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Efficacy of *Nutūl-i-Ḥār* (Hot Irrigation), a Polyherbal Unani Formulation, in the Treatment of *Shaqīqa-i-Muzmin* (Chronic Migraine): An Open Single-Arm Exploratory Clinical Trial

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Abstract

Shaqīqa-i-Muzmin (chronic migraine) is a type of migraine that is usually caused by cold humours (*bārid akhlāṭ*), specifically by phlegm (*balgham*) and to lesser extent by black bile (*sauda*). The aim of this study was to evaluate the effect of *Nutul-i-Ḥār* (hot irrigation) in the treatment of chronic migraine. *Nutul* (irrigation) therapy is widely and successfully used in diseases of head as described in *Unānī* system of medicine. This open, single-arm, exploratory clinical study was conducted in 30 patients of chronic migraine selected by convenient sampling method. One litre decoction prepared with 12 g each of *Astragalus hamosus* L. (*Iklilul malik*), *Matricaria chamomilla* L. (Babuna), *Artemisia absinthium* L. (*Afsanteen*), *Origanum vulgare* L. (*Marznjosh*) and *Trigonella foenum graecum* L. (*Hulba*) was poured over painful side of head for 45 minutes on every alternate day for a period of 30 days (15 sittings). The patients, thereafter, were followed untill 90th day of the study for various outcome measures comprising headache intensity, headache frequency, Migraine Disability Assessment Scale (MIDAS), and rescue medication. The reduction in headache frequency, MIDAS score and use of rescue medication was significant ($p < 0.001$) after the treatment. Reduction in headache intensity at 30th day, 60th day and 90th day was significant as compared with baseline values ($p < 0.001$) but not statistically significant at 90th day with respect to 60th day ($p > 0.05$). Statistical analysis was done using parametric (paired t-test) and non-parametric tests (Wilcoxan sign ranked test, Freidman with Dunn's multiple comparison tests). Hot irrigation with medicated decoction was found effective in the treatment of chronic migraine.

Keywords: Unani medicine; Therapeutic irrigation; Hydrotherapy; Classical migraine

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Introduction

Headache (*suda'*) was first described as a disease or true medical condition by *Buqrāṭ* (Hippocrates). He distinguished different types of headaches and described aura-related symptoms. He also mentioned the severe pain in one half of the head associated with disturbance of sight. *Jālīnūs* (Galen) differentiated migraine from other common headaches and named it as 'Hemicrania' which transformed to 'Hemicranium' in Latin, 'megrim' in old English and migraine in French [1,2]. *Shaqīqa* (migraine) is derived from the word 'Shaq', which means 'to part' [3].

The signs and symptoms of *Shaqīqa* (migraine) fairly correlate with those of migraine as described in modern medicine. The diagnostic criteria of migraine entail repeated attacks of headache lasting 4-72 h with a normal physical examination, no other reasonable cause for the headache; and at least 2 of the following features: (a) Unilateral pain, (b) Throbbing pain, (c) aggravated by movement, (d) Moderate or severe in intensity; plus at least 1 of the following features: (a) Nausea/vomiting, (b) Photophobia and phonophobia [4]. *Shaqīqa* (migraine), as mentioned in classical *Unānī* literature, is usually episodic [5], unilateral or sometimes bilateral [3] pulsating in nature, and controlled by compression of pulsating arteries [6]. It is sometimes associated with nausea, vomiting, pricking and burning pain [3,7] and inability to hear sharp sound or long conversations (phonophobia) and see scattered light (photophobia) [8]. The clinical features thus described in *Unānī* literature largely resemble with those of migraine as mentioned in modern medicine.

Chronic migraine is caused by cold humours, characterized by long-standing hemicranias occurring on most of the days with photophobia, phonophobia and vomiting [5,9]. *Bukhārāt* (vapours) and *akhlāṭ-i-ghalīẓa* (viscid humours) produced in different parts of the body ascend and accumulate in head to cause headache [10,11].

The prevalence of migraine in Southeast Asian region is 10.9% [12] and approximately 109 million Indians are suffering from migraine [13]. One-year population prevalence of headache disorder in Karnataka is 25.6% [14] with a prevalence higher in females (32.4%) than males (18.6%) [15]. The migraine headache influences 11.4% population (7.9% males and 14.8% females) worldwide [16] with a prevalence of chronic migraine approximately 2% [17]. Global Burden of Disease Study identified that migraine is the third most prevalent disease worldwide and seventh leading specific cause of disability [18].

The goals of managing migraine are to reduce migraine frequency, severity, disability of patients and improve the quality of life. Hence, treatment is divided into two categories: *Halat-e-Sukun ka Ilaj* (Prophylactic management) and *Dore ka Ilaj* (Management during episode) [19,20]. Despite having effective treatment in conventional system of medicine such as Triptans for acute migraine attacks, the response rate varies from 44-70%. Some patients do not get relief by two hours after taking oral migraine medications, and some experience adverse effects such as dyspepsia, gastrointestinal irritation, and nausea [21].

Unānī physicians have successfully treated chronic migraine since ancient times without observation of significant side effects on the basis

of the principles of *Tanqia wa Tadeel* (cleansing and rejuvenation) achieved by *Munzij wa Mushil Advia* (concoctive and purgative drugs) including various regimenal modalities [5,22,23]. The concoctives and purgatives in the treatment follow to achieve the goal of anti-temperament (allopathic) principle of the treatment which lays out that the drugs selected to treat a disease should possess temperament opposite to that of the treated disease.

Since, chronic migraine is usually caused by cold humours; therefore, drugs used in the treatment should be *Ḥār* (hot) in temperament according to the anti-temperament principle of treatment. The drugs used in the test formulation possess hot temperament which is opposite to that of the disease to balance out the deviated temperament back to normal in order to alleviate the symptoms and cure the disease. Furthermore, the test drugs have *Daf'-i-alam* (Analgesic) [24], *Musakkin* (Sedative) [25,26,27,28,29] *Moḥallil-i-Awrām* (Anti-inflammatory) [11,25,27,29,30,31,32,33], *Mulayyin-i-awrām* (Resolvent) [26,27,30,31,32], *Munzij Mawād* (Concoctive) [31,34,35], Mufaṭṭiḥ (Deobstruent) [29] *Muqawwi dimagh wa A'sab* (brain and Nerve tonic) [30,31], Qabiḍ (astringent) and *Rādi'* (repellent) [5] properties which help reverting the pathology of chronic migraine and control the accompanying symptoms.

Several experimental studies confirm anti-inflammatory, immunomodulatory, antianxiety, antistress activities [36] of the test drugs which further corroborate the properties of the drugs as mentioned in classical *Unānī* literature, employable to control and treat the chronic migraine.

Nutūl (Irrigation) is one of the several regimenal modalities used in many diseases such as Sudaa' (headache), *Shaqīqa* (migraine), *Sarsaam Saudavi* (meningitis), *Sahar* (insomnia), *Malankholia* (melancholia), *Mania wa Da-ul-Kalb*, *Nisyan* (amnesia), *Fālij* (paralysis), *Sara'* (epilepsy), and *Sakta* (stroke) [20].

Nutūl (Irrigation) is a procedure of slowly and steadily dripping of medicated liquid from a pre-fixed height over selected body part for a pre-determined period of time [37,38]. Ibne Sina classified it into *Nutūl-i-Ḥār* (hot irrigation) and *Nutūl-i-Bārid* (cold irrigation) and suggested the use of both alternatively for the purpose of resolution of causative pathological substances and strengthening of diseased part. It stimulates local nerve endings and trigeminal nerve; changes somato-autonomic reflexes and levels of various neurotransmitters including serotonin and catecholamine, resulting in sympathetic suppression and physio-immunological changes of peripheral circulation and natural killer cell activity [39,40]. Sensory stimuli due to continuous irrigation may dominate the painful stimuli by activation of large diameter myelinated fibers. This may lead to loss of gate to small nociceptive impulses. Both hypo and hyperthermia are known to exert strong physiological and hemodynamic effects on the body [41]. Studies have shown that warm water exposure decreases sympathetic power and increase vagal tone [42,43]. It is plausible that vasogenic inflammation and constriction that are hallmarks of migraine may be modulated by thermal applications resulting in clinical improvement. Keeping this in view, a study was planned to evaluate the efficacy of *Unānī* treat-

ment in management of chronic migraine using hot irrigation on affected side.

Materials and Methods

Ethical Approval

The study was approved by the Institutional Ethics Committee vide registration number NIUM/IEC/2016-17.023/IBT/01 and conducted in accordance with the Helsinki declaration, and the Good clinical practice guidelines of Ministry of Health and Family Welfare, Government of India. The trial was registered on clinical trial registry of India (www.ctri.nic.in) bearing a number CTRI/2018/03/012584.

Study design

This was a prospective, open-label, single-arm, pre and post individual controlled clinical trial conducted in National Institute of Unani Medicine, Bengaluru during February, 2019 to March, 2020.

Study participants

Clinically diagnosed patients of chronic migraine as per The International Classification of Headache Disorders (ICHD)-3 criteria having at least ≥15 headache days per month between the ages of 18 to 60 years of either gender were included in the study by convenient sampling method. Participants below 18 years and above 68 years of age, those with neuropsychiatric illness, familial hemiplegic migraine, mental illness, renal, hepatic, respiratory or cardiac comorbidities, pregnant and lactating women, and unwilling to participate were excluded from the study.

Sample size

The sample size was calculated on the assumption that mean change of visual analogue scale (VAS) for pain assessment from baseline to the end of treatment was expected as one. The standard deviation ($\sigma = 2.5$) was obtained from a study done earlier [44]. By using the following formula, the required sample size was 30 to achieve an 80% power at $\alpha = 0.05$. With projected dropout rate of 20%, 36 patients were required for the completion of the study (Figure 1). $N = (Z\alpha)^2S^2/d^2$) was the formula used for sample size calculation in this single group study [45].

Informed Consent

Eligible patients were provided with detailed information about treatment procedure and total duration of study protocol. Patients were given sufficient time to go through the information sheet and allowed to ask any doubt regarding the study procedure. The patients willing to participate in the study were asked to sign the consent form.

Intervention

Enrolled patients received 15 sittings of irrigation therapy with decoction of polyherbal *Unāni* formulation, (Table 1) on alternate days during the treatment phase of 30 days. The decoction was prepared freshly on every sitting.

Preparation of Decoction

All the drugs were pounded and soaked in 2 litres of water at least before 4 h of preparation of decoction for irrigation. All the drugs were boiled on medium heat until half the water

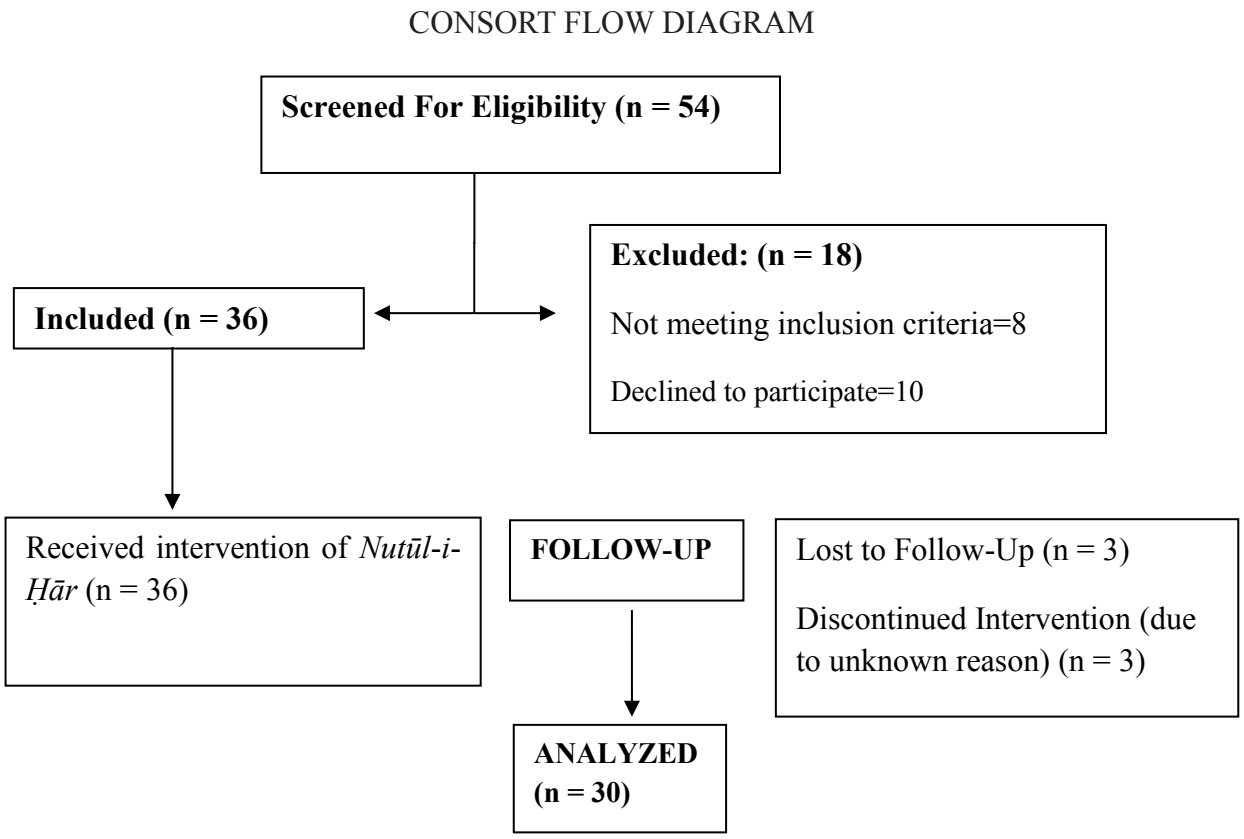

Figure 1. Flow diagram of study participation

Table 1. Ingredients of decoction (per sitting)

S. No.	Name of Drug	Scientific Name	Dose	Parts used in the Study
1	*Ikleel ul malik*	*Astragalus hamosus* L.	12 g/day	Pods
2	*Baboona*	*Matricaria chamomilla* L.	12 g/day	Flowers
3	*Hulba*	*Trigonella foenum-graecum* L.	12 g/day	Seeds
4	*Afsanteen*	*Artemisia absinthium* L.	12 g/day	Whole plant
5	*Marzanjosh*	*Origanum vulgare* L.	12 g/day	Leaves and seeds

evaporated. The decoction, thus prepared, was filtered in a pot and allowed to turn lukewarm. Decoction of medicine was prepared fresh on every treatment visit.

Procedure of Intervention

Before starting the treatment, vitals of the patients were recorded and the treatment procedure explained in language acquainted to them. The patient was asked to lie in supine position with both the eyes covered with wet cotton pads. The irrigation pot containing decoction was mounted at arm length height (approx. 1 meter) on a stand and fixed to focus on the painful site of head. The decoction was released to pour in continuous stream from the pot by turning on the knob and the flow controlled at a rate of approximately 45 mL/min to finish the procedure in 45 min. After completion of each sitting of irrigation therapy, patients were instructed to dry

their hair with a towel and cover their heads for 30 min.

Outcome Measures

The outcome measures were assessed on the basis of 11-point numeric rating scale (VAS), headache frequency, Migraine Disability Assessment Scale (MIDAS) [46], and total number of rescue medicines used.

After selection of patients, detailed history was taken; general physical examination carried out and data recorded in prescribed pro forma. Patients' socioeconomic status was assessed by Kuppuswamy Socioeconomic Scale-Modified 2017. Kannada translated version was used for patients' convenience [14].

All the patients having at least ≥ 15 headache days in a month were enrolled and asked about their detailed disease history including onset of disease, medications used for acute treatment and prophylaxis. Female patients were asked about any relation of headache frequency or headache intensity with menstrual cycle. Headache frequency was recorded in number of days, the patient had in last three months.

Number of Rescue medication used in previous three months before starting the test treatment and three months afterwards were recorded for the comparison. The patients were advised to take ibuprofen, 400 mg, as rescue medication as and when required but not more than 1200 mg in 24 h.

Follow-up and efficacy assessment

The overall duration of the protocol was 90 days (30 days treatment period and 60 days post-treatment follow-up). The patients were assessed clinically on 0 day (baseline), 15th day, 30th day, 45th day, 60th day, and 90th day.

Statistical analysis

Analysis of the data was performed by an intention to treat analysis. The participant who received at least one sitting of treatment procedure and had been assessed once post baseline was included in the final assessment. MIDAS and Number of rescue medication used were assessed by Wilcoxan matched pair signed-rank test. Headache intensity was assessed by Freidman with Dunn's multiple comparison tests; while headache frequency was assessed by paired t-test.

Results

Thirty-six out of 54 screened patients having at least ≥ 15 headache days per month were selected for irrigation therapy. Out of 36 patients, 30 patients were analysed statistically for any change in assessment parameters; while 6 patients were not assessed due to not having at least one post treatment assessment.

The demography of the participants is depicted in table 2. The mean age of the participants observed in the study was 36.9±9.9. In the present study, 23 (76.66%) patients were female, 26 (86.66%) participants were married, 17 (56.66%) were unemployed and 23 (76.66 %) participants had no family history of migraine. Out of 23 female participants, 20 (86.95%) showed no relation of migraine with menstrual cycle.

Table 2. Participants demographics

Demographic Variables	Values in Mean ± SD or %
Age (years)	36.9 ± 9.9 (30)
Female	76.66 (23)
Married	86.66 (26)
Non-employed	56.66 (17)
No family history of migraine	76.66 (23)
No relation with menstrual cycle	86.95 (20)

SD = Standard Deviation

Table 3 depicts the effect of intervention on the frequency of headache score after the treatment. There was statistically significant reduction ($p < 0.001$) in headache frequency from base line (51.800 ± 2.096) to 90th day (11.066 ± 4.643) with a mean difference of 40.734.

The mean changes in intensity of pain on 11 points numeric rating scale (VAS) are depicted in table 4. A statistically significant reduction ($p < 0.001$) in mean pain score was observed from base line (6.196 ± 1.327) to 30th day (4.44 ± 1.758), 60th day (3.223 ± 2.102) and 90th day (4.72 ± 1.398). This difference persisted up to 60th day. No statistically significant change ($p > 0.05$) was observed in pain score between 60th (3.223 ± 2.102) and 90th days (4.72 ± 1.398). Rank sum difference from base line was 47at 30th day, 69 at 60th day and 44 at 90th day and Freidman calculated was 55.276.

Table 3. Effect of intervention on the frequency of headache

Frequency of Pain	Before Treatment (3 months)	After Treatment (3 months)	Difference from Baseline	p value
Mean ± Standard deviation	51.800 ± 2.096	11.066 ± 4.643	40.734	$p < 0.001$*

Table 4. Effect of intervention on the intensity of pain

Results	Baseline	30th day	60th day	90th day
Mean ± SD	6.9166 ± 1.327	4.44 ± 1.758	3.223 ± 2.102	4.72 ± 1.398
Difference from baseline	-	2.477	3.693	2.197
Sum of rank	115	68	46	71
Rank sum difference	-	47	69	44
Fr* = 55.276				
P values vs. baseline	-	< 0.001	< 0.001	< 0.001

*Freidman Test

Table 5 showed the results of efficacy of tested regimenal modality on MIDAS after the treatment. Change in MIDAS score was statistically significant ($p < 0.001$) from base line (3.96 ± 0.18) to 90th day (2 ± 0.52).

Table 5. Effect of intervention on MIDAS

Mean ± SD		Median		Difference	Sum of all signed rank (W)	Sum of all positive rank (T+)	Sum of all negative rank (T-)	p value
BT	AT	BT	AT					
3.96 ± 0.18	2 ± 0.52	4	2	2	465	465	0.000	< 0.001*

*Wilcoxon matched pairs test

BT = Before treatment AT = After treatment

Table 6 shows a statistically significant reduction ($p < 0.001$) in use of rescue medication from base line (32.46 ± 10.43) to 90th day (7.82 ± 3.14) with a mean difference of 22.25 tablets.

Table 6. Effect of intervention on the use of Rescue Medication

Mean ± SD		Median		Difference	Sum of all signed rank (W)	Sum of all positive rank (T+)	Sum of all negative rank (T-)	p value
BT	AT	BT	AT					
32.46 ± 10.43	7.82 ± 3.14	29	7	22.25	465	465	0.00	< 0.001

*Wilcoxon matched pairs test

BT = Before treatment AT = After treatment

Discussion

In present study, significant reduction ($p < 0.05$) in headache frequency, VAS score, migraine-related disability and rescue medication was observed. These significant changes on various parameters confirm the hypothesis that therapeutic irrigation is effective in the treatment of chronic migraine.

Migraine is represented as a spectrum of disease characterized by high rates of attacks associated with high levels of pain at one end and mild attacks with fewer pain scores at another. This wide variability in illness representation has implications in the treatment for migraine. MIDAS questionnaire can be used as an effective clinical measure to identify the severity of illness and can be an inevitable tool in planning treatment for migraineurs [46]. The mean age of the participant observed in this study was 36.9 ± 9.9 which is in accordance with the previous studies conducted by Bigel et al. [47] and Rejinith V. et al [14]. The female preponderance (76.66%) in the present study corresponds with the findings of the study by Ruscheweyh et al. [48] and Blumenfeld et al [49].

Chronic migraine usually occurs due to the ac

cumulation of cold humours in brain and treatment needs cleansing and rejuvenation which is achieved by pharmacotherapy as well as regimenal therapy such as *Zimad* (paste), *Tila* (liniment), *Nutūl* (irrigation), and *Hijama* (cupping) [5,6,7,10,11,19,50]. Irrigation therapy works on the principle of *Taḥlīl* (resolution), *Taskīn* (sedation), *Tartīb* (moistness) and *Tadīl-i-Mizaj* (temperamental rejuvenation). The ingredients of tested polyherbal Unani formulation are known to have *Muḥallil-i-Awrām* (anti-inflammatory), *Mulaiyyan-i-Awrām* (resolvent), and *Daf-i-Alam* (analgesic) properties [11,25-35].

Anti-inflammatory, sedative, antiseptic, and spasmolytic properties of *M. chamomilla* were reported by Sharafzadeh S. et al [51]. The use of chamomile for centuries has been reported as anti-inflammatory, antioxidant, mild astringent, and sedative by Srivastava et al. [52]. It has been reported that *Astragalus hamosus* possesses the anti-inflammatory, and analgesic activities [53]. Artemisia absinthium has been claimed to possess the anti-inflammatory, and analgesic activities by Hadi et al. [54]. Vyas et al. reported the anti-inflammatory, and analgesic activities of *Trigonella foenum-graecum* seed extract [55]. Analgesic activity of Origanum vulgare was reported by Raveendran et al. & Afarineshe Khaki et al. [56,57].

Current studies and researches explain mechanism of action of irrigation therapy. Pouring of liquid from a distance has multiple effects like stimulation of nerve plexus, glands and brain cells [38], resulting in decreased heart rate, lowered sympathetic tone, slowing of alpha waves in EEG, decreased tidal volume and CO_2 excretion [33,58]. Psycho-physiological changes of irrigation therapy may be related to the tactile stimulation of the skin or hair follicles innervated by the occipital branch of trigeminal nerves [58]. Biochemical changes include suppression of noradrenaline due to continuous pouring of liquid over skin; decrease in PMN/Lymphocyte ratio and alpha receptors, resulting in sympathetic suppression leading to relaxation [59]. Studies have shown that warm water exposure decreases sympathetic power and increase vagal tone [42,43]. Sensory stimuli of irrigation therapy may dominate the painful stimuli by activation of large diameter myelinated fibres. This may lead to loss of gate to small nociceptive impulses. Both hypo and hyperthermia are known to exert strong physiological and hemodynamic effects on the body [41]. The impulses from the forehead cause stimulation of the trigeminal nerve and also a somato-autonomic reflexes and changes in levels of various neurotransmitters including serotonin and catecholamine, resulting in sympathetic suppression and physio-immunologic changes of peripheral circulation and natural killer cell activity [39,58].

Strength and Limitations

The use of this therapy externally is the real strength of this clinical trial which can safely be used in those patients who cannot take NSAIDs for painful conditions due to chronic systemic diseases. This clinical trial has several limitations such as relatively small sample size, single arm and no standard control.

Conclusion

The result of the present study showed that irrigation therapy with specific decoction is effective in the treatment of chronic migraine. Reduction in headache frequency, headache intensity, MDAS and use of rescue medication is highly significant statistically, with no reported adverse events. Repeated stimuli are needed to consolidate these effects which need 5-10 minutes and about one hour for stronger consolidation. Irrigation therapy exerts its effect by the virtue of its sheer streaming effect on the forehead as well as by using the medicated liquid in the procedure. To achieve long-lasting effect of this therapy, it must be performed at least 15 times. Regular or continuous pressure input generates continuous impulse to the central nervous system thereby continuously stimulating CNS. The anti-inflammatory, analgesic, sedative and antioxidant properties of tested drugs and the specific procedure of pouring the decoction of drugs cumulatively decrease the pain intensity, frequency and chronicity in migraine. Though the results of present study are promising but standard controlled, blinded clinical trials with large sample size and adequate follow-up are required to establish the efficacy of this regimenal modality in the management of chronic migraine.

Conflict of Interest

There is no conflict of interest regarding this article.

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References

[1] Larus SG. Migraine, Blood Pressure and Inflammation in Relation to Cardiovascular Disease and Mortality [PhD Thesis]. University of Iceland, 2010.
[2] Pearce JM. Historical aspects of migraine. J Neurol Neurosurg Psychiatry 1986; 49:1097-1103.
[3] Tabri M. Moalajat-e-Buqratiya. Vol 1. Central Council for Research in Unani Medicine. New Delhi 1995; pp 284-290.
[4] Longo DL, Fauci AS, Kasper DL, Hauser SL, Jameson JL, et al. Harrison's Principles of Internal Medicine. 18th ed. Vol 1. The McGraw Hill Companies. USA 2012; pp 114-128.
[5] Khan A. Ikseer-e-Azam. (Urdu translation by M Kabeeruddin). Idara-Kitab-ush-Shifa. New Delhi 2011 p 11.
[6] Arzani A. Tib-e-Akbar. (Urdu translation by HM Hussain). Deoband. Faisal Publications. YNM; pp 20-21.
[7] Zohar I. Kitab ul Taiseer. Central Council for Research in Unani Medicine. New Delhi 1986; pp 77-78.
[8] Razi Z. Kitab Al Hawi. Vol 1. Central Council for Research in Unani Medicine. New Delhi 1997; pp 192-198.
[9] Ibne Sina. Al Qanoon Fil Tib (urdu translation by Hkm GH Kintoori). Part 1. New Delhi: Aijaz Publishing House; 2010.
[10] Tabri R. Firdous-ul-Hikmat. Idara-Kitab-ush-Shifa. New Delhi 2010; pp 155-156.
[11] Majoosi A. Kamil-us-Sana. (Urdu translation by G H Kantoori). Vol 2. Central Council for Research in Unani Medicine. New Delhi 2010; pp 544-545.
[12] World Health Organization. The World Health Report 2001. Geneva: WHO; 2001.
[13] Extrapolation Statistics on Prevalence Rate of Migraine to Countries and Regions 2012. Available from: http://www.rightdiagnosis.com/m/migraine/statscountry.
[14] Renjith V, Pai M, Castelino F, Pai A, George A. Clinical profile and functional disability of patients with migraine. J Neurosci Rural Pract 2016;7:250-256.
[15] Kulkarni GB, Rao GN, Gururaj G, Stovner LJ, Steiner TJ. Headache disorders and public ill-health in India: Prevalence estimates in Karnataka State. J Headache Pain 2015;16:67.
[16] Atif M, Hussain S, Sarwar MR, Saqib A. A review indicating the migraine headache as a prevalent neurological disorder: Still under-estimated, under-recognized, underdiagnosed and under-treated. J Pharm Pract Community Med 2017;3:3-11.
[17] Manack AN, Buse DC, Lipton RB. Chronic migraine: epidemiology and disease burden. Curr Pain Headache Rep 2011;15:70-78.
[18] Gururaj GK, Kulkarni GB, Rao GN, Subbakrishna DK, Stovner LJ, et al. Prevalence and socio demographic cor-

relates of primary headache disorders: results of a population based survey from bangalore, india. Indian J Public Health 2014;58:241-248.
[19] Jurjani AH. Zakheera Khawarzam Shahi. (Urdu translation by Hadi Hussain Khan). Vol 6. Idara-Kitab-ush-Shifa. New Delhi 2010; pp 105-106.
[20] Baghdadi H. Mukhtarat Fil Tib. Vol 3. Central Council for Research in Unani Medicine. New Delhi 2004; pp 19-20.
[21] Nikhat S, Fazil M. An analytical review on nutool (irrigation) therapy. J Drug Deliv Ther 2015;5:1-4.
[22] Nayab M, Kouser H, Ansari AN. Tanqiya wa tadeel (evacuation and rejuvenation): the unani concept as evolutionary basis for conventional stroke management. J Drug Deliv Ther 2021;11:195-200.
[23] Kouser H, Khan F, Tehseen A, Nayab M, Ansari AN, Understanding the concept of Purgation (Ishal) in Unani Medicine: A Review, J Drug Deliv Ther 2021;11:241-246.
[24] Khare CP, Indian Medicinal Plants an Illustrated Dictionary Springer Science, Business Media. LLC 2007.
[25] Kazrooni SA. Al Mughni Fil TibMaroofba Al Sadeedi. Munshi Naval Kishor. Lucknow 1311; pp 18-19.
[26] Ibn Nafees. Ilmul Advia Nafeesi Ma Zamima (Urdu). Aijaz Publishing. New Delhi 2007; pp 70-72.
[27] Ghani N. Khazain ul Advia. Idara Kitab ush Shifa. New Delhi 2001.
[28] Khan MA. Moheete Azam. Vol. I. Matba Nizami. Kanpur 1885; p 144.
[29] Lubhaya R. Bayanul Advia. Vol.I. Goswami Pharmacy. Gali Qasim Jaan. New Delhi 1984.
[30] Kabiruddin. Makhzanul Mufradat al Maroof Khawas ul Advia. Aijaz Publishing House. New Delhi 2001.
[31] Hakeem MA. Bustan Al Mufradat (Musawwar Edition). IdaraKitabus-shifa. New Delhi 2002
[32] Betar I. Al Jame ul Mufradat al Advia wa al Aghziya (Urdu translation Ziauddin Abdulla bin Ahmad Undlasi). Vol. 1. Central Council for Research in Unani Medicine. New Delhi 1998.
[33] Razi Z. Kitab Al Hawi. Vol. X. Central Council for Research in Unani Medicine. New Delhi 1997.
[34] Khan MM. Tohfatul Momineen. Matba Nawal Kishore. Lucknow 1846.
[35] Attar Z. Ikhtiyarat-i-Badiyee. Matba Munshi Nawal Kishore. Lucknow 1888.
[36] Miraj S, Alesaeidi S. A systematic review study of therapeutic effects of matricaria recuitta chamomile (chamomile). Electron Physician 2016;8:3024-3031.
[37] Nayab M, Khan F, Ansari AN, Khan TN, Itrat M, Nutūl as an effective and time tested regimenal modality in unani system of medicine – an overview. J Drug Deliv Ther 2021;11:132-137.
[38] Khan S, Nayab M, Ansari RA. Effect of nutool with roghan-e-banafsha in sahar (primary insomnia). Int J Res Anal Rev 2019;6:1271-1281.
[39] Azam R, Nisar S, Jabeen A, Jilani S, Jahangir U, et al. Nutool therapy (irrigation) and its practical applications in unani system of medicine. World J Pharm Res 2016;5:599-607.
[40] Azam R, Mushtaq S, Fassihuzaman A. Jabeen Z, Zaidi S. Nutool (irrigation) - an effective mode of treatment in ilaj bit tadbeer (regimenal therapy). Indo Am J Pharm Res 2014;4:5787-5791.
[41] Mooventhan A, Nivethitha L. Scientific evidence-based effects of hydrotherapy on various systems of the body. N Am J Med Sci 2014;6:199-209.
[42] Perini R, Veicsteinas A. Heart rate variability and autonomic activity at rest and during exercise in various physiological conditions. Eur J Appl Physiol 2003;90:317-325.
[43] Nishimura M, Onodera S. Effects of water temperature on cardiac autonomic nervous system modulation during supine floating. J Gravit Physiol 2001;8:65-66.
[44] Hollanda L, Monteiro L, Melo AS. Botulinum toxin type A for cephalic cutaneous allodynia in chronic migraine: a randomized, double-blinded, placebo-controlled trial. Neurology Int 2014;6:70-73.
[45] Suresh KP, Chandrashekara S. Sample size estimation and power analysis for clinical research studies. J Hum Reprod Sci 2012;5:7-13.
[46] Lipton RB, Stewart WF, Sawyer J, Edmeads JG. Clinical utility of an instrument assessing migraine disability: The migraine disability assessment (MIDAS) questionnaire. Headache 2001;41:854-861.
[47] Bigal ME, Rapoport AM, Lipton RB, Tepper SJ, Sheftell FD. Assessment of migrainedisability using the migraine disability assessment (MIDAS) questionnaire: a comparison of chronic migraine with episodic migraine. Headache 2003;43:336-342.
[48] Ruscheweyh R, Müller M, Blum B, Straube A. Correlation of headache frequency and psychosocial impairment in migraine: A cross-sectional study. Headache 2014;54:861-871.
[49] Blumenfeld AM, Bloudek LM, Becker WJ, Buse DC, Varon SF, et al. Patterns of use and reasons for discontinuation of prophylactic medications for episodic migraine and chronic migraine: results from the second international burden of migraine study (IBMS-II). Headache 2013;53:644-655.
[50] Razi Z. Kitab ul Faqir. Vol 1. Part 1. Central Council for Research in Unani Medicine. New Delhi 2005; pp 71-72.
[51] Sharafzadeh S, Alizadeh O. German and roman chamomile. J App Pharm Sci 2011;1:1-5.
[52] Srivastava JK, Shankar E, Gupta S. Chamomile: A herbal medicine of the past with bright future. Mol Med Rep 2010;3:895-901.
[53] Shojaii A, Motaghinejad M, Norouzi S, Motevalian M. Evaluation of anti-inflammatory and analgesic activity of the extract and fractions of astragalus hamosus in animal models. Iran J Pharm Res 2015;14:263-269.
[54] Amrollahi H, Nazari H, Parvini S, Nazari N, Mohammadi A. Anti-inflammatory and analgesic activities of Artemisia absinthium and chemical composition of its essential oil. Int J Pharm Sci Rev Res 2014;24:237-244.

[55] Vyas S, Agrawal RP, Solanki P, Trivedi P. Analgesic and anti-inflammatory activities of trigonella foenum-graecum (seed) extract. Acta Pol Pharm 2008;65:473-476.
[56] Raveendran S, Rajadnya V, Kothari R, Tilak AV, Das S, et al. A study to evaluate the analgesic activity of origanum vulgare in mice using tail flick method. Int J Basic Clin Pharmacol 2019;8(10):2254-2257.
[57] Afarineshe Khaki MR, Pahlavan Y, Sepehri G, Sheibani V, Pahlavan B. Antinociceptive effect of aqueous extract of origanum vulgare l. in male rats: possible involvement of the GABAergic system. Iran J Pharm Res 2013;12:407-413.
[58] Uebaba K, Xu FH, Tagawa M, Asakura R, Itou T, et al. Using a healing robot for the scientific study of shirodhara. altered states of consciousness and decreased anxiety through indian dripping oil treatments. IEEE Eng Med Biol Mag 2005;24:69-78.
[59] Uebaba K, Xu FH, Ogawa H, Tatsuse T, Wang BH, et al. Psychoneuroimmunologic effects of ayurvedic oil-dripping treatment. J Altern Complement Mede 2008;14: 1189–1198.