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Journal of Medical Case Reports and Case Series ISSN: 2692-9880

Case Series Volume 2 Issue 19

Efficacy of 2-DG intervention in COVID-19 as assessed by 6-Minute Walk Test: A case series

Ajit Vigg[1*], Anuradha K[2]

[1]MBBS, DTDC, DNB FCCP, FICA, Former Head, Dept. of Chest Diseases, Apollo Hospital, Jubilee Hills, Hyderabad, Telangana, India. Consultant Chest Physician, Dr. Vigg Clinic, Hyderabad, Telangana, India.

[2]MBB Hospitals, DTCD, Associate Junior Consultant, Century Hospital, Hyderabad, Telangana, India.

[*]**Corresponding Author:** Ajit Vigg, MBBS, DTDC, DNB FCCP, FICA, Former Head, Dept of Chest Diseases, Apollo Hospital, Jubilee Hills, Hyderabad, Telangana, India. Consultant Chest Physician, Dr. Vigg Clinic, Hyderabad, Telangana, India

Received date: 10 December 2021; **Accepted date:** 20 December 2021; **Published date:** 28 December 2021

Citation: Vigg A, Anuradha K (2021) Efficacy of 2-DG intervention in COVID-19 as assessed by 6-Minute Walk Test: A case series. J Med Case Rep Case Series 2(19): https://doi.org/10.38207/JMCRCS/2021/0219260

Abstract

Purpose: To evaluate the effect of 2-deoxy-D-glucose (2-DG) and its impact on the 6-minute walk test (6MWT) in COVID-19 patients before hospital discharge.

Methods: The 6MWT report of the patients hospitalized with acute COVID-19 were analyzed retrospectively. All enrolled patients received 2-DG therapy as an adjunct for ten days to the standard of care in the management of COVID-19. A 6MWT was performed to determine any possible cases of silent hypoxemia before and after 2-DG administration. Data obtained during the tests were compared to evaluate the effect of 2-DG on the clinical condition of the patients and improvement in 6MWT.

Results: A significant improvement in the mean heart rate (86.5 ± 5.6/min, 91.1 ± 5.7/min), Borg scale breathlessness score (2.0 ± 0.5, 2.6 ± 0.7), and fatigue score (1.8 ± 0.6, 2.9 ± 0.6) was observed during the 6MWT post-2-DG therapy. Additionally, an optimum SpO_2 level of > 95 % was achieved and maintained post-2-DG therapy compared to the baseline SpO_2 level (< 90 %) pre-2-DG therapy. Improvement in these clinical parameters demonstrated a considerable improvement in the mean walking distance by 85% during the 6MWT with a marked development in the number of laps, speed, and metabolic equivalent (METS) compared to results obtained before 2-DG therapy.

Conclusion: 2-DG, as an adjunct therapy improved the clinical condition by achieving an optimum oxygen saturation level (> 95 %) in moderate to severely ill COVID-19 patients. It exhibited a positive impact on the 6MWT by improving the mean walking distance. 6MWT may be useful and can be considered as an effective tool to differentiate the hypoxemic patients before hospital discharge.

Keywords: COVID-19, 2-deoxy-D-glucose, 6-minute walk test, oxygen saturation, 2-DG

Introduction

COVID-19 pandemic, caused by novel coronavirus virus SARS-CoV-2, **[1]** continues to have major consequences in terms of morbidity, mortality, and financial expenses, necessitating the development of successful treatment strategies with new pharmacological interventions. Especially so because an effective preventive treatment remains elusive with the emergence of new variants.

Even as the pandemic was raging with healthcare systems around the globe under pressure, there were reports of sudden rapid deterioration of patients with initially mild symptoms. **[2]** Evidence that moderate to severe ventilatory mismatch in COVID-19 patients manifests as 'silent' or 'happy' hypoxia has mounted. **[3,4]** A patient in the state of 'happy hypoxia' fails to seek timely medical attention as their subjective respiratory distress is disproportionate to peripheral hypoxia. This resulted in home monitoring with a 'pulse oximeter' becoming a norm. However, it still failed to identify and triage at-risk patients whose oxygen saturation fell below normal at exertion. **[5]** This triggered the need to repurpose rapid exercise tests to identify exertional dyspnea early. Identifying exertional dyspnea became important not only to improve patient outcomes by identifying hypoxia early but also acted as an important tool to triage patients in resource strained settings to categorize patients for home monitoring versus in-hospital care. **[6]** Identifying hypoxia early and immediate supplemental oxygen therapy is the critical intervention to achieve target oxygen saturation (SpO_2) > 94 % and to avoid further deterioration of the clinical condition. **[7]**

One such rapid exercise test is the Six-Minute Walk Test (6MWT), the use of which has been validated for patients with face masks, relevant to the current pandemic scenario. The 6MWT was developed by the American Thoracic Society as a simple measure of aerobic exercise capacity that helps monitor patients' post-treatment for heart or lung diseases. **[8]**

Repurposing and repositioning of previously approved treatments, as well as immunization and rapid drug development, have been adopted

towards finding an effective remedy. 2-deoxy-D-glucose (2-DG), a glucose analog has recently received emergency use authorization from the Drug Controller General of India (DCGI) as adjuvant therapy in COVID-19 patients. **[9]** The drug inhibits viral replication inside the host cells, therefore, decreasing viral load, reducing the need for supplemental oxygen, and enabling faster recovery from COVID-19. **[9]**

The current retrospective case series is the first to study the efficacy of 2-DG by using the 6MWT pre and post 2-DG administration.

Material and methods

This retrospective case series included 52 adult patients (≥18 years of age) who availed of consultation for COVID-19 at Dr. Vigg's clinic, Hyderabad between June 21 and July 29, 2021. Medical records of ICU patients with laboratory-confirmed COVID-19 infection, characterized by a positive result on reverse transcription-polymerase chain reaction (RT-PCR) assay of a throat or nasopharyngeal swab sample, were included in the study. The patients were given 2-DG for 10 days in addition to the physician-prescribed standard of care for COVID-19. Pregnant women, and children (≤ 18 years of age) were excluded.

Data on patient demographics, comorbidities, medications, the requirement of supplemental oxygen and/or gait aid, and perceived exertion were collected retrospectively through a review of patients' medical records at baseline (day 1 of 2-DG administration). 2-DG was administered twice a day (morning and evening) for a maximum duration of 10 days as an adjunct to the physician-prescribed standard of care. A pre-filled sachet of 2-DG containing 5.85 g of pure 2-DG consisted of a single dose. The entire contents of one sachet were dissolved in 100 mL potable water 1-hour before administration. The volume of the 2-DG solution was determined as per the following formula:

Volume of one dose of 2-DG = 0.77 x (body weight of the patient [in kgs]) mL

Each dose of 2-DG was freshly prepared before administration and the excess 2-DG solution was discarded.

6MWT was performed under the supervision of a healthcare professional as per the previously described protocol **[10]** to determine the effect of the 2-DG intervention on respiratory parameters of COVID-19 patients. Briefly, patients were asked to walk for 6 minutes on a pre-measured flat surface with good traction and the duration was timed using a stop-clock. The test's endpoint was 6 minutes or the point at which the patient was unable to complete the test due to acute dyspnea. Parameters like heart rate, Borg dyspnea score, Borg fatigue score, and oxygen saturation levels were monitored at baseline (t=0 min) and the end of 6MWT. This test was administered on day 1 and day 10 of the 2-DG of intervention. Additionally, the total distance walked in 6 minutes was calculated using the number of laps, walking speed (in miles per hour) and metabolic equivalent (METS) recorded from the 6MWT.

Descriptive statistics were used to summarize the data and results are reported as mean and standard deviations, as applicable. Categorical variables were summarized as counts and percentages. Missing data were not included in estimations of averages. Analysis was performed with MS Excel software (Microsoft). Comparative analysis was performed to determine the effect of 2-DG on the improvement of clinical conditions in moderate to severe COVID-19 cases. Changes in heart rate, breathlessness, fatigue, SpO_2, no. of laps, distance covered in the test, etc. were assessed by paired *t*-test (two-tailed). *p*-value < 0.05 was considered statistically significant for differences between groups.

Results

Baseline characteristics and clinical characteristics of patients have been described in **Table 1**. The mean age of the patients was 58.5 years, and the majority were males (59.6 %). Most of the patients belonged to the age group of 61-70 years (59.6 %), whereas patients < 40 years were least common (7.7 %). Three patients (5.7 %) had comorbidities such as asthma, overlap chronic obstructive pulmonary disease (COPD), acute lower respiratory tract infection (LRTI), non-insulin-dependent diabetes mellitus (NIDDM), hypertension (HTN), and hypothyroidism **(Table 1)**.

For treatment of respiratory problems, oral medication was most preferred (71.2 %) followed by combined therapy with an inhaler and oral medication in 13.5 % of patients. Twelve patients (23.1 %) were on supplemental low flow oxygen via nasal cannula at the time of 2-DG administration. Breathlessness among patients was categorized using Borg Scale. Fifty percent of the patients had moderate breathlessness and 34.6 % were noted to have a severe degree of breathlessness at admission. Similarly, Borg's rating of perceived exertion was moderate in 46.2 % of the patients and severe in 36.5 % of patients **(Table 1)**.

Table 1 Baseline demographic and clinical characteristics of study participants

Age, years, Mean (SD)	58.5 (11.5)
Age category	**N (%)**
< 40 years	4 (7.7)
41-50 years	9 (17.3)
51-60 years	15 (28.8)
61-70 years	16 (30.8)
> 70 years	7 (13.5)
Gender	**N (%)**
Male	31 (59.6)
Female	21 (40.4)
Co-morbidity	**N (%)**
Asthma	1 (1.9)
Overlap COPD, Acute LRTI	1 (1.9)
NIDDM, HTN, Hypothyroidism	1 (1.9)
Medication	**N (%)**
Oral tablets	37 (71.2)
Inhaler	3 (5.8)
Inhaler and Oral tablets	7 (13.5)
O2 supplementation	**N (%)**
Yes	12 (23.1)
No	37 (71.2)
Not reported	2 (3.8)
O2 supplement 2L/min via nasal cannula	1 (1.9)
Distribution based on Borg scale: degree of breathlessness	**N (%)**
Mild	2 (3.8)
Moderate	26 (50)
Moderate to severe	2 (3.8)
Moderately severe	1 (1.9)
Severe	18 (34.6)
Perceived Exertion N (%)	
Moderate	24 (46.2)
Moderate to severe	3 (5.8)
Severe	19 (36.5)

Abbreviations: N: Number of patients; COPD: Chronic obstructive pulmonary disease; LRTI: Lower respiratory tract infection; NIDDM: Non-insulin dependent diabetes mellitus; HTN: Hypertension

A significant improvement in the clinical parameters was observed in patients post-2-DG therapy when compared to pre-2-DG. The clinical parameters during the 6MWT before and after 2-DG therapy are given in **Tables 2 and 3**.

The percentage change in heart rate from the start to the end of 6MWT pre and post-2-DG was 13.76% and 5.39%, respectively and this decrease was statistically significant ($p < 0.0001$). The mean differences pre and post 2-DG treatment were also significantly lower for heart rates both at the start and end of 6MWT **(Table 3; Figure 1)**.

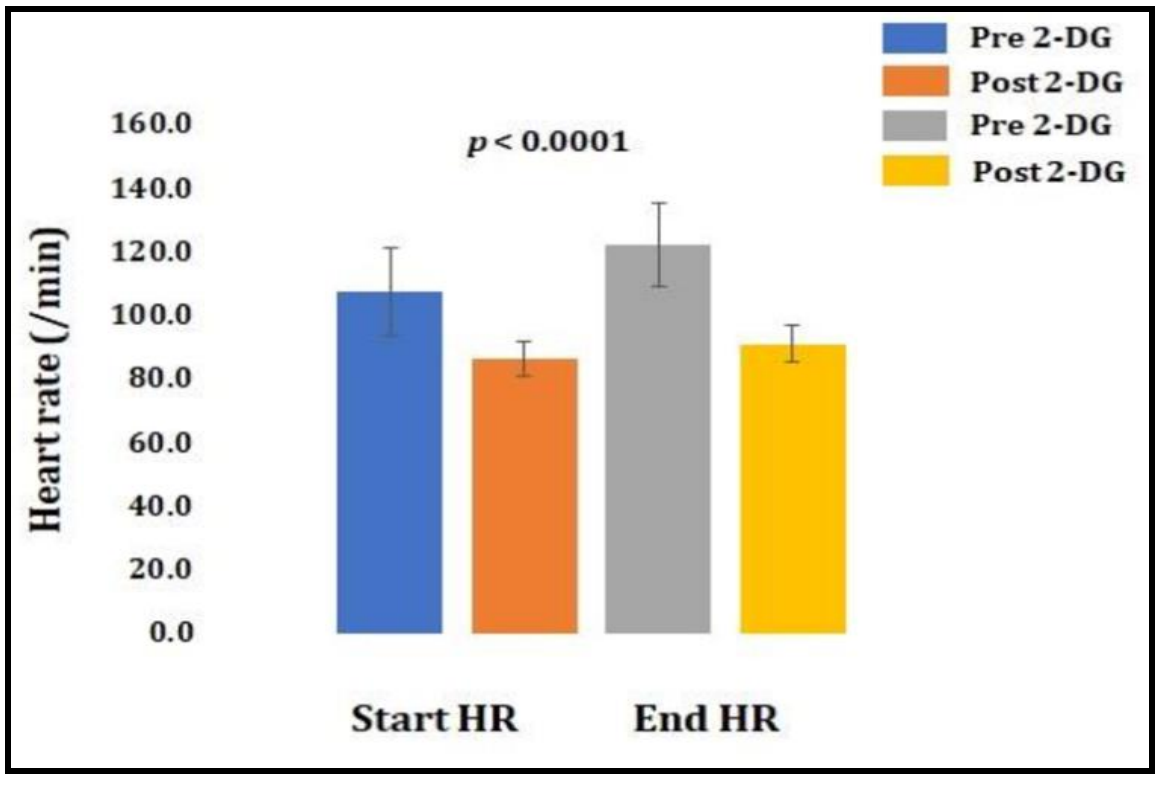

Figure 1 Improvement in heart rate with 2-DG therapy assessed by 6MWT

Table 2 Impact of 2-DG on start and end rates of clinical parameters

Parameters	**Pre 2-DG (Day 1)**			**Post 2-DG (Day 10)**			***p*-value**
	Start t=0	**End t=6 min**	**% Change**	**Start t=0**	**End t=6 min**	**% Change**	
Heart rate (/min)	107.2 ± 13.9	122.4 ± 13.1	13.76	86.5 ± 5.6	91.1 ± 5.7	5.39	< 0.0001
Breathlessness	4.8 ± 1.5	7.4 ± 1.6	54.36	2 ± 0.5	2.6 ± 0.7	30.75	< 0.0001
Fatigue	4.4 ± 1.5	6.9 ± 1.6	56.81	1.8 ± 0.6	2.5 ± 0.8	41.67	< 0.0001
SpO_2 (%)	90 ± 0.0	79 ± 0.1	-12.22	97 ± 0.0	96 ± 0.0	-1.03	< 0.0001

Table 3 Comparison of respiratory parameters before and after 2-DG intervention assessed by 6MWT test

Parameters		**Pre 2-DG**	**Post 2-DG**	**Mean differences**	**95% CI**	***p*-value**
Mean heart rate (min)	**Start**	107.7 ± 13.9	86.5 ± 5.6	-21.2 ± 9.9	-23.9 to -18.4	< 0.0001
	End	122.4 ± 13.1	91.1 ± 5.7	-31.3 ± 10.5	-34.2 to -28.4	< 0.0001
Breathlessness (Borg scale - /10)	**Start**	4.8 ± 1.5	2.0 ± 0.5	-2.8 ± 1.4	-3.2 to -2.4	< 0.0001
	End	7.4 ± 1.6	2.6 ± 0.7	-4.8 ± 1.4	-5.1 to -4.4	< 0.0001
Fatigue (Borg scale - /10)	**Start**	4.4 ± 1.5	1.8 ± 0.6	-2.6 ± 1.4	-3.0 to -2.3	< 0.0001
	End	6.9 ± 1.6	2.9 ± 0.6	-4.4 ± 1.5	-4.8 to -3.9	< 0.0001
SpO_2 (%)	**Start**	90 ± 0.0	97 ± 0.0	7 ± 2.3	6.7 - 7.9	< 0.0001
	End	79 ± 0.1	96 ± 0.0	17.1 ± 6.3	15.3 - 18.8	< 0.0001

Abbreviations: Start: t=0; End: t=6 min; CI: confidence interval

A statistically significant decrease in breathlessness as estimated by 6MWT pre and post-2-DG was observed in this study (2.6 and 0.6 decrease on Borg scale respectively) **(Table 3; Figure 2)**. The mean difference in breathlessness before and after 2-DG administration was likewise significantly lower, both at the beginning and end of the 6MWT. Similar results were obtained for fatigue as estimated on the Borg scale. Changes in Borg scale reading for fatigue from the start to end of 6MWT pre and post 2-DG were 2.5 and 1.1 respectively, which was statistically significant ($p < 0.0001$). The mean differences for fatigue at the start and end of the 6MWT were similarly considerably lower pre and post 2-DG therapy **(Table 3; Figure 3)**.

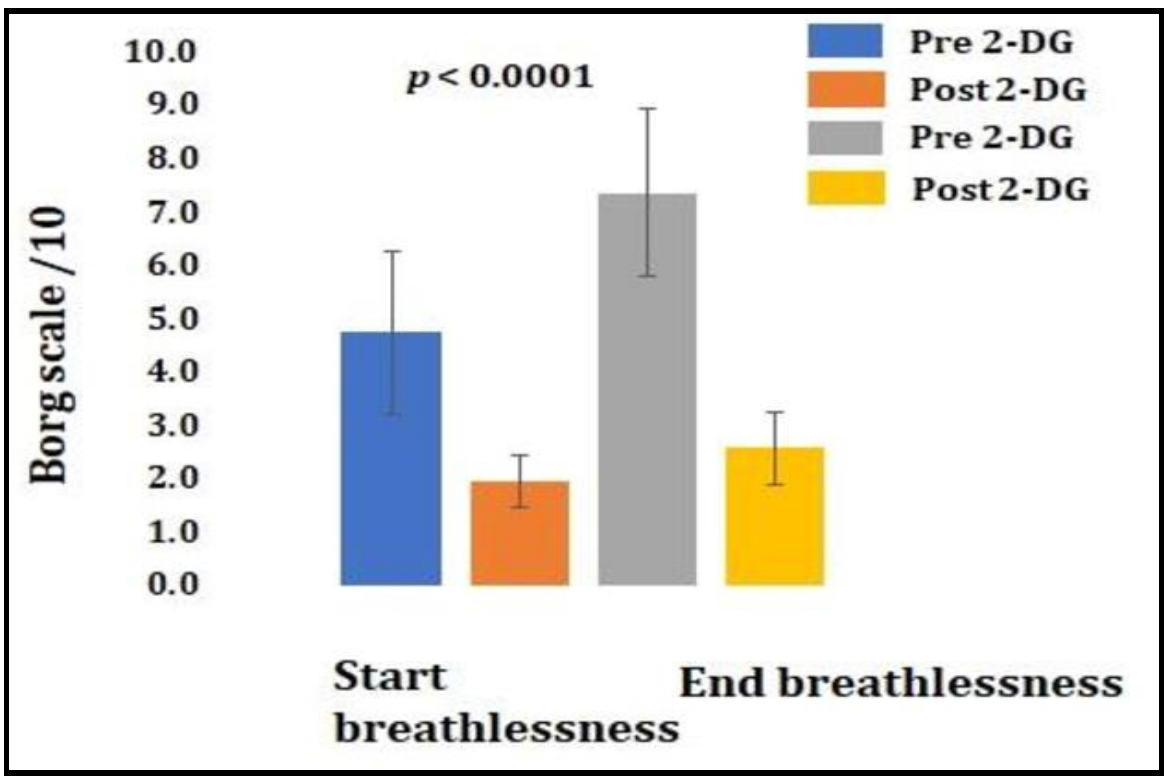

Figure 2 Improvement in breathlessness with 2-DG therapy assessed by 6MWT

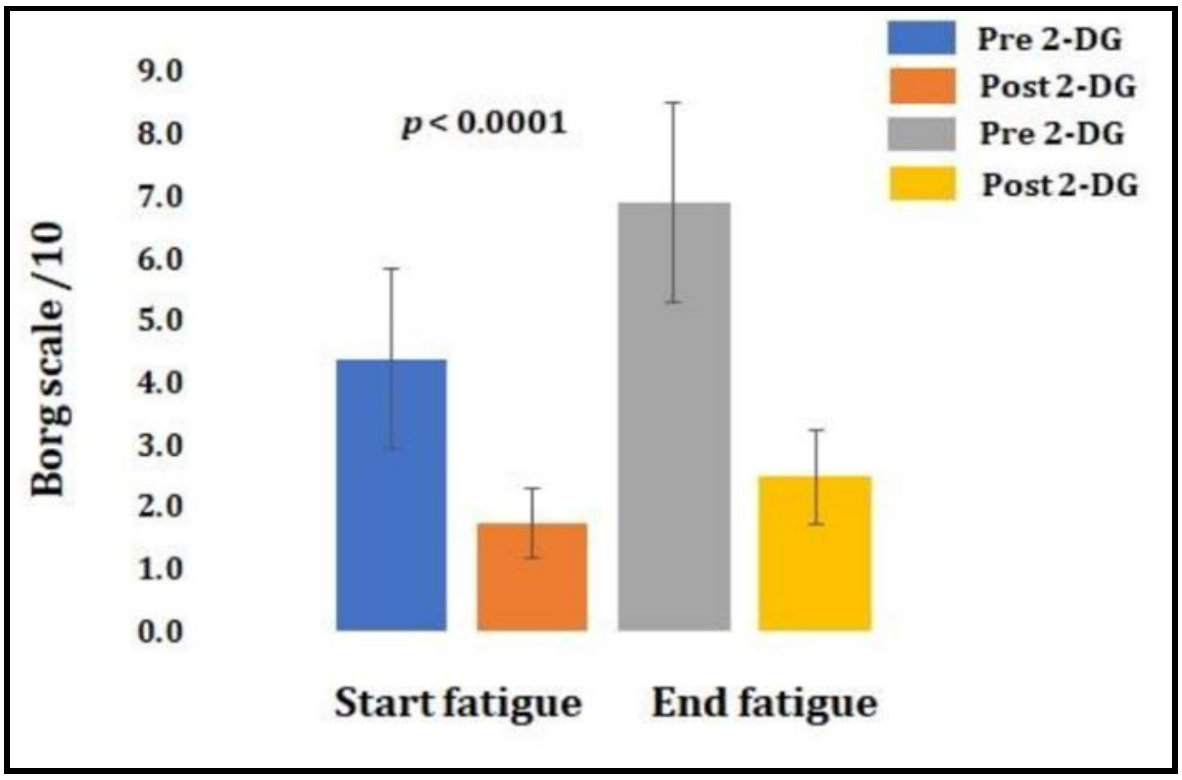

Figure 3 Improvement in fatigue with 2-DG therapy assessed by 6MWT

Differences in the start and end SpO_2 levels pre and post 2-DG was also significant and lower SpO_2 levels were observed post-2-DG (1 %) compared to pre-2-DG (11 %). > 95 % oxygen saturation was achieved in patients post-2-DG therapy **(Table 3; Figure 4)**. This indicates the efficacy of 2-DG in maintaining O_2 levels in COVID-19 patients.

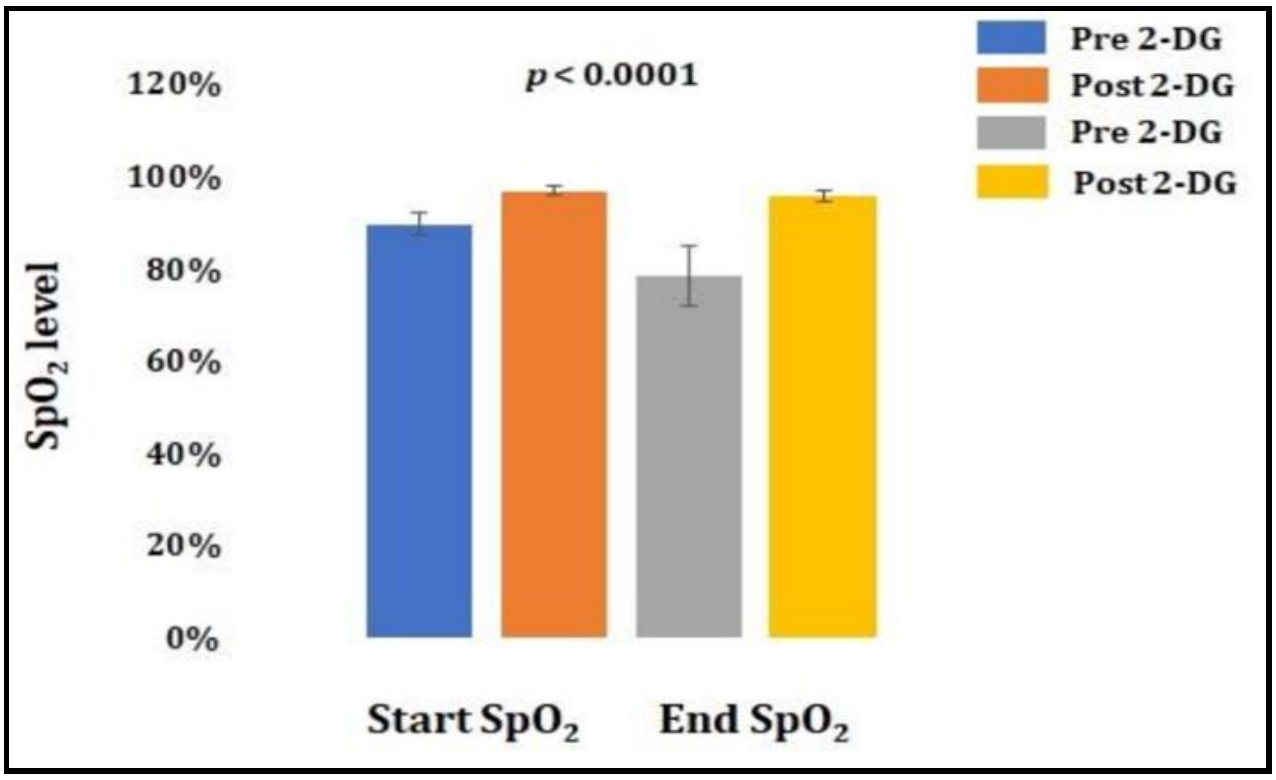

Figure 4 Improvement in SpO_2 level with 2-DG therapy assessed by 6MWT

Significant improvement in 6-minute walking distance (6MWD) distance ($p < 0.0001$) was observed after 10 days of 2-DG intervention in COVID-19 patients **(Table 4)**. Compared to baseline, a significant increase in the no. of laps (82.2 %), walking speed (83.3 %), METS (65.8 %), and 6MWD (84.6 %) were observed in patients after 2-DG intervention ($p < 0.0001$) **(Table 4)**. However, data in speed miles per hour (MPH), METS, and 6MWD could not be obtained from one patient and baseline data was not obtained for four patients. These patients were excluded from the final analyses.

Table 4 Improvement on distance parameters with 2-DG therapy assessed by 6MWT

Parameters	Pre 2-DG	Post 2-DG	% Change in parameter	Mean differences	95% CI	*p*-value
No. of Laps	10.6 ± 4.9	19.4 ± 4.4	82.2	8.731 ± 3.163	7.85 - 9.61	< 0.0001
Speed MPH	0.6 ± 0.3	1.1 ± 0.3	83.3	0.4935 ± 1.802	0.44 - 0.54	< 0.0001
METS	5.7 ± 2.2	9.4 ± 1.9	65.8	3.743 ± 1.393	3.35 - 4.13	< 0.0001
Distance covered in 6 minutes (ft.)	314.6 ± 161.4	575.5 ± 134.8	84.6	260.9 ± 101.8	231.0 - 290.8	< 0.0001

Abbreviations: MPH: Miles per hour; METS: Metabolic equivalent; CI: Confidence interval

Discussion

The extent of lung involvement in COVID-19 determines the presentation of symptoms, which range from moderate upper respiratory tract infections to acute respiratory distress syndrome (ARDS). For some patients, the transition from a mild illness with minor symptoms to a severe or critical state can happen rapidly. Hypoxemia, along with the requirement for supplemental oxygen, has been reported to be an important indicator of the degree of COVID-19 severity, particularly in hospitalized patients. **[6,7]**

In India, a higher frequency of viral pneumonia with ARDS was seen during the 'second wave' of COVID-19, resulting in considerable morbidity and mortality. Hence, research into the compassionate use of repurposed medications and novel compounds was prioritized and several molecules were evaluated for their efficacy in treating COVID-19. In India, 2-DG, a cancer treatment agent, was evaluated for COVID-19 treatment and approved by the DCGI as an emergency adjunct treatment for COVID-19 patients. **[11]** In addition, considering the high case-load and case-fatalities due to respiratory distress, reliable and cost-effective methods are required to identify patients in need of advanced medical care early. Several studies have analyzed the use of exertional tests in assessing and predicting disease progression in COVID-19 in ambulatory patients. **[6,10,12]** 6MWT has been proposed as an effective assessment tool for detecting hypoxemia in hospitalized patients prior to discharge **[13]** and to identify COVID-19 patients who will need hospitalization. **[14]**

In this case series, 6MWT was employed to evaluate the effect of 2-DG on improvement in respiratory parameters of COVID-19 patients. This case study yielded two important conclusions:

i. 2-DG is effective in improving respiratory parameters in COVID-19 patients, as demonstrated by the findings of 6MWT pre and post 2-DG therapy.
ii. ii. 6MWT is a simple and most tested method to identify silent hypoxemia, which is a harbinger of clinical deterioration in COVID-19 infection.

The beneficial effect of a 2-DG intervention on improving the clinical parameters was established from the findings. In hypoxemic patients, deterioration in oxygen saturation and cardiovascular compensation can occur rapidly. **[15]** The patients who are not capable of adequate cardiovascular compensation, especially the elderly population, are reported to experience more hypoxemic stress than the younger population. **[15]** However, none of the patients appeared to be hypoxemic during or at the end of the test, and an optimum SpO_2 level of above 95% was maintained even at the end of 6MWT with 2-DG administration. Additionally, elevated heart rate as a result of breathing response to hypoxemia was improved upon achieving a normal oxygen saturation level. **[15]** This demonstrates the minimal or no dependence on supplemental oxygen in patients administered with 2-DG in improving respiratory outcomes in COVID-19.

Furthermore, we observed that patients had a lower 6MWD at baseline, which improved after 10 days of 2-DG intervention. Improvement in 6MWD was in tandem with the improvement in fatigue and breathlessness after the 2-DG intervention, as estimated by the Borg scale, indicating a positive association of 6MWD with both fatigue and breathlessness. In a previous study, it has been reported that lower 6MWD was independently associated with exertional dyspnea and hypoxemia **[16]**. There was an 84.6 % improvement in 6MWD after the 2-DG intervention compared to baseline, which points to the efficacy of 2-DG in mitigating dyspnea and hypoxemia. The ease of availability and cost-effectiveness makes this drug suitable for developing countries like India. No side effects due to 2-DG were observed in this case series.

6MWT improves the margin of safety by early identification of cases that are likely to progress to severe conditions. **[6]** Considering the

economic viability and practical applicability, the COVID-19 care centers with mild cases in low and middle-income countries are suitable for this screening test. **[6]** A more effective modification of 6MWT was proposed by Mantha *et al*., which has been recommended for use in the management of mild COVID-19 cases at the clinic level and in identifying cases with progression to severity for referrals to larger hospitals and early intervention. **[6]**

The retrospective design and the small study population without a comparator arm were limitations of this study.

Conclusion

6MWT is an easy and effective tool for uncovering silent hypoxia, thus enabling early identification of COVID-19 patients at risk for deterioration and in need of in-hospital care. Since the parameters measured in the 6MWT reflect the immediate physiologic response to treatment, it can be used to monitor response to 2-DG therapy. Treatment with 2-DG has shown statistically significant improvement on the 6MWT parameters, indirectly demonstrating improvement in lung involvement and function post therapy. Future studies with a standard of care comparator arm can further establish the role of 6MWT in monitoring response to 2-DG therapy in COVID-19 patients.

In moderate to severely ill COVID-19 patients, administration of 2-DG improved the clinical condition by achieving an optimum oxygen saturation level. In addition, it improved the mean walking distance and exhibited a positive impact on the 6MWT. This test may be useful to differentiate hypoxemic patients and recommend advanced clinical care to avoid further worsening of the clinical condition, and also to assess the efficacy of new/novel drugs in the treatment of COVID-19.

Disclosure: The author reports no conflicts of interest in this work.

Acknowledgments The authors acknowledge Molecular Connections Pvt. Ltd., Bengaluru, India for the medical writing support and Dr. Reddy's Laboratories, India, for providing financial support towards medical writing.

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