Effect of Vinica Alkaloids Iontophoresis on Post-Mastectomy Shoulder Pain

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ABSTRACT

Background: Iontophoresis is a non-invasive technique used to increase the penetration of substances through the skin through the dermal layer (epidermis, dermis and parenchyma) in a controlled manner. Technological advances in recent decades have lowered the cost of equipment for implementation, which allowed for the expansion of this technique.

Objective: To evaluate effect of vinica alkaloids iontophoresis on post-mastectomy shoulder pain**.**

Patients and Methods: A randomized controlled study that was carried out on thirty females with age ranging from 35 to 50 years and suffering from post-mastectomy shoulder pain. The patients were randomly divided into two equal groups, each one included 15 patients. Patients in group A **(**Study group**)** received 45-60 minutes of vincristine iontophoresis (20 ml vincristine) 3 times/week in addition to conventional medical care, for eight weeks. While, patients in group B (Control group) received placebo 45-60 minutes of only 20 ml saline iontophoresis (3 times/week), in addition to conventional medical care, for eight weeks.

Results: Significant improvements in VAS and shoulder range of motion (ROM) were reported in the study group compared to the control group ($p < 0.001$). In the study group, the percents of improvement of shoulder flexion, abduction, internal and external rotation were 22.9%, 24.62%, 35.85%, and 39.97% respectively. While, in the control group, they were 0.5%, 0.67%, 2.8%, and 3.35% respectively. VAS scores achieved higher percentage of improvement (54.05%) compared to control group (10.15%).

Conclusion: Vinica alkaloids iontophoresis achieved significant improvements in shoulder pain and ROM following mastectomy.

Keywords: Vinica alkaloids, Iontophoresis, Mastectomy, ROM, VAS.

INTRODUCTION

Mastectomy could be a general expression for eradication of the breast, typically to get rid of cancerous tissue [(1, 2)]. Following mastectomy, some patients complain from pain, numbness, edema, weakness, or prickling within the arm and shoulder region in the affected side where surgery was applied [(3)]. Combination of shoulder pain and muscle strength diminution can contribute to shoulder dysfunction. It was reported that about 60% of females with mastectomy suffer from shoulder pain, while 67% have a decrease in upper limb strength. Mastectomy with lymph node dissection or extensive radiotherapy can predispose more to shoulder dysfunction comparing to patients with breast conserving surgeries or limited radiotherapy. Additionally, age, weight, previous shoulder complications, surgical procedures, using of aromatase inhibitor, and cervical dysfunction also contribute to shoulder limitations [(4)]. Several studies demonstrated that the muscles usually are directly influenced by surgical procedures or radiation, the pectoral muscles and the serratus, do not seem to be those that have long dysfunction. Rather, muscles like the trapezius muscle and rhomboids that do not act properly as they do not contract in a synchronous pattern throughout shoulder ROM. This dysfunction may be attributed to biomechanical changes starting with pectoral muscles and serratus shortening and subsequent nonadaptive changes within the supporting muscles [(5, 6)].

Iontophoresis is a strategy for bringing ionized substances inside the body tissues, which has demonstrated to be valuable in various clinical applications. The strategy frequently uses direct electrical flow to drive ionic substances for example, synthetics or medications put on the skin over the intact skin or other body surface to the body interior. Drug transmission via iontophoresis has many characteristics, as it is considered a safe, nonpainful and noninvasive modality.

It eliminates systemic drug adverse effects and increases the therapeutic efficacy of the drug by bypassing hepatic first-pass metabolism. It introduces few amounts of drug in comparison with other drug delivery modalities and also reduces the dosage frequencies and improves patient compliance [(7-9)].

Use of iontophoresis for electrically encouraged particle transport across natural films has been fruitful in management of neurological pain conditions. Such pain conditions incorporate postherpetic neuralgia, diabetic neuropathy, constant regional pain disorders and phantom pain [(10, 11)]. The fundamental agents utilized are the vinca alkaloids involving vincristine and vinblastine. It has been recommended that vinca alkaloids can cause settlement of neurogenic pain through blockade of microtubules in the neuron. The valuable impact of this treatment is

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most likely because of transganglionic degenerative atrophy of primary central sensory terminals in the Rolando substance by blockage of retrograde axoplasmic transmit in sensual nerves [12].

Above 33% of post mastectomy patients have reviewed their pain as moderate or serious. Regardless of the evident WHO proposals, shoulder pain following mastectomy is yet a significant issue [13, 14]. Therefore, this study strived to examine the efficiency of vinica alkaloids iontophoresis as a new physiotherapy modality in shoulder pain management following mastectomy, in term of improving pain and shoulder ROM. This study may provide a safe, effective, and non-invasive treatment modality for-post mastectomy shoulder pain in a trial to avoid invasive modalities and oral medications that cannot be tolerated for a long period due to their systemic adverse effects.

PATIENTS AND METHODS

A randomized controlled study that was carried out on thirty females with age range from 35 to 50 years and suffering from post-mastectomy shoulder pain were chosen and randomly divided into two equal groups, each one included 15 patients. Patients in group A **(**study group**)** received 45-60 minutes of vincristine iontophoresis (20 ml vincristine) 3 times/week in addition to conventional medical care for eight weeks. While, patients in group B (Control group) received placebo 45-60 minutes of only 20 ml saline iontophoresis (3 times/week), in addition to conventional medical care for eight weeks. Methods of assessment included visual analogue scale (VAS) and goniometer for shoulder pain and range of motion (ROM) respectively. Patients in both groups were assessed before treatment and after 8 weeks of treatment.

Female outpatients with post-mastectomy shoulder pain referred to our outpatient clinic from the National Institution of Oncology in Cairo, Egypt. They were eligible for the study if they fulfilled the following requirements: (a) moderate or severe pain of a tight, burning, or constricting nature following the surgery, (b) altered sensitivity of the skin in the painful area, (c) absence of other causes of arm pain (brachial plexus neuropathy owing to radiotherapy or to lymphedema entrapment, cervical radiculopathy and pericapsulitis of shoulder joint), (d) patients with shoulder pain not relieved by narcotics and (f) patients with limitation of ROM of shoulder flexion and abduction.

Patients were excluded in case of (a) open skin lesions, (b) other skin conditions, (c) recent scar tissue, (d) vinica alkaloids drugs allergies, (e) Electrically sensitive support systems as pacemakers and (f) severe or moderate impaired sensations or loss of skin.

Ethical approval and patients' consent:

An approval of the study was obtained from Cairo University Academic and Ethical committee. Every patient signed an informed written consent for acceptance of the operation.

Procedures of the study:

1-Measurement procedures:

a. **Visual analog scale (VAS):** VAS is considered the gold standard technique in pain-related research. It consisted of a 10-cm line marked 'no pain' at one end and 'pain as bad as it could be' at the other [15]. The patient marked the line according to the pain intensity experienced at that time

b. **Standard goniometer:** EMI Plastic 12" Goniometer 360 Degree ISOM was used to evaluate patients' shoulder ROM. Goniometer is objective and helpful way of quantifying even small range of motion improvements [16, 17] to establish a normal baseline and goal for the rehabilitation process. Abduction and forward flexion were measured with the patient standing, supine in respectively. External and internal rotation were measured with the patient supine and the arm abducted at 90 degrees. All participants were assessed before treatment and after 8 weeks of treatment.

2-Treatment Procedures: The intervention periods of both groups were identical, eight consecutive weeks, three sessions per week and duration of the session was about 45 to 60 min according to the ability of each patient.

Group A **(**study group**)** received vincristine iontophoresis (20 ml vine). A lint pad soaked with the blinded solution was covered by a sponge of the same size and shape as the electrode and soaked with distilled water. This in turn covered by the positive electrode (anode). The sponge was used to allow optimal electrode contact with the patient while avoiding direct contact with the skin. The lint, sponge, and anode were placed over the dermatomes affected by cancer and held in place using a crepe bandage. The cathode was placed over a sponge soaked in distilled water and applied to a non-hairy area on the ipsilateral arm. A direct current of 2–5 mAmp, as tolerated by the patient, were applied for 45- 60 minutes. Group B **(**Control group**)** received placebo (20 ml saline) iontophoresis, in addition to conventional medical care.

Statistical analysis

Descriptive statistics and t-tests were conducted for the comparison of subject characteristics between the groups. t-tests were conducted to compare the mean values of VAS and ROMs between both groups and paired t-tests were conducted to compare the pre- and post-treatment mean values of the measured variables in each group. Chi-square tests were conducted to compare outcome measures between the groups. The level of significance for all statistical tests was set at $p \leq 0.05$. All statistical tests were performed using the Statistical Package for Social Sciences (SPSS) version 19 for Windows (IBM SPSS, Armonk, NY, USA).

RESULTS

Subject characteristics:

Thirty females with post-mastectomy shoulder pain participated in this study. The mean age of the study group was 41 ± 6.83 years, and that of the control group was 43.06 ± 5.87 years. There was no significance difference between both groups in the mean age values ($p = 0.38$).

Effect of treatment on VAS and shoulder ROM:

- ***Within group comparison:*** There was a significant decrease in VAS post-treatment in the study group compared to that of pretreatment ($p < 0.001$) with a percent of decrease 54.05%. In addition, there was a significant increase in shoulder flexion (22.9%), abduction (24.62%), internal rotation (35.85%) and external rotation (39.97%). ROM in the study group post-treatment compared with that of pretreatment ($p < 0.001$). There was no significant difference in VAS and shoulder ROM in the control group between pre and post-treatment ($p > 0.05$) as shown in table (1).
- ***Between groups' comparison:*** There was no significant difference in VAS and shoulder ROM between both groups pre-treatment ($p > 0.05$). Comparison between the study and control groups post-treatment revealed a significant decrease in VAS and significant increase in shoulder ROM of the study group compared to that of the control group ($p < 0.001$) as shown in table (1).

Table (1): Mean VAS and shoulder ROM pre- and post-treatment of the study and control groups.

	Study group	**Control group**			
	X ± SD	**X ± SD**	**MD**	**t- value**	**p value**
VAS					
Pre treatment	6.66 ± 1.17	6.6 ± 1.18	0.06	0.15	0.87
Post treatment	3.06 ± 0.88	5.93 ± 1.38	-2.87	-6.75	0.001
MD	3.6	0.67			
Percentage of change	54.05%	10.15%			
t- value	12.43	1.78			
	p = 0.001	***p = 0.09***			
Flexion ROM (degrees)					
Pre treatment	129.86 ± 10.62	131.46 ± 11.16	-1.6	-0.4	0.69
Post treatment	159.6 ± 6.6	130.8 ± 10.45	28.8	9.01	0.001
MD	-29.74	0.66			
Percentage of change	22.9%	0.5%			
t- value	-24.35	0.94			
	p = 0.001	***p = 0.36***			
Abduction ROM (degrees)					
Pre treatment	126.73 ± 6.71	129.8 ± 11.12	-3.07	-0.91	0.36
Post treatment	157.93 ± 8.32	128.93 ± 10.33	29	8.46	0.001
MD	-31.2	0.87			
Percentage of change	24.62%	0.67%			
t- value	-26.81	1.25			
	p = 0.001	***p = 0.22***			
Internal rotation (degrees)					
Pre treatment	44.46 ± 3.46	45.06 ± 6.11	-0.6	-0.33	0.74
Post treatment	60.4 ± 9.02	43.8 ± 6.01	16.6	5.92	0.001
MD	-15.94	1.26			
Percentage of change	35.85%	2.8%			
t- value	-9.12	1.88			
	p = 0.001	***p = 0.08***			
External rotation (degrees)					
Pre treatment	42.53 ± 3.4	43.93 ± 3.41	-1.4	-1.12	0.27
Post treatment	59.53 ± 8.18	42.46 ± 4.06	17.07	7.23	0.001
MD	-17	1.47			
Percentage of change	39.97%	3.35%			
t- value	-11.1	1.59			
	p = 0.001	***p = 0.13***			

x, **Mean; SD, Standard deviation; p value, Probability value**

DISCUSSION

Post-mastectomy patient might have numbness, tingling or a shooting pain in armpit, upper arm and shoulder or chest wall. This is due to damage to the nerves during surgery. The nerves usually repair themselves, but it can take many weeks or months. The shoulder might become stiff and painful after breast surgery or removal of the lymph nodes [(18)]. Hence, this study was designed to evaluate the therapeutic effects of vinica alkaloids iontophoresis in reducing and improving shoulder pain and ROM in post-mastectomy patients.

In this trial, the statistical analysis revealed that there was a significant decrease in VAS post-treatment in the study group compared to that pretreatment ($p < 0.001$) with a decrease of 54.05%. In addition, there was a significant increase in shoulder flexion (22.9%), abduction (24.62%), internal rotation (35.85%) and external rotation (39.97%) ROM in the study group post-treatment ($p < 0.001$). While, there was no significant difference in VAS and shoulder ROM in the control group between pre- and post-treatment ($p > 0.05$). The improvement in shoulder ROM is due to pain decrease. The possible explanation for pain improvement could be the underlying mechanism of vinica alkaloids in depletion of substance P and calcitonin gene-related peptide, which are pain mediators, from lamina I–III from the segmentally related, ipsilateral Rolando substance of the spinal cord hence, decreasing nociception.

Use of iontophoresis for cutaneous drug delivery of vinca alkaloids has significantly enhanced dermal penetration to produce local anesthesia with acute pain [(19)]. **Penickova *et al.*** [(20)] examined iontophoresis application of vincristine injection in 16 participants with continuous pain secondary to lumbar disc bulging, and in 20 participants with continuous pain in the radicular skin zones. The beneficial impact was assessed from the participants' subjective reports on pain alleviation in percent, from the actual pain intensity and its interference with activities of daily living. The results revealed an improvement in 29 patients (81%). The therapeutic impact of the treatment was seen from the eighth to tenth application. A significant pain alleviation was reported in 69%, and 90% of patients in the first and second group respectively, with percent of pain improvement 24.1%, and 47.7% respectively.

Besides**, Csillik *et al.*** [(21)] evaluated the impacts of vinca alkaloids on patients with continuous pain due to different diagnoses ranging from intercostal neuralgia to terminal pain, at one-year follow-up, 78% of the subjects had demonstrated no pain recurrence, 16% had partial or temporary pain relief, while 6% experienced no diminish in pain. The study concluded that vinca alkaloids possess the ability to block the retrograde transmission within the peripheral nervous system. Moreover, **Layman *et al.*** [(22)] conducted a study on patients with post-herpetic neuralgia who were unresponsive to interventions, which involved TENS, sedative analgesics, antidepressants, and subcutaneous infiltration of lignocaine or hydrocortisone. The experimental group received a solution containing 0.01% vincristine, 0.9% saline, and 5% dimethyl sulfoxide, while the control group received only saline iontophoresis. At the close of treatment, 80% of the experimental group reported improvement on the VAS (mean improvement 59%, $P < 0.05$) compared to 10% in the control group. At six weeks, 60% of the experimental group showed improvements on VAS (mean improvement 27%, $P < 0.05$). However, in contrast to this trial and to the aforementioned studies, **Dowd *et al.*** [(23)] studied the effect of 0.01% vincristine iontophoresis in PHN cases, daily for 20 days, while the control group received saline iontophoresis. By the end of the treatment, there was a significant decrease of pain scores in each group compared to pre-treatment. However, no significant difference between both groups was reported. The study concluded that pain improvement may be attributed to analgesic effects of iontophoresis.

To our knowledge, this is the first study that investigates the vinica alkaloids iontophoresis in shoulder pain management following mastectomy. The trial results revealed prominent amelioration in both shoulder pain and ROM and no adverse effects were reported during the trial. However, this study was limited by small sample size and lack of secondary outcomes measurement as the disabilities of the arm, shoulder and hand (DASH) questionnaire, which may have enabled better statistical analysis. Moreover, lack of patients' follow up is considered one of the study's limitations, so further studies with larger sample size are in demand to investigate the treatment effects on patients' quality of life. Follow up studies are required to illustrate the impact of vinca alkaloids on shoulder pain and ROM on the long-term and recurrence rates of pain.

CONCLUSION

According to the current study results, vinca alkaloids has a significant effect in reducing and improving shoulder pain and range of motion (ROM) in post-mastectomy patients.

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