Safety, Efficacy and Mechanism of Action of *Fasd* (Blood Letting through Venesection) in Cases of Osteoarthrosis —A Randomized Controlled Study

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Abstract

Osteoarthrosis is the commonest life style disorder encountered by the society. In the western countries radiographic evidences of this disease is present in majority of persons by 65 years of age and about 80% persons more than 75 years of age; despite exhaustive work, still no satisfactory answer has been placed forward by the modern medicine, conservative measures are ineffective and produce various Adverse drug reactions. Whereas, the Unani physicians e.g. *Galen*, *Ibn Sina*, *Razi*, *Majoosi*, *Akbar Arzani*, *Azam Khan* & *Kabiruddin* has suggested *Fasd* as an adjuvent regimenal therapy for various types of Arthritis. Though venesection is in vogue, but its scientific validation has not been carried out so far about its safety, efficacy and mechanism of action. Therefore, to explore new alternatives and for scientific validation of *Fasd*, this study has been designed and carried out to evaluate the safety and efficacy; and to explore the mechanism of action of *Fasd* in the cases of Osteoarthrosis.

Keywords: Bloodletting, Venesection, Fasd, Osteoarthrosis.

Introduction

As per Unani Medical doctrine derangement of the temperament is occurred due to the presence of morbid humours in the body and the blood circulation as well, which are responsible for production of the disease. Hence, the bloodletting is applied for the purpose of *Tanquia-e-mawad* (Elimination of morbid material) from the body(Arzani, ynm) in order to restore the bodily humors and hence maintaining health. There are three important modes of bloodletting described in the Unani literature namely, *Fasd* (Venesection), *Hijamat* (Cupping therapy) and *Taleeq* (Leech therapy). Jalinoos, Ibn Sina (1927), Arzani (1956), Razi (ynm), Majoosi (ynm), Arzani (ynm), Khan (ynm), (Kabiruddin, 1916; Kabeeruddin, 2003) have recommended the application of venesection as an adjuvent therapy in the treatment of *Wajaul Mafasil*. Osteoarthrosis is a kind of disease, *Wajaual Mafasil*. Hence, *Fasd* is equally applicable to Osteorthrosis as in other types of arthritis.

Osteoarthrosis is a life style disorder commonly encountered by the society, in western countries. Radiographic evidence of this disease are present in majority of persons by 65 years of age and about 80% of persons more than 75 years of age(Lawrence *et al*.,1989). Approximately 11% of persons more than 64 years of age have symptomatic O.A. of knee (Felson & Zhang, 2004). In Indian

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population knee O.A. is more common than any other joint; the same type is more common in caucasions than black or Chinese(Christopher *et al*.,1991).

American college of Rheumatology defines the disorder as; a heterogeneous group of conditions that lead to joint symptoms and signs which are associated with defective integrity of articular cartilage, in addition to related change in the underlying bone at the margins(Cooper,1988). This condition characterized clinically as joint pain, morning stiffness of less than 30 minutes, muscular weakness, swelling/effusion, Restriction of joint movements. Though the classics of Unani medicine have not described the disease as such but the symptomatology of O.A. has been described under the heading of 'Wajaul Mafasil'.

Despite exhaustive work in the field of management of this agony, still no satisfactory answer has been placed forward by modern medicine. The conservative treatment for subsiding the pain and stiffness produces a lot of adverse reactions. This handicap drives us to explore the safe and effective alternatives. Present work is based on this rationale.

Since the application of venesection has been recommended by various Unani physicians as an adjuvant therapy in the cases of arthritis, we selected this intervention to combat the sign and symptoms of O.A. Though this intervention is in vogue since centuries together but no scientific validation was carried out for its safety and efficacy. Therefore, we designed and carried out this study to evaluate the safety and efficacy of this regimen in the cases of Osteoarthrosis in comparison to conservative treatment of Unani system of medicine. An attempt was also done to explore its mechanism of action on scientific lines in combating the existing sign and symptoms of O.A.

Methodology

(i) Study Design

This was a prospective, single-centered, randomized controlled trial. All patients underwent a treatment period of 6 weeks. The protocol was approved by the ethics committee of Jamia Hamdard University, New Delhi. The trial was conducted under the Good Clinical Practice (GCP) guidelines. All patients gave written informed consent.

(ii) Patients

We screened all our patients, aged 35 to 65 years, who attended the Unani as well as Orthopedic OPDs in Majeedia hospital, New Delhi. The patients,

who had definite osteoarthritis of the knee as defined by American College of Rheumatology, were included. In bilateral knee pain, the investigator selected the more painful knee. Additionally, only those patients were included in the study that could perform 50 ft. walk test without the support of crutches or assisted devices. Exclusion criteria included pregnant and breast feeding women, anemic individuals, diabetics, patients having past history of blood disorders, ischemic heart disease and hypertension, ESR > 40 mm/hr (Westergren), CRP > 5 mg/l, any knee surgery in the previous three months, other types of arthritis, patients with any intercurrent disease(s) or condition(s) that might interfere with the free use and evaluation of the affected knee and might predispose them to a high probability of interfering with the completion of the 6 wk. follow-up (severe osteoarthritis associated with disability, neurological problems, severe congenital defects, peptic ulcer, severe liver disease, mental state, or other clinically significant conditions). *Mizaj* (temperament) of each subject was assessed on the basis of ten classical parameters prescribed in unani medical literature.

(iii) Procedures

A total of 40 patients, 20 in each group, were randomly allocated to both groups by a non-stratified block randomization with equal block lengths. Sequentially numbered envelopes containing the treatment assignment were prepared. When a patient met the inclusion criteria and consented for participation, the investigator opened the lowest numbered envelope, which determined the group of assignments. Since the intervention was invasive, hence we could not blind our study. The trial was performed after getting prior approval by institutional committee of medical ethics Jamia Hamdard, New Delhi. Patients were informed regarding the nature of the study in detail and were provided the informed consent form.

The cases randomly selected for test group i.e. group ‘B’ were administered the oral + local drugs and venesection simultaneously.

In group ‘A’ (Control group) - (i) Cap. ‘AUJAI’ were given 2 BD after meals

(ii) Roghan Surkh – was provided to apply locally on affected joints once at night

(Both formulations from Hamdard (Wakf) Lab Delhi, a GMP certified company)

In group ‘B’ (Test group) - Same drugs and dosage was administered as group ‘A’ with application of venesection on the indicated vein. The total duration of treatment was fixed 6 weeks (42 days) for both groups.

Before application of venesection, the vein to be venesected was identified properly, then as preoperative measure the site was shaved off and cleaned thoroughly with an antiseptic solution. A tourniquet was applied then on the proximal end of the extremity to expose the vein. Keeping all the sterilization measures a small cut in the longitudinal axis was made on the targeted vein.

Since all the cases were having knee osteoarthrosis; hence either small saphenous or popliteal vein was selected for venesection. The blood was allowed to be let out till it stopped itself. Then the tourniquet was released and the wound was closed by applying a piece of gauze containing antiseptic solution. On day 14th, patients returned for the second visit; day 28th for third visit and on 42nd day the final visit took place.

Outcome Measures

The outcome measures were change in knee pain, joint stiffness, joint swelling, muscular weakness and restriction of joint movement as derived from the mean Visual Analog Score of each component. The Each question was assessed by a 10 cm horizontal VAS score. For the fifty meter walk test, patients were asked to walk, at their own naturally preferred 'comfortable' pace, across a distance of 50 feet. The time taken to complete the distance was measured using a hand-held stop watch. Three repetitions of the walk were undertaken and the mean was used for subsequent analysis. Radiological assessment of the joint was also done pre and post treatment intervention.

Tolerability

Vital signs were monitored at every visit. Laboratory investigations were also performed including hematology, liver function test (Serum Bilirubin, SGOT, SGPT and Alkaline phosphatase), Serum Creatinine, Blood Urea and Uric acid at day 0 and 42.

Statistical analysis

Standard statistical tests were employed. Mann-Whitney U test was used to see the between the group difference while Wilcoxon signed rank test was used to compare the within the group difference.

Results

The improvement in joint pain is shown in table no. 2. In group A, the mean percentage of change in grading score was reported 73.33 while in group B, it

was found 93.75. As far as the morning stiffness is concerned in group A, the mean percentage of change in grading score was reported 81.66, whereas in group 'B', it was found 85.00 (Table 3). In muscular weakness the percentage of change was 66.66 in group A, whereas 85.83 in group B (Table 4). In swelling/effusion the percentage of change was 45.83 in group A, while 55.00 in group B (Table 5). The change in restriction of movement was found 78.78 in group A, whereas 90.47 in group B after the treatment (Table 6).

The statistical significance in subsidence of clinical features between the two groups was found at P-value 0.001, 0.806, 0.020, 0.467 and 0.130 respectively in pain, morning stiffness, muscular weakness, swelling/effusion and restriction of movement. However, the reduction in all clinical features was found significant in both the groups individually at P-value <.001 (Table 1 to 7).

Table 1: Baseline characteristics of study patients (n = 40)

Variable		Test Group (n = 20)	Control Group (n = 20)
Age (years)		49.90 ± 2.79	47.85 ± 7.49
Sex	Male(n)	8	6
	Female (n)	15	11
Previous regular NSAID intake (n)		16	14
Duration of knee OA (Yrs)		4.5	3.2
BMI (kg/m2)		27.12 ± 0.31	28.47 ± 0.33
VAS Pain Score		3.4 ± 0.50	3.2 ± 0.52
VAS Stiffness Score		2.05 ± 0.82	1.80 ± 0.89
VAS Joint swelling score		1.45 ± 1.31	1.2 ± 1.28
VAS Muscular weakness score		2.0 ± 0.91	1.8 ± 0.83
VAS Restriction of joint Movement		1.70 ± 1.21	1.35 ± 1.30
Fifty Meter Walk Test		37.35± 0.58	39.71± 0.78

***** Values with plus/minus signs are expressed as means ± SD

The effect on walking time was found significant in both the groups individually and the difference in both the groups comparatively was found insignificant (Table 7).

As far as the laboratory investigations are concerned, it was noted that there was no significant change in the status of Hb%, TLC, DLC and ESR after the intervention in both groups (Table No. 8 & 9).

Table 2: Effect on Joint Pain (VAS)

Groups	Items	Before treatment	After treatment	% of change
A	Mean Std. Dev. Std. Error of Mean	3.2 0.52 0.11	0.90 0.71 0.16	73.33 20.34 4.54
B	Mean Std. Dev. Std. Error of Mean	3.40 0.50 0.11	0.25 0.44 0.09	93.75 11.10 2.48
P value	< 0.001			

Table 3: Effect on Morning Stiffness (VAS)

Groups	Items	Before treatment	After treatment	% of change
A	Mean Std. Dev. Std. Error of Mean	1.80 0.89 0.20	0.30 0.47 0.10	81.66 31.48 07.03
B	Mean Std. Dev. Std. Error of Mean	2.05 0.82 0.18	0.25 0.44. 0.09	85.00 26.98 06.03
P value	< 0.806			

Table 4: Effect on Muscle weakness

Groups	Items	Before treatment	After treatment	% of change
A	Mean Std. Dev. Std. Error of Mean	1.80 0.83 0.18	0.65 0.48 0.10	66.66 31.06 6.94
B	Mean Std. Dev. Std. Error of Mean	2.0 0.91 0.20	0.30 0.47 0.10	85.83 26.08 5.83
P value	< 0.020			

The difference in change was found insignificant individually as well as between the two groups in LFTs & KFTs (Table No. 10 &11). Hence, it was concluded that the intervention is safe and tolerable.

The Radiographic assessment showed no any significant improving effect in both groups. However, Acute Soft Tissue Swelling (ASTS) was relieved in both groups after intervention.

Table 5: Effect on Joint Swelling

Groups	Items	Before treatment	After treatment	% of change
A	Mean Std. Dev. Std. Error of Mean	1.20 1.28 0.28	0.25 0.44 0.09	45.83 44.87 10.03
B	Mean Std. Dev. Std. Error of Mean	1.45 1.31 0.29	0.15 0.36 0.08	55.00 47.48 10.61
P value	< 0.467			

Table 6: Effect on Restriction of joint Movement

Groups	Items	Before treatment	After treatment	% of change
A	Mean Std. Dev. Std. Error of Mean	1.35 1.30 0.29	0.30 0.47 0.10	78.78 21.20 6.39
B	Mean Std. Dev. Std. Error of Mean	1.70 1.21 0.27	0.20 0.41 0.09	90.47 15.62 4.17
P value	< 0.130			

Table 7: Effect on Fifty meter walk test

Groups	Items	Before treatment	After treatment
A	Mean Std. Dev. Std. Error of Mean	39.71 0.78 0.52	17.20 1.60 0.36
B	Mean Std. Dev. Std. Error of Mean	37.35 0.58 0.675	16.25 1.02 0.228
P value	< 0.01		

As far as the Arthritic Profile is concerned, no case was found positive for R. Factor, ASO Titre and C-Reactive Protein. Change in Uric Acid and ESR was reported significant in both groups individually after the treatment but insignificant in between the two groups (Table No. 12 & 13).

Table 8: Effects on Haematological Parameters
(Significance in between the two groups)

	% change in Haemoglobin	% change in TLC	% change in Neutrophils	% change in Lymphocytes	% change in Monocytes	% change in Eosinophils
Mann-Whitney-U	181.50	152.00	195.50	183.00	200.00	179.00
P-value	0.617	0.194	0.903	0.645	1.000	0.663

Table 9: Effects on Haematological Parameters
(Within the group significance)

Significance	Groups	Hb% AT-BT	TLC AT-BT	Neutrophils AT-BT	Lymphocytes AT-BT	Monocytes AT-BT	Eosinophils AT-BT
P. value	A	0.001	0.008	0.026	0.471	1.000	0.001
	B	0.001	0.003	0.001	0.043	1.000	0.002

AT = After Treatment, BT = Before Treatment

Table 10: Effect on Biochemical Parameters
(Significance in between the two groups)

	Liver function tests (% change in)				Kidney function test (% change in)	
	S. Bilirubin	SGOT	SGPT	S. Alk phosphatase	Blood urea	S. creatinine
Mann-Whitney-U	187.50	99.00	47.00	144.00	175.500	190.500
P-value	0.725	0.006	0.001	0.130	0.507	0.795

Adverse Events

Neither group experienced any adverse effects as evidenced by the safety parameters.

Discussion

Since long term therapy for Osteoarthritis (OA) of the knee has limited options and treatment carries substantial risk for serious adverse effects, new therapeutic approaches should be considered. *Fasd* (venesection), although extensively used for treating various disorders in Unani system of medicine, has never been evaluated in a modern scientific context in accordance with GCP. We have followed the GCP as close as possible when conducting the study. We found that *Fasd* (Venesection) significantly improved scores of

pain, stiffness, restriction of joint movement, muscular weakness and 50 meter walk test performance over 6 weeks. OA is a disease in which compliance and persistence are known to be rather poor. In this study, venesection was found safe and well tolerated. Baseline characteristic of both the groups were comparable.

While evaluating the therapeutic effects of *Fasd* it was observed the subsidence of pain was quite significant in group B in comparison to group A, perhaps due to the expulsion of morbid materials, pain producing substances and relieving the congestion, since the drugs used in both the groups locally as well as internally were the same. Hence, venesection had an added value in relieving the pain. There was significant difference in walking time after the treatment in both groups and the difference between the groups was found insignificant.

The possible mechanism of action of venesection can be understood by exploiting the knowledge of haemodynamics; biophysical and biochemical dimensions of Biohemorrheology (Wang and Cheng Sun,1988;Poiseuille, 1835;Poiseuille,1830). Different mechanisms explain the observed effects of the venesection. After performing venesection, the hydrostatic pressure of capillaries of that local area becomes suddenly decreased, resultantly the movement of waste-metabolites and other morbid humours increase considerably from tissue spaces to the capillaries. It also increases the perfusion and relieves the engorgement of veins. O.A. leads to subchondral bone remodeling which results into subchondral irregular thickening with sclerosis and cyst formation. Increment in intraosseous pressure due to these changes in subchondral bone produces pain. Hence, relief of this pressure which is thought due to obstruction of various out flow can relieve pain. Therapeutic intervention of *Fasd* releases this pressure and is helpful in relieving pain. Furthermore, this procedure is thought to clear out the pain producing indigenous chemical stimuli (Algogenic substances) such as serotonin, substance P, Bradykinin, Prostaglandins and Histamines. It is also worth to mention here that application of *Fasd* (venesection) enhances the local blood flow, removes the stasis which helps in normalizing the local pH, removes the cell rigidity, in which the cells lost their elasticity and behave like Ghost cells of spherical nature instead of biconcavity, this phenomenon hampers the microcirculation and further increases hypoxia and acidosis. It checks the rouleaux formation and clears the already formed clumps, decreases the viscosity, and removes the acidosis and hypoxia. Hence it is helpful in relieving pain, stiffness and muscular weakness. Since the venesection's resources the hypoxia which is supposed to be an important

contributory factor in production of OA, might be helpful in delaying the destruction of articular cartilage.

Our present data suggest that re-treatments will be necessary for this therapy to become clinically valuable in the long term management of OA. Venesection, as applied in this study, was safe and well tolerated.

In conclusion, this study suggests that *Fasd* (Venesection) seems to be an effective treatment for Osteoarthrosis. However, because of the above mentioned limitations, we emphasize the preliminary nature of this study. The effectiveness of this treatment, especially when applied repeatedly, should be further evaluated in larger randomized studies. In addition, further advanced capillary haemodynamic studies are needed to have deeper and firm insight into its exact mechanism of action.

Table 11: Effect on Biochemical parameters
(Within the group Significance)

Significance	Groups	Liver Function Tests (AT-BT)				Kidney Function Tests (AT-BT)	
		S. Bilirubin	SGOT	SGPT	S. Alk phosphatase	Blood urea	S. creatinine
P-Value	A	0.5126	0.040	0.117	0.003	0.001	0.002
	B	0.452	0.001	0.001	0.001	0.003	0.033

AT = After Treatment, BT = Before Treatment

Table 12: Effects on Arthritic Profile
(Significance in between the two groups)

	% change in uric acid	% change in ESR
Mann-Whitney U	136.50	118.00
P-value	0.086	0.026

Table 13: Effects on Arthritic Profile
(Within the group significance)

Significance	Groups	Uric Acid AT-BT	ESR AT-BT
P-value	A	0.001	0.001
	B	0.001	0.001

AT = After Treatment, BT = Before Treatment

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