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REVISITING THE ROLE OF LOW DOSE RADIATION THERAPY AGAINST COVID-19 PNEUMONIA

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ABSTRACT: Background: The entire world is battling the coronavirus disease (COVID-19) that potentially leads to pneumonia, Acute Respiratory Distress Syndrome (ARDS), multi-organ failure, often resulting in death. Therefore, the utmost challenge from a medical perspective is to improve lung function before the patient requires intubation and critical care. In the same light, the use of low dose radiation therapy (LDRT) that has been used to treat various non-malignant inflammatory conditions can be exploited as a promising approach to combat ARDS in COVID-19 patients. LDRT is a century-old popular treatment of viral pneumonia that has been reported to reduce inflammation and prevent the cytokine storm, thus mitigating the severity of pneumonitis. Given the outcomes of pilot clinical studies, the administration of LDRT should be kept as an option in clinical situations where benefits outweigh the risks. Therefore, the present communication highlights the anti-inflammatory role of LDRT so as to revisit its prospective role in COVID-19 pneumonia treatment. **Conclusions:** In the COVID-19 pandemic, LDRT appears as a cost-efficient, potent, non-invasive, anti-inflammatory treatment option that can decrease the patient burden of the hospital set up and help in mitigating the life-threatening symptoms associated with COVID-19 pneumonitis, especially in patients who are at a progressive stage of infection and unfit for conventional anti-inflammatory treatments.

INTRODUCTION: The onset of novel coronavirus disease (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) was first reported in Wuhan, China in December 2019 and rapidly spread to many countries across the globe [1]. World Health Organization (WHO) declared it as a global pandemic on 11th March 2020.

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Based on WHO's report, 16th October 2020, the number of confirmed cases of COVID-19 are 38,394,169, and the numbers of deaths are 1,089,047, with 216 countries affected globally.

With a death toll far exceeding that of the SARS-CoV-1 outbreak in China during 2002-2004, the onset of novel SARS-CoV-2 in 2019 has led to a public health emergency of international concern, putting all health organizations on high alert. At present, no drug or vaccine has been found suitable for the treatment of COVID-19 pneumonia as they are still in the trial stage. The elderly population with multiple co-morbidities are at a higher risk of developing SARS-CoV-2 pneumonia due to a compromised immune system.

Such patients after infection are prone to show a severe inflammatory response, which can be treated with Low Dose Radiation Therapy (LDRT). LDRT is well known to induce an anti-inflammatory response by activating cytokines such as TGF-β1 and IL-10 [2]. Benefits of LDRT outweigh the risk as reported by certain recent pilot studies [3, 4].

LDRT appears to be an economically viable, non-invasive treatment option and helps in mitigating the life-threatening symptoms associated with COVID-19 pneumonitis. Therefore, the administration of LDRT should be kept as an option in critically ill patients with acute respiratory distress.

Pathogenesis of COVID-19 Pneumonia: The clinical symptoms of COVID-19 range from mild (common cold, dry cough, fever, myalgia) to severe (dyspnea leading to pneumonia, Acute Respiratory Distress Syndrome (ARDS), sepsis, multi-organ failure) even resulting in death [5]. SARS-CoV-2 pneumonia causes an inflammatory response characterized by a sudden increase in the level of many pro-inflammatory cytokines (IL-1β, IL-2, IL-6, IL-7, IL-8, IL-12, granulocyte-macrophage colony-stimulating factor (GM-CSF), macrophage inflammatory protein-1α (MIP-1α), TNF- α, ferritin, and D-dimer) and is refereed as the Cytokine Release Syndrome (CRS) [6].

The continuous production of pro-inflammatory cytokines is accompanied by chemokines such as CCL2, CCL3, CCL5, IFNγ-inducible protein-10 (IP-10), and Reactive Oxygen Species (ROS) [6]. This acute inflammatory response damages the endothelial cells and the alveolar epithelial cells, which is the main cause of COVID-19 related ARDS. This results in the accumulation of fluid inside the alveoli causing diffuse alveolar damage [2]. Neutrophils are activated by cytokines, recruited to the lungs, and release inflammatory markers, which is important in the pathogenesis of ARDS. ARDS is also referred to as macrophage activation syndrome (MAS) because of the significant role of macrophages in generating cytokine storm responsible for irreversible lung damage. Based on the microenvironment in different pathological conditions, the M1 macrophages secrete pro-inflammatory cytokines (IL-1, IL-6, TNF-α), whereas the M2 macrophages secrete anti-inflammatory cytokines [2]. In the acute stage of ARDS, resident alveolar macrophages, which primarily express the M2 phenotype, alter to M1 phenotype and release various pro-inflammatory markers. Therefore, cytokine storm is the major cause of ARDS, so suppressing it can prevent the deterioration of patients and save their lives.

Pharmacological Intervention for COVID-19: A multitude of pharmacological studies have shown some drug candidates previously approved for different clinical conditions that may have potential against SARS-CoV-2 infection. However, only large-scale clinical trials on COVID-19 patients will be able to determine their safety and efficacy. Remdesivir, an RNA polymerase inhibitor, has shown merit in human trials only in shortening the recovery time by a few days, resulting in increased transaminases and kidney injury.

Tocilizumab, an IL-6 inhibitor, has also been clinically exploited for its use in COVID-19 patients with severe inflammation. However, high costs and safety risks lead to a barrier for its potential use in treating COVID-19 [7]. Also, the antimalarial drugs, Hydroxychloroquine and Chloroquine, have demonstrated antiviral activity against SARS-CoV-2, but it also induces the risk of cardiac toxicity in critically ill patients [8]. Thus, the lack of an effective and economically viable treatment option presents a dire need to investigate new anti-inflammatory therapies.

Low Dose Radiation Therapy (LDRT) – Mechanism of Action against Inflammation: The relationship between ionizing radiation and inflammatory response is dichotomous and depends on the amount of radiation dose. Radiation exposure at high doses induces inflammation by activating transcription factors (NF-κB) and cytokines such as IL-6, IL-1β, and TNF-α. While low doses of radiation (0.5–1.5 Gy) induces an anti-inflammatory response by activating cytokines such as TGF-β1 and IL-102. The clinical evidence comes from the LDRT usage during the first half of the 20th century in successfully treating pneumonia especially, viral pneumonia [9].

An early event in the inflammatory cascade involves local vasodilatation, increased blood flow, and microvascular permeability, resulting in

erythema and edema. At the site of infection, endothelial cells in the lungs are activated by pro-inflammatory cytokines mainly produced by resident macrophages and dendritic cells, which causes the recruitment of leukocytes from peripheral blood to endothelial cells. The first contact between endothelial cells and leukocytes occurs due to the adhesion molecules E-selectin and P-select on the surface of the endothelial cells, which bind to the L-selectin and corresponding carbohydrate ligands present on the surfaces of the leukocytes [10]. The effector phase of inflammation is characterized by an accumulation of monocytes and their differentiation into macrophages and dendritic cells. The immune cells support inflammation by performing a plethora of functions like phagocytosis, antigen presentation, cytotoxicity, secretion of cytokines, ROI, and inducible Nitric Oxide Synthase (iNOS) that results in the production of nitric oxide (NO)[2]. Various studies have shown that LDRT lowers the adhesion of leukocytes to endothelial cells by increasing the expression of TGF-β1 and decreasing the expression of E-Selectin on endothelial cells [11]. LDRT induces apoptosis in Peripheral Blood Mononuclear cells (PBMC) by lowering the levels of pro-inflammatory cytokines like TNF-α, IL-1β while increasing the levels of anti-inflammatory cytokine like IL-10. The activated macrophages respond to LDRT by reducing the expression of iNOS. This resulted in decreased NO production and lowered levels of ROI. LDRT has been shown to alleviate inflammation and facilitates healing by enabling the polarization of macrophages from pro-inflammatory M1 phenotype to anti-inflammatory M2 phenotype [12].

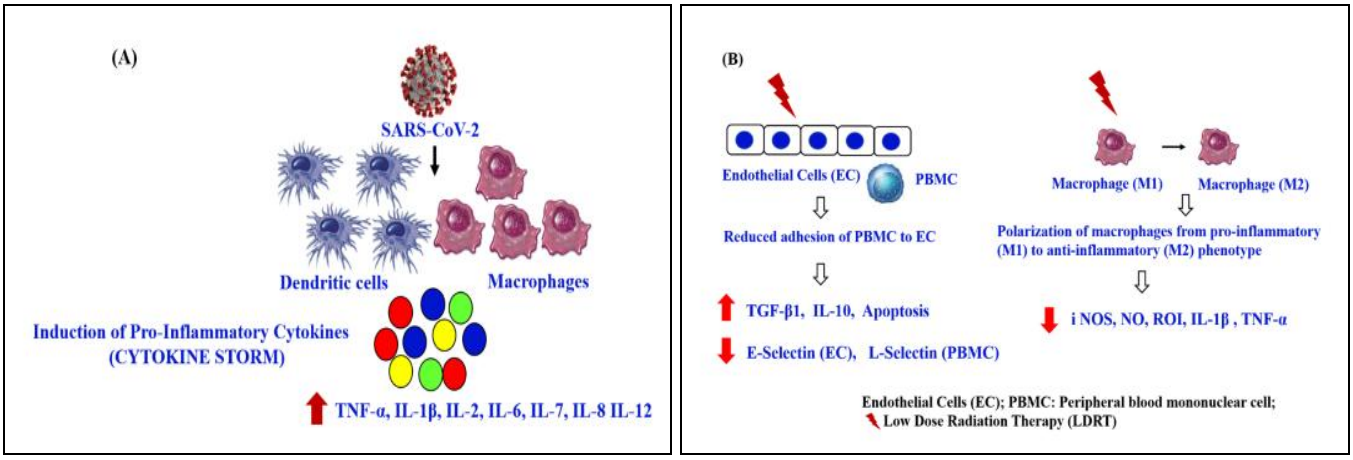

FIG. 1: (A) THE EFFECT OF SARS-COV-2 IN GENERATING CYTOKINE STORM BY STIMULATING THE PRO-INFLAMMATORY CYTOKINES; (B) THE MODULATORY EFFECT OF LDRT ON THE ENDOTHELIAL CELLS, PERIPHERAL BLOOD MONONUCLEAR CELLS AND MACROPHAGES AFTER INDUCTION OF CYTOKINE STORM

TABLE 1: ANTI-INFLAMMATORY EFFECT OF LDRT UNDER VARIOUS PATHOLOGICAL CONDITIONS

Clinical/Experimental Pathology	Radiation Dose	Mechanism of action
Arthritis (Rabbit and Mice)	0.5-1.5 Gy	↓ inflammation symptoms, ↓ iNOS and ↑ HO [15]
Mice granulomatous disease	2 Gy	↓ inflammation [15]
Mice superficial dorsal air cell model	0–5 Gy	↓ iNOS, ↑ HSP-70 and ↑ HO-1 [15]
Mice systemic inflammation	0.1-0.6 Gy	↓ leukocyte adhesion
model with Lipopolysaccharide (LPS)		ICAM not modified↑TGF-β1 [15]
Plantar Fasciitis	0.25-1 Gy	Pain relief: 90% [16]
Bursitis Trochanterica	0.5-1 Gy	Pain relief: 72% [16]
Periarthritis Humeroscapularis	1 Gy	Pain relief: 91% [16]
Systemic Lupus Erythematous	0.5 Gy	↓ CD (+), CD4(+), CD8(-), B220 (+), T cells, ↑ Fox P3 [11]
Autoimmune Encephalomyelitis	0.5 Gy	↓ TNF-α, IL-6, IL-17 [11]

The M2 phenotype results in lowering the levels of ROS, NO, iNOS, TNF-α, and TGF-α while increasing the levels of heme oxygenase, IL-10, TNF-β, NF-κB, AP-1. **Fig. 1A** depicts the Cytokine Storm in response to SARS-CoV-2 infection, and **Fig. 1B** shows the modulatory effect of LDRT on endothelial cells, PBMC, and macrophages. LDRT has also been found to enhance the anti-viral immune response by stimulating the natural killer cell activity and production of interferons with no

effect on the viability of the virus [13]. Keeping in view the anti-inflammatory role of LDRT, it has been employed to treat a myriad of inflammatory or infectious disease ranging from bronchial asthma, arthritis, sinusitis, ear infection, necrotizing fasciitis, carbuncles and furuncles (boils), and potentially deadly infection such as pneumonia and gas gangrene [14]. **Table 1** shows the anti-inflammatory effect of LDRT in different experimental models.

Why LDRT in COVID-19 pneumonia?: In the present global pandemic, LDRT to the lungs of patients with COVID-19 pneumonia could be useful in mitigating inflammation and life-threatening symptoms based upon convincing recent evidence, availability, economic viability, and rapidity towards the relief of symptoms.

Recent Evidence: As reviewed by Calabrese and others [9], low-dose X-rays has been shown effective in broad range of pneumonia (cure rate of 83.1%) covering 863 cases. It is worth pondering that out of 863 cases, 85 cases were of virus-induced pneumonia, in which the cure rate was 78.8%. The optimal outcome of this treatment seems to be dependent on the stage of infection. LDRT ameliorates inflammation when given in the early to medium stages of SARS-CoV infection. In a study on patients with progressive interstitial pneumonia, a low radiation dose of 0.5 Gy given in the first 14 days of infection responded successfully to therapy, whereas the response was reduced to half when therapy was administered 14 days after the development of disease [9]. Based on available evidence and the underlying mechanism of action of LDRT, a single dose range of 0.3-0.5 Gy has been proposed to be useful in treating COVID-19 patients in the acute stage of illness when cytokine surge occurs [12]. One of the reports from researchers at Emory University in Atlanta completed a pilot study using LDRT in COVID-19 pneumonia. In a group of five COVID-19 patients, both lungs were irradiated with 1.5 Gy of radiation for over 10-15 minutes. Four patients showed rapid improvement in their breathing within 24 h. Repeated imaging and blood tests confirmed that LDRT appeared effective and safe in ameliorating COVID-19 symptoms [4]. In Iran, another pilot study was conducted in 5 patients who were older than 60 years. The whole lung was irradiated at a single fraction of 0.5 Gy, and the response rate was observed to be 80% with no acute radiation-induced toxicity [3]. Therefore, LDRT to the lungs of patients with COVID-19 pneumonia could be useful in mitigating inflammation and life-threatening symptoms.

Availability and Viability: Patients at a higher age with multiple co-morbidities are at a higher risk of developing SARS-CoV-2 pneumonia due to a compromised immune system. The COVID-19 pandemic has burdened health care to the extent that supportive oxygen therapy and mechanical ventilators, which is the only treatment available presently, are not enough to meet the needs of all the patients. Therefore, the health of many patients, especially the higher age group people, is greatly compromised, and the data globally suggest more mortality in elderly and comorbid patients than healthy and young enrolments [17]. The development of a suitable drug or vaccine is still in its infancy, and subsequent upscale production will take further time. In all this, the healthcare of COVID-19 patients, especially in developing countries, will be greatly compromised. Thus, the potential of LDRT as an anti-inflammatory agent can be utilized in older patients and in patients who are at a progressive stage of infection and unfit for conventional anti-inflammatory treatments. Other benefits of using radiation therapy over pharmacological treatments are its easy availability and portability. It allows a convenient way of delivering radiation doses to patients. Therefore, LDRT appears as a cost-efficient, potent, non-invasive, anti-inflammatory treatment option.

Rapidity towards Symptom Relief: There are few historical studies reporting relief of symptoms within the order of hours after LDRT [18, 19]. In the same line, an animal model study suggested LDRT could reduce the acute phase of pneumonia by half [20].

LDRT and Associated Risk: Though the possibility of long-term radiation-induced stochastic effects such as aging and cancer cannot be ruled out, however because of the low dose, radiation toxicities are very much unlikely. The radiation dose used to treat pneumonia is much below (<1%) than that used for anti-cancer therapy. Therefore, it does not exceed the tolerance dose in critical

organs such as the heart, thyroid, stomach or kidneys. Epidemiological studies suggest that the risk of cancer in adjacent organs is < 1%, which, if occurs has a long latent period of > 10 years [21]. Therefore, this can be explored as a treatment modality in severely ill elderly patients.

CONCLUSION: Patients with COVID-19 pneumonitis may benefit from LDRT and improve their quality of life and survival. This treatment option is economically viable and can decrease the patient burden of the hospital setup and help in mitigating the life-threatening symptoms associated with COVID-19 pneumonitis. Given the outcomes of pilot clinical studies, the administration of LDRT should be kept as an option in clinical situations where benefits outweigh the risks.

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