Exogenous Surfactant Versus Placebo in the Treatment of Moderate and Severe ARDS in COVID-19: The Pilot Study of a Clinical Trial

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Abstract

**Background:** COVID-19 pandemic has created a global health challenge. Many pharmaceuticals have been repurposed as potential treatments; though many have not been promising. Due to the inflammatory and destructive effects of the virus on alveolar cells, the effect of exogenous surfactant was assessed as a potential treatment of lung dysfunction in COVID-19 patients.

**Methods:** In this pilot study of the clinical trial, 49 patients aged 35-80 years with COVID-19 admitted in ICU entered the study (22 patients intubated and 23 had face masks; 4 patients in the control arm). The treatment arm patients received two consecutive doses of surfactant. P/F ratio (based on serial blood gas analyses before and 12 hours after 2 doses of surfactant) and also, clinical outcomes were assessed.

**Results:** in COVID-19 adult patients, surfactant significantly improved pulmonary P/F ratio both in intubated and face mask COVID-19 patients (increasing from 119.2 ±51.7 to 179.4±115.5). The rate of extubation was much better than similar country-wide studies.

**Conclusions:** Surfactant significantly alleviates the respiratory status in moderate to severe COVID-19 ARDS with two consecutive 100 mg doses of surfactant (with 6 hours’ interval); though previous studies have been controversial, regarding the effect of surfactant in general forms of ARDS. Higher doses might have better effects, mandating more trials.

**Introduction**

The new coronavirus disease (COVID-19) outbreak due to the novel coronavirus SARS-CoV-2 started in China in late 2019; transforming very rapidly into a dramatic global pandemic with great health and societal impacts. Pulmonary involvement remains among its serious complications (1–3).

Many pharmacological and non-pharmacological agents have been proposed as treatment hopes; none have been conclusive yet, necessitating more research (4–6). Many of the current therapeutic options are repurposed potential pharmaceuticals (7–10).

Meanwhile, "hyaline membrane formation lesions indicating acute respiratory distress syndrome (ARDS)" are among the postmortem pathologic findings in pulmonary samples of COVID-19 patients; these lesions "much resemble the lungs of wet drowning" (11, 12).

Surfactant, combined of proteins and lipids, secreted into the alveolar space by type II alveolar cells, reduces alveolar surface tension and modulates immunological homeostasis and inflammatory mediators in the alveoli; these mechanisms are failed in alveoli of COVID-19 patients, partially due to surfactant shortage after the destruction of alveolar cells by virus-induced lung injury, leading a floating state in alveoli rendering gas exchange and augmenting inflammatory cascade (12–15).
This study was performed to assess the effects of intratracheal and inhalational surfactant on the pulmonary status and clinical outcome of moderate and severe stages of ARDS in COVID-19 patients.

Methods

The study proposal was approved by the Research Ethics Committee, Vice-Chancellor of Research Affairs, Shahid Beheshti University of Medical Sciences (SBMU) March 28, 2020, coded IR.SBMU.RETECH.REC.1399.016. Besides, the protocol was approved by the Iranian Clinical Trials Registry (IRCT; https://www.irct.ir/) “IRCT20091201002804N12” on 06/01/2020. Informed written consent was taken from all the patients or when unconscious, from their relatives. Patient recruitment started immediately after 06/01/2020, in COVID-19 patients admitted in Intensive Care Units, in two university hospitals, Tehran, Iran.

The surfactant vials were provided by Tekzima Drug Alborz Company, Tehran, Iran which provided the drugs as support to the study. The drug was provided as “Beraksurf” as 100 mg in 4 mL vials. Except for the drugs, there is no relationship between the researchers and the latter company or any other company. Besides, this research project is funded by the Anesthesiology Research Center, SBMU, Tehran, Iran with grant number 22959. Besides, support was provided solely from institutional and/or departmental sources.

The primary protocol is published before (16). The recruitment of the patients started with a pre-pilot phase; in which the patients were randomly assigned into two groups; i.e. they received Surfactant or placebo using an intra-tracheal approach. However, after assessing the results of the first group of patients (4 patients in each group), due to the major clinical improvements seen in patients who had received surfactant, the researchers decided not to deprive anyone of the benefits of the study drug (surfactant), shifting all the patients to the surfactant group which could be considered as compassionate treatment. So, the current manuscript includes a pre-pilot and the “treatment arm of the study”; though the authors know this might decrease the external validity of the study. A summary of the designed patient flowchart and its changes are presented in the CONSORT flow chart of this manuscript.

The clinical diagnosis and treatment protocol, including imaging and laboratory diagnostic features and therapeutic approaches, strictly followed the National Iranian Guideline for Diagnosis and Treatment of Adult COVID-19 Patients (first released on February 29, 2019) and its updates throughout the study (17–21). The diagnosis was confirmed using a combination of clinical and nasopharyngeal swab sampling for the Reverse transcription-polymerase chain reaction (RT-PCR) test, added with a list of para-clinical tests including imaging studies; besides, serial arterial blood gas assessment was performed to manage the respiratory status. computed tomography scanning (CT scanning). CT studies were not included in all the study patients; because not all of the patients tolerated being transferred to the CT unit; though in a large number of the patients, CT was used for clinical purposes; meanwhile, all of the patients had at least portable chest X rays.
Inclusion criteria were:

- adult COVID-19 patients admitted to Intensive Care Unit (ICU); age range of 18 to 80 years
- moderate to severe ARDS; based on the definition of the Arterial Pressure of Oxygen to Inspirational Fraction of Oxygen (PaO2/FiO2 Ratio; P/F Ratio)
- it was mandatory to use auxiliary respiratory devices (including either intubation or face mask)
- ARDS was due to COVID-19

Exclusion criteria were:

- any patient needing extracorporeal membrane oxygenation (ECMO)
- ARDS was primarily due to any other reason rather than COVID-19
- The primary source of pulmonary involvement was bacterial pneumonia or any other etiology except for COVID-19 induced lung involvement
- Those who refused to continue the study (either the patient or his/her family)
- any patient had any sign of healing before entering the study leading to patient discharge from ICU in less than 12 hours

All the patients received exogenous surfactant in 2 doses with 6 hours’ interval; each dose included 100 mg surfactant in 4 mL vials. In those who were intubated, the drug was administered directly into the endotracheal tube and in the others, a constant face mask with a nebulizer was used.

For outcome measurement, the results of the proportion of Arterial Pressure of Oxygen to Inspirational Fraction of Oxygen (i.e. PaO2/FiO2 or simply P/F ratio) was analyzed using arterial blood gas samples throughout the study and the first P/F ratio was checked before administering surfactant (called P/F ratio 1) while the second P/F ratio was checked 12 hours after administration of the 2nd surfactant doses (called P/F ratio 2). A P-value of less than 0.05 was considered significant. A T-test was used to compare the results.

Result

A total of 49 patients entered the study; 8 in the pre-pilot stage and 41 in the treatment arm. The current data represent the 45 patients which were related to the treatment arm (4 + 41) of the study. The results of the data analysis are presented in Table 1.
Table 1
Data analysis of the study patients

|                          | Intubated (received intra-tracheal surfactant) | Non-intubated (received surfactant through nebulizer) | Global study data |
|--------------------------|-----------------------------------------------|------------------------------------------------------|------------------|
| Number of patients       | 22                                            | 23                                                   | 45 (41 + 4)      |
| Age in years (mean ± standard deviation) | 58.1 ± 15.2                                   | 65.2 ± 14.8                                          | 61.6 ± 15        |
| Minimum/Maximum of Age in years | 38/80                                         | 34/80                                                | 35/80            |
| Female/Male ratio        | 8/14                                          | 10/13                                                | 18/27            |
| P/F ratio 1 *            | 78.6 ± 44.1                                   | 159.7 ± 59.3                                         | 119.2 ± 51.7     |
| P/F ratio 2 **           | 143.2 ± 116.6                                 | 214.4 ± 105.7                                        | 179.4 ± 115.5    |
| P value (between P/F ratio 1 & P/F ratio 2) | 0.000 (df = 21) | 0.000 (df = 22) | 0.000 (df = 44) |

* P/F ratio 1: PaO2/FiO2 i.e. Arterial Pressure of Oxygen to Inspirational Fraction of Oxygen just before starting surfactant

* P/F ratio 2: PaO2/FiO2 i.e. Arterial Pressure of Oxygen to Inspirational Fraction of Oxygen 12 hours after surfactant administration

There was a statistically significant difference in the trend of the P/F ratio after surfactant administration; in both intratracheal and inhalation modes. Besides, among the 22 intubated patients, 7 were extubated and transferred to the ward after their course improved; 15 others have died; the extubation discharge was much higher than the total extubation rates in other studies; both compared with results of another cohort in the same geographic and demographic setting and the results of studies country-wide (22–24). The data of the 7 extubated patients are summarized in Table 2.
Table 2
Data of the extubated patients

| Patient No | Age (years) | Gender | Duration of intubation (Days) | Lowest saturation level ever | Days to extubation after surfactant administration |
|------------|-------------|--------|------------------------------|------------------------------|-----------------------------------------------|
| 1          | 80          | Male   | 6                            | 40                           | 5                                             |
| 2          | 48          | Male   | 3                            | 30                           | 2                                             |
| 3          | 50          | Male   | 3                            | 60                           | 2                                             |
| 4          | 41          | Male   | 4                            | 52                           | 3                                             |
| 5          | 50          | Male   | 4                            | 30                           | 3                                             |
| 6          | 51          | Female | 6                            | 35                           | 3                                             |
| 7          | 39          | Male   | 4                            | 41                           | 4                                             |

Discussion

The results of our study demonstrated that a low dose regimen of surfactant administered either through intratracheal route or by inhalational method (nebulizing face mask) could improve respiratory function in COVID-19 induced ARDS. To the best of our knowledge, this is the first clinical study assessing the role of exogenous surfactant in COVID-19 attributed ARDS patients. Surfactant seems effective in alleviating the respiratory status in moderate to severe COVID-19 ARDS with two consecutive 100 mg doses of surfactant (with 6 hours’ interval); though previous studies have been controversial, regarding the effect of surfactant in general forms of ARDS. However, among other designed clinical studies, none has been finished yet and this is the earliest registered one, approved on March 28, 2020, and patient recruitment started immediately afterward.

The results of this study demonstrated that surfactant could improve the P/F ratio of the patients, increase the chance of extubation in intubated patients and decrease the chance of intubation in non-intubated cases compared with a larger sample in the same geographic and demographic setting; in which 459 confirmed COVID-19 patients were assessed in which 396 survived and 63 expired (22). While the latter study was performed in Tehran, Iran; similar findings were demonstrated in similar studies from Tehran and Isfahan, two major cities in Iran (23, 24). Compared with studies in a similar level of care, geographic and demographic status, our results demonstrate a significant role for surfactant in COVID-19 pneumonia patients.

In COVID-19 patients, Weaning from mechanical ventilation and extubation are among the main determinant of outcome (25, 26). Besides, we considered the P/F ratio as one of our main indicators due to its role in defining ARDS severity (26–28).
Before the COVID-19 pandemic, there was a great controversy regarding the role of surfactant in ARDS patients especially in adult patients; many studies failed to demonstrate any benefit from surfactant administration in adult ARDS regarding mortality rate, ventilator-free days, or improvement in oxygenation status (29, 30), or even might improve the oxygenation status of adult ARDS but could not improve mortality (31, 32).

However, the current study demonstrated that in COVID-19 patients with moderate and severe stages of ARDS, when we consider the pulmonary effects of exogenous surfactant things go a bit different. Part of the explanation might result from the differences in the mechanisms of COVID-19 and the resulting cytokine storm which has specific features for COVID-19 lung involvement, much different from other versions of adult ARDS (33–36). Also, the pathologic findings in COVID-19 patients’ lungs, much resemble the findings in water drowning alveoli, added with "hyaline membrane formation lesions" are among the postmortem pathologic findings in pulmonary samples of COVID-19 patients (11, 12). These findings might be among the main explanations for the results of exogenous surfactant effectiveness in COVID-19 patients with moderate and severe stages of ARDS. From a demographic point of view, our results confirmed improved outcomes for critical patients compared with similar studies in the same country where there was no use of exogenous surfactant use in COVID-19 ARDS (22–24).

Finally, we used a very low dose of surfactant yet received acceptable results. Compared with neonates receiving surfactant with respiratory distress syndrome, this dose was much lower (37–39). However, there might be some explanations: in neonates, there is a total paucity of surfactant in neonatal lung tissue; while, this is not the same case in COVID-19 attributed ARDS patients (11, 12). Possibly, this could be the reason why our doses have been relatively effective. However, more experiments with higher doses of surfactant might be even more promising.

**Limitations of the study**

there are some limitations to this study

1- for ethical reasons we performed the treatment arm of the study; since the early results suggested significant improvements. Though we tried not to deprive any of our patients of exogenous surfactant after the primary stage of the study, we could not assess our results in a fully performed clinical trial.

2- we did not assess the postmortem lung tissues of the patients who had been expired albeit had received exogenous surfactant. Possibly this could help future studies in uncovering the role of surfactant.
3- we have not followed our patients yet; considering their respiratory indices compared with other patients which could have important findings. However, we tried to report our results to possibly benefit more patients worldwide.

**Conclusions**

Surfactant significantly alleviates the respiratory status in moderate to severe COVID-19 ARDS with two consecutive 100 mg doses of surfactant (with 6 hours’ interval); in terms of the P/F ratio after surfactant administration; in both intratracheal and inhalation modes and also, the chance to extubation; though previous studies have been controversial, regarding the effect of surfactant in general forms of ARDS. However, higher doses might have better effects, mandating more trials.

**Abbreviations**

ARDS: acute respiratory distress syndrome
COVID-19: The new coronavirus disease
CT scan: computed tomography scan
ECMO: extracorporeal membrane oxygenation
IRCT: Iranian Clinical Trials Registry
PaO2/FiO2 Ratio; P/F Ratio: Arterial Pressure of Oxygen to Inspirational Fraction of Oxygen
RT-PCR: Reverse transcription-polymerase chain reaction
SBMU: Shahid Beheshti University of Medical Sciences

**Declarations**

**Ethics approval and consent to participate:**

The study proposal was approved by the Research Ethics Committee, Vice-Chancellor of Research Affairs, Shahid Beheshti University of Medical Sciences (SBMU) March 28, 2020, coded IR.SBMU.RETECH.REC.1399.016. Besides, the protocol was approved by the Iranian Clinical Trials Registry (IRCT; [https://www.irct.ir/](https://www.irct.ir/)) “IRCT20091201002804N12” on 06/01/2020. Informed written consent was taken from all the patients or when unconscious, from their relatives. Patient recruitment started immediately after 06/01/2020, in COVID-19 patients admitted in Intensive Care Units, in two university hospitals, Tehran, Iran.
Consent to participate:
all the authors have informed written consent to participate. No other consent seems applicable. Besides, written informed consent was waived by the IRB.

Consent for publication:
Not applicable

Availability of data and material:
_Ali Dabbagh_ holds all the data available

Competing interests:
The surfactant vials were provided by Tekzima Drug Alborz Company, Tehran, Iran which provided the drugs as support to the study. The drug was provided as “Beraksurf” as 100 mg in 4 mL vials. Except for the drugs, there is no relationship between the researchers and the latter company or any other company.

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Author role statement and contribution:
All authors have read and approved the manuscript

MG: This author helped Conceptualization; Methodology; Investigation; Formal analysis; Writing – review & editing

MF: This author helped Conceptualization; Methodology; Writing – review & editing

NM: This author helped Conceptualization; Methodology; Data curation; Formal analysis; Writing – review & editing

ST: This author helped Conceptualization; Methodology; Writing – review & editing

KF: This author helped Conceptualization; Methodology; Writing – review & editing
NN: This author helped Conceptualization; Methodology; Writing – review & editing
NMA: This author helped Conceptualization; Methodology; Writing – review & editing
SB: This author helped Conceptualization; Methodology; Writing – review & editing
ANA: This author helped Conceptualization; Methodology; Investigation; Writing – review & editing
AP: This author helped Conceptualization; Methodology; Investigation; Writing – review & editing
MAKK: This author helped Conceptualization; Methodology; Investigation; Writing – review & editing
MAP: This author helped Conceptualization; Methodology; Writing – review & editing
SR: This author helped Conceptualization; Methodology; Writing – review & editing
AD: This author helped Conceptualization; Data curation; Formal analysis; Funding acquisition; Investigation; Methodology; Project administration; Resources; Software; Supervision; Validation; Visualization; Writing – original draft; Writing – review & editing

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