Effect of ultrasound-enhanced bee venom on selected post inguinal hernioplasty complications: a single-blind randomized controlled trial

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Abstract. – OBJECTIVE: Bee venom (BV) phonophoresis has been recommended as a non-invasive treatment for a variety of inflammatory conditions and for reducing post-operative pain. This study aimed at evaluating the impact of bee venom phonophoresis around incisions and on selected acupuncture points for the treatment of pain, inflammation, and mobility of the hip following inguinal hernioplasty.

PATIENTS AND METHODS: Sixty-six male patients who had acute pain and decreased mobility of the hip after having an indirect unilateral inguinal hernioplasty with a mesh participated in this study. Patients were randomly assigned into two equal groups of 33. The bee venom phonophoresis group (Group A) received low-intensity pulsed ultrasound using BV gel, and the control group (Group B) received low-intensity pulsed ultrasound using only plain gel without BV gel. Both groups received the same regular medical care and 5 minutes of therapy each, three times a week, for three weeks postoperative. The visual analogue scale (VAS), serum C-reactive protein (CRP), and hip ROM measurements were used to assess the acute pain, inflammation, and ROM pre-application (pre-treatment) and post-3 weeks of treatment (post-treatment) for both groups.

RESULTS: The findings have exhibited an extremely significant difference in VAS, CRP, and hip ROM measurements in the BV phonophoresis group compared to that of the control group ($p < 0.05$).

CONCLUSIONS: BV delivered by phonophoresis around incisions and on selected acupuncture points has a beneficial effect in the treatment of pain, inflammation, and mobility of the hip following inguinal hernioplasty with mesh.

Introduction

Inguinal hernia is a major health concern in Egypt, with an approximate frequency of 7%[1]. Inguinal hernia repair is among the most popular surgical treatments globally. Mesh repair, whether open or laparoscopic endoscopic, is the most effective way to repair an inguinal hernia[2]. Inguinal hernioplasty causes discomfort in about 11% of patients[3]. Patients should experience as few problems and postoperative pain as feasible after inguinal hernia repair, in addition to a quick recovery and the ability to resume normal activity[4]. Postoperative pain in the right lower abdominal area and inguinal region is a common condition[5]. The common cause of inguinal discomfort is nerve injuries, which can be due to thermal or mechanical injury during surgical incision and repair, nerve trapping from stitches, staples, mesh, and contractures, as well as injuries associated with the inflammatory reaction to the prosthetic mesh material[6]. Nerve damages sustained during surgery can result in severe pain shortly after the procedure[7].

Several studies[8,9] have looked at how inflammatory serum indicators change following inguinal hernioplasty, depending on the mesh used and/or

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the surgical method used. Inadequate postoperative pain and inflammation management has been linked to an increased risk of surgical wound infections[10], lower patient's satisfaction with pre-operative knowledge[11], increased patient distress, decreased range of motion, and an increased risk of respiratory and cardiovascular complications[12]. Furthermore, immediate postoperative pain severity has been associated with the onset of chronic pain[13]. Narcotics have been linked to negative impacts such as pulmonary collapse, drowsiness, nausea, and vomiting. Therefore, supplementary strategies for postoperative pain and inflammation control may help to decrease narcotic adverse reactions. According to some studies[14], acupuncture has been shown to improve pain management, minimize analgesic requirements, promote postoperative mobility, reduce postoperative adverse effects, and relieve pulmonary problems.

Acupuncture stimulates the autonomic nervous system and raises endorphin levels in the body[15]. Acupuncture needles are inserted into traditional acupuncture points. Pressure, heat, electrical current, ultrasound, laser, bee venom, and other methods may be used to trigger these sites[16].

Bee venom (BV) is an animal venom that is made up of enzymes, polypeptides, non-peptide compounds, and bioactive amines[17]. Application of BV to an acu-point produced a considerably stronger anti-nociceptive and anti-inflammatory impact than a non-acu-point application[18]. Traditional BV therapy was by direct bee stings, which caused pain and inflammation, as well as an inability to control the exact amount, which may result in poor patient comfort, or BV injections into acu-points, which is an invasive technique that causes extreme pain[19]. For these reasons, the necessity for a different technique of applying BV is critical.

Trans-dermal drug delivery (TDD) has many benefits over systemic application methods such as orally administrated and intravenous delivery[20]. While the trans-dermal patch is a beneficial early TDD method, due to the stratum corneum's boundary action, only tiny-molecule medicines can be ingested[21].

Bee Venom Gel (BVG) may affect the body's immune system processes and contribute to increased cortisol secretion, making it analgesic and anti-inflammatory[22]. After using a lot of venom administration methods such as bee stings, apipuncture, infusions, electrophoresis, and application with ultrasound waves (phonophoresis), resulted in success rates ranging from 60 to 90%[23]. Reliable with the viewpoint of improving post-operative pain, our current study aimed at determining the efficacy of bee venom phonophoresis for the treatment of pain, inflammation, and mobility of the hip following inguinal hernioplasty.

Patients and Methods

Study Design

This prospective pre-post-test study was a single-blind randomized controlled trial, started in March 2021 and ended in February 2022. All procedures were conducted following the Declaration of Helsinki.

Subjects

A total of sixty-six male patients who had acute pain and decreased mobility of the hip following indirect unilateral inguinal hernioplasty with mesh were selected on day one post-operatively from the surgery units of Al-Kasr Al-Aini Hospital and OM El-Massrien Hospital, Cairo, Egypt. The diagnosis was made clinically by the physician. Eligible patients ranged in age from 28 to 50 years old. They had not previously undertaken another physical therapy modality for pain, and all of them were non-smokers and under their own medications prescribed by their physician. Patients were ruled out of the research if they had non-mesh inguinal hernioplasty and/or suffered from open or infected wounds and/or any systemic diseases that may interfere with the study's objectives such as using chemo or radiotherapy. They were also excluded if they had an allergy to bee venom and/or had associated disorders, such as immunodeficiency, HIV, diabetes, or anemia.

Interventions

Participants were divided into two groups at random with a total of 33 participants each. The bee venom phonophoresis group (Group A) received low-intensity pulsed ultrasound using BV gel; and the control group (Group B) received low-intensity pulsed ultrasound using only plain gel without BV gel. Both groups received 5 minutes for each session, three times a week, for three consecutive weeks postoperative and received the same regular medical care.

Randomization

Each participant has signed an informed consent after being well-versed about the structure, goal, and effect of the treatment and measurement methods, as well as their right to withdraw or de-

cline at any time with gathering information privacy. The participants were also told to describe any negative effects they experienced throughout the treatment, such as itching. Based on their gender, the participants were randomly divided into two groups (groups A and B): it was done by making 66 closed envelopes with carbon paper inside, 33 envelopes for each group. Then the 33 closed group A envelopes with the 33 closed group B envelopes were mixed, as if they were playing cards. Once it was certain that the stack of envelopes had been thoroughly mixed, by using a firm hand for writing distinct serial number over the front of each envelope, they were ordered from 1 to 66. The carbon paper inside the envelope would transfer this number to the allocation paper inside. Then, these envelopes were put in the appropriate plastic holder and arranged numerically[24]. No subjects dropped out of the research after allocation, as shown in Figure 1.

Procedures

Measurement protocol

For both groups of the study, visual analogue scale (VAS), serum C-reactive protein (CRP) and hip range of motion (ROM) measurements were used to assess the acute pain, inflammation, and ROM pre-application (pre-treatment) and post-3 weeks of treatment (post-treatment).

Visual analogue scale (VAS)

The visual analogue scale (VAS) is a 10-cm-long line with the ends labelled as the pain intensities (e.g., no pain to unbearable pain). Between "no pain" and "worst pain", patients were asked to mark the spot on the line that best described their pain experience. The operator then measured in millimeters the gap between zero and "no pain"[25].
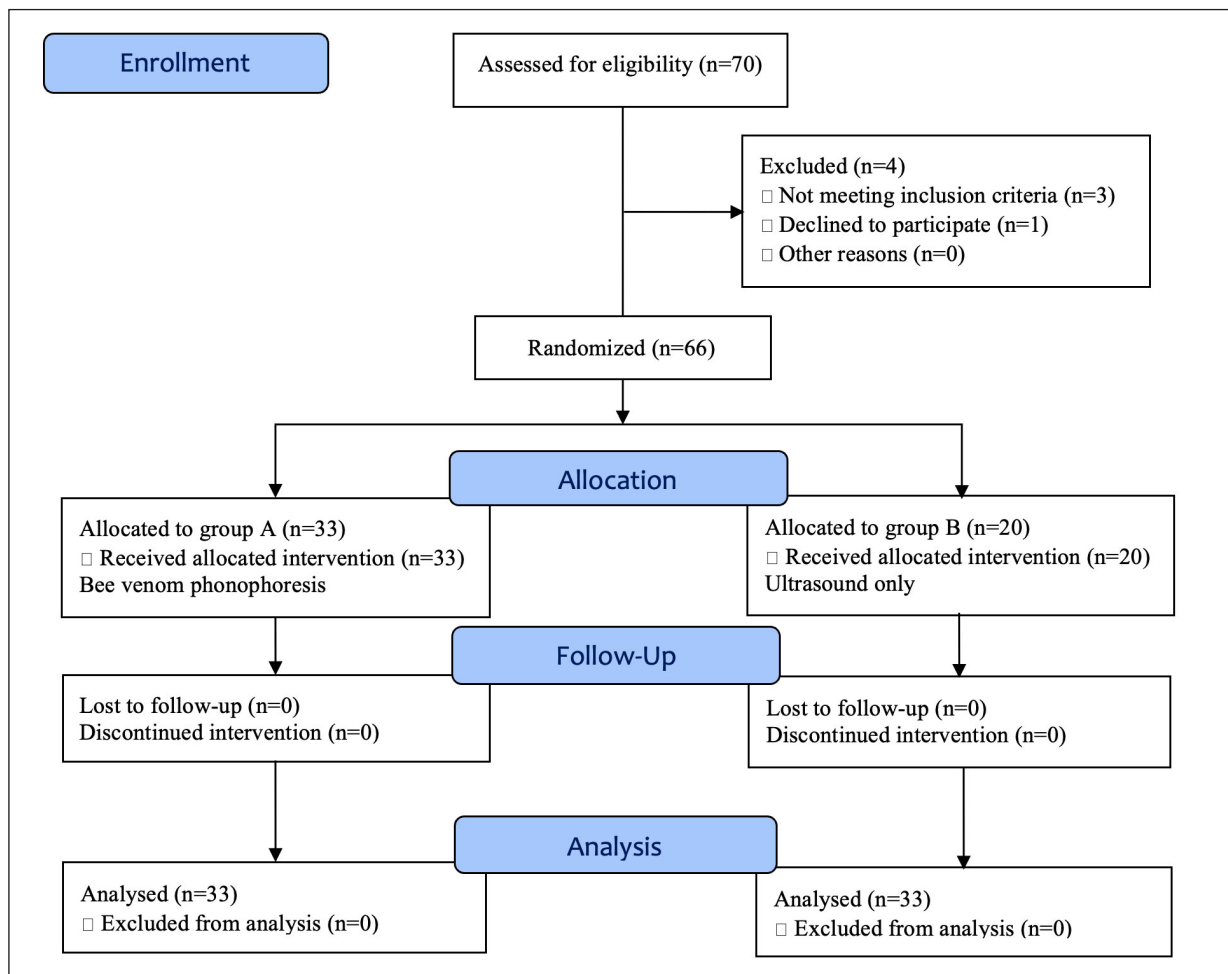

Figure 1. The flowchart of the study.

Serum C-reactive protein (CRP)

Venous blood (3 ml) was collected postoperatively before starting the study in both groups and at the end of all sessions after 3 weeks. Blood is drawn from a vein, generally from underneath the elbow or the back of the hand. The needle is removed after the blood is drawn, and the puncture site is wrapped to prevent bleeding. Venous blood was put into the lab rotator to separate the serum from the plasma. Pipette 50 ul of CRP test reagent onto a glass slide, then 50 ul of patient serum onto the glass slide and mix for 2 minutes. Check for clumping, then compare the results to the CRP positive and negative control serums. The titrated serum was diluted (1:2, 1:4, 1:8, etc.) in saline, and one drop of each diluted serum was added to one drop of the reagent in a glass slide to see if the latex particles suspension agglutinated. The dilution factor (i.e., 2, 4, etc.) was multiplied by the detection limit (6 mg/L) to get the CRP concentration. A result of less than 6 mg/dl is considered normal[26].

Manual goniometer

A simple long-arm goniometer (Orthopedic Equipment Co.; Bourbon, MO, USA) with a 360° scale labeled in one-degree intervals was used. A manual goniometer was used for the assessment of hip flexion, extension, abduction, and adduction ROM. The participant was lying in a supine position for hip flexion, abduction, and adduction ROM assessments, and then in a side-lying position for assessment of hip extension ROM.

For hip flexion range of motion assessment, the goniometer's fulcrum was on the greater trochanter; the stationary arm was parallel to the trunk and the movable arm was parallel to the thigh. The participant was asked to flex his hip joint as much as he could, and then flexion ROM was recorded. For hip extension ROM assessment, the fulcrum of the goniometer was on the greater trochanter; the fixed arm was parallel to the trunk and the movable arm was parallel to the thigh. The participant was asked to extend his hip joint as much as he could, and then extension ROM was recorded. For hip abduction and adduction ROM assessment, begin at the neutral zero position, where the thigh's long axis is perpendicular to the transverse line across the pelvis' anterior superior iliac spines. These last anatomical features were also employed to orient the goniometer's fixed arm. The fulcrum of the goniometer was centered on the unilateral anterior superior iliac spine, and the movable arm of the goniometer was placed over the midline of the femur, directed at the center of the patella. To ensure that the pelvis did not shift during abduction and that the leg was not constricted during adduction, the subject had the ipsilateral leg dangling on the treatment table's side.

Treatment protocol

All patients in both groups of the study (A) and (B) would receive a noncontact low-frequency pulsed ultrasound [(Chattanooga Intelect MOBILE Model-2776), manufactured in Mougueree, France] delivered through a fine mist of sterile saline or alcohol at the incisional site of inguinal hernioplasty, REN 4 and REN 6. Treatment sessions were 3 sessions a week for 3 consecutive weeks. Before and after each patient exposure, the ultrasonic applicator's performance was tested on a regular basis, and each test included all essential acoustic field characteristics (pressure amplitude, frequency), as well as the uniformity of the field distribution[27].

Ren 4: on the anterior midline 2 sun higher to the top boundary of the pubic symphysis or 3 sun lower to the umbilicus on the anterior midline. Ren 6: 3.5 suns higher to the upper edge of the pubic symphysis or 1.5 suns lower to the umbilicus.

For the bee venom phonophoresis group (A): a single clinical dosage of diluted BV in normal saline, 0.05 ml (1 g/ml), was administered into the elbow *via* either an intradermal or subcutaneous method to test for BV allergy. Subjects might take part in this study if the evaluated lesion created a camel hump with a size of less than 10 mm and redness with a size of less than 26.5 mm after 10 to 15 minutes[28]. Participants were given a topical application of BV initially made gel using an ultrasonic therapy apparatus with frequency, 0.5-MHZ pulsed mode (applicator 1.9 cm^2) applied around the incision site, Ren 4 and Ren 6. The movement was over the incision margins with a pulsed duty cycle of 40% (4 ms on, 6 ms off), an energy output of 0.5 W/cm2, and time was 5 minutes each session. Each participant was put in the most comfortable and relaxed position as a supine lying position, and the patient was instructed to expose the incision site to avoid any restriction for receiving phonophoresis around the incisional site, REN 4, and REN 6. The incision margin was cleaned with alcohol or normal saline, the ultrasound unit's plug was inserted into the main current supply, and the treatment approach (phonophoresis application for bee venom gel) was prepared; each

participant received a total amount of about 0.6 mg to 1 mg of BV gel each session for a total of 5 minutes[29]. The participants in the control group (Group B) received only low-intensity pulsed ultrasound applied around the incisional site, REN 4, and REN 6 for 5 minutes, as in Group A, using only plain gel without BV gel[30].

Outcome Measures

The VAS, CRP, and hip ROM were measured before starting the study program and again at the completion of the study after 3 weeks of the treatment.

Statistical Analysis

The Statistical Package for Social Science (SPSS, IBM Corp., Armonk, NY, USA) application version 22 for Windows was used to run all statistical analyses and the significant level was set at $p < 0.05$. The test included three dependent variables (VAS, CRP, and ROM of the hip joint). Descriptive statistical analysis using histograms with the normal distribution curve presented that the data were normally distributed and did not breach the parametric supposition for the dependent variables. The Box's test was used to analyze covariance homogeneity and the Shapiro-Wilk test was used to analyze data normality. For the age comparison of the two groups, descriptive statistics and an unpaired t-test were used. For the contrast of affected side distribution among groups. To compare the mean values of VAS and hip ROM between groups A and B, an unpaired t-test was used. Within every group, a paired t-test was used to compare pre- and post-treatment. For sample size calculation to avoid type II error, the data analysis test that was used to identify the effect size was established using the G*power program (G*power 3.1.9.2), which anticipates a large variance between groups. A power analysis showed that 33 patients per group were adequate to attain a power level of 80% [power = 0.80, α =

0.05; effect size = 0.4]. This effect size was selected because it produced a reasonable sample size. We examined 70 patients over the course of the three-week study.

Results

Sixty-six patients from both groups were matched with consideration given to age and affected side (Figure 1). In terms of age and affected side distribution, there were no statistical significances ($p > 0.05$) among subjects in both groups as shown in Table I.

Effect of Treatment on VAS, CRP, and Hip ROM

Within group comparison

In groups A and B, there was a significant difference in VAS, CRP and hip ROM post-treatment compared to pre-treatment ($p < 0.001$) in favor of group A. The VAS improvement in Group A was 77.2%, while the improvement in Group B was 45.25%. The CRP in group A improved by 39.62 %, while in group B, it improved by 12.33 %. The percentage of improvement in flexion, extension, abduction, and adduction in group A was 31.47%, 265.8%, 99.21%, and 147.93%, respectively, while the percentage of improvement in group B was 22.36%, 210.34%, 80.5% and 91.6% respectively (Table II).

Between group's comparison

Pre-treatment, there was no significant difference in VAS, CRP, or hip ROM between the two groups ($p > 0.05$). When the VAS, CRP, and hip ROM of groups A and B were evaluated after treatment, there was a significant difference in VAS, CRP, and hip ROM of group A compared with that of group B ($p < 0.001$) as displayed in Table II.

Table I. Comparison of subject characteristics between groups A and B.

	$\bar{x} \pm SD$		*p*-value
	Group A	**Group B**	
Age (years)	37.42 ± 7.25	38.70 ± 6.47	0.46[a]
Affected side			
Right side	19 (58%)	23 (70%)	0.38[a]
Left side	14 (42%)	10 (30%)	

$\bar{x}$: mean; SD: standard deviation; *p*-value: probability value; [a]: non-significant.

Table II. Within and between group comparison for both groups A and B.

	Group A	Group B			
	$\bar{x} \pm SD$	$\bar{x} \pm SD$	MD	*t*-value	*p*-value
VAS					
Pre-treatment	7.85 ± 1.25	7.69 ± 1.38	0.15	0.47	0.64
Post-treatment	1.79 ± 1.11	4.21 ± 1.6	-2.424	-7.16	0.000
MD	1.35	3.49			
% of change	77.2%	45.25%			
t-value	25.89	10.33			
p-value	$p = 0.000^b$	$p = 0.000^b$			
CRP					
Pre-treatment	140.9± 21.74	138.55± 16.73	2.36	0.49	0.62
Post-treatment	85.09± 20.37	121.45± 16.5	-36.36	-7.97	0.000
MD	55.82	17.09			
% of change	39.62%	12.33%			
t-value	34.46	20.57			
p-value	$p = 0.000^b$	$p = 0.000^b$			
Flexion ROM (degrees)					
Pre-treatment	107.36 ± 5.75	108.0 ± 6.12	-0.64	-0.44	0.67
Post-treatment	141.15 ± 5.25	132.15 ± 5.22	9.0	6.98	0.000
MD	-33.79	-24.15			
% of change	31.47%	22.36%			
t-value	-26.48	-16.71			
p-value	$p = 0.000^b$	$p = 0.000^b$			
Extension ROM (degrees)					
Pre-treatment	5.12 ± 3.33	4.45 ± 3.45	0.67	0.80	0.43
Post-treatment	18.73 ± 5.16	13.82 ± 3.44	4.91	4.55	0.000
MD	-13.61	-9.36			
% of change	265.8%	210.34%			
t-value	-15.29	-15.38			
p-value	$p = 0.000^b$	$p = 0.000^b$			
Abduction ROM (degrees)					
Pre-treatment	16.55 ± 4.42	15.09 ± 3.01	1.46	1.56	0.12
Post-treatment	32.97 ± 4.36	27.24 ± 6.18	5.73	4.35	0.000
MD	-16.42	-12.15			
% of change	99.21%	80.5%			
t-value	-18.22	-14.14			
p-value	$p = 0.000^b$	$p = 0.000^b$			
Adduction ROM (degrees)					
Pre-treatment	12.33 ± 2.17	11.91 ± 2.57	0.42	0.72	0.47
Post-treatment	30.58 ± 5.29	22.82 ± 3.48	7.76	7.04	0.000
MD	-18.24	-10.91			
% of change	147.93%	91.6%			
t-value	-17.03	-15.22			
p-value	$p = 0.000^b$	$p = 0.000^b$			

$\bar{x}$: mean; SD: standard deviation; MD: mean difference; *p*-value: probability value; [b]: Statistically significant.

Discussion

The therapeutic efficacy of bee venom phonophoresis around incisions and on specific acupuncture points was examined in this study among two different groups (groups A and B) in the reduction of pain, inflammation, and hip ROM after inguinal hernioplasty using VAS, CRP, and manual goniometer. According to the findings of this study, all outcome variables within every group showed a substantial change before and after 3 weeks of treatment. There was a highly significant difference ($p < 0.05$) between the BV phonophoresis groups (group A) and the control group (group B) in the (pre *vs.* post treatment). In terms of VAS and CRP, the current study's findings indicated a highly significant difference ($p < 0.05$) in the BV phonophoresis groups (group A) in the (pre *vs.* post treatment) with a percentage of improvement of 77.2 % and 39.62 % respectively compared with the control group (group B) with a percentage of improvement of 45.25% and 12.33% respectively. Furthermore, there was a highly significant difference ($p < 0.05$) in flexion, extension, abduction, and adduction of the hip (pre *vs.* post treatment) in the BV phonophoresis groups (group A), with a percentage of change of 31.47%, 256.8%, 99.21%, and 147.93%, respectively, compared to that of the control group (group B), with a percentage of change of 22.36%, 210.34%, 80.5%, and 91.6% respectively. This improvement could be due to how phonophoresis can alter structural lipids in the stratum corneum by increasing BV penetration through the skin during and after cavitation therapy. The confusion in the epidermis also increases skin permeability, allowing topical BV to infiltrate the dermis, especially when it has a low molecular weight. According to Tsai et al[31], BV may cause the endogenous pain inhibitory system to generate neurotransmitters or neuropeptides to minimize pain transmission. BV treatment has been proven to increase cortisol levels in the pituitary gland and adrenal gland cortex[32]. The descending serotonergic pathway, opioid receptors, and 2-adrenoceptors are also activated[33]. Bee venom's anti-inflammatory and analgesic properties are due to melittin and adolapin suppressing prostaglandin synthesis. It inhibits the activities of cyclooxygenase and lipoxygenase[34].

Tertiapin works to reduce inflammation by inhibiting potassium channels[35]. Furthermore, animal models have shown that the mast cell degranulation peptide (MCDP) has anti-inflammatory properties. Many studies[34] have found that BV injections have both initial nociceptive and long-term antinociceptive effects. Injecting bee venom into an acupoint has been proven to have anti-nociceptive and anti-inflammatory effects in rats and humans[36]. The findings of this research concerning the efficacy of bee venom phonophoresis in reducing acute pain, inflammation, and ROM of the hip in patients following indirect inguinal hernioplasty were observed and recorded by Yasin et al[37], who stated that phonophoresis improves BV penetration into the skin during and after cavitation therapy, disrupting structural lipids in the stratum corneum, may account for the decreased discomfort, promotes skin permeability, allowing topical BV to permeate the dermis, especially when it has a low molecular weight. According to Park et al[38], BV gel phonophoresis for pelvis inflammation was found to significantly reduce C-reactive protein levels and pain severity due to its anti-inflammatory and analgesic qualities.

De Santana et al[39] noted that BV therapy is used for a variety of disorders despite its toxicity. It is known to be useful for musculoskeletal problems such as arthritis and immune-related diseases. According to Lee et al[40], melittin, apamin, and adolapin are the primary peptides in BV that have potent anti-inflammatory and analgesic properties. By injecting BV into lesions, cortisol levels rise in the blood and prostaglandin formation is blocked. In a study by Jang and Kim[41], who reported that the use of an ultrasonic apparatus for BV delivery in the treatment of biceps brachii muscular soreness, phonophoresis was proven to be a beneficial method for minimizing pain and improving range of motion. BV was shown to inhibit COX-2 and prostaglandin E2 in the body suggesting lower inflammation in various joints. Treatment outcomes demonstrated that it improved hip joint mobility with hip osteoarthritis.

On the other hand, there are some studies[42-44] that don't support the hypothesis of this study. Altan et al[42] stated that cellular injury due to cavitation was seen in many *in vitro* types of research utilizing 1-MHz continuous US at spatial peak doses equal to or more than 1 W/cm^2. High-intensity US applications are also known to create pain and a heated sensation. To maximize beneficial thermal properties while avoiding tissue injury, in accordance with the previous suggestions, we used a pulsed mode for our US dose in our experiment. Kołaczek et al[43] reported that regrettably, BV might cause side effects when used. During BV application, patients hypersensitive to bee venom were shown to have a greater chance of a systemic allergic response. According to Shim et al[44], there was minor adverse effects and temporary skin reactions such as itching, rash, and edema appeared. However, each participant in this study got a bee venom allergy test to avoid those negative effects.

Utilized an ultrasonic device for BV delivery in the treatment of biceps brachii muscle soreness since phonophoresis is a useful method for reducing pain and increasing range of motion.

Limitations

There are several limitations in this study; first, there was a small sample size, secondly only male patients were included in the study, and this should be considered when the results are evaluated. Also, there were many types of hernia repair not included and the unfavorable reactions with a low chance of occurrence may have gone unnoticed. Furthermore, double blinding was not possible. Further studies should be conducted using different parameters of ultrasound (intensity, frequency, and treatment duration) or with other physical therapy modalities that decrease pain following indirect unilateral inguinal hernioplasty. Further studies are needed to compare between males and females (sex factors), different age of patients (age factor), and their effects on rate of recovery by using bee venom phonophoresis with unilateral indirect inguinal hernioplasty.

Conclusions

According to findings of related research, the findings of this study support the assumption that bee venom phonophoresis plays a major role in the treatment of acute pain, inflammation and mobility of the hip following indirect inguinal hernioplasty, it is non-invasive, simple method improving pain, inflammation and mobility of the hip proved by highly significant difference of VAS, CRP, and hip ROM measurements in bee venom phonophoresis group than low intensity ultrasound group alone.

Conflict of Interest

There are no conflicts of interest declared by the authors.

Ethics Approval

The institutional review board of Cairo University's Faculty of Physical Therapy granted ethical permission prior to the start of the investigation, which was given the number P.T.REC/012/002764. This study was registered at Clinical Trials.gov with the reference number: NCT05286463.

Informed Consent

Each participant has signed an informed consent after being well-versed about the structure, goal, and effect of the treatment and measurement methods, as well as their right to withdraw or decline at any time with gathering information privacy.

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