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ASSESSING THE EFFICACY AND SAFETY OF A TREATMENT REGIMEN COMPRISING ASPIRIN, PROMETHAZINE, AND MULTIVITAMIN COMBINATION FOR MILD TO MODERATE SYMPTOMATIC SUBJECTS OF COVID 19: A RANDOMIZED CONTROLLED TRIAL

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ABSTRACT

Introduction: The COVID-19 pandemic with the emergence of numerous variants is concomitant with high morbidity and mortality. To assess the efficacy and safety of treatment regimen comprising aspirin, promethazine, and multivitamin combination for mild to moderate symptomatic subjects of COVID-19. **Trial design:** A randomized controlled clinical trial was conducted using an interventional drug regimen, APMV2020, comprising two tablets A: a combination of aspirin and promethazine, B: multivitamins and trace elements, on 60 COVID-19 positive subjects. **Methodology:** The subjects were randomized to receive either the control intervention (clinical management protocol for COVID-19 advocated by the Indian Council of Medical Research (ICMR), Ministry of Health and Family Welfare, Government of India) or the test intervention (Treatment with APMV2020 tablets along with the standard control treatment. The assessment days were baseline, day 5 and 10. **Results:** APMV2020 significantly (<0.05) improved symptoms of COVID-19 like cough, breathlessness and fatigue, myalgia, headache, diarrhea, anosmia as compared to the control group. APMV2020 treatment also reduced inflammatory markers like LDH, ferritin and CRP. **Conclusion:** The APMV2020 treatment for COVID-19 provides better and faster clinical recovery of subjects suffering from COVID-19 symptoms, besides averting the possible disease progression. This may be the promising approach to recover patients of COVID-19.

KEYWORDS: Aspirin, Vitamin C, promethazine, zinc, selenium, vitamin D, COVID-19.

1. BACKGROUND

The emergence of the corona virus (SARS-CoV-2) infection leading to a global pandemic, affecting 220 countries and territories, has resulted in unprecedented changes in our daily life.[1] The COVID-19 pandemic posed extraordinary stress over the administrations and healthcare systems around the world. The virus's extreme ability for transmission with an incredibly wide range of clinical scenarios, ranging from asymptomatic carriers to critically ill patients, warrants extensive research efforts directed towards the prevention, cure, and management of COVID-19-related complications.

The clinical spectrum of COVID-19 infection is highly variable as the patients with mild disease can present with symptoms of fever, cough, and fatigue,[2] while some patients deteriorate quickly after a short period of mild symptoms. Sepsis and septic shock, respiratory failure, acute respiratory distress syndrome (ARDS), and heart failure are commonly observed with disease progression.[3] The disease severity is assessed by

imaging of the lung tissue, along with serum levels of certain inflammatory markers, like C - reactive protein (CRP), low-density lipoprotein (LDH), and ferritin. Symptom alleviation, reduction of elevated inflammatory markers, minimal or no need for hospital admission, combined with no need for supplemental oxygen can be considered as features indicating clinical recovery from COVID-19.[4]

The virus has undergone numerous mutations, presented as several phases or waves of the disease. [5] There are reports of evolutionarily important mutations and deletions that have emerged in the SARS-CoV-2 gene-encoding proteins that interact with the host immune system,[5, 6] and the rate of mutations in these proteins continues to increase after the first outbreak. The cross-reactivity on one hand and the viral mutations, on the other hand, explain the evolution of the pandemic until the summer of 2020. The primary mutations observed during the summer appeared in the spike protein, particularly in N439K in RBD,[5] comprise the most frequent mutations in the spike (including D614G, N439K, and S477N) which have noticeably increased its transmissibility. The strain with D614G associated with mutations at RBD is more infective and resistant to some neutralizing antibodies, with poor implications on the disease recovery.[6]

1.1 Rationale of the study

Considering clinical scenario, viral mutations, and ongoing waves of infections, there is a need for a validated intervention that can attain faster clinical recovery, manage long-term complications, improve prognosis, and support host immunity.

We propose an intervention (APMV2020), which consists of component A (aspirin and promethazine tablet) and component B (Nutraceutical Tablet) (Table 2). The ingredients in the formulation may serve as a precisely tailored therapy for the symptomatic treatment of COVID- 19, combined with nutraceutical constituents to help boost the host immunity. The ingredients are reported in scientific literature and can synergistically support symptom recovery, provide antiviral effects, and a natural boost to immunity.

Therefore, the current study was conducted to clinically validate the safety and efficacy of the APMV2020 tablets.

Table 2: Composition of component A.

Component A tablet	
Aspirin IP	150 mg
Promethazine Hydrochloride IP	5 mg
Component B tablet	
Vitamin D3	2000 IU
Vitamin C	750 mg
Niacinamide IP/BP	80 mg
Zinc Sulphate Monohydrate IP/USP eqvt. to Elemental Zinc	15 mg
Potassium Iodide IP/BP eqvt to. Elemental Iodine	100 mcg
Sodium Selenate Eqvt. to Elemental Selenium	82.5 mcg

1.2 **Objectives of the study**

The objectives of the study were to assess effectiveness of APMV2020 combination in alleviating symptoms, reducing inflammatory markers, faster clinical recovery in mild to moderate COVID 19 patients along with the assessment of safety and tolerability of the intervention.

2. MATERIALS AND METHODS

2.1 Study design

We conducted a prospective randomized controlled trial involving COVID-19 patients recruited from the outpatient department of Lokmanya Medical Research Centre, Lokmanya Hospital, Chinchwad, Pune, India. The study was approved by the Institutional Ethics Committee, Lokmanya Medical Research Centre, and was registered with the Clinical Trial Registry of India (CTRI/2021/06/034254). The trial involved parallel design, two groups i.e. APMV2020 and control allocated as 1:1. The consolidated standards of reporting trials (CONSORT) flow of the entire study is depicted in Figure 1.

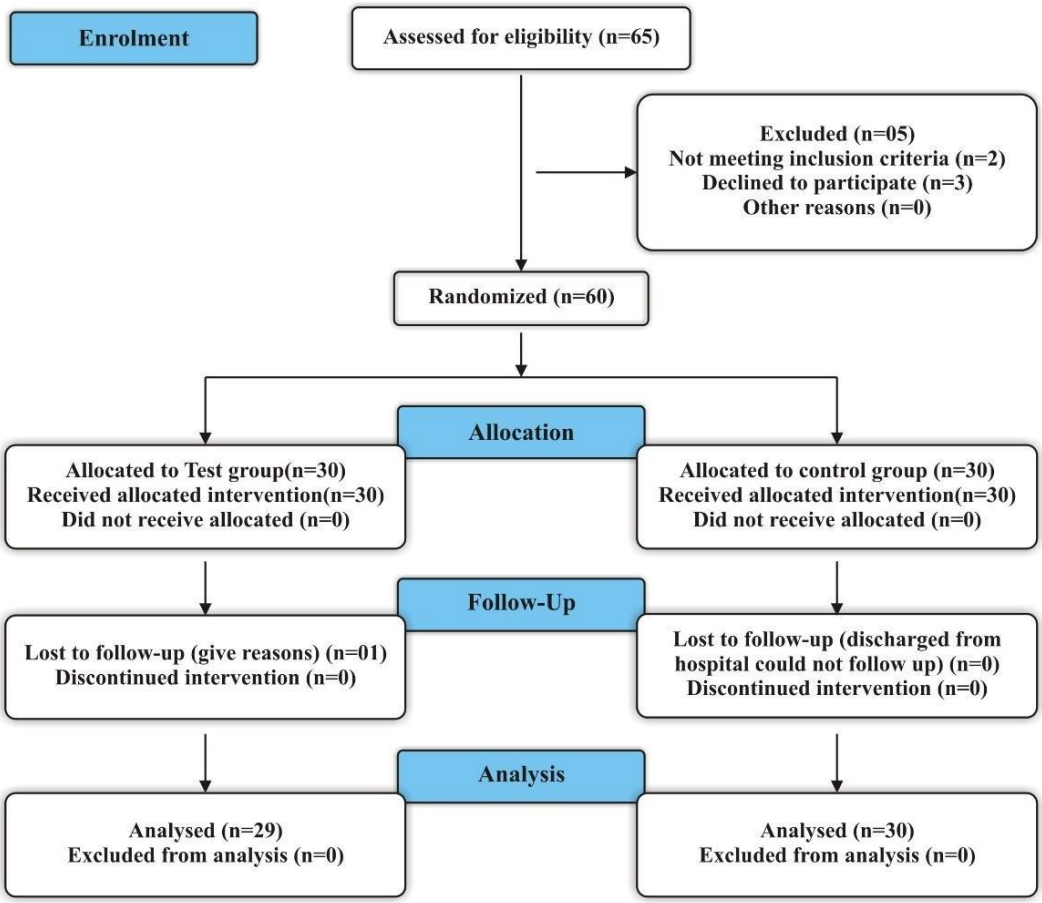

Figure 1: CONSORT flow diagram.

2.2 Inclusion criteria

Mild to moderate symptomatic patients (having no symptoms of severe disease) aged 18 to 60 years, males and females, confirmed as COVID-19 positive based on the RT-PCR report, were screened for the study. Subjects willing to provide consent and follow up were included in the study. There were no changes in the inclusion criteria throughout the study.

2.3 Exclusion criteria

Patients with autoimmune disease and compromised immunity were not included in study.

Pregnant or lactating women, patients requiring hospital admission at the time of screening, and for those aspirin is contraindicated were excluded. Subjects with comorbidity at critical stage at screening were excluded.

2.4 Study groups

We screened 65 participants based on the inclusion-exclusion criteria, of which 60 participants were found suitable and were randomized using a computer-generated randomization sheet to receive either in the standard treatment (Control Group), or APMV2020 tablets (Treatment Group). All the subjects were provided with conventional care advocated by the Indian Council of Medical Research (ICMR), Ministry of Health and Family Welfare, Government of India. Figure 1 presents the flow of events for the trial. Mechanism used to implement the random allocation sequence was sequentially numbered containers, as the trial is open label there is no blinding. We received randomization schedule from qualified statistician, investigator enrolled the participants to respective study groups.

2.5 Sample size

We intended to enroll 300 subjects to get 240 evaluable cases. We have considered subjects getting relieved of cough in AMPV2020 group is 40% and 20% in control group. Based on this assumption from clinical experience, a qualified statistician evaluated the sample size of Total 240 (120 cases in each arm) completed cases needed to assess the study objective at 90% power and alpha 0.05. However, in this manuscript we have only depicted results of first 60 subjects as that was mentioned in the protocol to be the sample size for the interim analysis.

2.6 Intervention and dosage

The dose of AMPV2020 was 1 tablet of components A and B twice a day with water for 10 days.

To assure a standard of care treatment to AMPV2020 group, antiviral, antipyretic and antibiotics were used as per discretion of investigator. To control group additionally antihistaminic, multivitamin supplements

were prescribed along with antiviral, antibiotics and antipyretics.

2.7 Outcome measures

As AMPV2020 contains ingredients such as aspirin and promethazine though to be reducing symptoms and inflammation in COVID 19 and multivitamin composition aiding early recovery, the primary study outcomes were, improvement in clinical symptoms including fever, headache, diarrhea, breathlessness, cough, anosmia, fatigue, and myalgia, a reduction in elevated levels of inflammatory markers and changes in SpO_2 levels.

The symptom scoring was done using a 0-10 visual analog scale (VAS) – 0-1: no symptoms, 2-5: mild symptoms, i.e. symptoms interfering with the daily activities, 6-8: moderate symptoms, i.e. symptoms interfering too much in daily activities, and 9-10: severe symptoms requiring medical assistance. The secondary outcomes were the requirement of hospitalization and admission to ICU, and the adverse events occurring baseline to end of the study. There were no changes in the outcome assessment and amendment to protocol.

2.8 Methodology

After attaining ethical approval, the study was registered on the CTRI website. The subjects were considered for further evaluation as per the inclusion and exclusion criteria. On the screening visit, written informed consent was obtained from subjects. Demographic details, medical, surgical, and treatment history, current medication, were noted in the case record form (CRF), along with the vital signs, followed by detailed clinical examination and lab investigations. The record of concomitant medication was properly maintained. The eligible subjects were randomized in respective groups. The treatment was followed till day 10. Assessment of treatment compliance, SpO_2, symptom grading was done using the patient's diary. All subjects were advised to follow their diet routine. The presence of any adverse events was strictly monitored and reported. On day 10, all lab investigations were repeated.

2.9 Data analysis

Patients without any major protocol violation, consumed at least one dose of intervention, and those who did not take any prohibited medications during the study period were considered for analysis. Continuous variables, such as age and other demographical characteristics, were summarized by using summary statistics, i.e. frequency, and mean, and standard deviation. Categorical values like gender and clinical examination were summarized using frequencies and percentages.

2.9.1 Analysis of primary efficacy parameters

Percentage of the population relieved of symptoms on days 5 and 10 were analyzed and compared between groups using the Chi-square test. Other primary efficacy variables, such as inflammatory markers and symptom scoring, were analyzed by student t test, Wilcoxon signed rank test and Mann Whitney test.

2.9.2 Secondary efficacy parameters

Secondary variables, namely requirement of hospitalization and ICU, and days of oxygen supplementation, were represented as percentages.

3. RESULTS

Total of 65 subjects screened and five were screen failure, total 60 were randomized and evaluated further (30 in each groups) in this manuscript. Out of five two subjects were not fitting in inclusion criteria and three declined the participation. There were no drop outs. The trial continued recruitment as decided after completing 60 subjects.

3.1 Demographic characteristics

Both groups were comparable in terms of the mean age of the male and female subjects, ranging from 33.52 to 39.53 years. The male to female ratio in both test and control groups was approximately 63:35 (Table 1).

Table 1: Demographic details of study subjects.

Parameter	Treatment		Control	
Group	Male (n=20)	Female(n=9)	Male(n=18)	Female(n=12)
Age (years)	34.4±8.99	31.56±5.51	39.56±10.36	39.5±11.01
Total Age (years)	33.52±8.13		39.53±10.53	

3.2 Primary study outcomes

3.2.1 Change in the COVID-19 symptoms

Clinical symptoms, such as cough, breathlessness, fatigue, myalgia, headache, diarrhea, and anosmia, were assessed from baseline to day 10. There was significant reduction ($p<0.05$) in symptoms in both groups from their respective baseline to day 10. However, it was evident that the treatment group had a faster relief of symptoms compared to the control – more subjects were relieved of cough, breathlessness, fatigue, and myalgia in the treatment group at day 5 as compared to the control (Table 3).

Table 3: Symptom scores for both groups.

Duration/ score	Treatment			Control		
	No symptoms	Mild	Moderate	No symptoms	Mild	Moderate
Cough						
Baseline	0	13	16	0	13	17
5	12*	16	1	6	18	6
10	24*	4	1	15	11	4
Breathlessness						
Baseline	0	15	14	0	18	12
5	11	17	1	14	12	4
10	22*	6	1	12	15	3
Fatigue						
Baseline	0	14	15	0	15	15
5	19	3	7	10	15	5
10	20*	5	4	12	16	2
Myalgia						
Baseline	0	18	11	0	20	10
5	17*	4	8	9	7	14
10	18*	7	4	9	8	13
Headache						
Baseline	0	14	15	0	15	15
5	18	8	3	11	15	4
10	19	8	2	18	10	2
Diarrhea						
Baseline	0	20	9	0	20	10
5	18	11	0	14	16	0
10	20	9	0	14	16	0
Anosmia						
Baseline	0	18	11	0	20	10
5	15	14	0	16	14	0
10	21	8	0	12	18	0

The faster resolution of symptoms is denoted by a greater reduction score at day 5 in the treatment group than the control. Furthermore, on day 10, the treatment group showed significantly ($p<0.05$) reduced symptom scores (cough, breathlessness, fatigue, and myalgia) (Table 4)

Table 4: Between-groups comparison for change in symptom scores.

(Mean ± SD) Cough Score			
Duration	**Test**	**Control**	**p-value**
Baseline	5.31±2.14	5.73±2.24	0.4651
5	2.45±1.75	3.20±2.07	0.4286
10	1.03±1.20	2.27±2.21	0.1672
(p value)	<0.05	<0.05	
(Mean ± SD) Breathlessness Score			
Duration	**Test**	**Control**	**P value**
Baseline	5.21±2.14	4.97±2.31	0.6829
5	2.48±1.69	2.63±2.19	0.4336
10	1.17±1.24	2.20±1.75	0.0042
(p value)	<0.05	<0.05	
(Mean ± SD) Fatigue Score			
Duration	**Test**	**Control**	**P value**
Baseline	5.28±2.07	5.37±2.25	0.8734
5	2.38±2.64	2.90±2.10	0.1945
10	1.69±2.02	2.30±1.92	0.1865
(p value)	<0.05	<0.05	
(Mean ± SD) Myalgia Score			
Duration	**Test**	**Control**	**P value**
Baseline	4.76±2.08	4.90±2.02	0.7939

5	2.52±2.71	4.07±3.01	<0.001
10	1.76±2.15	3.77±2.69	<0.001
(p value)	<0.05	<0.05	
(Mean ± SD) Headache Score			
Duration	**Test**	**Control**	**P value**
Baseline	5.14±2.06	5.40±2.19	0.6409
5	2.03±2.21	2.97±2.11	0.0546
10	1.45±1.69	2.07±2.02	0.443
(p value)	<0.05	<0.05	
(Mean ± SD) Anosmia Score			
Duration	**Test**	**Control**	**P value**
Baseline	4.93±2.31	4.67±2.27	0.6621
5	2.00±1.96	1.90±1.61	0.5848
10	0.97±1.14	2.03±1.57	0.0008
(p value)	<0.05	<0.05	
(Mean ± SD) Diarrhea Score			
Duration	**Test**	**Control**	**P value**
Baseline	4.38±2.21	4.73±2.31	0.5536
5	1.62±1.73	2.27±1.80	0.3442
10	1.03±1.08	1.87±1.47	0.2429
(p value)	<0.05	<0.05	

Data analyzed by using student t test. Significant at $p<0.05$

3.2.2 Changes in SpO_2 levels

The average SpO_2 level in both groups were maintained in normal range and thus the difference was not significant. Around 20% subjects from control group maintained oxygen saturation on supplemental oxygen. There were no subjects from both groups required mechanical ventilation.

3.2.3 Changes in inflammatory markers

Inflammatory markers, namely CRP, LDH, D-dimer, and ferritin were elevated in both groups at baseline. There was a statistically significant ($p<0.05$) reduction in the elevated levels of serum.

LDH and ferritin in the treatment group compared to control (Table 5). There was more reduction in elevated CRP levels in treatment group than placebo. (63.33% in the treatment group compared to 55.34% in the control group).

Table 5: Changes in mean inflammatory markers between groups.

Changes in D-Dimer (µg/ml) between groups			
Duration	**Treatment**	**Control**	**P Value between**
Baseline	0.32±0.36	0.36±0.35	0.50
Day 10	0.33±0.36	0.32±0.31	0.40
P value within	0.72	0.34	
Changes in LDH (U/L) between groups			
Baseline	301.45±117.73	317.52±107.70	0.6
Day 10	261.79±70.06	367.17±190.36	0.01
% change	13.16	-15.63	
P value within	0.16	0.27	
Changes in Ferritin (ng/ml) between groups			
Baseline	144.08±280.54	130.88±95.16	0.81
Day 10	73.13±66.17	158.93±132.91	0.04
% change	49.24	-21.43	
P valuewithin	0.24	0.22	
Changes in CRP (mg/l) between groups			
Baseline	9.98±17.21	10.01±13.75	0.87
Day 10	3.66±4.84	4.47±5.92	0.94
% change	63.33	55.34	
P value within	0.08	0.05	

Analyzed by Wilcoxon signed-rank test for within-group analysis and Mann Whitney U test for between-group analyses of D-Dimer and Student t test for LDH, Ferritin and CRP. Significant atp<0.05.

3.3 Secondary study outcomes

3.3.1 Requirements of hospitalization

In the control group, 20% of subjects (n=6) developed a need for hospitalization at the Lokmanya Hospital, a dedicated COVID setup. No subject from the treatment group required hospitalization, i.e. 100% of subjects recovered clinically in home isolation.

3.3.2 Requirement of supplemental oxygen

In the control group, all subjects (n=6) who were admitted at Lokmanya Hospital during the course of the study required supplemental oxygen, of which, three subjects (50%) required oxygen supplementation on and off till 5-6 days. The other three subjects required high-flow oxygen supplementation for 8-9 days. No subject from the treatment arm required supplemental oxygen, i.e., 100% of subjects maintained the oxygen saturation on room air.

3.3.3 Requirements of ICU admission

Three subjects (10%) in the control group required ICU admission, whereas, none of the treatment group patients required ICU admission. There was no mortality in both groups.

3.4 Safety outcomes

Hematological parameters were assessed on baseline and day 10, and there were no significant changes in the parameters between groups (Table 6).

Table 6: Changes in hematological parameters.

Parameters	Treatment		Control	
	Baseline	Day 10	Baseline	Day 10
Total Leukocyte (/cumm)	8.36±2.39	7.82±2.19	6.88±2.32	9.84±3.93
Neutrophils (%)	66.49±12.77	61.82±8.36	72.58±13.89	68.48±9.97
Lymphocytes (%)	26.72±11.24	30.23±6.80	21.14±11.85	26.40±9.74
Monocytes (%)	3.02±0.97	3.34±1.11	4.73±3.46	3.17±1.95
Eosinophil (%)	3.31±3.28	4.13±3.64	1.17±0.97	1.43±0.78
Basophils (%)	0.18±0.04	0.18±0.04	0.17±0.19	0.24±0.19
Total RBC Count (million/cumm)	4.94±0.74	4.93±0.77	4.62±0.68	4.88±0.59
Hemoglobin (G/dl)	13.80±2.50	13.88±1.97	13.29±1.93	13.88±1.56
Hematocrit (%)	42.97±5.47	42.72±4.34	41.04±4.93	44.07±4.02
Platelets (/cumm)	287.14±71.05	269.97±74.49	215.05±65.81	334.93±98.41
Platelet Distribution (fL)	11.81±1.35	11.88±2.36	11.98±2.28	12.53±3.29
Mean Platelet Volume (fL)	10.36±0.64	10.35±0.85	9.82±1.47	10.50±1.16

Data analyzed by Student's t-test; Non-significant.

3.5 Adverse events

No adverse events related to study medication or possible engagement of test intervention were reported throughout the study period.

4. DISCUSSION

This randomized controlled trial evaluated the effects of the APMV2020 tablets in COVID-19.

APMV2020 significantly improved symptoms of COVID-19, such as cough, breathlessness and fatigue, myalgia, headache, diarrhea, and anosmia and reduced serum levels of inflammatory markers like LDH, ferritin, and CRP. Overall, the inclusion of APMV2020 in the treatment protocol of COVID-19 resulted in faster clinical recovery (operationally defined as symptomatic relief for this study) with an improved prognosis. In general, COVID-19 patients who develop ARDS have a high mortality rate which is may be attributed to a hyper-inflammatory state induced by the infection, leading to multi-organ dysfunction syndrome.[7] APMV2020 administration is crucial in supporting the immune system, thereby promoting faster symptomatic recovery and halting the disease progression.[8] In the present research, the participants of the treatment group did not warrant the need for hospital admission, neither supplemental oxygen. Six subjects (20%) from the control group required hospitalization, ICU admission, and supplemental oxygen for over 5-9 days. These results highlight the valid implications of incorporating APMV2020 in the standard of treatment to reduce the overall burden on healthcare systems and ease out the economic proposition for patients.

Assessment of hematological parameters suggested no significant change post-treatment and no adverse events throughout the 10-day protocol, indicating the safety of the intervention. All patients were compliant with the APMV2020 regimen for 10 days.

In COVID-19 dyspnea is a predominant symptom, and it is extremely important to maintain SpO2 levels > 96% for better clinical outcomes.[9] Though statistically non-

significant, treatment with APMV2020 demonstrated maintained SpO2 levels during the study period in line with reduced breathlessness, further lowering the risk profile of the disease. There is a strong relationship between symptom regressions and recovery in COVID 19.[10] Our results suggest that subjects treated with APMV2020 were relieved of cough, breathlessness, and fatigue and myalgia more effectively than the control within five days of treatment, which further mitigates the risk of disease progression or severity.

It is well researched fact that immuno-inflammatory responses play a critical role in the progression of COVID-19.[11,12] Triggered inflammatory responses are the result of rapid viral replication of SARS-CoV-2, resulting in cellular destruction that can stimulate the release of cytokines and chemokine through macrophages and monocytes,[13] leading to cytokine storms in COVID-19.[14] Inflammatory markers, such as serum LDH, ferritin, CRP, and interleukin-6 (IL-6) have been positively allied to the high risks of severity and fatality in COVID-19.[14] Further, elevated inflammatory markers bear the risk of lung involvement possibly forecasting fatality in COVID- 19.[15] One of the main objectives of all clinicians treating COVID-19 is always to lower the aggravated cytokine response to mitigate the risk. In the present study, treatment with APMV2020 demonstrated excellent anti-inflammatory activity by significantly reducing serum levels of LDH, ferritin, and CRP than control. APMV2020 is a potential interventional candidate with balanced immunomodulatory and anti-inflammatory activities.

Aspirin from APMV2020 inhibits platelet aggregation and cyclooxygenase activity causing inhibition of Thromboxane-A2, which is responsible for inflammation and thrombosis.[16] which accounts for pulmonary and cardio-protective benefits of Aspirin. Aspirin can help in the prevention of thrombo-inflammation, pulmonary embolism, and thrombosis found commonly in COVID-19 patients.[16]

Aspirin is a commonly studied molecule with antiviral activity against the influenza-A H1N1 virus.[17] Aspirin via the COX pathway block the synthesis of proinflammatory molecules like thromboxane and prostaglandins preventing systemic inflammatory responses. Aspirin downregulates the superoxide radicals' generation from activated neutrophils, and stabilizes lysosomal membranes and enzymes. It limits the release of inflammatory mediators and provides hemodynamic protection while inhibiting oxidant injury, especially if given early at the onset of inflammation. Notably, multiple researchers worldwide have used aspirin in the early stages of COVID-19 to inhibit acute inflammation and alter platelet biology to prevent thrombo-inflammatory lung changes.[18]

Promethazine from the APMV2020 combination is an antihistaminic widely known to treat the symptoms of lower respiratory tract infections, pneumonia and asthma. It blocks airway inflammation and bronchoconstriction caused by histamine release from mast cells. There is mast cell activation, histamine release and systemic upregulation of pro-inflammatory cytokines (TNF- α, IL-6) in patients with COVID-19. Promethazine also act in COVID-19 patients as a cough suppressant.[19]

Modern studies explains that vitamin D deficiency in COVID-19 patients are associated with the severity of condition and mortality. Consequently, optimal Vitamin D levels is suggested to have benefit in terms of immunomodulatory and anti-inflammatory properties in the patients.[20] Similarly, the vitamin C administration to pneumonia patients can reduce chances of severity and duration of the disease. Vitamin C possess antioxidant, anti-inflammatory, antithrombotic, and immuno-modulatory functions. There is plenty of evidence suggesting the immunomodulatory and antioxidant potential of Vitamin C for improving the disease prognosis in COVID 19.[21]

The primary receptor for the SARS Cov2 is the ACE2 receptor; upon binding, the virus enters the host cell via endocytosis, leading to viral multiplication. Minerals like selenium and selenoproteins possess antiviral action. Selenium supports structural integrity and intactness of the respiratory epithelial barrier, which will lower viral entry to respiratory cells. Selenium is required for the activities of phagocytic cells, which are a major component of the innate immune system.[22]

Zinc (Zn) owns antiviral effects through generating innate and acquired (humoral) immune responses, stabilization of cell membrane inhibiting the entry of the virus, and inhibition of viral replication through interference with the viral genome transcription, protein translation, polyprotein processing, viral attachment, and uncoating. Multiple antiviral effects of Zn have been demonstrated in a variety of viral species, including SARS-CoV-2, and there is strong evidence for the usefulness of zinc supplementation in reducing the risk and severity of COVID-19.[23]

Undeniably, nutrition is a key denominator for maintaining good health. Our results further substantiate the idea that dietary components such as vitamins C, D, selenium, and zinc from APMV2020 have well-established antiviral, antioxidant, and immunomodulatory potential in COVID-19.[24]

The assessment of effectiveness of APMV2020 with higher sample size is warranted. To summarize, there are three approaches by which APMV2020 can prove as a good candidate be integrated into the COVID-19 standard care protocol. First, offering speedy clinical recovery to reduce the burden on healthcare infrastructure

and ease the economic drain of the patients. Second, the combination shows significant anti-inflammatory potential to improve prognosis. Lastly, the immunomodulatory properties offer long-term protection through multivitamins and trace element combinations.

5. CONCLUSION

It can be concluded that APMV2020 treatment for COVID-19 patients provides several advantages over the standard of care treatment alone. There was an early clinical recovery of subjects from COVID-19 symptoms, along with a significant reduction in inflammatory markers like LDH ferritin, and CRP. The reduced oxygen supplementation and hospital admissions further substantiate its efficacy in reducing the burden on the healthcare infrastructure.

Treatment with APMV2020 can potentially avert the progression of COVID-19 offering speedy clinical recovery, reducing the overall financial burden on healthcare infrastructure and the patient by lowering the need for hospitalization, demonstrating the anti-inflammatory potential to improve prognosis, and promising immunomodulatory effects to offer long-term protection through multivitamin and trace element combination. This study serves as preliminary evidence for further researches using aspirin, promethazine, vitamin D, C, and micronutrient therapy as an intervention in the management of COVID-19.

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9. REFERENCES

1. Lai CC, Shih TP, Ko WC, Tang HJ, Hsueh PR. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and coronavirus disease-2019 (COVID-19): The epidemic and the challenges. *Int J Antimicrob Agents*, 2020; 55(3): 105924.
2. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet, 2020 Mar 28; 395(10229): 1054-1062.
3. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, Cereda D, Coluccello A, Foti G, Fumagalli R, Iotti G, Latronico N, Lorini L, Merler S, Natalini G, Piatti A, Ranieri MV, Scandroglio AM, Storti E, Cecconi M, Pesenti A; COVID-19 Lombardy ICU Network. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA, 2020 Apr 28; 323(16): 1574-1581.
4. Corman VM, Landt O, Kaiser M, Molenkamp R, Meijer A, Chu DK, Bleicker T, Brünink S, Schneider J, Schmidt ML, Mulders DG, Haagmans BL, van der Veer B, van den Brink S, Wijsman L, Goderski G, Romette JL, Ellis J, Zambon M, Peiris M, Goossens H, Reusken C, Koopmans MP, Drosten C. Detection of 2019 novel coronavirus (2019-nCoV) by real-time RT-PCR. Euro Surveill, 2020 Jan; 25(3): 2000045.
5. Becerra-Flores M, Cardozo T. SARS-CoV-2 viral spike G614 mutation exhibits higher case fatality rate. Int J Clin Pract, 2020 Aug; 74(8): e13525. doi: 10.1111/ijcp.13525.
6. Banoun H. Evolution of SARS-CoV-2: Review of Mutations, Role of the Host Immune System. Nephron, 2021; 145(4): 392-403.
7. Hasan SS, Capstick T, Ahmed R, Kow CS, Mazhar F, Merchant HA, Zaidi STR. Mortality in COVID-19 patients with acute respiratory distress syndrome and corticosteroids use: a systematic review and meta-analysis. Expert Rev Respir Med, 2020 Nov; 14(11): 1149-1163.
8. Seifert G, Jeitler M, Stange R, Michalsen A, Cramer H, Brinkhaus B, Esch T, Kerckhoff A, Paul A, Teut M, Ghadjar P, Langhorst J, Häupl T, Murthy V, Kessler CS. The Relevance of Complementary and Integrative Medicine in the COVID-19 Pandemic: A Qualitative Review of the Literature. Front Med (Lausanne), 2020 Dec 11; 7: 587749.
9. Li Y, Xia L. Coronavirus Disease 2019 (COVID-19): Role of Chest CT in Diagnosis and Management. AJR Am J Roentgenol, 2020 Jun; 214(6): 1280-1286.
10. Mahmud R, Rahman MM, Rassel MA, Monayem FB, Sayeed SKJB, Islam MS, Islam MM. Post-COVID-19 syndrome among symptomatic COVID-19 patients: A prospective cohort study in a tertiary care center of Bangladesh. PLoS One, 2021 Apr 8; 16(4): e0249644.
11. Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, Qiu Y, Wang J, Liu Y, Wei Y, Xia J, Yu T, Zhang X, Zhang L. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet, 2020 Feb 15; 395(10223): 507-513.
12. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ; HLH across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet. 2020 Mar 28; 395(10229):1033-1034.

13. Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D, and Richardson P. COVID-19: combining antiviral and anti-inflammatory treatments. Lancet Infect Dis., 2020 Apr; 20(4): 400-402.
14. Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP. The trinity of COVID-19: immunity, inflammation and intervention. Nat Rev Immunol, 2020 Jun; 20(6): 363-374.
15. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, Liu S, Zhao P, Liu H, Zhu L, Tai Y, Bai C, Gao T, Song J, Xia P, Dong J, Zhao J, Wang FS. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med, 2020 Apr; 8(4): 420-422.
16. Haque S, Jawed A, Akhter N, Dar SA, Khan F, Mandal RK, Areeshi MY, Lohani M, Wahid M. Acetylsalicylic acid (Aspirin): a potent medicine for preventing COVID-19 deaths caused by thrombosis and pulmonary embolism. Eur Rev Med Pharmacol Sci., 2020 Sep; 24(18): 9244-9245.
17. Glatthaar-Saalmüller B, Mair KH, Saalmüller A. Antiviral activity of aspirin against RNA viruses of the respiratory tract-an in vitro study. Influenza Other Respir Viruses, 2017 Jan; 11(1): 85-92
18. Alegbeleye, Bamidele & Akpoveso, Oke-Oghene & Alegbeleye, Adewale & Mohammed, Rana & Esteban Zubero, Eduardo. The Novel Aspirin as Breakthrough Drug for COVID-19: A Narrative Review, 2020; 2(4): 335-350;10.5281/zenodo.3970519.
19. Dabbish, A. M. et al. Inflammatory pathways and potential therapies for COVID-19: A mini review', European Journal of Inflammation, 2021; 19: 1-22.
20. Güven M, Gültekin H. The effect of high-dose parenteral vitamin D3 on COVID-19-related inhospital mortality in critical COVID-19 patients during intensive care unit admission: an observational cohort study. Eur J Clin Nutr, 2021 Sep; 75(9): 1383-1388.
21. Carr AC, Rowe S. The Emerging Role of Vitamin C in the Prevention and Treatment of COVID- 19. Nutrients, 2020 Oct 27; 12(11): 3286.
22. Khatiwada S, Subedi A. A Mechanistic Link between Selenium and Coronavirus Disease 2019 (COVID-19). Curr Nutr Rep, 2021 Jun; 10(2): 125-136.
23. Kumar A, Kubota Y, Chernov M, Kasuya H. Potential role of zinc supplementation in prophylaxis and treatment of COVID-19. Med Hypotheses, 2020 Nov; 144: 109848.
24. Shakoor H, Feehan J, Al Dhaheri AS, Ali HI, Platat C, Ismail LC, Apostolopoulos V, Stojanovska L. Immune-boosting role of vitamins D, C, E, zinc, selenium and omega-3 fatty acids: Could they help against COVID-19? Maturitas, 2021 Jan; 143: 1-9.