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Investigating the effectiveness of artcure transdermal diffusional patch in patients with cervical disc herniation: A randomized placebo-controlled study

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Abstract

This study aims to investigate the effectiveness of Artcure Diffusional Transdermal Patch treatment on pain and functional status in patients with cervical disc herniation. A total of 48 patients (15 males, 33 females; mean age 48 years; range 20 to 60 years) who were diagnosed with cervical disc herniation were included in this double-blind, randomized, placebo-controlled study. Participants were randomized into 2 groups. Artcure Transdermal Patch was implemented in the 1st Group, and a placebo transdermal patch was given to the 2nd Group. Artcure and placebo patches were applied once to both patient groups, remaining for 24 hours as was recommended in their usages. All individuals were examined at the onset, in the 4th week, and the 12th week. Visual Analog Scale (VAS) was used to evaluate pain, neuropathic pain intensity was measured using the Leeds Assessment of Neuropathic Symptoms and Signs Scales (LANSS), and the functional level was measured by the Neck Pain and Disability Scale (NPDS). It was determined that the pain level decreased, neuropathic symptoms reduced, and functional level improved compared to initial parameters in the diffusional transdermal patch group. There were significant differences among the groups in the 4th and 12th weeks concerning pain, neuropathic symptoms, and functional status, and it was also determined that this difference was conspicuous in the transdermal diffusional patch group. Based on these data, Artcure Diffusional Patch may be an alternative for conservative treatment of patients with cervical disc herniation.

Keywords: Cervical disc herniation, diffusional transdermal patch, artcure, neuropathic symptoms

Introduction

Cervical disc herniation is a disease that occurs with anatomical and physiological changes of the intervertebral disc upon the exposure of the cervical region to mechanical and traumatic stresses [1]. It results from a wide range of factors such as repetitive micro-traumas, heavy lifting, occupational activities, diabetes, smoking, long-term driving, and congenital spinal diseases. The disease affects about 45% of individuals in the general population [2,3]. It is more common in the middle and old age group as pathological changes in intervertebral discs. Degeneration increases with a gradual decrease in the water content of the disc structure. It is more common in women than in men [4].

Conservative treatments and surgical methods are used in its treatment. Conservative treatment includes pharmacological therapy, physical therapy agents such as superficial and deep heaters [hot pack (HP), therapeutic ultrasound (US), etc.], electrotherapy [transcutaneous electrical nerve stimulation (TENS), etc.], exercise programs, injections, orthoses, and acupuncture applications [5].

As an alternative to other medical treatments, transdermal diffusional patch treatment has recently started to be used in cervical disc herniation patients, who could not benefit from classical conservative treatments. Artcure transdermal diffusional patch contains low-density herbal lipids. These lipid molecules are in the structure of terpene and terpenoid in a gel consistency. It can be applied in median or paramedian disc protrusion and extrusion cases. The herniated disc begins to lose its water content, and tears emerge on the outer annulus fibrosus fibers. The disc content becomes hyperosmolar. The terpenoids in the diffusional transdermal patch content diffuse through the polar cavities of the herniated disc, which is in the collagen structure, into the nucleus pulposus. Because of these low-density lipid molecules, intra-disc osmolarity decreases to 150-200 mOsm and the inner disc becomes

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hypo osmolar and the surrounding tissue becomes hyperosmolar. The liquid molecules in the disc content move outward with this diffusion difference, and the herniated disc fragment begins to shrink. In this way, pain and other neuropathic symptoms can recede. The most common side effect is allergic or irritable skin reactions observed in the application area [6,7].

When the literature was examined, it was observed that there was no placebo comparative study investigating the effectiveness of transdermal diffusional patch treatment on pain and functional status in cervical disc herniation. This study aimed to investigate the effectiveness of diffusional transdermal patch treatment on pain, neuropathic symptoms, and functional status in individuals with cervical disc herniation.

Materials and Methods

The participants of this study were 48 patients who were between 20-60 years old and who were admitted to the Physical Medicine and Rehabilitation Outpatient clinic of our hospital. The study was carried out following the Helsinki Declaration and approved by the Inonu University Clinical Research Ethics Committee with the number 2018/54.

All participants were informed about the study and their written consents were taken. It was calculated that a total of 48 individuals should be enrolled, with at least 24 subjects from each group when $\alpha = 0.05$ and $1 - \beta = 0.80$ were taken in the power analysis. Inclusion criteria for the study are having pain spreading to and around the neck, having neuropathic pain and/or sensory deficit in the upper extremities, and having at least one protrusion, extrusion, sequestrum disc herniation in cervical MRI imaging. The exclusion criteria are having another disease that creates pain around the neck apart from the cervical disc herniation, having a previous cervical surgery, asthma, or a history of atopic skin disease, having been diagnosed with diabetes mellitus, pregnancy, or lactation status, having a muscle in the upper limb muscles decreased to or under 3/5 and having cognitive impairment.

The study was planned as a prospective, randomized, and double-blind study. The same clinician who was blind to the treatment method performed pre-treatment and post-treatment evaluation, and the same nurse performed patch treatment.

Patients participating in the study were randomized into 2 groups by the sealed envelope method. Artcure transdermal patch was implemented to the first group, and a placebo transdermal patch was applied to the second group. On all the participants, the transdermal patch was fixed in the cervical area with hypoallergenic tapes and was applied for 24 hours. Patients were offered bed rest in the supine position during the application, except for their basic physical needs. For the first few hours, patients were monitored, and those who did not have an allergic reaction were sent home. Patients were told that non-steroidal anti-inflammatory drugs, myorelaxant drugs should not be used, and/or cold/hot application should not be done. They were informed about allergic reactions that may occur during or after the implementation, emphasizing that, in case of any systemic allergic symptoms, the application should be discontinued by removing the tapes and should apply to the emergency department of the nearest hospital. They were told that after 24 hours, they could remove the hypoallergenic tapes with the help of their relatives and continue their daily lives by removing the patch.

To assess the effectiveness of the treatment, patients were evaluated before treatment, 4, and 12 weeks after treatment for pain, functional status in daily life activities, and neuropathic symptoms. Visual Analog Scale (VAS) was used to determine the pain status of patients [8]. They were asked to show the pain they felt on a 10 cm ruler. In the assessment, the value “0” indicates no pain, while the value “10” indicates the most severe level of pain. Distances between points were recorded in centimeters.

Neck Pain and Disability Scale (NPDS) was used to assess how neck pain affects performing daily life activities. The Neck Pain and Disability Scale (NPDS) consists of 20 parameters. Each item is scored between 0 and 5 points. Bicer et al. [9] conducted its translation and adaptation to the Turkish language. Parameters evaluate the severity of pain, the effect of pain on daily basic functional activities, and their relationship with emotional changes. In this way, it measures the effects of neck pain on the quality of daily life and disability. The total score consists of the sum of the scores in each item, ranging from 0 to 100.

Whether chronic pain that can spread to the upper extremities is of neuropathic origin was evaluated through the Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale (LANSS). LANSS consists of a first part, which is filled by the patient considering his/her neuropathic symptoms, and a second part, which includes a brief physical examination of the doctor. In the first part, five questions answered by the patients identify complaints related to their neuropathic pain, while the physical examination in the second part is applied to detect whether there is any allodynia by touching on painful and painless areas using pieces of cotton [10].

Statistical analysis

Statistical analysis was conducted through the SPSS (Statistical Package for Social Sciences) for Windows 24.0 (SPSS Inc, Chicago, IL). Descriptive statistics were described as mean±standard deviation and percentage. Pearson Chi-Square Test and Fisher's Exact Test were used to evaluate categorical variables. Whether the variables were normally distributed was evaluated using visual and analytical methods (Shapiro-Wilk Test). In statistical analyses between two independent groups, the independent group’s t-test was used for variables with normal distribution, and the Mann-Whitney U test for variables without normal distribution. In comparing the pre-treatment and post-treatment values between two dependent groups, the independent t-test was used for variables with normal distribution, and Wilcoxon signed-rank test was used for the variables without normal distribution. In all statistical analyses, the significance value of p was taken as 0.05.

Results

48 patients (24 patients in each group) aged 20-60 years were included in the study. The average age of all patients participating in the study was 48.33±8.99 years, 68.75 % (n=33) of whom were female and 31.25 % (n=15) were male (Table 1).

Radiologically, 81.25% (n=39) of the participant patients had protruded disc herniation and 18.75% (n=15) had extruded disc

herniation (Table 1). Groups of patients with apparent cervical spondylosis or spinal stenosis were not included in the treatment. Of the patients, 47.9% (n=23) were treated for one herniated disc, 37.5% (n=18) for two herniated discs, 12.5% (n=6) for three, and 2.08% (n=1) for four discs. Radiologically, 27.08% (n=13) of the participant patients with cervical disc herniation had central disc herniation, and 72.91% (n=35) had posterolateral disc herniation. Both groups were similar concerning age, gender, type of cervical disc herniation, and localization (P>0.05) (Table 1).

Table 1. Demographic data and baseline values of outcomes

		Artcure	Placebo	p
		n=24(50)	n=24(50)	
Age		46.75±8.09	49.91±9.72	0.794 [a]
Gender	**Female**	15(62.5)	18(75)	0.350 [b]
	Male	9(37.5)	6(25)	
Type of Herniation	**Protrusion**	18(75)	21(87.5)	0.267 [b]
	Extrusion	6(25)	3(12.5)	
Herniation Localization	**Central**	8(33.3)	5(20.8)	0.330 [b]
	Posterolateral	16(66.6)	19(79.16)	
Number of Herniation	**Single**	13(54.16)	10(41.66)	0.055 [b]
	Multiple	11(45.83)	14(58.33)	

a: Independent t test b: Pearson Chi-Square test

Intra-group and inter-group average VAS values for pre-treatment, 4th and 12th post-treatment weeks are given in Table 2. It was determined that there was a significant decrease in the VAS values at the 4th and 12th weeks in the 1st group of Artcure patients compared to the 2nd group of placebo patients (p<0.05). In the placebo group, the VAS values at the 4th and 12th weeks were similar (p>0.05).

Although there was a significant difference concerning the NPDS values between the pre-treatment and 4th and 12th post-treatment weeks in the Artcure group, there were no significant changes in patients in the placebo group concerning the values of pre-treatment and 4th and 12th post-treatment weeks (p>0.05) (Table 3).

Intra-group and inter-group averages of the LANSS values for pre-treatment, 4th, and 12th post-treatment weeks are given in Table 4. Evaluating the VAS values at the 4th and 12th post-treatment weeks between the groups, it was determined that there was a significant difference in favor of the Artcure group (p<0.05). However, it was determined that there was no significant change between the pre-treatment and post-treatment values in the placebo group (p>0.05) (Table 4).

Table 2. Comparison of intra and inter-group VAS parameters

		Artcure (n=24)	Placebo (n=24)	p
NPDS	**Pretreatment**	7.91±0.14	7.83±0.14	0.685[a]
	4th week	3.83±0.50	7.87±0.23	<0.001[a]
	12th week	5.50±0.43	8.16±0.20	0.001[b]
	p	P1: <0,001[d]	P1: 0.405 [d]	
		P2: <0,001[c]	P2: 0.070[c]	
		P3: <0,001[c]	P3: 0.035[c]	

VAS: Visuel analog scale a: Independent T test b: Mann-Whitney U test c: Wilcoxon signed rank test d: Paired sample T test P1: Comparison of pretreatment and 4th week P2: Comparison of pretreatment 12th week P3: Comparison of 4th week and 12th week

Table 3. Comparison of intra and inter-group NPDS parameters

		Artcure (n=24)	Placebo (n=24)	p
NPDS	**Pretreatment**	31.45±0.39	28.41±0.83	0.37[a]
	4th week	17.08±1.93	29.16±1.01	<0.001[a]
	12th week	21.20±1.84	29.91±0.97	0.006[b]
	p	P1: <0.001[d]	P1: 0.09[d]	
		P2: <0.001[c]	P2: 0.1[c]	
		P3: <0.001[c]	P3: 0.68[c]	

NPDS: Neck Pain and Disability Scale [a]: Independent T test [b]: Mann-Whitney U test [c]: Wilcoxon signed rank test [d]: Paired sample T test P1: Comparison of pretreatment and 4th week P2: Comparison of pretreatment 12th week P3: Comparison of 4th week and 12th week

Table 4. Comparison of intra and inter-group LANSS parameters

		Artcure (n=24)	Placebo (n=24)	p
LANSS	**Pretreatment**	16.54±0.66	14.58±0.75	0.113[a]
	4th week	8.54±0.97	15.37±0.83	<0.001[a]
	12th week	11.08±1.05	15.41±0.82	<0.001[b]
	p	p1 <0.001[d]	p1= 0.114[d]	
		p2 <0.001[c]	p2= <0.084[c]	
		p3 <0.001[c]	p3= 0.739[c]	

LANSS: Leeds Assessment of Neuropathic Symptoms and Signs Pain Scale [a]: Independent T test [b]: Mann-Whitney U test [c]: Wilcoxon signed rank test [d]: Paired sample T test P1: Comparison of pretreatment and 4th week P2: Comparison of pretreatment 12th week P3: Comparison of 4th week and 12th week

Discussion

In this study, we investigated the effectiveness of diffusional transdermal patch administration on pain and functional status in patients monitored for cervical disc herniation. Following the administration, we observed significant improvement in the participant patients concerning their pain scores and neuropathic symptoms in the 4th and 12th weeks after the treatment compared to those in the pre-treatment. Although there are many studies in the literature on treatment methods used in cervical disc herniation, there is a limited number of studies investigating the effectiveness of transdermal diffusional patch therapy.

Currently, transdermal patch treatments are often used in many areas such as pain management, post-menopausal hormone replacement, hypertension treatment, and nicotine addiction. However, there is a limited number of studies conducted on its use in disc herniation. The most important limitation of transdermal drug administration is the difficulty in overcoming the stratum corneum barrier in the skin and absorption problems. In recent studies, it has been suggested that terpene and terpenoid molecules, which increase the absorption power and amount especially in transdermal treatment systems, demonstrate nociceptive and anti-inflammatory effects and synergistic effects [7,11]. Furthermore, by osmotic diffusion through the collagenase cavities of the herniated disc, whose structure is impaired, these substances mechanically move into the nucleus pulposus, turning the hyperosmolar disc environment into a hypo osmolar environment. In some clinical and in-vitro studies, osmotic changes were shown to affect cell proliferation [11-15].

The disc medium with decreased osmolarity ceases cell proliferation, preventing the accumulation and synthesis of intermediates in the matrix. In addition, liquid molecules in the disk content move towards the surrounding tissue, which turns into a relatively more hyperosmolar medium. In this way, the diameter and mass of the herniated disc decrease, and the pressure inside the degenerated disc decreases. In this way, improvements can be observed in discogenic pain and radicular symptoms in patients with median and paramedian cervical and lumbar disc herniation [7]. In our study, similar effects were observed in the patients following the administration of Artcure diffusional transdermal patch, there was a significant improvement in neck pain, radicular symptoms spreading to the upper extremities, and general health criteria compared to the pre-treatment status.

In the application of the Artcure diffusional transdermal patch, the patient can easily resume his/her normal life after 24 hours. It has no repetitive use such as every day or several times a day like analgesic transdermal patch treatments. However, if necessary, there may also be a second application after about 2 weeks. Furthermore, unlike other transdermal treatments, it can cause shrinkage in disc diameter as it shows its effect mechanically.

The effectiveness of transdermal patch treatment on discopathy was evaluated by clinical studies. In a prospective randomized placebo-controlled study conducted by Akseki et al. on 49 patients with protruded and extruded lumbar disc herniation, it was determined that, after the transdermal patch administration, there was a statistically significant decrease in the average VAS and Oswestry scores in the 1st and 2nd days and 4th week; additionally, a significant improvement was observed in physical examination results and active joint movement spans compared to the initial state [16]. In general, a significant decrease was observed in the VAS scores of all patients within 48 hours. It was determined that the post-treatment effectiveness was not related to herniation level, the existence of pressure, herniation type, and clinical severity according to the Oswestry scale. Similarly, in our study, it was determined that there was an improvement in the 4th and 12th week-VAS values of the patients, who underwent the transdermal patch treatment.

In a study conducted by Ocak et al., on patients with lumbar discopathy, it was demonstrated that there was a significant reduction and decline in herniated disc size in the lumbar MRI monitoring at the 6th and 14th weeks after transdermal patch treatment [7]. In another clinical study by Cagli et al., the effectiveness of the transdermal patch treatment was evaluated on 30 patients who applied with lumbar and leg pain complaints and who were diagnosed with protruded and extruded disc herniation on MRI examination. In that study, it was determined that there were statistically significant changes in the average VAS and Oswestry scores of the patients in the 24th and 48th hours and at the end of the 1st month after the treatment compared to the pre-treatment status. In addition, 46.7% of patients had a straight leg stretching (SLS) test, 50% had positive femoral nerve stretching (FNS) test, 40% had a paravertebral muscle spasm, in the physical examination conducted at the 1st month after the patch treatment, the SLS test was 23.3%, and the paravertebral muscle spasm was 26.7%. In parallel to these studies, we observed significant improvement in pain, functionality, and neuropathic complaints of patients in our study.

Transdermal Patch Treatment is accepted as an alternative to oral medical treatments owing to its treatment success, patient

compliance, and certain advantages for the patients undergoing the treatment [17]. Oral medications can lose their effectiveness when they have a first-pass effect in the liver and cannot be adequately absorbed in the gastrointestinal tract. Therefore, in such cases, oral medication treatments may need to be given in repeated doses or changed. However, transdermal treatment applications are placed on the skin in the appropriate area, and the drug it contains is released in a controlled manner and joins the circulation system. In addition, not every drug can be administered in this way with transdermal systems, and especially several allergic side effects can lead to difficulty in use. Despite all this, transdermal medical treatments have begun to appear more in scientific studies and literature, especially owing to their advantages such as not causing gastrointestinal symptoms, simple and easy application, and better patient compliance [18]. In our study, patients who had undergone a transdermal patch showed easy adaptation to treatment and did not quit treatment for reasons such as difficulty in use. In addition, no local or systemic side effects were observed, except for dermatitis-like skin reactions.

The reasons for the diffusional transdermal patch treatment can be explained as follows: (I) it is safe owing to its narrow side effect scale and no systemic side effects, (ii) patients have no difficulty in adapting to the treatment, (ii) it is an alternative treatment method for patients with protruded and extruded disc herniation without severe neurological deficits.

There are certain limitations of this study such as the relatively small number of patients participating in the study, the inability to evaluate the results of the application from a radiological point of view since some of our patients cannot perform a control cervical MRI examination for various reasons, and the lack of heterogeneous distribution of gender.

As a conclusion, it was observed that the application of the Artcure transdermal diffusional patch has a positive effect on pain, neuropathic complaints, and functional status of patients diagnosed with cervical disc herniation; based on this fact, it can be considered as an easy-to-apply, cheap and effective treatment option in cases where conventional treatment methods are not effective.

Conflict of interests
The authors declare that they have no competing interests.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The study was carried out following the Helsinki Declaration and approved by the Inonu University Clinical Research Ethics Committee with the number 2018/54).

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