Original article

Evaluation of safety and efficacy of Unani Add-on regimen in preventing the progression of severity of the disease in hospitalized SARS-CoV2 tested positive asymptomatic /mild to moderate symptomatic COVID-19 cases- A Randomised Controlled Clinical Trial

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Abstract

Objectives: The study aimed to establish the effectiveness of Unani add-on regimen by comparing theduration required for change in disease status from COVID-19 positive asymptomatic / mildto moderate symptomatic patients to asymptomatic negative. ***Methods:*** This single-centric, randomized, twin arm, controlled, clinical trial was carried out on a totalnumber of 62 RT-PCR confirmed COVID-19 patients. The Intervention group (IG) receivedUnani Regimen (Khameera Marwareed and Unani Joshanda) in addition to the conventional management, while the Control group (CG) received only conventional management. ***Results:*** It was observed that 16 (51.6%) patients in Intervention Group and 3 (9.4%) patients incontrol group became negative for COVID-19 at day 7 and remaining 13 out of 15 (93.5%) patients in Intervention Group and 20 out of 28 (74.1%) patients in control group becamenegative for COVID-19 at day 14 .This effect of the Unani Regimen in comparison to thecontrol group was statistically significant (p =0.003). ***Conclusions*:** It can be concluded that the change of COVID-19 positive asymptomatic / mild to moderate symptomatic patients to RT-PCR negative was much earlier in the add-on Unani regimen group as compared to control group.

Keywords: COVID-19; Immunity; Quality of life; Randomized Controlled Trial; WHO QoL; RT-PCR

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Introduction

COVID-19 is an infectious clinical condition caused by SARS-CoV-2. The pathogenesis and clinical appearances are almost the same as *Amraz-e-Wabai* (epidemic diseases) which was described by Hippocrates, Galen, Aristotle, Razes, Avicenna, Jurjani, etc. The classical Unani literature says that *Tabi'at* (Medicatrix naturae) is the supreme power, when *tabi'at* remains strong, then diseases do not occur easily but once it weakens, it increases the

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susceptibility to illnesses in an individual[1].Therefore, the diseases occur due to weakened *Quwwat-i-Mudabbira-i-Badan* / *Tabi'at* (Medicatrix naturae) and may be cured if we strengthen it (including immune-modulation). Unani formulations have been used during epidemics (*waba*) to treat various *Amraz-e-Wabaiya* (Infectious diseases of epidemics) such as plague, small-pox and cholera by Unani physicians since long. As per the classical literature of Unani medicine, clinical manifestations are identical to *Nazla-e-Wabāiya* (epidemic influenza), characterized by fever, sore throat, sneezing, nasal irritation, malaise, cough, diarrhoea, and delirium, when the patient develops pleurisy or pneumonia, it worsens the prognosis.[2, 3, 4]

The current COVID-19 pandemic requires the development of potential strategies on an urgent basis to protect people at high risk of novel coronavirus infection. 80% people infected with COVID-19 develop only mild to moderate symptoms, 15% develop severe symptoms, and 5% have critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, neurological symptoms [16] thrombo-embolism and/or multi-organ failure.[5] Therefore, there is considerable concern as India's COVID-19 graph is rising despite stringent surveillance, tracing of contacts and isolation of COVID-19 suspected individuals and active cases.

The immune system plays an important role in various diseases and disorders and is an important health determinant. An adequately functioning immune system is essential for the body to recognize and defend itself against exposure to foreign bodies, including bacteria, and viruses.

To address these challenges and accelerate the research needed in resource-limited settings, the study was proposed with the aim to establish the effectiveness of Unani add-on regimen by comparing the duration required for change in disease status from COVID-19 positive asymptomatic / mild to moderate symptomatic patients to asymptomatic negative.Unani classical literature lists various single drugs and compound formulations for prevention of diseases through immunomodulation. Single drugs for enhancing immunity include *Crocus sativus* L.,[6] *Withania somnifera* L.,[7] *Punica granatum* L.,[8,9] *Cassia fistula* L.,[10] *Viola odorata* L.,[10] *Cordia myxa* R.,[10] *Cydonia oblonga* M.,[11] *Zizyphus jujuba* M.,[12]

The study drug *Khameera Marwareed*(KM)is a combination of herbs namely; *Marwareed kalan nasufta* (*Mytilus margaritiferus*), *Tabasheer safaid* (*Bambusa bambos* L.), *Sandal safaid* (*Santalum album* L.), *Ambar ashhab* (Ambergris), *Qand safaid* (Sugar), *Arq-e-Gulab* (distillate of *Rosa damascene* M.), *Arq-e-Bed Mushk* (*Salix caprea* L. distillate.), *Asl* (Honey); whereas Unani Joshanda contains herbs namely; *Unnab* (*Zizyphus jujuba*), *Saistan*(*Cordia myxa*) and *Behidana*(*Cydonia oblonga*). Additionally, subjects were also given *Habb-Mubarak, Habb-Surfa, Habb-Hindi-Zeeqi* and *Safoof-e-Teen* as and when required. Antiviral, antimicrobial, anti-inflammatory, immunomodulatory and antioxidant activity of all the individual ingredients have already been reported in literature[13, 14.]

Methods

Study design and participants

This is single-centre open label, randomized, parallel arm, controlled, clinical trial conducted on RT-PCR confirmed COVID-19 subjects. The present study was conducted on 62 subjects, 31 in each arm. All the subjects with positive RT-PCR for COVID-19, either asymptomatic or mild symptomaticwere referred from a tertiary care centre and hospitalized in the isolation ward of a Dedicated COVID Health Care (DCHC) approved by Delhi State Government in the year 2020.

Patients with a positive reverse-transcriptase–polymerase-chain-reaction (RT-PCR) assay were assessed for eligibility in the trial . Adult individuals aged between 18-65 years, asymptomatic or mild to moderate symptomatic with respiratory rate < 30 per min and Oxygen saturation >90% and willing to take part in this trial were included in the study. Pregnant or lactating women, suspected COVID-19 cases not tested positive for COVID-19 by RT-PCR, severe primary COVID-19 patients with symptoms classified as severe or critical, severe illness such as cardiovascular, patients with liver or kidney diseases, severe primary respiratory disease or pneumonia, cancer or mental illness, and COVID-19 positive cases simultaneously participating in any other clinical trials were excluded from the study.

Clinical and laboratory assessment

Subjects were assessed for clinical parameters including vitals, oxygen saturation, temperament and quality of life at baseline, day 7 and day 14. Similarly, adverse events during the therapy were also recorded on day 7, day 14, and until discharge or death. A standard WHO QoL-BREF questionnaire was used

to assess the impact of *Unani regimen* on the quality of life of the study subjects[15, 16]. Serial oropharyngeal swab samples were obtained at baseline, day 7 and day 14. Data regarding the drug safety was shared with the Data and Safety Monitoring Board (DSMB) of the Ministry of AYUSH, at regular intervals.

The protocol was approved by the Central Ethics Committee of CCRUM and registered in Clinical Trial Registry of India (2020/07/026462). 71 confirmed cases of COVID-19 which were referred to the In-patient Department of A & U Tibbiya College & Hospital (AUTCH), New Delhi were evaluated. Out of these, 62 patients fulfilling the inclusion and exclusion criteria, were enrolled in the study after taking the written informed consent.

Procedure

Registered subjects who met the selection criteria were assigned to Intervention or Control group. 31 patients were enrolled in the intervention group whereas 31 patients were enrolled in the control group using the block randomization method.

The Intervention group received *Unani Regimen (Khameera Marwareed* and *Unani Joshanda)* in addition to the conventional management, while the Control group received only conventional management.Both the Unani drugs were procured from Indian medicine Pharmaceutical Corporation Limited (IMPCL), India. KM was given in the dose of 5gm once along with *Unani Joshanda* 125ml daily orally for 14 days as an add-on treatment to conventional therapy. In addition, subjects were given *Habb-Mubarak, Habb Surfa, Habb Hindi Zeeqi* and *Safoof e Teen* in case of fever, cough, breathlessness and diarrhoea respectively as and when required. In Control group, subjects were given conventional management.

A detailed history, physical examination including temperament and Quality of Life assessment and baseline investigations were done in all subjects. The total duration of the study was 14 days and subjects were assessed at baseline, day 7 and day 14 for outcome measures. The proportion of subjects who became COVID-19 negative, or progressed to the next stage with regards to severity were determined. The change in the status of each patient was recorded in specially designed Case Record Form (CRF) for each group.

Statistical analysis

Statistical analyses was carried out using SPSS (Statistical Package for the Social Sciences) Statistics Software (version 25). Data were presented as number (%), mean ±standard deviation (SD) or as median (range) wherever appropriate. Baseline categorical and continuous variables were compared between the group using Chi-square / Fisher's exact test and student's't' test/ Paired 't' test respectively.

Table 1: Demographic and clinical profile of COVID-19 positive subjects (n= 62)

Variable	Unani group n=31	Control group n=31	Total n=62
Age (in years) Mean ±SD	38.54±13.08	36.32±10.12	37.44±11.75
Gender n (%)			
Male	27 (87.1%)	31(100%)	58 (93.54%)
Females	4(12.9%)	0	4 (6.46%)
BMI (Mean ±SD)	20.83+3.21	20.92±3.78	20.87±3.50
Health Worker n (%)			
Yes	1 (3.2%)	0	1 (1.61%)
No	30 (96.8%)	31(100%)	61 (98.39%)
Mizaj (Temperament) n (%)			
Damvi	9 (29%)	9 (29%)	18 (29.04%)
Saudavi	2 (6.5%)	0	2 (3.23%)
Safravi	7 (22.06%)	9 (29%)	16 (25.80%)
Balghami	13 (41.9%)	13 (41.9%)	26 (41.93%)
Vital signs (Mean ±SD) at Admission			
Temperature(°C)	98.40 ±0.95	98.37±1.23	98.38 ±1.09
Pulse rate (per min)	84.00±7.04	84.58±10.35	84.36±9.10
Systolic BP (mm Hg)	120±9.85	118.84±9.94	119.37±9.92
Diastolic BP (mm Hg)	78.66±5.90	80.28±6.28	79.55±6.07
Oxygen saturation (SpO2) (%)	97.75±1.93	96.31±1.83	96.95±1.74
Co-morbidities			
COPD	0	1(3.2)	1 (1.6%)
Hypertension	1 (3.2)	1(3.2)	2 (3.2%)
Diabetes mellitus	3 (9.7)	1(3.2)	4 (4.8%)
HIV	1 (3.2)	0	1 (1.6%)
Obesity	0	1(3.2)	1 (1.6%)
Chronic alcoholic	2(6.4)	7 (22.6)	9 (29%)
Current Smoker	1 (1.6%)	1 (1.6%)	2 (3.2%)

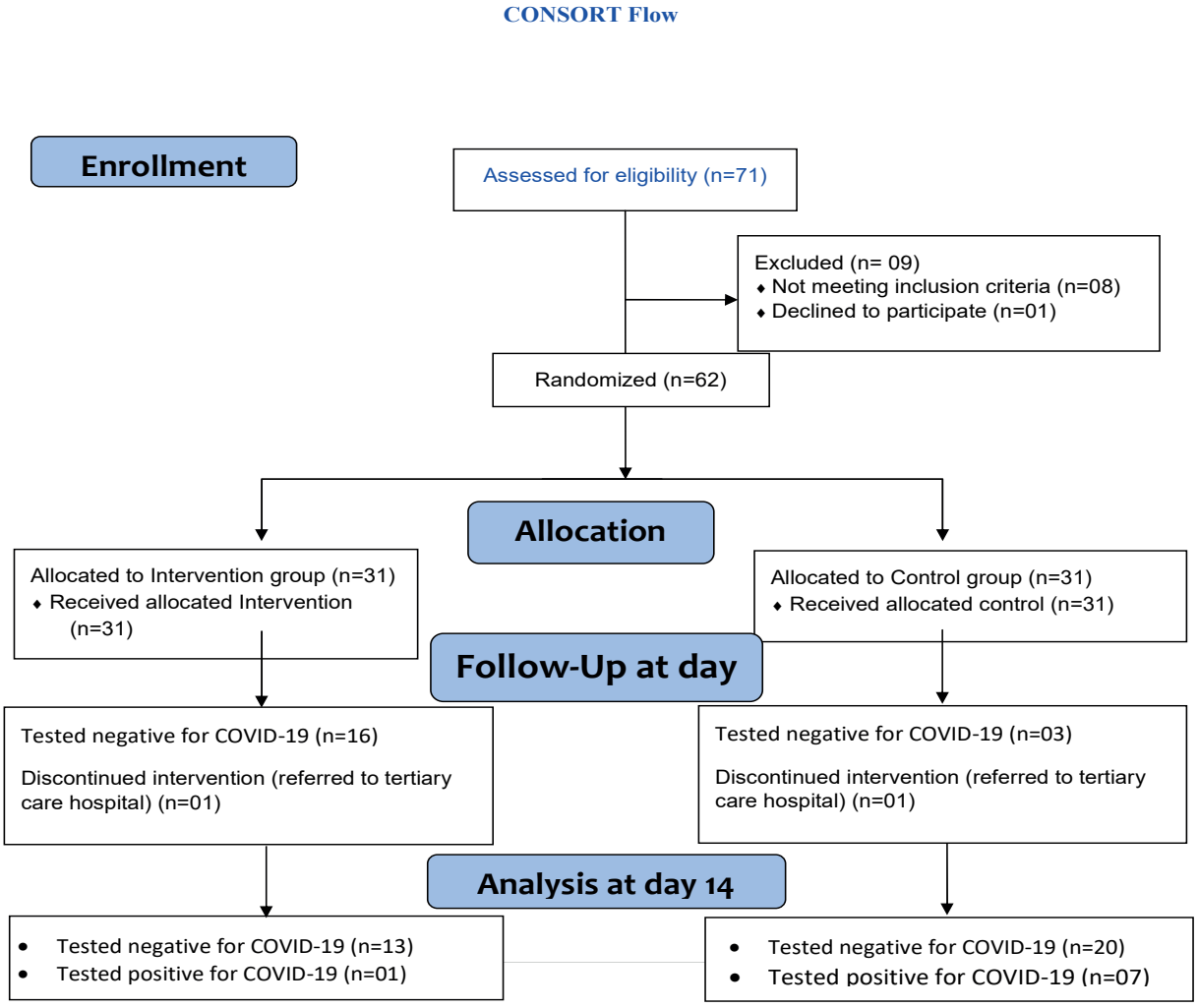

Figure 1. Consort flow chart of recruitment and allocation of subjects to Unani add-on intervention and control groups

Outcomes

Per protocol analysis was performed to determine the effectiveness of Unani regimen *vis-a-vis* control. The outcome of the study was to compare duration required for change in the disease status from RT-PCR positive to RT-PCR negative in admitted subjects in Intervention group with those in Control group. Quality of life was assessed by change in the WHOQOL-BREF scores from baseline to end of the study.[15, 16]

RESULT

A total of 71 laboratory confirmed SARS-CoV-2 RT-PCR positive cases were assessed for eligibility during July 2020 to September 2020. Of these, eight subjects did not fulfil inclusion criteria and one patient did not agree to participate in the study. Thereafter 62 subjects were registered in the study which were randomized in 1:1 ratio into two groups with 31 subjects in each group i.e. Intervention group and Control group using a computer generated sequence. Two subjects, one in each group discontinued their respective interventions in the Intervention group due to breathlessness referred to tertiary care hospital and one patient withdrew consent during the study in Control group. The CONSORT flow chart of patient recruitment in the study is shown in Figure 1.

Demographic and clinical profile of COVID-19 positive subjects

The demographic and clinical profile of the subjects was noted at baseline and it was observed that subjects in the two groups were similar in demographics and disease characteristics (Table 1). The mean age of sample population was 38.54 years (with an SD ± 13.08 years) in the Intervention group and 36.32 years (with an SD ± 10.12 years) in Control group with male preponderance (93.5%) in both groups has been observed. Assessment of *Mizaj was* done at baseline on a *10 point scale* based on Body Complexion, Built, Touch, Hair, Movement, dietary preferences, most suitable weather , Sleep, Pulse, Emotions and it was observed that majority of the subjects 42% were having *Balghami* i.e. Phlegmatic temperament followed by 29% *Damvi i.e.* Sanguineous temperament, 25.8% *Safrawi* i.e. Choleric temperament and 3.2% *Saudawi* i.e. Melancholic temperament. The underlying co-morbidities observed in both the groups are summarized in Table 1. Overall, 8 subjects in Intervention group and 12 in Control group had pre-existing diseases. Although all subjects had oxygen saturation above 94% with mean 97.74±7.89 in Intervention group and 96.31±1.83 in control group (Table 1). Therefore significant difference was observed in both the groups in terms of age, gender and vital signs at baseline. The data for age, gender, vital signs at admission are balanced between both the groups and were statistically not significant (p>0.0.5).

Clinical presentation of COVID 19 positive subjects

The most common presenting symptoms in the order of frequency were fever (35.5%), followed by dry cough (17.7 %), headache (16.1%), sore throat (9.7%), rhinorrhea (9.7%), fatigue (4.8%), myalgia (3.2%), shortness of breath (3.2 %), and diarrhea (1.6%). (Table 2)

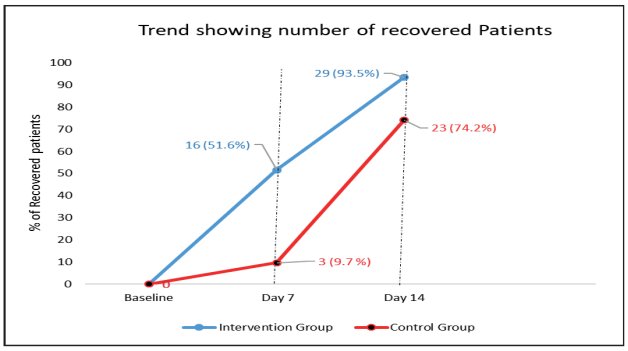

Figure 2. Trend showing study subjects becoming RT-PCR negative at Day 7 and Day 14 of the treatment.

Table 2. Clinical presentation at baseline in the enrolled COVID 19 positive subjects

	Number (percentage)		
Symptoms or signs	**Unani group (n=31)**	**Control Group (n=31)**	**Total**
Fever	15 (48.4)	7 (22.6)	22(35.5)
Dry Cough	8 (25.8)	3 (9.7)	11(17.7)
Sore Throat	3 (9.7)	3 (9.7)	6(9.7)
Runny Nose	3 (9.7)	1 (3.2)	6(9.7)
Muscle Aches (myalgia)	0 (0)	2 (6.5)	2(3.2)
Joint Pain (arthralgia)	0 (0)	1 (3.2)	1(1.6)
Fatigue/Malaise	1 (3.2)	2 (6.5)	3(4.8)
Shortness of Breath	0 (0)	2 (6.5)	2(3.2)
Headache	6 (19.4)	4 (12.9)	10(16.1)
Vomiting / Nausea	1 (3.2)	0 (0)	1(1.6)
Diarrhea	2 (6.5)	1 (3.2)	3(4.8)

RT-PCR conversion in Intervention and Control groups

It was observed that16 (51.6%) patients became RT-PCR negative at day 7in Intervention Group, whereas, only 3(9.4%) patients became RT-PCR negative at day 7 in control group (P<0.001).

The RT-PCR tests were repeated at day 14 in both the groups. It was observed that out of 15 patients in Intervention group, 13 (41.9%) patients became RT-PCR negative, whereas, 20 (64.6%) patients became RT-PCR negative out of 28 patients in control group (p <0.003). (Table 3, Figure 2)

Change in WHO QoL-Bref Scores

Changes in 26 items in the four domains i.e physical, psychological, social, and environmental of WHO QoL-BREF were also evaluated after the study. The mean scores of WHO QoL in both the groups were calculated on day 0 and day 14, higher scores denote better quality of life. Comparing the four domains of the subjects, social domain was the lowest with a mean score of 10.42± 1.08 in Intervention group and 10.77± 1.76 in control group, while the environmental domain was the highest with a mean score of 22.48± 3.05 in Intervention group and 22.00± 2.03 in control group at admission. In the intergroup analysis, little change in the mean score was reported in all the four

Table 3. Proportion of subjects with negative RT-PCR in COVID-19 subjects treated with Unani regimen and control subjects.

Group	Day 7 post inclusion (n=31)			Day 14 post inclusion (n=31)			Cumulative % of Negative subjects
	Number (%) of Negative Subjects	% of Negative Subjects	Number of Positive subjects	Number of Negative Subjects	% of Negative Subjects	Number of Positive subjects	
Intervention Group	16	51.6%	15	13	41.9%	2	93.5%
Control Group	3	9.6%	28	20	64.6%	8	74.2%
P-value	<0.001			0.003			

Table 4: WHO-QOL-BREF Questionnaire wise distribution of subjects

Domain	Intervention Group		Control Group		Intervention Group			Control Group		
	Mean ± SD		Mean ± SD		Mean changes					
	Base Line	End of the study	Base Line	End of the study	Base Line vs End of the study		p-value	Base Line vs End of the study		p-value
Domain1 (Physical)	22.81± 2.49	23.97± 2.67	22.35±2.99	22.90± 2.99	1.161	↑	0.086	0.548	↑	0.234
Domain2 (Psychological)	18.29± 2.47	20.00± 2.91	19.55± 2.21	19.71± 3.20	1.710	↑	0.022	0.161	↑	0.764
Domain3 (Social)	10.19± 1.13	10.42± 1.08	10.77± 1.76	10.81± 2.41	0.226	↑	0.408	0.032	↑	0.904
Domain4 (Environmental)	22.48± 3.05	22.97± 5.08	22.00± 2.03	22.13± 5.03	0.484	↑	0.673	0.129	↑	0.891

domains of quality of life however, the difference between both the groups was found statistically non-significant.(Table 4)

Intergroup Analysis of outcome indicators before and after treatment

The results of analysis of outcome indicators in 62 subjects in both the groups before and after treatment showed that there were significant differences in Total Leukocyte Count, Neutrophil count, Absolute lymphocyte count, ESR, HS-CRP, Ferritin, D-dimer, LDH, IgG, SGOT and SGPT (Table 5). Among these indicators, Total leukocyte count, Neutrophil count, and Absolute lymphocyte count were increased, while Ferritin levels, D-dimer, SGOT, SGPT, S. creatinine and ESR were decreased after treatment in the Intervention group (Table 5).

The **Lactate Dehydrogenase (LDH)** levels were found elevated at baseline in 24 subjects in both the groups which after the treatment was remained elevated in 17 subjects of Control group and 24 subjects in Intervention group. However, there was no significant difference in the levels of LDH before and after treatment in either of the two groups (Table 5).

At admission, D-dimer was elevated in 21 subjects of the Intervention group and in 10 subjects of the control group, which after treatment remained elevated in only 8 subjects in the Intervention group and 5 subjects in control group. The baseline mean value of D-dimer reduced in the Intervention group relative to the mean value at day 14 ($p = 0.004$), the difference between the mean values is statistically significant in contrast to the control group ($p=0.18$)

IgG was elevated in only 2 subjects of the control group in contrast to none in the Intervention group. Hs-CRP levels were elevated in 13 subjects in the Intervention group which was remained elevated in only three subjects at day 14 in contrast to 8 subjects in the control group at baseline which at day 14 remain elevated in none of the subjects. There was no significant difference in the mean scores of HS-CRP before and after treatment in the Intervention group (0.824).However, the mean scores of HS-CRP decreased in the control group (p=0.019)

It was observed that subjects with positive RT-PCR had significantly lower TLC and absolute lymphocyte count at baseline which was elevated at day 14 in both the groups (p <0.001). The Total leucocyte count at baseline (5.68±1.86) increased to (7.45±1.84) in Intervention group which is statistically significant (p <0.001). While in Control group Neutrophils at baseline (52.97±9.95) was increased to (59.03±8.02) at day 14, this difference is statistically significant (p=0.004).

The important finding is that mean value of D-dimer which was elevated in the Intervention group at baseline (280.60±168.75) reduced to 193.57±124.99 at day 14, this difference is statistically significant (p=0.004) in contrast to control group which was reduced from baseline 183.41 ±95.38 to 155.55 ±61.01 at day 14.However, there was no significant difference in the mean values of D-dimer before and after treatment in the control group.

The mean value of Serum creatinine in the Intervention group at baseline was 0.87±0.29, which reduced to 0.66±0.23 at day 14, this difference is statistically significant (p=0.002) in contrast to control group which was reduced from baseline 0.90±0.27 to 0.87±0.17 at day 14 (p=0.002).

However, no apparent differences in haematological, hepato or renal toxicity were seen between the groups (Table 5).

Table 5: Laboratory findings of COVID-19 subjects on admission to hospital

		Unani group (n=31)				Control Group (n=31)			
		Baseline (Mean ± SD)	**At Day 14 (Mean ± SD)**	**Mean changes from baseline**	**P value**	**Baseline (Mean ± SD)**	**At Day 14 (Mean ± SD)**	**Mean changes from baseline**	**P value**
Hemoglobin <6:non		14.17±2.16	14.01±1.9	0.153	0.407	14.87±1.05	15.21± 1.21	-0.34	0.024
TLC		5.68±1.86	7.45±1.84	-1.775	<0.001	6.10±1.96	7.72±1.50	-1.62	<0.001
DLC	N	52.97±9.95	59.03±8.02	-6.067	0.004	56.30±9.44	55.90±8.41	0.40	0.83
	L	37.17±10.39	32.50±7.29	4.667	0.022	34.97±9.89	34.77±7.32	0.20	0.91
	M	6.43±2.50	4.67±1.24	1.767	0.004	6.73±6.75	5.40±1.35	1.33	0.28
	E	3.50±2.50	3.87±2.89	-0.367	0.473	3.20±3.67	4.07±2.37	-0.87	0.27
	B	0.13±0.43	0.00±0.00	0.133	0.103	0.03±0.18	0.20±0.40	-0.17	0.02
Absolute lymphocyte count 710-4530		1995.83±548.02	2368.37±629.88	-372.533	0.003	2088.33±625.25	2702.07±780.88	-613.73	<0.001
ESR 2-10		17.80±13.97	12.47±9.30	5.333	0.058	9.97±3.18	11.13±8.57	-1.16	0.48
Blood Sugar Fasting 70-110		94.73±8.66	90.67±12.01	4.067	0.055	96.07±14.93	90.97±22.87	5.10	0.19

	Unani group (n=31)				Control Group (n=31)			
	Baseline (Mean ± SD)	**At Day 14 (Mean ± SD)**	**Mean changes from baseline**	**P value**	**Baseline (Mean ± SD)**	**At Day 14 (Mean ± SD)**	**Mean changes from baseline**	**P value**
HbA1c	5.04±0.78	5.22±0.86	-0.183	0.027	4.93±1.01	5.54±0.63	-0.61	0.024
Blood urea	21.63±6.81	21.87±6.01	-0.233	0.880	20.20±5.25	21.37±5.49	-1.17	0.36
Serum Uric acid	5.28±1.90	5.35±2.16	-0.070	0.795	5.21±1.66	5.01±1.59	0.20	0.46
Serum creatinine	0.87±0.29	0.66±0.23	0.20	0.002	0.90±0.27	0.87±0.17	0.03	0.45
AST/SGOT	43.37±29.34	36.17±29.87	7.200	0.278	38.93±17.84	30.07±16.33	8.87	<0.001
ALT/SGPT	43.43±35.55	41.60±50.79	1.833	0.829	39.13±19.76	37.20±29.81	1.93	0.61
Total Protein	7.38±0.86	7.59±0.78	-0.213	0.301	8.42±0.90	7.98±0.88	0.43	0.029
Serum Albumin	4.58±0.60	5.18±3.66	-0.593	0.372	4.73±0.60	4.58±0.35	0.15	0.18
Serum Globulin	2.77±0.81	3.08±0.71	-0.310	0.073	3.74±0.81	3.38±0.83	0.36	0.06
A/G Ratio	1.87±0.80	1.54±0.36	0.326	0.030	1.34±0.42	1.47±0.59	-0.13	0.32
Serum Bilirubin	0.74±0.29	0.84±0.54	-0.109	0.131	0.72±0.54	0.79±0.42	-0.07	0.39
Conjugated Bilirubin	0.21±0.07	0.22±0.09	-0.011	0.414	0.19±0.81	0.21±0.78	-0.02	0.08
Un Conjugated Bilirubin	0.52±0.23	0.62±0.45	-0.100	0.101	0.53±0.47	0.57±0.34	-0.04	0.55
Serum alkaline phosphatase	131.83±47.38	90.61±38.59	41.217	<0.001	114.03±38.94	104.27±33.02	9.77	0.22
HS CRP	5.21±7.58	6.00±17.90	-0.792	0.824	2.81±3.69	1.463±1.84	1.35	0.019
Ferritin (ng/mL)	202.55±180.25	164.43±135.49	38.113	0.022	152.70±105.27	131.39±83.34	21.31	0.074
IgG	1497.77±223.57	1501.51±269.44	3.746	0.878	1560.84±538.38	1668.15±393.36	-107.31	0.25
D-dimer 0-200	280.60±168.75	193.57±124.99	87.031	0.004	183.41±95.38	155.55±61.01	27.85	0.18
LDH	277.83±89.82	289.50±59.12	-11.667	0.536	272.81±102.35	240.94±59.23	31.87	0.13

Adverse effects

During the study, none of the patient has reported any adverse event, however five patients (1.6%) from Intervention group and nine (29%) patients in the control group reported mild adverse effects, i.e. Malaise, Headache, Nausea, Skin Rash / Pruritus, Diarrhea. The total number of subjects who developed adverse effects was much higher in the control group (09; 29%) than in the Intervention group (05; 16.1%). (Table 6).

Table 5: Adverse effects

Symptoms	Intervention group (n=31)			Control group (n=31)	
	At day 7	At day 14	Total side effects	At day 7	At day 14
Malaise	1	0	1	0	2
Headache	1	1	2	2	2
Nausea	0	1	1	1	0
Skin Rash/Pruritus	0	1	1	0	0
Diarrhea	0	0	0	1	1
Total n(%)	**2(6.5)**	**3(9.7)**	**5 (16.1)**	**4(12.9)**	**5(16.1)**

Discussion and Conclusion:

In this randomized controlled trial, the main study outcome was change in disease status from positive to negative in subjects receiving Unani interventions with those receiving conventional management in hospital admitted RT-PCR confirmed COVID-19 subjects on day 07 and day 14. In most subjects, after seven days of therapy or tested positive for coronavirus, a substantial improvement was observed in Intervention group, and when the RT-PCR test for COVID-19 was done as per the protocol, the majority of the subjects 16 (51.6%) in Intervention group turned COVID-19 negative in contrast to control group where only 3 (9.4 %) subjects turned COVID negative at day 7 of the treatment. These tests were repeated at day 14, in which 13 out of remaining 15 subjects in Intervention group and 20 out of 28 subjects in control group tested negative which is statistically significant (p = 0.003) leaving only one patient in the Intervention group and 07 subjects in the control group who remained RT-PCR positive after day 14. The result showed that the Unani add-on regimen is significantly effective in clearing viral nasopharyngeal carriage of SARS-CoV-2 subjects within seven days of the treatment. The effect may be attributed to the immunomodulatory, antioxidant and anti-influenza properties of the ingredients of the *Unani Joshanda*, anti-allergic property in *Behi dana* (*Cydonia oblonga* M.), anti-pyretic in *Unnab* (*Zizyphus jujube* M.) and tracheal smooth muscle relaxant property in *Sapistan* (*Cordia myxa* L.)[17-20].These properties may be due to the presence of the bioactive components such as Kaempferol, Quercitin glycosides, gallic acid, ascorbic acid, citric acid present in Cydonia, Polyphenol, tannin, Glutathione (GSH) in *Zyziphus*, Phenolics, tannins, steroids in Cordia. Further, it can also be attributed to the administration of *Khamira Marwareed*, which is reported to increase delayed-Hypersensitivity response DTH and Ig 2A and Ig 2B level.[13] This type of immune-modulatory activity may have impact in early clearing of viral nasopharyngeal carriage of SARS-CoV-2 patients.

The impact of the disease on patient's quality of life (QoL) was also assessed using WHO Quality of Life-BREF (WHOQOL-BREF). Each domain of WHO-QoL was recorded at day 0 and day 14 and the mean percentage change in each domain was calculated on day 14. According to the QoL questionnaires (WHOQoL-26), there was no statistical difference noted between the Intervention group and Control in all the four domain scores viz. on physical, psychological, social, and environmental. It was observed that in the Intervention group, there was a significant (p< 0.005) increase in the scores of psychological domain after 14 days of Unani add-on therapy.

Some subjects in both the groups showed deranged values of haematological indices of COVID-19 at baseline. The haematological analysis at baseline showed that out of 62 subjects, 31(50%) had high D dimer (≥200), 40(64.5%) had elevated ESR. 21 (33.9%) subjects had elevated Hs-CRP levels and LDH levels were found elevated in 50 (80.6%) subjects. However, Ferritin levels were not elevated in any of the group. Previous studies have showed that high values of C-reactive protein (CRP), Ferritin, D-dimer, LDH, glutamic-pyruvic transaminase (SGPT), Blood urea, and Serum creatinine are risk factors for more severe disease, thromboembolic complications, myocardial damage, and/or worse prognosis[21]. Tsui et al. and Fan et al. reported

elevated LDH level were independent predictors of an adverse clinical outcome and were associated with higher rate of ICU admissions[22-23]. Chen et al., found that LDH had significantly increased in most subjects[24].But, after the treatment it was found that the elevated values of D-dimer was reduced significantly (< 0.005) and none of the patient required Oxygen support, or administration of mechanical ventilator or not even death was reported during the trial. This indicates that Unani regimen when given as an add-on to conventional management helps in the reduction of the severity of the disease. It can also be inferred that no significant differences were seen after the Unani treatment in haematological, hepatic or renal parameters.

In this study on hospitalized asymptomatic or mild COVID-19 patients, the conversion from RT-PCR positive into negative was much earlier on day 7 in the Intervention group, compared to control group. Also it was observed that the Unani regimen along with conventional management helped in the reduction of the disease severity. The Unani add-on regime may be used as after treatment for the management of asymptomatic to mild COVID-19 patients.

Conclusion

It can be concluded that the Unani regimen when given as an add-on to conventional management helps in the reduction of the severity of the disease. It can also be inferred that the study regimen is safe as no significant differences were seen after the Unani treatment in haematological, hepatic or renal parameters. Further it is Unani treatment when added to conventional care, the Unani regimen inculcates a positive attitude in subjects which helps them to recover earlier than the subjects in the control group who received only conventional management.

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