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## PILOT ANALYSIS OF INTRAVENOUS LIPID INFUSION ROLE IN COVID-19 MORTALITY

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### ABSTRACT

**INTRODUCTION.** How to reduce the fatality of coronavirus disease (COVID-19) is still challenging. A proper nutritional support has been always a matter of attention in critically ill patients.

**MATERIAL AND METHODS.** We assessed COVID-19 patients who had received intralipid infusion due to medical indications and compared them with those who did not receive it regarding fatality rate and prognosis. As a part of a data mining project using data of observational cohort of COVID-19 patients hospitalized in the educational centers of Iran University of Medical Sciences, Tehran, Iran, an inferential case series was performed. A total of 19 patients with SARS-CoV-2 infection were selected from the cohort. Briefly, 13 patients survived and 6 patients died, and 12 patients were admitted in intensive care unit (ICU). All dead cases were ICU admitted. The association of intralipid infusion and survival rate was examined using Fisher exact test. No association was observed between intralipid infusion and survival.

**CONCLUSIONS.** No significant protecting effect was observed for patients who received intralipid for medical indications. Since intralipid was administered according to medical indications, surviving of all the non-ICU admitted patients despite having underlying diseases was remarkable. Despite the fact, due to several bias factors that could not be controlled in such a retrospective study, the results might be accidental. We suggest to assess such an effect retrospectively in other centers as well.

**Key words:** *COVID-19, intravenous fat emulsions, nutrition, immune modulation*

### INTRODUCTION

Coronavirus disease 2019 (COVID-19) has had a serious burden on health system. Up to the time of this paper (23 July 2022), more than 569 million cases have been confirmed with more than 6.38 million mortalities (1).

A proper nutritional support has been always a matter of attention in critically ill patients of different diseases. Many of these patients might not be able to eat orally as per their need (2, 3). Moreover, enteral nutrition might be harmful in some conditions. Therefore, a parenteral nutritional support might be used (4). COVID-19 and sepsis due to COVID-19 are not exceptions in this regard, especially in those hospitalized for a quite long-term in intensive care unit (ICU) who need a proper nutritional support (5).

Regulation of energy consumption under stressful condition of different diseases is very complex. Fat is the most important source of energy in prolonged starvation. Calorie enriched formula is suggested to be used in patients with fluid restriction. Nevertheless, excess energy in certain phases of some diseases may be harmful. In patients with pulmonary insufficiency, the total calorie should be made of up to 50% lipids (4). Hence, we proposed a hypothesis that lipid enriched formulae can be beneficial for hospitalized COVID-19 patients.

Intralipid® serum is a fat emulsion containing: soybean oil, glycerin and egg phospholipids. Intralipid is used in addition to aminofusin as a part of total parenteral nutrition for those patients with characteristic indications. Immunomodulatory effects of soybean oil have been mentioned in the literature (6). It has been

shown that intralipid did not affect blood cytokines or ex vivo T cell proliferation in critically ill patients who need hyperalimentation. Moreover, those with essential fatty acid deficiency need intralipid infusion to remove the burden of infection susceptibility to some extent (7).

There is only a single report to our knowledge to use intralipid infusion in COVID-19 patients (8). The objective of this study was to compare case fatality rate among those COVID-19 patients who had received intralipid due to medical indications with those who did not.

## MATERIAL AND METHODS

As a part of a data mining project on a cohort of COVID-19 patients hospitalized in the educational centers of Iran University of Medical Sciences, Tehran, Iran (with ethical registration number IR.IUMS.REC.1399.194), an inferential case series study was performed. The source of the primary data was Iranian integrated care electronic health record (locally called SEPAS). The inclusion criteria were being hospitalized due to COVID-19 infection and receiving intralipid infusion already due to medical conditions such as short bowel syndrome, post-op build up, enterocutaneous fistula etc. All patients with these criteria were selected between 20 March 2020 and 11 August 2020.

The reference group comprised all individuals hospitalized due to COVID-19 infection between 20 March and 11 August 2020 recruited to the cohort. The reported variables were age, gender, length of stay (LOS), receiving antiviral therapy, ICU admission and surviving from the disease.

The case finding and data selection process from the source dataset were performed using Stata 12 software (StataCorp LLC, US). Fisher exact and independent t tests were used for inferential statistics at two tailed significance level of 0.05.

Ethically, no drug intervention was performed by the researcher, and the confidentiality of the information was regarded under supervision of the research and technology deputy of our institution.

## RESULTS

A total of 19 patients with COVID-19 infection were selected from the cohort according to the inclusion criteria. The source population (our cohort) consisted of 6 054 confirmed and hospitalized COVID-19 patients with a mean age of  $56.89 \pm 20.95$ . About 56% of the source population were male and the frequency of ICU admission was 27.3%. The preliminary report of this cohort has been previously reported (9). The demographic and underlying characteristics of the 19 patients who had received intralipid are shown in

Table 1. Baseline characteristics of patients who received intralipid

ID	Gender	Age (year)	LOS (day)	Antiviral receiving	ICU admission
Survived					
1	Female	77	2	Yes	No
2	Female	69	6	Yes	No
3	Male	47	7	Yes	No
4	Female	38	5	Yes	No
5	Female	69	4	Yes	No
6	Female	31	6	Yes	No
7	Female	73	3	No	No
8	Male	50	43	No	Yes
9	Male	55	3	Yes	Yes
10	Male	79	9	No	Yes
11	Male	71	13	No	Yes
12	Male	69	1	Yes	Yes
13	Male	49	35	Yes	Yes
Non-survived					
14	Male	81	4	Yes	Yes
15	Male	82	27	No	Yes
16	Female	83	18	Yes	Yes
17	Female	65	19	Yes	Yes
18	Male	70	16	Yes	Yes
19	Male	86	8	Yes	Yes

LOS: length of stay. ICU: intensive care unit.

Table 1. Briefly, 13 patients survived and 6 patients died, and 12 patients were ICU admitted. All non-survived patients were ICU admitted (Table 1).

There was no significant association between intralipid infusion and survival from COVID-19 using Fisher exact test ( $p=0.252$ ). Considering ICU admitted patients, there was no significant association ( $p=0.556$ ) as well. Despite survival of all non-ICU admitted patient those who received intralipid, no significant protective association was found in this subgroup ( $p=0.605$ ) (Table 2).

Moreover, to find a possible confounding effect for age, we compared age of survived and non-survived patients using independent t test. The mean age was significantly higher in non-survived patients ( $p=0.013$ ). Similar result was observed in ICU admitted patients ( $p=0.029$ ). The low number of observations was not suitable for multiple regression modeling (Table 3). In addition, the mean age in the intralipid infusion group (65 years  $\pm$ 16) was significantly higher than the mean age in the rest of the cohort (56.89  $\pm$  20.95), ( $p=0.0459$ ).

### DISCUSSION

The present case series with inferential approach was performed to show the possible role of intralipid

infusion on survival from COVID-19. It was the first report of multiple cases. Before this study, there was only one case report.

Javid et al. (2020) in Iran, reported a COVID-19 case with pulmonary complications, who was rescued after receiving intralipid infusion. Pulmonary dysfunction substantially improved after 48 hours of starting intralipid infusion. They hypothesized that the plausible cause of death was progressive cardiopulmonary involvement by viral load and viral intoxication (8). However, this was only a case report but triggered the idea to for the current retrospective assessment.

Our rationale is different. We did not believe that intralipid infusion might be helpful for viral clearance since there is no scientific evidence. We hypothesised that its protecting effects might be due to improving nutritional and metabolic status as well as role of some fatty acids in immune system. Rothschild et al. (2010), described the mechanism called “lipid sink” in which intralipid serum acts as emulsified fat droplets to provide an intravascular lipid compartment to remove lipophilic substances (10). Vasilieva et al. (2020), proposed lipid standard therapy against COVID-19 as a target treatment of lipid peroxidation disorders caused by oxidative stress. In these studies, the patient recovered quickly with a decrease in endogenous

Table 2. Association of receiving intralipid with fatality of COVID-19 divided by disease outcome.

Outcome	Intralipid positive (n,%)	Intralipid negative (n)	Total cohort (n)	Fisher exact test p-value (effect)
ICU admitted				0.556
Non-survived	6 (50%)	659 (39%)	665 (39%)	
Survived	6 (50%)	1019 (61%)	1025 (61%)	
Total	12	1678	1690	
Non-ICU admitted				0.605
Non-survived	0	575 (13%)	575 (13%)	
Survived	7 (100%)	3782 (87%)	3789 (87%)	
Total	7	4357	4364	
All				0.252
Non-survived	6 (32%)	1234 (20%)	1240 (20%)	
Survived	13 (68%)	4803 (80%)	4814 (80%)	
Total	19	6035	6054	

Table 3. Association of age with survival from COVID-19 in patients who received intralipid using independent t test.

Group	Observations	Mean (year)	Standard deviation	p-value
All				0.013
Survived	13	50.08	15.36	
Non-survived	6	77.83	8.33	
Pooled	19	65	16.02	
ICU admitted				0.029
Survived	6	62.17	12.50	
Non-survived	6	77.83	8.33	
Pooled	12	70	13.02	

intoxication markers (such as cytolytic enzymes, C-reactive protein and platelets) and tissue hypoxia and general status were improved (11). The probable mechanisms of protecting effect of intralipid infusion are shown in Figure 1.

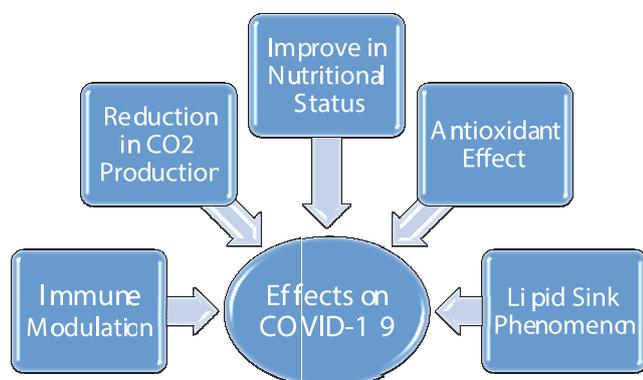


Figure 1. The probable effects of intralipid infusion on COVID-19

(Important: the probable harmful effects such as thrombotic events are not in the graph)

We found no significant association of intralipid infusion with survival prognosis. However, persons who received intralipid infusion were on average older and suffering from underlying diseases, which required parenteral nutrition. These two factors could explain the lack of protective association. Still the fact that no death occurred among patients who received intralipid infusion and were not admitted to ICU, as compared to 13% in the reference group is remarkable.

Our study had some limitations. Low number of cases and possible confounding due to age and receiving the drug by previous indications can be mentioned. However, this could be retrospectively addressed by pooling larger datasets and we suggest further investigations to compare the mortality rate in other centers in patients who received intralipids due to their own medical indications. We deeply believe that our results might have been accidental but worth further assessment. It might pave the way for new studies as the treatment of COVID-19 is not well understood yet. Our study can only be considered as a hypothesis generating and of course poses many biases. Intralipids never does a miracle.

#### Conflicts of interest.

None to declare.

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