the area treated and applying ultrasound for at least 7 or 8 min in order to achieve a rise in temperature. We applied US for a duration of 10 min in our study.

In one of the recent randomized controlled studies on the efficacy of PP on musculoskeletal system, Ay et al. [4] showed significant improvement in pain, disability, and range of motion of neck with both diclofenac PP and US in myofascial pain syndrome. In another randomized controlled study, diclofenac PP showed better improvement over US treatment in reducing pain in myofascial pain syndrome [35]. Üstün et al. [37] reported superior improvement with eutectic mixture of local anesthetics cream (EMLA) PP over conventional US therapy in the parameters of pain and neck disability in myofascial pain syndrome.

Kozanoglu et al. [20] obtained significant improvement in pain severity and walking performance both with 5% ibuprofen PP and US but failed to show the superiority of PP in knee osteoarthritis. In a study conducted on patients with acute calcific tendinitis of shoulder, diclofenac PP with methylprednisolone injection provides better shoulder function and excellent pain reduction [7]. Klaiman et al. [18] found no additive effect of 0.05% fluocinonide, PP in the patients with tendinitis, epicondylitis, and tenosynovitis. In another study performed in the patients with carpal tunnel syndrome, ketoprofen PP was found to be effective in pain relief as a supplementary treatment to splinting [42]. There are few studies on evaluation of the effect of PP in back pain. Durmus et al. [13] compared US plus exercise, PP plus exercise, and exercise alone for treatment of 60 chronic low back pain patients in a study where they applied US with 1 MHz frequency at 1.5 Wt/cm² for 10 min and Gluco Gel containing capsaicin as the topical agent. They observed the best improvement in the group that received PP plus exercise and suggested that that regimen was optimal for improving pain, disability, depression, and sleep quality in the patients with CNP. Since the patients in our study had acute pain, we did not include exercise in our treatment protocol in any group.

Another difference of our study is that the combination of a NSAID and a myorelaxant was used for the first time to the best of our knowledge. Since muscle spasm accompanies acute low back pain in most cases, the positive results obtained in our study can also be attributed to the beneficial effect of the myorelaxant.

5. Conclusion

Although the relatively low number of the patients should be noted as a limitation of our study, the results have shown the superiority of PP treatment according to the evaluations performed at the end of the sixth week. We suggest that further studies with larger patient groups are required for better understanding of the effects of phonophoresis in acute and chronic back pain.

Conflict of interest

Lale Altan, Meliha Kasapoğlu Aksoy, Esra Kösegil Öztürk declare that they have no conflict of interest.

Ethical statement

Ethical approval was obtained from institutional research committee and with the 1964 Helsinki declaration and comparable ethical standards.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.ultras.2018.08.008>.

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