The Impact of Deep Local Lung Hyperthermia on COVID-19 Cancer Patients

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Abstract

Background: The goal of this study was to assess the impact of deep local hyperthermia on oxygen (O_2) saturation and infected volumes of lungs on coronavirus disease 2019 (COVID-19) cancer patients.

Materials and Methods: Fifty patients who suffered from COVID-19 (according to their computed tomography (CT) images and laboratory findings) were included in this study. The mentioned patients were divided into two groups (I and II) with thirty-five participants. The infected volumes and COVID-19 infectious locations were diagnosed using their CT images, and deep local hyperthermia was performed for group II. After three consequent days, the SPO_2, D-dimer, and infected volumes of lung parenchyma of both groups were compared to each other.

Results: For group II, the mean ± SD (standard deviation) of O_2 pressure saturation (SPO_2) before/after hyperthermia was $85 ± 0.0/91.3 ± 0.5$, respectively, while for group I, the mean ± SD of SPO_2 before/after 3 days was $85 ± 0.0/88 ± 0.2$, respectively. For infected volumes of lungs before/after hyperthermia in group II, the mean ± SD was $31.36 ± 3.13/4 ± 1.53$, respectively. Nonetheless, the infected volumes of lungs for group I were $34.21 ± 3.41/10 ± 2.12$ before/after three days. For group II, the amount of D-dimer before/after hyperthermia was $3200 ± 106/510 ± 121$, respectively. However, for group I, it was $3100/740$ before/after the consequent three days, respectively.

Conclusion: Deep local lung hyperthermia for COVID-19 cancer patients is suggested, as a result of its positive impacts on SPO_2 improvement and also D-dimer serum level, C-reactive protein, and Lactate dehydrogenaze reduction for the mentioned patients.

Keywords: Cancer, COVID-19, D-dimer, hyperthermia, lung, SPO_2

INTRODUCTION

Based on literature and studies, coronaviruses are a diverse group of viruses that may pose a threat to infect several animals, and according to a large amount of evidence, they may cause mild-to-severe respiratory infections in the human body.[1] At the end of 2019, a novel type of coronavirus emerged known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in Wuhan, China.[1] A vast number of investigations showed that the mentioned virus may cause an outbreak of unusual viral pneumonia. As a result of the highly transmissible nature of the virus and the fast spread of it around the world, the disease is known as coronavirus disease 2019 (COVID-19). Nowadays, many types of COVID-19 including delta (delta coronavirus) and lambda (γ coronavirus) emerged in many countries. To the best of our knowledge, it may cause infection to the lung and decrease the oxygen (O_2) saturation of blood cells. From the beginning of its spread to now, several studies have evaluated the effects of different methods on COVID-19 and discussed the clinical modalities,

Access this article online

Quick Response Code:

Website: www.advbiores.net

DOI: 10.4103/abr.abr_75_23

How to cite this article: Tavakoli M, Moghareabed R, Taheri H, Noorbakhsh Dehkordy M, Nasri E, Saeb M, et al. The impact of deep local lung hyperthermia on COVID-19 cancer patients. Adv Biomed Res 2024;13:92.

which may lead to decreased lung infections. COVID-19 may inject its genome into lung cells and pose to infect lung parenchyma, which may lead to some devastating impacts on the human body. Therefore, it would seem that trying to shape the deformation of lung cell receptors or creating some defects in intracellular enzyme may have considerable positive impacts on treating COVID-19 patients.

According to reading different studies, hyperthermia has a prominent role in treating lung cancer patients using radiofrequency (RF) waves.[2-4] David *et al.* have discussed the tolerance of the lung to hyperthermia and found that using 44.9 degrees of Celsius may increase lung perfusion without any adverse effects.[5,6] Hyperthermia can lead to some effects on extra- and intracellular proteins, which may be useful for treating the lung cells of COVID-19 patients.

Therefore, the purpose of this work was to evaluate the impact of deep local hyperthermia of the lung on the O_2 saturation of COVID-19 cancer patients.

MATERIALS AND METHODS

This study was performed at Sayed-Al-Shohada Hospital (Isfahan, Iran) from June to November 2021. The protocol of this cross-sectional study was approved by the ethical board of Isfahan University of Medical Sciences, Isfahan, Iran (IR. MUI. REC. 1399. 684).

Patient selection

Fifty patients who suffer from moderate-to-severe COVID-19 were included in this study. The patients are included in this work based on the following criteria: positive nasopharynx or oropharynx Polymeraze chain reaction (PCR), highly suggestive COVID-19 evidence on the computed tomography (CT) images, non-autoimmune disease, non-diabetic, non-lung cancer (non-primary or metastatic tumors) patients, and O_2 saturation higher than 85% ($SPO_2 > 85\%$). Patients who aged higher than 75 years, suffer from autoimmune disease, and had decreased SAO_2 after hyperthermia were excluded from
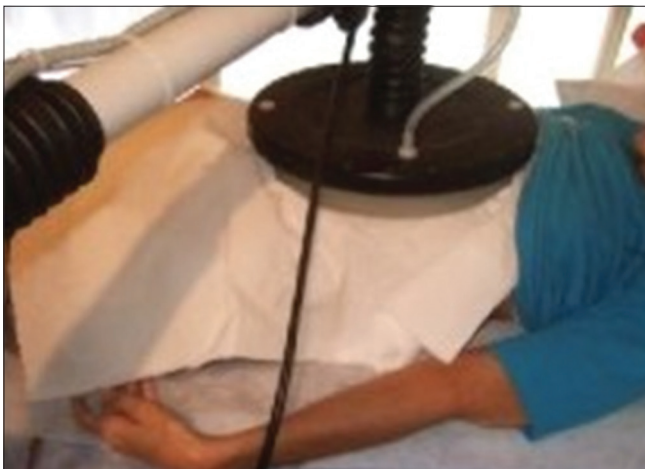

Figure 1: Deep local hyperthermia of lung

this study [Figure 1]. In addition, patients who had decreased SPO_2 (48 hours after hyperthermia) were excluded from this work. In this work, the studied patients were divided into two groups (I and II) as follows.

Patients who just received the routine modalities of COVID-19 treatment (such as remdesivir, corticosteroid, and actemra) were included in study group I, and patients who were treated with the mentioned routine modalities plus deep local lung hyperthermia were included in control group II.

Deep local hyperthermia

For group II, the whole lungs were contoured on CT images of the patients using a treatment planning system (TPS) (TiGRT, LinaTech, China). Therefore, a three-dimensional volumetric map guide of lesions based on the patient's geometry was provided. The Anterior Posterior- Posterior Anterior (AP-PA) diameter of the chest and the chest wall–lung interface thickness were measured using patient CT scan data. Moreover, the lungs were irradiated by a maximum of 41 degrees of Celsius RF waves (Novin Teb, Isfahan, Iran), which are located at the chest wall surface [Figure 1]. The mentioned patients were subjected to deep local hyperthermia (7–10 MHz RF waves) two times per day for three subsequent days. Each fraction time was 20 minutes. In this study, lower frequencies (7–8.7 MHz) were used to penetrate RF waves inside the lung. The SPO_2 of patients was evaluated before using an O_2 saturation measurement device, during and after 1 hour, 6 hours, and then daily after hyperthermia. A daily chest X-ray (CXR) was performed for the stated patients, and a second CT scan was applied for patients who had suitable clinical situations for CT.

RESULTS

Table 1 illustrates the clinical features of the studied patients. Table 2 indicates the impact of lung hyperthermia on the SPO_2

Table 1: Clinical, biological, and demographic characteristics of the studied patients

	Group I	Group II (hyperthermia)
Sex	Male: 12	Male: 14
	Female: 13	Female: 11
Age (the minimum–maximum, mean±SD/range)	42.71-68.23, 61.27±2.36	39.46-68.56, 63.40±3.25
*are expressed in years		
Autoimmune disease	None	None
Anemia	None	None
Hospitalization days	7	4
Vaccination	All	All
Addicted smoke	None	None
Laboratory findings		
Oropharynx/nasopharynx PCR	Positive	Positive
Lung CT images (COVID-19 infection diagnosis)	All	All

Table 2: SPO$_2$, infected volumes of lungs, and laboratory findings of studied patients before and after hyperthermia		
	Group I (before/ after treatment)	Group II (before/ after hyperthermia)
SPO$_2$		
Maximum	88/90	89/92
Minimum	85/87	85/89
Mean	85±0.0/88±0.2	85±0.0/91.3±0.5
Infected lung volumes		
Mean	34.21±3.41/10±2.12	31.36±3.13/4±1.53
LDH		
Mean	857±115/569.7±13.3	851±23.6/541.4±12.4
Ferritin		
Mean	1006±112/302±41	1011±143/281±47
D-dimer		
Mean	3100±117/740±126	3200±106/510±121

of COVID-19 patients. The table also compares D-dimer, ferritin, and LDH for the patients.

Based on our findings, for group II, the mean ± SD of SPO$_2$ before hyperthermia was 85 ± 0.0, while it was 91.3 ± 0.5 after local hyperthermia. For the other patients (group I), the mean ± SD of SPO$_2$ before and after their treatment was 85 ± 0.0 and 88 ± 0.2, respectively.

Furthermore, for group II, the maximum and minimum SPO$_2$ before/after hyperthermia was 89/92 and 85/89, respectively. However, for group I, the maximum and minimum SPO$_2$ before/after their treatment was 88/90 and 85/87, respectively. In this study, it was found that, although the SPO$_2$ of the patients increased with hyperthermia, it decreased 1 hour after hyperthermia. In addition, our data showed a sharp increase in their SPO$_2$ 6 hours after hyperthermia ended.

For the effect of hyperthermia on the infected volumes of lungs (Figure 2 shows lung CT of 74 years old patients), it was found that the mean ± SD of the infected volume of the lung for group II before/after hyperthermia was 31.36 ± 3.13 and 4 ± 1.53, respectively. Nevertheless, the infected volumes of lungs for group I were 34.21 ± 3.41/10 ± 2.12 before/after their treatment.

According to our analysis, D-dimer, ferritin, and LDH before/after hyperthermia were 3200 ± 106/510 ± 121, 1011 ± 143/281 ± 47, and 851 ± 23.6/541.4 ± 12.4 for group II, but for group I, they were 3100 ± 117/740 ± 126, 1006 ± 112/302 ± 41, and 857 ± 115/569.7 ± 13.3 before/after hyperthermia, respectively.

Moreover, it is considered that group II treatment time (three consequent days) was lower than group (I). Table 3 indicates the impacts of hyperthermia on the SPO$_2$.

DISCUSSION

Nowadays, COVID-19 and other types of the virus (delta, lambda, and mu), which result from different mutations, are

spread around the world. A wealth of studies have investigated different ideas and modalities, which may reduce or eliminate the toxicity of COVID-19 in the human body. According to different studies, it is considered that there is no experimental study about the impact of deep local lung hyperthermia on O$_2$ saturation of COVID-19 patients. Moreover, a large number of studies have shown that hyperthermia is a safe method, which applies non-ionizing RF waves. Therefore, this study was performed to evaluate the advantages and disadvantages of hyperthermia with regard to the adverse effects of COVID-19 on critical organs such as lungs.

Based on the results, hyperthermia may lead to an increase in SPO$_2$ in all patients who were included in group II. Moreover, although the SPO$_2$ of the patients was increased during hyperthermia, it decreased about 1 hour after hyperthermia. In addition, our data showed a sharp increase in the SPO$_2$ 6 hours after hyperthermia ended. Furthermore, the amount of D-dimer in patients who underwent hyperthermia decreased after hyperthermia.

In this study, it was found that hyperthermia may cause a considerable decrease in the infected volumes of lungs for the studied patients.

It is considered that deep local hyperthermia takes its toll on infected lungs using short RF waves, which may lead to higher transmittance inside the lung parenchyma.

These results are highly due to the high temperature of the lungs, which resulted from hyperthermia, and also the increased kinetic energy of the organ, leading to consuming more O$_2$, as a result of the increasing metabolic rate of the cells and growing blood flows to the lung parenchyma. In addition, the higher temperatures of the lung parenchyma and lower levels of O$_2$ in the cells may cause damage to intra- and extracellular proteins including membrane proteins, receptors, nucleoid proteins, and cytoplasmic enzymes resulting in a vast number of defects in the genome synthesis of the virus in the nucleus. Furthermore, damaged proteins of the cytoplasm and membrane may lead to some delays in interphasic cycles and cell death, respectively, as a result of many defects in the mineral transmitters in the cell.[6,7] Moreover, the shape deformation of receptors, which stems from the higher temperature of the lung parenchyma, may lead to the disability of antigens to bind them.

It would seem that high temperatures may damage COVID-19 in an *in vitro* situation, as a result of denaturation of virus proteins or its capsid,[8] but it is considered that the effect of RF waves and high temperature in an *in vivo* situation may be different, because the virus merely injects its genome into the lung cells without any capsid.[9] Therefore, intracellular enzymes may be used to produce virus proteins (pneumocyte type 2).[8] Also, this would seem that the Golgi device may produce a new capsid for COVID-19.[8] According to the results of Sarah *et al.*,[9] temperature may have a substantial role in the immune system of the body and phagocytose process, which may have an impact on coronavirus. Moreover, deep

local hyperthermia may have a prominent role in increasing the immune system response including increased macrophage, lymphocytes, Tumour necrose factor (TNF-α), interleukin II, and cytotoxicity effects on antigens.[10] Hyperthermia may excite the adaptive immune system and natural killer cells against COVID-19 lung cells [Figure 3]. Baronzia *et al*.[10] have evaluated the impact of local and whole-body hyperthermia on the immune system and found that the effect of local hyperthermia on the immune system is time-dependent and it is considered that the local hyperthermia may not increase the cytokines (except TNF-α and interleukin II). Based on the results of David *et al*.,[11] using 44.9 degrees of Celsius may increase lung blood perfusion without any significant damage to the lungs.

Furthermore, ribonucleicacide (RNA) templates, which are known as messenger RNA (mRNA), are commonly employed by cell ribosomes to produce amino acids. Moreover, ribosomes may link to each other to assemble polyribosomes, which can enhance protein synthesis. Nakamura and Hall have found that temperature-dependent reductions in polyribosomes may lead to a reduction in protein synthesis. McCormick and Penman have reported that using 42 degrees of Celsius may disaggregate polyribosomes, which can cause lower protein synthesis.[12] Also, using 42 degrees of Celsius may decrease rRNA production to only 3% after 1 hour[13,14] and it can cause a significant reduction in protein translation, which may be useful to preserve energy. Moreover, 42 degrees of Celsius can alter other mechanisms of certain mRNA production[15] and also polyadenylation.[16] Some studies have shown that polyadenylation of the coronavirus RNA may promote virus survival through translation enhancement and replication.[17] This would seem that the inhibition of protein synthesis and polyadenylation of viral RNA may significantly dampen COVID-19 infectivity. Cortese *et al*. have concluded that the cellular organelles may be remodeled in the mentioned virus-infected cells, and the inhibition of cytoskeletal rearrangements in the infected cells may lead to suppression of production of viral particles.[18] Therefore, it seems that hyperthermia[19] may alter the cytoskeleton dynamics and decrease the infectivity of COVID-19. In addition, the stated virus can alter lysosomal trafficking, because it can release new virions. Chosh *et al*.[20] stated that the deacidification of

lysosomes (which may lead to the inactivation of lysosomal enzymes) during the COVID-19 infection can impair antigen processing and presentation in the cells. Mao *et al*.[21] have shown that the acidification of lysosomes may be done by increasing temperatures, and thus, hyperthermia could limit the release of new viral particles and also enhance antigen recognition by cells of the immune system.

Hyper-inflammatory state (also known as cytokine storm) is one of the hallmarks of severe COVID-19 patients who progress to severe forms of the disease, characterized by increased serum levels of Interlukine IL-1b, IL-6, IL-8, and TNF-a, which have been associated with a decreased survival rate.[22,23] Increasing fibrinogen production (via IL-6) and promoting rapid clot formation (via IL-8, IL-1b, and IL-6)[24,25] may contribute pro-inflammatory cytokines to thrombosis for a reason, which may lead to identifying hypercoagulability in COVID-19 as "thrombo inflammation."[26] In this sense, hyperthermia could be a suitable choice, because the downregulation of pro-inflammatory gene expression through exposition of the stated cells to heat (41 degrees of Celsius for as short as 10 min) can result in inhibition of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-jB) and mitogen-activated protein kinase (MAPK) for up to 20 h.[27] Furthermore, after exposing mononuclear blood cells from healthy donors to 39 degrees of Celsius, lymphocytes are increased with no predilection of lymphocyte subtype as determined through flow cytometry, and levels of IL-1b, IL-6, and Interfron (IFN-c) are decreased.[28-33]

In this study, there was not any evidence of coagulation in our patients, which could be a suitable choice for applying hyperthermia to treat COVID-19. Based on our findings, deep local hyperthermia could be a good choice to treat COVID-19 patients.
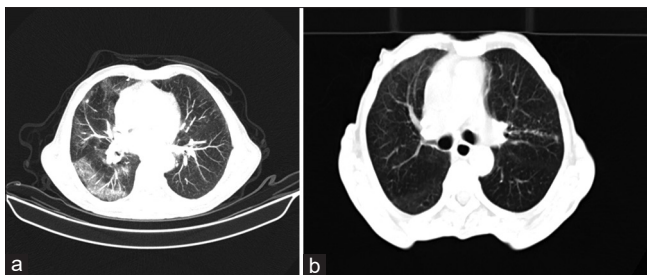
Table 3: Implication of hyperthermia on the SPO$_2$ of group II ($n=35$)

	Before	During	1 hour after hyperthermia	6 hours after hyperthermia
SPO$_2$				
Maximum	89	91	87	92
Minimum	85	86	84	89

Figure 2: Lung CT of a 74-year-old patient before (a) and after three consequent days of hyperthermia (b)
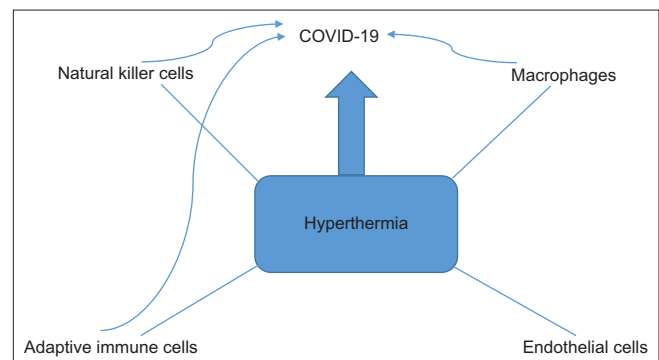

Figure 3: Schematic effect of hyperthermia on COVID-19

CONCLUSION

In this paper, the impacts of deep local lung hyperthermia on COVID-19 patients were investigated.

According to our findings, applying deep local lung hyperthermia for COVID-19 patients is suggested, as a result of its prominent effects on SPO_2 increase in the patients. Furthermore, hyperthermia may lead to a decrease in D-dimer and ferritin (CRP and D-DIMER) in the mentioned patients. Further research about the effects of deep local lung hyperthermia with larger sample sizes and longer-time follow-up is suggested.

List of abbreviations

CT = Computed tomography
CXR = Chest X-ray
O_2 sat = O_2 saturation.

Ethics approval and consent to participate

This study was approved by the Isfahan University of Medical Sciences, Isfahan, Iran (IR.MUI.MED.REC.1399.684).

Conflicts of interest

There are no conflicts of interest.

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