

Chronic non-bacterial prostatitis responses to pumpkin seeds phonophoresis: randomized control trial

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ABSTARCT

Background: It has been observed that out of all visits to the clinics by the young and middle age men for grievances including the genital and urinary frameworks, about 25% of the visits accounts for Prostatitis. Significant number of men, aged less than 50, visits to urologist due to Interminable prostatitis. Nevertheless just 5 to 10% of "prostatitis" cases are really caused by a bacterial contamination. The purpose was to investigate thoroughly the effect of pumpkin seeds oil phonophoresis among males who are diagnosed with chronic non-bacterial prostatitis. **Subjects and Methods:** The study population composed of sixty male outpatients diagnosed with chronic non-bacterial prostatitis. Through sample random sampling procedure the total study population was categorized in to three treatment groups; Group A, wherein patients received phonophoresis treatment using pumpkin seeds oil; Group B, where members of the group received trans-perineal continuous low-intensity ultrasound; and Group C, in which the participant received placebo low-intensity ultrasound. All of The three groups of the organized trail received their corresponding treatment daily up-to 3 weeks. The well-defined parameters of NIH Chronic Prostatitis Symptom Index (NIH-CPSI), urodynamic measurements of residual urine, and flow rate measures were utilized to analyze the outcome of the trail. White blood cell (WBC) was determined from prostatic secretion. **Results:** Both for Group A and B the study has observed significant difference in before and after treatment results measured in terms of values of urodynamic residual urine, urine flow rate, white blood cells, and NIH chronic prostatitis symptom index among group A and group B, where's no change has been observed in before and after treatment results for group C. the exact probability statistic, P-value suggests a statistically insignificant difference ($P > 0.05$) between Group A and B except for white blood cells, while group A and C, and group B and C as well differ significantly with the probability value of ($P < 0.05$). **Conclusion:** with the careful treatment procedures carried out during the organized trail the current study has significantly proved that pumpkin seeds oil phonophoresis can produce a tremendous effect in the management of nonbacterial prostatitis, hence can be considered as a safe, noninvasive method for the treatment of nonbacterial prostatitis.

Keywords: Pumpkin seeds oil, Phonophoresis, Ultrasound, Physiotherapy, Cucurbitapepo, Chronic non-bacterial prostatitis.

Introduction

It has been observed that Ultrasound (US) technology is most frequently used as a therapeutic modality in the field of physiotherapy and sports medicine. Also it is widely used in the clinical management of traumatic and acquired conditions which affect the musculoskeletal system. Similarly, by the practitioners the use of ultrasound has been advocated in the enhancement of the transdermal penetration of medications such as phonophoresis. Pharmacologic-based substances such as proteins, indomethacin, corticosteroids, and large-size molecules have been used for this purpose [1].

Medically Phonophoresis is a term used to refer to the process of the enhancement of penetration of medications through the normal skin using ultrasonic waves. The use of cream or medication gel which acts as a coupling medium is applied over the ultrasound head which is administered over the target area of treatment. To facilitate the substance when applied using the gel or cream, it is important to determine the properties of a good ultrasonic conductor to achieve positive therapeutic outcomes otherwise the treatment may yield ineffective therapeutic results [2, 3].

Before processing to Ultrasound, gels are typically applied on skin area covering targeted tissue to eliminate air between the probe and the skin as sound is transmitted to the

tissue area. It is important that any substitute substance used other than the conventional ultrasound transmission gel possesses properties capable of exerting independent therapeutic and palliative effect for the patient. One of the important properties of any substance considered for this purpose is that the coupling substance must be able to minimize the perception of cold by the patient upon the application of the ultrasound head. Likewise, the substitute medium should exhibit properties that can be customized for a patient's specific medical condition [4].

When recommending oil for Ultrasound transmission, it should be priority tested and be able to demonstrate significant results when used for ultrasound. On the bases of proper examination and testing several examples or classification of essential oils are categorized as having properties which help in inflammatory conditions are; birch sweet, German chamomile, wintergreen, and camphor. Similarly geranium, clary sage, orange, parsley, rose geranium are some other essential oils which are categorized as showing significant therapeutic effects, specifically related to female hormonal and gynecologic symptoms. Best example of herbal oil which was studied for its properties is olive oil. Nakhostin-Roohi et al., (2016) [5] have assessed the special effects of virgin olive oil phonophoresis in case of female athletes' anterior knee pain. Further, the use of Chinese herbal

medicines, particularly its oil derivatives, have also been reported to be used in phonophoresis such as using Guizhi (cassia twig) and cinnamic aldehyde. [6].

Pumpkin Seeds oil, extracted from *Cucurbita* plant, has also been classified as one of the essential oils that may yield significant potential therapeutic effects when used as a coupling medium. The *Cucurbita* genus contains numerous species, and is widely obtainable in Europe, Asia, and America. One of the variants is *Cucurbitapepo* while the other is *Cucurbita maxima*. Current work has focused on *Cucurbitapepo* variant, *Cucurbita* is globally well-known and old-fashioned herbal medicinal product used over the past centuries. Further its medicinal and therapeutic use and significance has been described in many textbooks and traditional medicinal manuscripts. In Europe, *cucurbitapepo* in the form of ethanolic pumpkin seeds using its soft extract has been practiced widely. For several urological conditions this has primarily been registered as a remedy, specifically those related with an enlarged prostate gland and micturition problems connected with an overactive bladder [7, 8].

Pumpkin seeds oil is rich in antioxidants [9]. The lively composites in *Cucurbitapepo* L. seeds are: $\Delta 5$ -, $\Delta 7$ - and $\Delta 8$ -sterols. $\Delta 7$ -sterols are largely found in predominant proportion in *Cucurbitapepo*. These are significantly registered to be the vital active

components of pumpkin seeds in the treatment of gentle prostatic hyperplasia [10].

The significant fraction that consists of $\Delta 7$ -sterols is widely believed to be responsible for its therapeutic effects [11]. It is worth mention that these sterols have not been found in any other sterol-containing plant extracts used in benign prostatic hyperplasia (BPH) treatment.

Pumpkin seeds contain considerable amounts of D7-phytosterols, either in free form or inevitable to sugar molecules. A lipid-steroidal extract has also been confirmed to have an inhibitory effect on 5 α -reductase in cultured human prostate fibroblasts. The pharmacological mechanism of action of pumpkin seed oil is well-documented through the process of inhibition of 5-alpha-reductase which is primarily responsible for the conversion of testosterone into DPT (dihydrotestosterone) [12, 13].

A study conducted by Schilcher et al., (1987) reached to the conclusion that orally administered D7-phytosterol-rich *Cucurbitapepo* subsp. *pepo* seeds (3–4 days before prostatectomy) resulted in a reduced volume of dihydrotestosterone in prostate tissue of patients [14].

Another remarkable benefit is the great content of Omega 6 (Linoleic Acid) which is a necessary fatty acid. Omega-6 has been identified to relieve symptoms associated with benign

expansion and diminution prostate cancer risk. A clinical trial carried out in Hungary, utilized pumpkin seeds oil among male patients diagnosed with BPH. The results of the trial revealed that improvement has been recorded in night urination in 66% of participants, further, 86% of the participants of the trial noted positive and significant improvement in symptoms of difficulty in urination. The intake of Pumpkin seed oil also resulted in a decrease of prostatic sizer in 33% of patients when compared with a medical treatment. Also, it has been reported that pumpkin seed oil has been demonstrated to exert antimicrobial effects [15].

With its perceived therapeutic effects and other useful characteristics on the prostate, the possibility that pumpkin seeds oil can be used as coupling medium used for therapeutic ultrasound in the clinics should be given proper consideration. Though, it is predominantly made up of both linoleic and oleic acid, the proportion of linoleic acid is comparatively low, however its high unsaturated fatty acid property provides a high oxidative stability for use in different industrial settings [16]. Hence, the current work has been carried out to qualify and investigate the transdermal use of pumpkin seeds oil as a topical coupling ultrasound medium for therapeutic ultrasound application on non-bacterial prostatitis (CNBP).

Subjects, Instrumentations and Methods

Subjects:

Design

A randomized controlled comparative trial was conducted. Patients were screened accordingly. Bladder residual urine, urinary flow rate, white blood cells in prostatic specific specimens, and NIH- CPSI were recorded before and after three weeks of the treatment to ensure the benefits of the utilized modalities.

After screening, 60 male patients who complained from CNBP were randomly assigned to three different groups; Group A wherein patients received phonophoresis treatment using pumpkin seeds oil for, Group B who received continuous low intensity ultrasound (LIUS), and Group C wherein patients received placebo LIUS while the ultrasound machine is working and there was no output. The three groups received their pre-agreed protocol five times per week for three weeks

Participants

For the analysis participants were recruited from a registry of patients with a diagnosis of CNBP. To be included for the analysis a patient must be evaluated with a confirmed diagnosis. They were examined and diagnosed accordingly by a medical practitioner/urologist. The patients who were included in the study should have normal laboratory findings. Patients with concomitant infection, autoimmune diseases, diabetes mellitus, cancer, heart problems/pacemaker, implants (metal, silicone, saline), acute and post-acute injury, thrombophlebitis, impaired sensation, psychiatric diseases, and those with well-known

contraindications of ultrasound treatment were excluded from the study. Similarly, those with known hypersensitivity to pumpkin seeds oil and its derivatives, along with those who had received other forms of therapies that could influence the therapeutic outcomes of the study were excluded from the study sample. Complete blood count (CBC), urinalysis, urine culture, and routine biochemical tests were performed to rule out other diseases.

The trial was accomplished in accord to the principles specified in agreement with the values of the Statement of Helsinki. All the participants were prior informed about the complete study design thoroughly both in verbal and written form. Ethics Committee of the Faculty of Physical Therapy, Cairo University, permitted the study protocol. All patients were provided a written agreement to contribute in the trail.

Measures

To accumulate desired data for the analysis, for all subjects, bladder residual urine and urinary flow rate were measured through A DANTIC UD 5000/5500 Urodynamic examination system. Further white blood cells in prostatic specific specimens, and NIH-CPSI questionnaire were recorded before and after three weeks of the treatment. Monitoring of symptoms were conducted and recorded based on changes in terms of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) which was obtained before and after treatment for all the three groups.

Intervention

For group (A), a trans-perineal phonophoresis through the use of 3 ml pumpkin seeds oil as a coupling medium obtained from the Faculty of Pharmacy, Cairo University was applied for 8 minutes per session, five times a week for a total of three consecutive

weeks. The patient lies in lateral recumbent position while both lower limbs flexed toward the chest. The area to be treated was cleaned by using alcohol-based formulation. Continuous ultrasonic waves with a frequency of 1 MHz and a power density of 1.5 W/cm², 100% duty cycle, 8 minutes per session were applied while the ultrasound head was moved in a circular direction over the perineal area throughout the session. LIU device (Sonopuls 490 u. Manufacturer; ENRAF NONIUS B.V, Netherlands) was used in the current study.

For group B, low intensity ultrasonic waves using the same duty cycle, time, and manner of application was used trans-perineally, five times a week for three consecutive days. The coupling medium used was the regular gel.

For group C, placebo low-intensity ultrasound while the device is on mode wherever there was no output, five times a week for three consecutive weeks was used.

Statistical analyses

To analyse the data, Statistical Package for social sciences (SPSS) version 21 has been utilized. For all demographic and quantitative variables of interest, summary statistic, namely; mean \pm standard deviation was calculated. To assess the degree of differences based on before and after treatment among the three groups, independent and paired t-test procedures were applied, further the differences were analyzed for the same group on pre and post treatment basis, and also on pre and post treatment difference among groups. One-way analysis of variance (ANOVA) was used to assess inter-groups differences in various measurements.

RESULTS

Sample Characteristics

The study sample for the current study was sixty nine patients with CNBP. Out of the total study sample, nine individuals did not qualify to be included in the study and consequently were omitted from the results due to various reasons: reluctant to participate (n= 4), inadequate evaluation measures (n= 2), unwillingness to remain in the treatment procedures (n= 2), and have not received three sessions of the selected interventions (n= 1). As mentioned earlier, the study included sixty participants, with twenty in each group. There is no evidence of statistically significant difference the study groups as to age, height, weight and body mass index reflecting the homogeneity as demonstrated in Table 1 ($P > 0.05$).

The results displayed no significant differences in the starting point values of urodynamic residual urine, urine flow rate, white blood cells, and NIH chronic prostatitis symptom index among the three groups as shown in table 2.

After application of the treatment protocols, t-test results showed significant differences in comparison to pre intervention in values of urodynamic residual urine, urine flow rate, white blood cells, and NIH chronic prostatitis symptom index among group A and group B except for

group C. while ANOVA showed significant difference in favor of group A for all the measured parameters as shown in Table 2.

Pre and Post intervention Comparison

Post-intervention comparisons between groups using ANOVA test showed that all parameters differed significantly among groups in favor of Group A as presented in Table 3. Concerning the post hoc test, there was a non-significant difference ($P > 0.05$) between Group A and B except for white blood cells, while there was significant difference ($P < 0.05$) between Group A and C and between Groups B and C as displayed in Table 3.

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DISCUSSION

It has been confirmed from the findings of the current study that the use of ultrasound phonophoresis using pumpkin seeds oil can be used as a substitute in the treatment of CNBP. This was demonstrated through the significant reduction of white blood cells count (WBC), values of NIH-CPSI, and the residual urine in the urinary bladder while a significant increase was recorded in the urine flow rate. Till date researches don on the current area of interest has emphasized mechanisms by which trans-perineal phonophoresis exerts its effects through different pathways. Future research is recommended to clearly determine the principles concerning these influences in CNBP.

In 2013, Li et al., [17] appraised the clinical potency and safety of trans-perineal ultrasound using a low-intensity therapeutic ultrasound device to treat chronic prostatitis (CP). The study reported the results of NIH - CPSI scores in addition to regular prostatic testing and assessment of prostatic fluid. Findings showed that trans-perineal ultrasonic treatment is profoundly useful for CP, particularly in releasing prostatic discomfort and simultaneously holding the benefits of being safe, simple to use, easy handling, and general acceptability.

Trans-rectal low-intensity pulsed ultrasound (LIPUS) has also been expressed to be productive in counteracting the clinical manifestations of chronic prostatitis and chronic pelvic pain syndrome (CP/CPPS). LIPUS has been explained to produce its effects in controlling excretions of cytokines [18].

Furthermore, treatment by LIPUS could hinder IL-1 β -induced

COX-2 appearances via the integrin β 1 receptor served by the phosphorylation of ERK $\frac{1}{2}$, as COX-2 is the result of pain [19]. Therefore, LIPUS is considered as an effective clinical method to be prescribed for the treatment of CP/CPPS.

The ways of increasing skin permeability provoked through the clinical application of low-frequency ultrasound have been attributed to the temporary acoustic cavitation generated over the skin membrane via micro jets affecting the skin surface, although other mechanisms may play insignificant roles. Generally, low-frequency pulsed ultrasound has revealed a much greater potential to allow high-molecular-weight components to pass through the skin and affect deep structures [20].

The dispersion of low-intensity ultrasound through the skin has two principal real values: heating phenomenon and production of cavitation wherein both mechanisms might be combined as cavitation may result in heating [21].

The entire outcome is enhanced skin permeability as a result of developed fluidity of lipids between cells through the heating process or the mechanical force and/or through spreading intercellular space, or via building persistent or temporary holes within corneocytes and keratinocytes as a result of cavitation and/or by forcing the drug and the carrier throughout the permeabilized skin through the effects of convection [22].

Herbal medicine dispensed to males with symptomatic BPH and CNBP where practitioners designate phytochemical products in the corresponding way as they designate

medications, and investigated the mixture of saw palmetto with pumpkin seeds oil with notable improvement in maximum flow rate (MFR) value in BPH subjects after 3 months of therapy [23, 24].

Our study revealed a similar effectiveness on MFR in the ultrasound group, but the combination of pumpkin seed oil with ultrasound gained more benefits and results.

The effect of pumpkin seed oil is characterized by its restraint on 5- α -reductase that transforms testosterone into dihydrotestosterone (DHT) [25, 13] as well as epithelial compression in the prostate transition area as explained by Marks et al., (2000) [23]. Results from a study that utilized pumpkin seeds oil for patients with prostate problems revealed inhibition of testosterone-induced prostatic hyperplasia [25]. Similarly, ingestion of pumpkin seeds oil resulted in actual decrease of prostatic weight [13].

In our study, integration of treatment via pumpkin seeds oil and ultrasound phonophoresis resulted in significant symptomatic recovery with statistically significant difference in flow rate, residual urine, WBC, and NIH-CPSI. Further, more high-grade results can be achieved if the trial is re-conducted with larger sample over a more extended measurement period. Regarding the study outcomes, it could be proposed that pumpkin seeds oil phonophoresis is clinically supported and may be satisfactory as an alternative medicine for BPH.

Moon et al., (1990) found that the urinary flow rate of BPH subjects supplied with sitosterol has shown significant improvement from an

initial MFR after 4 weeks of therapy and remained to progress to a period of 12 weeks [26].

Essential omega-3 fatty acids are primarily associated with initiating anti-inflammatory responses; pumpkin seeds oil is rich in omega 3 fatty acids specifically α -linolenic acid (ALA). Its main property involves the following effects: anti-inflammatory, antioxidative, hypocholesterolemic, hypolipidemic, hypotensive, and vasoconstrictive. A plausible explanation for the reduction of symptoms in prostatitis with the application of phonophoresis may be due to enhancement of properties of pumpkin seeds oil as an omega 3 fatty acid exerting its effects on prostatic tissue. The immediate effects of the enhancement of ALA through phonophoresis result in a decrease in oxidation with a concomitant decrease in inflammation [27].

Evidence is rising that both inflammation and oxidation play a key roles in the development of prostate cancer. Chronic inflammation primarily exerts its cellular side effects mainly through excessive production of free radicals and depletion of antioxidants [28].

It has been revealed by the previous work done in the current area of interest the use of ultrasound Technology has adequately been registered to increase blood supply and also increase collagen synthesis to injured areas and consequently results in a faster healing process. Ultrasound helps in increasing production of blood vessels and fibroblasts and increases the permeability of the cell membrane. This may also possibly explain the enhancement observed in group B in

addition to the effects of the pumpkin seeds oil as a coupling medium to the physiological effects exerted on prostate tissue in group A[29].

A further comprehensive study revealed that pumpkin seeds oil can be favorably administered in combination with chemotherapy with significant beneficial consequences for prostatic cancer patients[30].

Furthermore, it was found that Pumpkin oil included high levels of delta-7-sterine that inhibits DHT receptors in the prostate gland that causes cancer. It is a mild steroid that competes with dihydrotestosterone. DHT is known to be a significant factor in enlarged prostate tissue as well as hair loss. Pumpkin seeds oils also contain phytosterols with beta-sitosterol particularly beneficial for men[10].

Glucocorticoids inhibit phagocytosis by both neutrophils and monocytes including the release of degradative enzymes, and production of inflammatory cytokines[31].

In summary, there is a possibility that the beta-sitosterol as a known glucocorticoid derivative in pumpkin seeds oil through the application of phonophoresis may induce the suppression of the inflammatory response in the prostate tissue mediated through inhibition of cytokine and arachidonic acid metabolite production which are known factors known to be involved in stimulating inflammation.

Abdel-Rahman et al., (2006), conducted a similar study to explore properly the impact of pumpkin seeds taken through diet supplementation on prostate hypertrophy and reported that ingestion of a high dose of pumpkin seeds inhibits prostate growth[32].

The advantages of pumpkin seeds therapy significantly depend on the tonic impact on the bladder, sphincter recreation and lessening of micturition signs. Therefore, it was suggested that pumpkin seeds might be employed in patients without significant impediment of

the prostate with low risk as the disease progresses. For patients who experience frequent urological problems; treatment through the use of Cucurbitapepo (pumpkin seeds oil) may be advised with micturition manifestations correlated to BPH during the initial disease stages, particularly those associated with an overactive bladder[33].

Limitations of the study

Small sample size due to some genuine reasons can be considered as a major limitation of the current study; hence it is suggested for future researches to examine larger sample size to get more generalizing results. Further to get evidence-based outcomes future researchers are directed to examine the use of other different herbal sources that can be presented to the body by using different modes of low-intensity ultrasound through the means of phonophoresis.

Conclusion

After in-depth analysis the current work reached to conclusion that chronic non-bacterial prostatitis can be treated effectively through many modalities that subside the inflammatory process and diminish the prostatic signs and symptoms. One of these existing modalities is the use of trans-perineal phonophoresis using pumpkin seeds oil and low intensity ultrasound which are considered to be an adjunct treatment with less or no side effects.

Authors contribution SA Tantawy and HM Elgohary: designed and conducted research. DM Kamel: collected the data and made statistical analysis. HM Elgohary and SA Tantawy: wrote the paper; DM Kamek: revised and edited the manuscript. All authors read and approved the final manuscript.

Compliance with ethical standards

Conflicts of interest

The authors declare that they have no conflict of interest.

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