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Original Research Article

Mechanism of Hijāma bi'l Shart (wet cupping) explained in view of piezo channels in Waja'al-Rukbah (knee osteoarthritis): an open labelled, randomised, controlled clinical trial

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ABSTRACT

Background: Osteoarthritis (OA), described as *Waja'al-Mafāṣil* in Unani medicine, results from an imbalance between degeneration and regeneration of articular cartilage and bone, where natural repair mechanisms become inadequate. It is a major public health issue and a leading cause of disability in developing countries. Wet cupping, an important Unani therapeutic modality, is explored here for its scientific basis through piezo-channels-mechanosensitive ion channels that convert mechanical pressure stimuli, a key component of wet cupping, into electrochemical signals that may influence joint pathology.
Methods: A non-inferiority RCT was conducted on 60 OA patients aged 40-70 years, randomized 1:1 into test (wet cupping) and control (Aceclofenac 100 mg twice daily) groups. The test group received five cupping sessions on days 0, 15, 30, 45 and 60, and both interventions lasted 8 weeks. Outcomes were assessed using WOMAC, 100-mm VAS, and active range of motion, along with subjective symptoms. Safety was evaluated through hemogram, LFT, KFT, and urine tests at baseline and week 8.
Results: Pre-protocol analysis included 60 patients (30 test, 30 control) who completed the study. Both groups showed significant improvement in objective parameters (VAS, WOMAC, AOR) and subjective measures. However, intergroup comparison revealed no statistically significant difference between the test and control groups.
Conclusions: Wet cupping's mechanotransduction effects explain intergroup differences, suggesting it can serve as an effective alternative treatment for knee osteoarthritis.

Keywords: *Hijāma bi'l Shart,* Knee osteoarthritis, Piezo channels, *Waja'al-Rukbah,* Wet cupping

INTRODUCTION

OA is a heterogenous disease characterized by progressive cartilage loss subchondral bone remodelling, osteophyte formation and Synovial inflammation with resultant joint and increasing disability[1].OA is characterized by a change in chondrocyte behaviour that leads to elevated production of proteolytic enzymes such as matrix metalloproteinase 13, cartilage damage and loss of joint function.[2] OA is one of the leading cause of disability and it's worldwide prevalence estimate for symptomatic OA is 9.6 % among men and 18% among women.[3] It is painful and debilitating disease of the synovial joints, affecting 12-15% of the population between 25-74 years of age.[4] Recent estimates suggest that worldwide 250 milliom people are burdened by the

incidence of knee OA.[5] Osteoarthritis affects all ages and has multifactorial etiologies.Several responsible genes are associated with the occurrence of this disease. Previous knee trauma increases the risk of knee OA by 3.86 times. Old age, female gender, overweight, obesity, knee injury, repetitive use of joints, bone density, muscle weakness and joint laxity, all play roles in the development of joint OA.[6] OA can be classified based on the etiology into primary (idiopathic) or secondary.[7] Primary OA is the most common type, it has no clear etiology but is thought to have genetic predisposition. Where as secondary OA is associated with known cause but the resulting pathology is the same as of primary OA.[8]

Despite excellent medical care, there is no more cure for OA in the modern era. Currently OA treatment is focused on control of symptoms, preventing disease progression, minimizing disability, improving quality of life and avoid over treatment with potentiality harmful pharmacologic agents.[9] These drugs have the undesirable side effects e.g. gastric ulcer, dyspepsia, renal impairment, hepatotoxicity and abdominal pain .Unani medicine may offer an alternative treatment for relieving the symptoms of OA and overcoming the side effects of the conventional medication.Unani medicine has an entirely differently approach to disease diagnosis and treatment than conventional medicine.

OA is clinically similar to the well-established disorder *Waja'al-Mafāṣil*.[10] *Ibn Sina* defined *Waja'al-Mafāṣil* as pain of the joints, which is caused by the retention of morbid matter, usually *Balghami Madda*.[11] *Akbar Arzani* mentioned that pain and inflammation of hands and legs as *Waja'al-Mafāṣil*. Likewise, *Ismail Jarjani* described *Waja'al-Mafāṣil* as the accumulation of morbid matter in the joints and cavities of the organs which produces pain and inflammation.[12] According to the *Ibn Sina* the etiology of *Waja'al-Mafāṣil* are divided into two types.[13] *Asbab-i-Faila* the factors which affect the joint and create susceptibility of disease and *Asbab-i-munfaila* which indirectly affect the joint and causes structural and functional disturbance in the joint, these include; congenital weakness of joints, acquired weakness of joints ,onset of a new un-natural passage due to movement, *tahallul, and takhalkhul*, which may be either congenital on acquired etc.[14]

The Unani treatment of OA is based on addressing the root cause of the disease for which different regiminal therapies are put into use.[15] Management of different types of *Waja'al-Mafāṣil* varies from each other. If it is due to *Sue-i-Mizaj Sada,* then it is to be treated with *T'adeel-i-mizaj* (alternation of temperament) whereas, in case of *maddah*, it has to be treated through *imala and istifaragh*, so as to correct the imbalance of *khilt*. For this purpose, a number of pharmacopial preparation and regiminal therapies are being put into practice by the ancient Unani physicians and *Hijama bilshart* is one of them.[16]

This study was carried-out to evaluate the efficacy of wet cupping in knee OA in comparison to tablet Aceclofenac and in this study, we also explained the add on benefits of wet cupping with the concept of piezochannels, which are the ion channels that represent key type of machanotransducers that effectively convert machanical stimuli into electrochemical signals which is important for both physiological and pathological process.[17] Piezo channels play crucial rule in numerous physiological and pathological process by functioning as cellular machanotransducers.[18] Wet cupping being one of the finest regiminal therapies, appears to work through the process of machanotransduction, as during the procedure of wet cupping one of the steps involved is the application of pressure (shear force),which is done for the purpose of increasing the blood circulation which activates the piezo channels through the process of Machanotransduction.

METHODS

Trial design and setting

The study was planned as comparative, open labelled, randomized trial and was conducted on 60 patients of knee OA at the Outpatient Department (OPD) of Regional Research Institute of Unani Medicine, Srinagar, India from April 2018 to June 2019.

Participants

The study recruited participants of either sex, aged between 40 to 70 years, who met American College of Rheumatology Criteria for osteoarthritis of different joints, had symptoms consistent with osteoarthritis of the joint involved for at least six months to screening, were willing to discontinue all NSAIDS or other analgesic medication taken for any condition, willing to sign the informed consent, follow the protocol and participate in clinical trial voluntarily.

However pregnant and lactating mothers, patients with renal dysfunction, liver diseases, gastrointestinal diseases, ischemic heart disease, hypertension, patients with the surgical history of joint involvement and patients unable to read/or understand the WOMAC questionnaire form were excluded.

Interventions

Participants of the test group were subjected to *Hijama bi'l Shart* on affected joint as per the standard schedule. Four cups were applied on the knee on each side (medial femorotibial, lateral femorotibial or patellofemoral junction) for a period of approximately 5-10 minutes. Participants of the control group received Tablet Aceclofenac 100 mg twice daily.

Parameters

Objective parameters

VAS (intensity of pain): VAS is a 10 cm numerical Linkart scale. Pain intensity was evaluated and measured along a 0-10 scale, where 0 is no pain,1-3 is mild pain,4-6 is moderate pain,7-10 is severe pain. The patient's maximum level of pain experienced in the preceding 48 hours recorded once in each follow ups with baseline.

WOMAC score: This functional assessment instrument consists of three sub scales; 1) Pain sub scale- which asks 5 questions about pain intensity during low level daily activities and at night in bed, 2) Severity of stiffness- 2 questions, 3) Physical function difficulty -27 questions.

The patient's answer was graded on a questionnaire scale (0-none, 1-mild, 2-moderate, 3-severe, 4-extreme). The measure takes approximately 5 to 10 mins to complete. The scores are totaled for each sub scale with maximum total of 108. The WOMAC score was recorded at the baseline and after the treatment.

Active range of motion (AROM): Severity of OA knee was evaluated through this scale. The patients report outcome according to 3 sub scales. The questionnaire focuses on pain and complaints felt by the patient, the maximum walking distance, and his ADL. Each answer is graded by points. This scale was recorded at the base line and post treatment.

X- ray knee joint: Subjective parameters included the following: a) Pain in knee joint, b) Morning stiffness, c) Difficulty in movement. All the subjective parameters were evaluated on each follow up.

Safety and adverse event monitoring

Both groups (test and control) were assessed for the safety parameters by means of hematological and biochemical tests which include hemogram, ESR, Blood urea, Serum creatinine, SGOT, SGPT and Urine routine with microscopy. No adverse effect was observed throughout the study in both the groups.

Withdrawal criteria

Participants were eliminated from the study if they experienced adverse effects, non-compliance to protocol.

Sample size

The total sample size of the study was 60, 30 in test and 30 in control group.

Randomization

The participants were randomly allocated into test and control group in a ratio of 1:1 by using computer generated allocation sequence.

Assessment of Mizaj

The *Mizaj* of the patients was determined on the basis of assessement of *Ajnas-e-Ashara*. 33 patients had *Balghami Mizaj,* 25 patients were *Damvi* and 2 patients had *safrawi mizaj*.

Informed consent

Enrolled patients after fulfilling the inclusion criteria were given the informed consent sheet to refer thoroughly, which possess details regarding the nature of the study, the drugs and regimens to be used method and duration of treatment, its risks and benefits and patients' association with the study is purely voluntarily his/her responsibilities and confidentiality of records etc. Patients were given the right to ask any query with the investigator, after acceptance to participate in the study, were requested to give written informed consent duly signed with date.

Duration of protocol therapy and follow ups

Hijama bi'l Shart (wet cupping) was applied on the affected joint as per the standard schedule. The duration of therapy was two months. The schedule of therapy was 60 days with 5 follow ups including baseline i.e. 0, 15th, 30th, 45th, 60th day.

RESULTS

Demographic and clinical profile

The duration of protocol therapy was completed by 60 patients. The majority of patients 24 (40%) were between the age of 40 to 45 years, 15(25%) in the age group of 46-51 years, 13 (21.67%) from 52-57 years, 5 (8.33%) from 58 -63 and 3 (5%) from 64 -69. This data indicates that the disease is more prevalent in 40-45 years of age. The female patients were found to be 37 (61.67%) and 23 (38.33%) were males which supports the fact that this disease is more common in females and coincides with the findings. All the 60, (100%) patients were married, and occupation-wise around 34 (56.66%) patients were stay-at-home wives, 8 (13.33%) were shopkeeper and rest are distributed in different business, this study gives the confirmation that observations coincides with the findings.

The dietary habits of most of patients was mixed type with 57 (95%) of them falling into this category and 3(5%) patients were vegetarian, which indicates the fact that OA has the specific relationship with dietary pattern as mixed diets induces weight gain which is a predisposing factor for knee OA. Around 29 (48.3%) patients were from upper lower class. On *Mizaj* assessment 33 (55%) patients had *Balghami Mizaj*, 25 (41.66%) were with Damvi Mizaj and 2 patients had *Safrāwī Mizaj*, this finding supports the facts of Unani

literature described by Ibni-e-Sina and Hakeem Azam khan that people with *Balghami Mizaj* are more likely to develop knee OA. Out of 60 patients 30 (50%) were having disease since <10 months, 26 (43.33%) were 10-20 months and 4 (6.66%) were >20 months. This disease is age related disorder with degradation and loss of the articular cartilage is a central feature that is sometimes attributed to 'wear and tear' and related to duration of illness.

Assessment of the effects of interventions on subjective parameters

Knee joint pain

The effect of the study on ''Knee joint pain'' was assessed with VAS, where the mean score with differences was observed in test group on baseline, 1st, 2nd, 3rd, and 4th and follow-ups as 8.600.50, 8.130.51, 6.470.86, 4.271.01, and 2.370.85 whereas, in control group 8.3330.55, 8.100.66, 6.400.77, 4.400.89, and 2.230.73 (Table 1).

Table 1: Pain- a comparison in two groups of patients studied.

Pain	Test group	Control group	Total	P value
Follow up 1	8.13±0.51	8.10±0.66	8.12±0.58	0.827
Follow up 2	6.47±0.86	6.40±0.77	6.43±0.81	0.753
Follow up 3	4.27±1.01	4.40±0.89	4.33±0.95	0.591
Follow up 4	2.37±0.85	2.23±0.73	2.30±0.79	0.051

Table 2: Morning stiffness- a comparison in two group of patients studied.

Morning stiffness	Test group	Control group	Total	P value
Before treatment	8.23±0.77	8.07±0.64	8.15±0.71	0.367
Follow up 1	7.40±0.81	8.03±0.41	7.72±0.72	<0.001
Follow up 2	6.20±1.06	7.20±1.10	6.70±1.18	0.001
Follow up 3	5.10±0.88	6.67±1.54	5.88±1.47	<0.001
Follow up 4	2.67±0.76	5.63±2.76	4.15±2.50	<0.001

Table 3: Difficulty in movements- a comparison in two groups of patients studied.

Difficulty in movements	Test group	Control group	Total	P value
Before treatment	8.67±0.48	8.57±0.68	8.62±0.58	0.513
Follow up 1	7.40±0.72	7.80±0.76	7.60±0.76	0.041
Follow up 2	5.97±1.03	6.97±0.76	6.47±1.03	<0.001
Follow up 3	4.63±0.89	5.10±0.80	4.87±0.87	0.037
Follow up 4	2.80±0.48	3.17±0.46	2.98±0.50	0.004

The pre and post treatment findings were compared statistically using Friedman test for intra group and Kruskall-Wallis test for inter group comparison with Dunns multiple pair comparison test. The intergroup comparison shows statistically in significant. However, improvement was observed in test and control group with p0.001. These findings may be due to increased muscle activity which results in pain reduction.

The effect of the study on "morning stiffness" was assessed with VAS where the mean scores with differences was observed in test group on baseline, 1st, 2nd, 3rd, and 4th follow ups as 8.230.77, 7.400.81, 6.201.06, 5.100.88, and 2.670.76 whereas, in control group 8.070.64, 8.037.201.10, 6.671.54, and 5.632.76 (Table 2). The pre and post treatment findings were compared statistically using Friedman test for intra group and Kruskall-Wallis test for inter group comparison with Dunns multiple pair comparison test.

The mean VAS scores in test group at 3rd follow-up was observed significant with p 0.01, and highly significant with p 0.001 at 4th follow-ups with reference to baseline. In control group the mean scores were found significant with p0.040 at 3rd follow up and highly significant with p0.001 at 4th follow-ups with reference to baseline.

The inter group comparison shows statistically in significant. However, improvement was observed in test and control groups with, p 0.001. This finding may be due to increased muscle activity and evacuation of morbid materials which results in morning stiffness reduction.

Difficulty in movement: The effect of the study on "morning stiffness" was assessed with VAS, where the

mean scores with differences was observed in test group on baseline, 1st, 2nd, 3rd, and 4th, follow ups as 8.670.48, 7.400.72, 5.971.03, 4.630.89, and 2.800.48, whereas, in control group 8.570.68, 7.800.76, 5.100.80, and 3.170.46 (Table 3). The pre and post treatment findings were compared statistically using Friedman test for intra group and Kruskall-Wallis test for inter group comparison with Dunns multiple pair comparison test.

The mean VAS scores in test group at 3rd follow-up was observed significant with p0.01, and highly significant with p0.001 at 4thfollow ups with reference to baseline. In control group the mean scores were found significant with p0.040 at 3rd follow up and highly significant with p0.001 at 4th follow-ups with reference to baseline.

The inter group comparison shows statistically in significant. However, improvement was observed in test and control groups with, p0.001. This finding may be due to evacuation of morbid materials and reduced the stiffness of joint.

Assessment of the effects of interventions on objective parameters

Effect on VAS score: The effect of the study was assessed with VAS, where the mean scores with differences was observed in test group before and after treatment are 8.260.52, and 2.130.62 whereas, in control group 8.330.54 and 4.300.72 (Table 4). The pre and post treatment findings were compared statistically using student t test (two tailed, independent).

Table 4: VAS score - a comparison in two groups of patients studied.

VAS score	Before treatment		After treatment		Percentage of improvement	P value
	Mean	SD	Mean	SD		
Test group	8.26	0.52	2.13	0.62	74.21	<0.001
Control	8.33	0.54	4.30	0.72	48.37	<0.001
P value (Test group vs Control)	<0.001					

Table 5: WOMAC- a comparison in two groups of patients studied.

WOMAC	Before treatment		After treatment		Percentage of improvement	P value
	Mean	SD	Mean	SD		
Test group	75.23	3.91	16.53	3.10	78.02	<0.001
Control	76.51	2.80	27.76	6.87	63.71	<0.001
P value (Test group vs Control)	<0.001					

Table 6: Flexion- a comparison in two groups of patients studied.

Flexion	Before treatment		After treatment		Percentage of improvement	P value
	Mean	SD	Mean	SD		
Test group	108.30	7.46	166.70	6.60	53.92	<0.001
Control	108.00	9.61	133.66	4.84	23.75	<0.001
P value (Test group vs Control)	<0.001					

The intergroup comparison shows statistically in significant. However, improvement was observed in test and control groups with p 0.001. Cupping superimposes acute inflammation on chronic inflammation. The chronic inflammation of cartilage that is deep seated has acute inflammation on the skin and muscle and these findings may be due to evacuation of morbid materials and reduced the severity of pain.[27]

The effect of the study on pain subscale of WOMAC index, where derived from the mean scores with differences before and after the treatment in test group observed as 75.233.91 and 16.533.10 whereas, in control group 76.512.80 and 27.766,87 (Table 5)**.** The inter group comparison shows statistically significant. However, improvement was observed in test and control groups with, 0.001.

The mean scores of both groups were compared statistically using Student t test (two tailed independent).

For active range of motion (AROM) (Flexion) in both groups i.e. test and control groups are equally effective for active range of motion with p0.001. Flexibility and range of motion are very important factors in sports performance, rehabilitation and musculoskeletal pain. Releasing of toxins and removal of wastes and heavy metals might be explained by 'Blood Detoxification theory' (Table 6). These theories may overlap or work interchangeably to produce various therapeutics effects in specific ailments and diseases and apparently, no single theory exists to explain the whole effects of cupping.

Effects of the study interventions on safety parameters

The effect of the study on safety parameters was assessed with reference to the findings of pre and post study through clinical. Haematological and biochemical parameters. The clinical findings like unusual effects or reaction were not observed. Similarly haematological and biochemical parameters were found within the normal range, and all safety parameters were found statistically insignificant (Table 7). Therefore, these studies methods were found free from ant adverse effects, hence, concluded safe and therefore may be used in the management of OA.

DISCUSSION

In this study, the mechanism of wet cupping in view of piezo receptors is explained. Wet cupping has been considered as the remedy for different musculoskeletal disorders, prophylaxis as well as important means for preventing the progression of disease.[22-29] Though wet cupping is put into practice from ancient times but the possible mechanism of it is not well known till date .This study attempts to prove that wet cupping works through mechanism of activation of piezo proteins, which are the special type of sensory receptors present in the skin, vessels, bones etc.[29] During cupping suction cups are applied to skin, near joints or areas of somatic pain, creating a negative pressure. Negative pressure can stimulate angiogenesis, improves blood circulation, promote the regeneration of bone possibly by enhancing the expression of vascular endothelial growth factor (VEGF) and bone morphogenetic protein (BMP)-2.[30] The piezo protein guided effect of cupping therapy is one of the most appropriate mechanisms that could be hypothesized in the current era. However more comprehensive research is needed to fully understand this newly hypothesized piezo protein theory of cupping therapy. Wet cupping, a well-known regiminal therapy of Unani medicine is a six step procedure i.e. skin demarcation, sterilisation, cupping (negative pressure), puncturing, cupping (negative pressure) and sterilisation.[31] As wet cupping involves the application of cups with negative force at the site of demarcation and this negative pressure induced during this procedure activates the process of machanotransduction which is considered to be responsible for providing the stimulus to piezo channels present in the body. Through piezo channels a number of benefits attributed to wet cupping in knee osteoarthritis include the following:

Maintenance of cartilage homeostasis; Bone cells include osteoblast lineage, osteocytes and osteoclasts. Osteocytes are terminally differenciated osteoblasts that are derived from MSC's. Osteocytes play a vital role in bone homeostasis by regulating the formation and activity of osteoblasts and osteoclasts.[32] In addition, the cartilage that connects the bones in the joints is also an intrensically machanosensitive tissue composed of chondrocytes as the only cell type. Chondrocytes one of the differenciation directions of MSC's regulate the metabolism of the cartilage extract cellular matrix to adapt to the machanical stress environment.[33] At present many studies have found that piezo 1 is expressed in bone and plays an important machanotransduction role there.[34] Morever piezo channel 1 and 2 are expressed in chondrocytes and participate in maintenance of cartilage homeostasis associated with machanotransduction.[35]

Osteocytes can generate signals to regulate bone forming osteoblasts and bone resorbing osteoclasts to renew bone.[36] Recently, Sasaki et al found that activation of piezo 1 activated by mechanical stretch in osteocytes can mediate phosphorylation of Akt (protein kinase B, encoding product of retroviral Ann gene v-Akt), which downregulates the expression of sclerotin. Since sclerotin could lead to decreased bone mass.[37] Piezo 1 in osteocytes inhibits the expression of sclerotin by activating the Akt signal pathway to promote bone formation.

Physical factors, such as mechanical strain, vibration and hydrostatic pressure, are important in the osteogenesis and differentiation of MSCs.[38] Sugimoto et al established a cell chamber capable of controlling hydrostatic pressure, in which the increased expression of piezo 1 was detected and the osteogenic differenciation was enhanced in primary MSC's and MSC's lines *in vitro* research.[38]

Recently it was proposed that piezo channels are of functional importance in chondrocyte machanotransduction. Lee et al Detected robust expression of piezo 1 and piezo 2 in primary chrondocytes of mice, pigs and humans.[39] *In-vitro* machanical stress can cause Ca ions to flow into chondrocytes through piezo channels, resulting in cell apoptosis (of damaged chondrocytes). Piezo 1 also plays an important role in the endochondrial ossification in which chondrocytes are involved.

This study has few limitations. The proposed mechanism of wet cupping through Piezo-protein activation is theoretical and not supported by direct molecular or electrophysiological evidence in this study. The study did not include objective assessment tools such as MRI, ultrasound, or biochemical markers to validate changes in cartilage homeostasis, osteogenesis, or bone remodeling. The negative pressure generated during cupping was not standardized, quantified, or analyzed in relation to Piezo receptor activation thresholds.

CONCLUSION

From the above mentioned discussion, it can be concluded that through the activation of piezo 1 and piezo 2 channels, wet cupping can yield number of benefits like improvement in the signs and symptoms of osteoarthritis, may promote cartilage maintenance, enhance bone remodelling, and support the regenerative processes

important in knee osteoarthritis. Hence these findings suggest that wet cupping may serve as a potential alternative or adjunct in the management of osteoarthritis. However, further comprehensive research is necessary to validate the Piezo-protein–guided mechanism of wet cupping and clarify its therapeutic role in musculoskeletal disorders.

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