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FULL PAPER

Low-dose radiation therapy for COVID-19 pneumonia: a pilot study

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Objectives: The World Health Organization (WHO) has declared coronavirus disease 2019 (COVID-19) as pandemic in March 2020. Currently there is no specific effective treatment for COVID-19. The major cause of death in COVID-19 is severe pneumonia leading to respiratory failure. Radiation in low doses (<100 cGy) has been known for its anti-inflammatory effect and therefore, low dose radiation therapy (LDRT) to lungs can potentially mitigate the severity of pneumonia and reduce mortality. We conducted a pilot trial to study the feasibility and clinical efficacy of LDRT to lungs in the management of patients with COVID-19.

Methods: From June to Aug 2020, we enrolled 10 patients with COVID-19 having moderate to severe risk disease [National Early Warning Score (NEWS) of ≥5]. Patients were treated as per the standard COVID-19 management guidelines along with LDRT to both lungs with a dose of 70cGy in single fraction. Response assessment was done based on the clinical parameters using the NEWS.

Results: All patients completed the prescribed treatment. Nine patients had complete clinical recovery mostly within a period ranging from 3 to 7 days. One patient, who was a known hypertensive, showed clinical deterioration and died 24 days after LDRT. No patients showed the signs of acute radiation toxicity.

Conclusion: The results of our pilot study suggest that LDRT is feasible in COVID-19 patients having moderate to severe disease. Its clinical efficacy may be tested by conducting randomized controlled trials.

Advances in knowledge: LDRT has shown promising results in COVID-19 pneumonia and should be researched further through randomized controlled trials.

INTRODUCTION

Currently, there is a global outbreak of COVID-19 caused by severe acute respiratory syndrome coronavirus 2 (SARS- CoV-2). On 11 March 2020, the WHO has declared COVID-19 as a pandemic and as of 31 January 2021, there have been a total of 101 561 219 confirmed cases and 2 196 944 deaths.[1] The clinical spectrum of COVID-19 varies from asymptomatic to clinical conditions characterized by respiratory failure that necessitates mechanical ventilation and intensive care unit (ICU) support. Severe pneumonia progressing to acute respiratory distress syndrome (ARDS) is the cause of death in majority of cases. The death rate ranges from 2 to 15% in different group of patients.[2–4]

Currently, there is no specific antiviral drug available for COVID-19. Although vaccines are available their efficacy on large scale is yet to be established. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Based on severity of symptoms, there are several scoring methods which can predict the outcome of disease. The National Early Warning Score (NEWS) is a popular scoring system used for non-ICU patients suffering from acute illness.[5] This score helps in quickly determining the degree of illness and intervention required. It also provides likelihood of death or admission to an ICU. Based on this score, any illness can be categorized as mild (Score <4), moderate (Score 5–6 or individual 3) and severe (Score ≥7).

According to this scoring system, COVID-19 patients having a score of 5–6 will have probability of 15.7% critical events (ICU admission or 30 day mortality) and those having a score ≥7 will have about 24.1% critical events.[5]

The pathogenesis of COVID-19 pneumonitis appears to involve a cytokine storm with elevated pro-inflammatory cytokines, such as IL-6 and TNFα among many others, leading to respiratory failure.[6] Radiation therapy (RT) in low doses (<100 cGy) is reported to have its anti-inflammatory action by downregulating pro-inflammatory macrophages and upregulating anti-inflammatory macrophages (interleukin-10, transforming growth factor β1) and natural killer (NK) T cells; thus, countering the immune reaction incited by COVID-19.[7] Low dose lung irradiation can potentially mitigate the severity of pneumonitis thereby reducing the risk of death. It was a popular treatment of viral pneumonias until 1940s.[8] Historical data[9–13] suggests that low dose radiation therapy (LDRT) to whole lung can possibly prevent cytokine storm and ARDS. A few recent trials,[14,15] although with small sample size and short-term results have shown the feasibility of LDRT doses ranging from 0.5 to 1.5 Gy. We, therefore, conducted a pilot trial to study the feasibility and clinical efficacy of LDRT to lungs in the management of patients with COVID-19.

METHODS AND MATERIALS

This pilot study was conducted at our Institute to assess feasibility and clinical efficacy of LDRT in patients with COVID-19. The study was initiated in May 2020 after approval by Institute of Ethics committee (Ref. No. IEC-465/22.05.2020, RP-01/2020). It is registered on ClinicalTrials.gov (NCT04394793) and Clinical Trials Registry India (CTRI/2020/06/025862). The study protocol was designed jointly by the radiation oncology team and Institute COVID Management Team (comprising of members from departments of Internal medicine, pulmonary medicine, intensive care and hospital infection control committee). The sample size of 10 patients was determined based on multiple factors like incidence of COVID-19 disease, severity of disease, risk of viral exposure to radiation oncology team, availability of radiation therapy resources, distance between the COVID-19 indoor unit, radiation therapy machine, etc. Eligible patients (as per inclusion criteria) were enrolled in the study after obtaining their consent. In order to avoid viral exposure to team, video conference facility was used while counseling them and taking their consent. Complete details about the trial, steps involved, benefits or side-effects of treatment were explained to every patient.

Eligibility criteria

Eligibility criteria included age more than 18 years, diagnosis of COVID-19 confirmed by RT-PCR and moderate to severe illness (NEWS ≥5). Generally, the febrile patients who were already admitted to our indoor unit for COVID-19 management and having respiratory rate of >24 per minute and/or oxygen saturation of <94% were screened for inclusion as they were likely to fulfill the eligibility criteria. Patients requiring mechanical ventilatory support or having unstable hemodynamic status were excluded. As COVID-19 virus is highly contagious and poses a risk to the various staff members during laboratory and radiological investigations, we adopted NEWS (Table 1) for inclusion of patients as well as response assessment as this is mostly based on clinical feasibility and efficacy of LDRT. The study outcome measures were: (1) number of ICU admissions or deaths; (2) improvement in NEWS score post LDRT; and 3) length of hospital stay post LDRT.

Treatment and workflow to RT machine

All patients were treated as per the Institute COVID-19 standard management guidelines along with intervention of LDRT to both lungs with a dose of 70 cGy in single fraction. The standard medical treatment generally consisted of oxygen supplementation, antibiotics, dexamethasone and general supportive care. LDRT was delivered employing two opposed antero posterior and postero anterior open portals. We did not use CT-based RT planning as the prescribed dose is very low and the expected dose to organs at risk (OAR) is negligible. Additionally, CT simulation would increase the risk of viral exposure to staff. For patient transport from indoor unit to RT machine (Varian True Beam Radiotherapy System Linear Accelerator), the corridor was isolated. Patients were made to wear personal protective equipment (PPE) or mask covering face and head before they were shifted to RT area. The patient was positioned supine with hands above head. Machine gantry was rotated to 90 degree and a lateral chest X-ray portal image was taken in order to guide in measuring dose prescription point. Gantry was rotated back to 0 degree; an adequate field size was opened in order to cover both lungs. Upper border of the field was kept above the superior edge of lateral end of clavicle extending 1 cm superior to lung apex on portal imaging. Lower border extended below at the level of the L1 vertebrae (transpyloric plane) in order to cover costophrenic angle. Lateral borders were in the air on both sides of chest. A dose of 70 cGy in single fraction was prescribed at the midpoint of anteroposterior chest separation using 6 MV X-ray photons. Oxygen saturation level was continuously monitored during the entire treatment by placing the pulse oximetry monitor facing the CCTV camera. After completion of treatment, the patient was transported back to indoor unit through the same corridor. The Linear Accelerator unit was sanitized as per the cleaning and disinfection guidelines provided by the vendor.

Response assessment

The response assessment was done mainly on clinical parameters as per the NEWS. Imaging, routine hematological investigations and serum markers levels (like C-reactive peptide, D-dimer, interleukin-6, ferritin, etc.) were done as and when needed, but not mandatorily for response assessment. The NEWS was recorded on Day 3, Day seven and Day 14 post LDRT. These scores were compared with baseline score recorded on the day of LDRT, that is, on Day 0. Clinical response was defined as subject achieving NEWS of 0 within 14 days following LDRT. Failure was defined as ICU admission anytime after LDRT or death within 30 days. Patients were generally discharged from the hospital after they attained NEWS of 0 along with negative test (by RT-PCR) for COVID-19. They were contacted on phone for any further required information.

Table 1. National Early Warning Score (NEWS) formula

Criteria	Point Value
Respiratory Rate (breaths/min)	
≤8	+3
9–11	+1
12–20	0
21–24	+2
≥25	+3
Oxygen Saturation (%)	
≤91	+3
92–93	+2
94–95	+1
≥96	0
Any Supplemental Oxygen	
Yes	+1
No	0
Temperature in °C (°F)	
≤35.0 (95)	+3
35.1–36.0 (95.1–96.8)	+1
36.1–38.0 (96.9–100.4)	0
38.1–39.0 (100.5–102.2)	+1
≥39.1 (≥102.3)	+2
Systolic BP	
≤90	+3
91–100	+2
101–110	+1
111–219	0
≥220	+3
Heart Rate (beats/min)	
≤40	+3
41–50	+1
51–90	0
91–110	+1
111–130	+2
≥131	+3
AVPU (Alert, Voice, Pain, Unresponsive)	
A	0
V, P, or U	+3

Adapted from: Royal College of Physicians. National Early Warning Score (NEWS): Standardizing the assessment of acute illness severity in the NHS. Report of a working party. London: RCP, 2012.

Interpretation

A low score (NEWS 1–4) should prompt assessment by a competent registered nurse who should decide if a change to frequency of clinical monitoring or an escalation of clinical care is required.

A medium score (*i.e.* NEWS of 5–6 or a RED score) should prompt an urgent review by a clinician skilled with competencies in the assessment of acute illness – usually a ward-based doctor or acute team nurse, who should consider whether escalation of care to a team with critical-care skills is required (*i.e.* critical care outreach team).

A RED score refers to an extreme variation in a single physiological parameter (*i.e.* a score of 3 on the NEWS chart in any one physiological parameter, colored RED to aid identification; *e.g.* heart rate.

A high score (NEWS ≥7) should prompt emergency assessment by a clinical team/critical care outreach team with critical-care competencies and usually transfer of the patient to a higher dependency care area.

RESULTS

A total of 10 patients were recruited and treated from June to September 2020. Table 2 shows various clinical characteristics of the patients. All the patients were male with a median age of 51 years (range 38 to 63 years). The shortness of breath was the most common symptoms, found in all patients. The median respiratory rate was 22 per minute (range 21–27/min). Majority of patients (8 out of 10) had NEWS of 5–6. Three patients had co-morbidities (hypertension, two and diabetes, 1).

LDRT was delivered after a mean of 3 days (range 1–9 days) of indoor admission (Table 3). None of the patients was admitted in ICU before LDRT. Two patients (patient no. 3 and 8) received LDRT after 6 and 9 days of hospitalization, respectively, as they were having mild symptoms initially. All patients completed the prescribed LDRT. Average time taken for LDRT (from entering to exiting treatment room) was 11 min (8–34 min). One patient took unexpectedly longer time during treatment (34 min) due to technical problem in switching on the machine. Another patient took 19 min since the radiation therapy technologist had difficulty in starting the treatment due to fogging inside wall of face shield. No patient required RT interruption due to deterioration of vitals or oxygen saturation.

Table 3 shows the progress in NEWS post LDRT. One patient, showed clinical deterioration and had to be intubated. He developed fungal pneumonia and finally succumbed of ARDS on day 24. Rest nine patients had complete clinical response and finally discharged from the hospital after their COVID test was negative. The average hospital stay of the cured patients was 15 days (range 10–24 days). Figure 1 depicts the speed of clinical recovery. Most patients achieved a NEWS of 0 by Day 7, but patients having age ≤50 years had faster recovery. Three of the five patients with age ≤50 years had achieved Day 3 NEWS of 0 while none of the patients older than 50 years could achieve this score (Table 3). Of the three patients having co-morbidities, one died and the rest two recovered. All seven patients without co-morbidities recovered. Day 30 clinical status was determined by communicating the patients or relatives on phone. All nine patients discharged from hospital were alive. No patients showed the signs of acute radiation toxicity.

DISCUSSION

The results of our study have proven the feasibility of using LDRT for treatment of COVID-19 patients with moderate to severe risk disease. All patients completed the prescribed treatment without any hurdles. None of the radiation therapy team members involved in LDRT of these patients acquired COVID-19 infection. We used simple, open field technique for RT to minimize the radiation planning and delivery time. No patient showed any signs of acute radiation toxicity and therefore it is clinically safe.

In terms of clinical improvement, we observed 90% clinical response rate in our study which suggests that LDRT is probably effective in COVID-19 patients with moderate to severe illness. Only one patient, who had associated co-morbidity (HT) did not respond to LDRT and died of ARDS. It is well known that the patients with co-morbidities have higher risk of mortality.

Table 2. Clinical Characteristics of the patients

Patient Serial No.	Age (year)	Sex	Co-morbidities	Respiratory Rate (per minute)	Oxygen Saturation (%)	Any Supplemental Oxygen	Temp.	Systolic BP (mm Hg)	Heart Rate (per min)	NEWS
1	52	Males	none	24	93	yes	98.0	110	76	6
2	45	Males	none	21	93	yes	98.6	138	88	5
3	43	Males	none	27	95	yes	97.6	136	87	5
4	58	Males	none	28	91	yes	98.0	159	77	7
5	38	Males	HT	22	91	yes	98.0	126	98	5
6	53	Males	HT	22	95	yes	98.8	105	80	5
7	56	Males	DM	24	93	yes	98.4	110	104	7
8	45	Males	none	22	93	yes	98.4	103	88	6
9	50	Males	none	22	92	yes	98.2	123	96	6
10	63	Male	none	22	95	yes	98.8	120	98	5

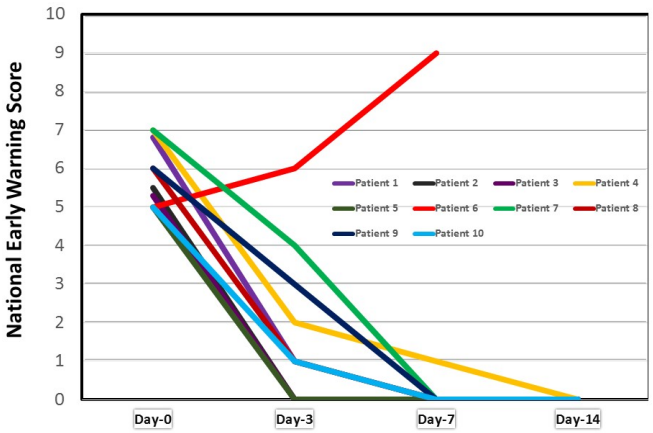
DM, Diabetes mellitus; HT, Hypertension; NEWS, National early warning score.

Table 3. Clinical Response post LDRT

Patient Serial No.	Age (year)	Hospital stay (days)	Interval between day of hospitalization and LDRT (days)	Day-0 NEWS (on the day of LDRT)	Day-3 NEWS	Day-7 NEWS	Day-14 NEWS	Day-30 clinical status
1	52	10	3	6	1	0	0	Alive
2	45	24	2	5	0	0	0	Alive
3	43	18	9	5	0	0	0	Alive
4	58	15	1	7	2	1	0	Alive
5	38	13	1	5	0	0	0	Alive
6	53	24	2	5	6	9	-	Dead
7	56	15	2	7	4	0	0	Alive
8	45	12	6	6	1	0	0	Alive
9	50	14	2	6	3	0	0	Alive
10	63	12	2	5	1	0	0	Alive

ICU, Intensive care unit; LDRT, Low dose radiation therapy; NEWS, National early warning score.

Figure 1. Graph showing post LDRT response as per National Early Warning Score.



The other two patients in our series (patient no. 5 and 7) with co-morbidities had recovered within a week and got discharged in less than 2 weeks of LDRT. Due to small population of patients with co-morbidities in our study; it is difficult to co-relate LDRT response with co-morbidities. LDRT can potentially help in averting the need of ICU admission, if its clinical efficacy is established in future trials. ICU care consumes lot of manpower resources and cost which are constrained in developing countries like India having high incidence of COVID-19.

The initial report using X-rays to treat patients with pneumonia was in 1907 by Edsall and Pemberton.[9] Subsequent reports till 1940s suggested that LDRT was successful in decreasing the mortality rate in untreated patients from about 30% to 5–10%.[10–13] In 1943, Oppenheimer[13] reported the results of LDRT using 50 roentgen in 56 patients of viral pneumonia and observed cure rate of 80%. During that time, there was no concept of lung correction factor and therefore the actual dose delivered to lungs in Oppenheimer's study was more than 50 roentgen. We, therefore, employed a prescribed dose of 70 cGy in our study. Oppenheimer[13] further observed that if radiation was delivered in the first week of disease phase, the cure rate was 100% as compared to 50% when delivered after 2 weeks. Despite good clinical results reported in these trials,[10–13] LDRT slowly vanished after the arrival of penicillin. Kirkby and Mackenzie first suggested the use of LDRT in current COVID-19.[16]

Recently, two studies,[14,15] to the best of our knowledge, have been published reporting the use of LDRT for COVID-19 and ours is the third one being reported here. Table 4 shows the comparison of these two studies with our present study. Our study has the largest sample size (10 *vs* 5 *vs* 5 patients). Both trials[14,15] had higher median age and co-morbidities as compared to ours. LDRT dose was highest in the study by Hess at al.[15] Although it is difficult to compare clinical outcome due to small sample sizes in all three studies (Table 4), the recovery rate was relatively higher in our study (90% *vs* 80% *vs* 80%). This is probably because our patients had relatively less severe disease, younger age and lower frequency of co-morbidities. As evident from Table 3, patients younger than 50 years of age had faster recovery rate in our

Table 4. Studies published so far using LDRT for Covid-19

Authors	NCT no.	No. of patients	Median age (year)	No. of patients having co-morbidities	Interval between hospitalization and LDRT (days)	RT dose (Gy)	No. of RT fields	Response/ recovery rate (%)	Acute toxicity
Hess et al[15]	NCT04366791	5	90	5	5	1.5	2 (AP-PA)	80	nil
Ameri et al[14]	NCT04390412	5	71.8	5	2	0.5	2 (AP-PA)	80	nil
Present Study	NCT04394793	10	51	3	3	0.7	2 (AP-PA)	90	nil

AP, Antero-posterior; LDRT, Low dose radiation therapy; PA, Postero-anterior; RT, Radiation therapy.

study. We believe LDRT is most effective in averting the cytokine storm and therefore may be used before the cytokine storm has set in. Therefore our study was designed to enroll patients with moderate to severe illness.

Castillo et al[17] have recently published a report of 64 year old patient treated with LDRT. They adopted CT-based planning prescribing a dose of 1.0 Gy with VMAT technique. Clinical target volume (CTV) consisting of whole lung and OAR were contoured. A circumferential 5 mm and craniocaudal 10 mm PTV expansion was created. Procedure duration consisted of 30 min planning and about 13 min of treatment delivery (including cone beam CT scan performance). The patient showed improvement after 3 days of LDRT and shifted out of ICU after 6 days. We do not encourage CT-based planning considering negligible dose to OAR due to low prescription dose.

Although it is hypothesized that LDRT potentially mitigate the COVID-19 pneumonitis by inducing an anti-inflammatory effect; animal, human and *in vitro* studies indicate that LDRT may have the potential to control bacterial pneumonia.[18] Therefore, LDRT may also be capable of reducing bacterial co-infections in patients with COVID-19. Additionally, LDRT might prevent accelerated viral drug-related mutation thus potentially improving the immune response by means of the enhanced RNA damage compared to antiviral therapy.[18,19]

Whenever RT is employed for benign conditions, concerns are expressed about risk of radiation-induced carcinogenesis. It is often ignored that even without radiation exposure; a healthy human being does carry a certain amount of life-time risk of developing cancer. At such low doses of RT, the risk of radiation-induced carcinogenesis is negligible considering the potential benefit of LDRT in the current pandemic. Another apprehension of LDRT in COVID-19 patients is lung fibrosis which may be a sequelae of both covid-19 pneumonia and LDRT. Emerging literature suggest that there could be a substantial risk of pulmonary fibrosis following COVID-19 infection.[20] Additional treatment with LDRT in COVID-19 patients may enhance this risk; however, none of the published trials,[14,15] although limited by the short-term data, have reported such complication of LDRT.

Our study has several limitations including small sample size and response assessment without radiological or laboratory investigations. We wanted to keep the study design simple and convenient for smooth conduction considering the fear of radiation exposure amongst the patient population and also the panic in radiation therapy team which is primarily a non-COVID team. Although, there are several ongoing trials (ClinicalTrials.gov Identifier: NCT04427566, NCT04572412, NCT04377477, NCT04493294 and NCT04393948) with primary outcome assessment based on clinical parameters,[21] future trials may be designed based on the guidelines suggested by the National Cancer Institute.[22]

CONCLUSION

The results of our pilot study suggest that LDRT is feasible in COVID-19 patients having moderate to severe disease. Its clinical efficacy may be tested by conducting randomized controlled trials.

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ETHICS APPROVAL

The ethical approval of the study was provided by Institute Ethics Committee, All India Institute of Medical Sciences, New Delhi (Ref. No. IEC-465/22.05.2020, RP-01/2020 dated 26th May 2020).

CLINICALTRIALS.GOV REGISTRATION NO

NCT04394793.

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