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ORIGINAL RESEARCH

Effect of Sofosbuvir on Length of Hospital Stay in Moderate COVID-19 Cases; a Randomized Controlled Trial

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Abstract: **Introduction:** Efforts to control the COVID-19 pandemic are still on. This study aimed to evaluate the effect of sofosbuvir on length of hospital stay and complications in COVID-19 cases with moderate severity. **Methods:** This randomized clinical trial was done on moderate COVID-19 cases, who were admitted to Shohadaye Tajrish Hospital, Tehran, Iran, from 4/2021 to 9/2021. Eligible patients were randomly allocated into two groups of intervention (sofosbuvir) and control, and their outcomes were compared regarding the length of hospital stay and complications. **Results:** 100 COVID-19 cases were randomly divided into two groups of 50 patients, as the intervention and control groups. The mean age of patients was 50.56 ± 12.23 and 57.1±14.1 years in the intervention and control groups, respectively (p = 0.02). The two groups were similar regarding distribution of gender (p = 0.15), underlying diseases (p = 0.08), the severity of COVID-19 (p = 0.80) at the time of admission, signs and symptoms (p > 0.05), and essential laboratory profile (p > 0.05). The length of hospital stay in the control and intervention groups was 7.7 ± 4.09 days and 4.7±1.6 days, respectively (p = 0.02). None of our patients needed ICU or mechanical ventilation. **Conclusion:** Sofosbuvir may decrease the length of hospital stay of COVID-19 cases with moderate severity, without a significant effect on the rate of intensive care unit (ICU) need and mortality.

Keywords: SARS-CoV-2; Treatment Outcome; Sofosbuvir; Duration of Therapy

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1. Introduction

Since the influenza pandemic in 1819, COVID-19 has been one of the deadliest diseases we have ever faced. It has affected so many different aspects of human life, including health, economy, social life, schooling, travel, etc. (1). Introduction of the first vaccines against it in 2020 with their high efficacy, promised a near COVID-19-free world (2). New variants, like delta and omicron, the different level of access to vaccine among different countries (3), and a variable acquired immunity among different individuals (4), especially immunocompromised patients (5), showed us that although vaccines are very effective, we are still far from an end to the pandemic.

So, the need for a therapeutic alternative is still on. This need is more evident in times of COVID-19 peaks, which put healthcare systems in danger of crash (6). One cheaper

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and more scalable approach is repurposing the already available drugs (7). Hepatitis C virus (HCV) and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) are both categorized as positive-sense Ribonucleic acid (RNA) viruses and have similar replication mechanisms. Sovodac (FDA approved) is standardly used to treat chronic HCV infection (8) and it functions by targeting the dependent RNA polymerase enzyme (9). It is one of the antiviral drugs considered for treatment of COVID-19and has been studied in different clinical trials (10). According to a study, which evaluated in vitro effecst of this medication on SARS-COV-2, sofosbuvir could prevent RNA synthesis via chain termination, and daclatasvir targets the folding process of secondary RNA units in SARS-CoV-2 (11). Moreover, clinical trials (10) showed an association between lower mortality rates and the need for ICU in COVID-19 patients treated with sofosbuvir/daclatasvir (12). Another aspect to consider is the financial burden of producing these drugs, in a nutshell, active ingredients for sofosbuvir and daclatasvir cost a reasonable amount of 700$/kg and 600$/kg, respectively. Some studies suggest that sofosbuvir shows more affinity to mRNA of the virus compared to daclatasvir, so the efficacy of each drug in treating COVID-19 patients may be different (13-15). In terms of safety, in a randomized clinical trial (RCT) with Sofosbuvir/Ledivaspir, no side effect leading to withdrawal from the study was reported (16). Similarly, in another RCT with Sofosbuvir/Daclatasvir, no severe side effects were reported (17).

Given sofosbuvir's availability in Iran, as well as it cost, efficacy, and safety background, we aimed to evaluate the effects of sofosbuvir alone (not in combination with any other drug) only in patients with moderate COVID-19.

2. Methods

2.1. Study design and setting

This randomized clinical trial was aimed to evaluate the safety and efficacy of sofosbuvir in management of moderate COVID-19 cases, who were admitted to the COVID-19 ward of Shohadaye Tajrish Hospital, a tertiary teaching hospital in Tehran, Iran, from 4/2021 to 9/2021. Eligible patients were randomly allocated to either the intervention or control group and their outcomes were compared regarding the length of hospital stay and complications.

The Ethics Committee of Shahid Beheshti University of Medical Sciences approved the study protocol (Ethics code: IR.SBMU.RETECH.REC.1399.1322). This trial was registered on the Iranian Registry of Clinical Trials (IRCT: IRCT20180302038915N1). All the patients were required to fill out the consent form to enter the trial. Researchers adhered to ethical considerations of Helsinki Declaration and confidentiality of patients' information.

2.2. Participants

Confirmed COVID-19 cases with ages ranging from 18 to 80 years, who were admitted to the hospital with at least one of the symptoms of: Fever (Oral temperature ≥ 38 °C), Respiratory rate >24/minutes, 90%<O2Saturation<93% in room air, or the Pa02/Fi02 ratio ≤ 300mgHg were included in the study without gender limitation. COVID-19 infection was confirmed using RT-PCR and spiral chest computed tomography (CT) scan. Patients with moderate COVID-19 were defined as cases with total severity score (TSS)< 7 in the first 7 days of infection (18) and 90% < O2 saturation < 93% in room air on admission.

Patients with history of allergic reaction to the drugs used in this clinical trial, those who were pregnant or breastfeeding, former recipients of any experimental treatment for COVID-19, those with heart rate < 60/minutes, those currently on amiodarone as a treatment regimen, patients showing multi-organ failure evidence, needing mechanical ventilation, having estimated glomerular filtration rate < 50 milliliters per minute per 1.73 meters, admitted in intensive care unit (ICU) ward, and those who were in shock were excluded. If one of these exclusion criteria occurred during the study, patients were pulled out immediately but included in the final analysis.

2.3. Intervention

Eligible patients were randomly assigned to intervention or control group using block randomization (using a web service www.sealedenvelope.com). In this trial, the analyzer and care givers were blind to patients' allocation group.

The intervention group received interferon + sofosbuvir + national protocol for COVID-19, and control group received interferon + national protocol for COVID-19. Interferon-beta 1a 44 micrograms (ReciGen, manufactured by CinnaGen, from Iran) was administered subcutaneously, one dose every other day for five doses for patients in both groups. Sofosbuvir 400 mg/d for seven days (myHep, manufactured by Mylan company, from India) was administered for intervention group. National protocol is an integrated flowchart for COVID-19 diagnosis and treatment (19).

2.4. Data Gathering

Demographic information of patients, presenting signs/symptoms, vital signs, medical and drug history, and length of hospital stay were recorded at the time of admission in a pre-designed checklist. Patients underwent daily assessments regarding the clinical course, disease progression, and laboratory and para-clinical tests during the hospitalization period.

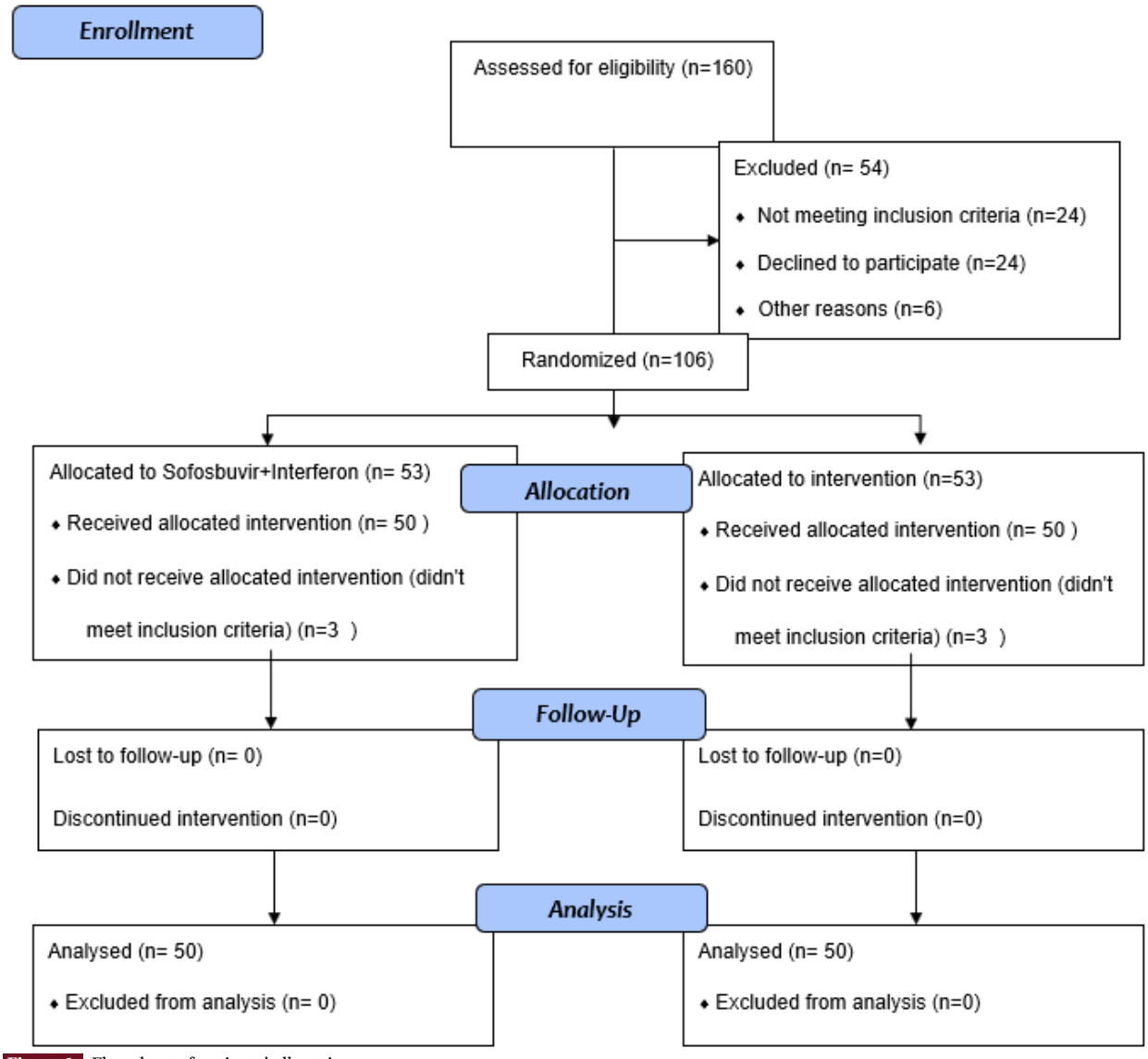

Figure 1: Flowchart of patients' allocation.

2.5. Outcome

The primary outcome was defined as length of hospital stay (patients were discharged after improvement in the signs and symptoms, tachypnea, saturation O2, fever, which were assessed by a daily physical exam). Patients were evaluated by experienced health providers every day during their hospital admission for clinical response to therapy, probable adverse effects, and complications according to the plan.

2.6. Statistical analysis

For statistical analysis, SPSS version 22.0 and Stata 14.2 were used. Shapiro-Wilk and Kolmogorov-Smirnov tests were performed to evaluate the normal distribution of quantitative data. The baseline characteristics were compared using the Chi-square test or one-way ANOVA. Quantitative data were presented as mean ± SD, and qualitative variables were expressed as number (percentages). The significance level was set at $p < 0.05$. Mean Difference was presented as effect size, and it was standardized using Cohen's d.

3. Results

3.1. Baseline characteristics of studied cases

100 COVID-19 cases were randomly divided into two groups of 50 patients, as the intervention and control groups (figure 1). 25 (50%) patients in the control group and 19 (38%) in the intervention group were male ($p = 0.15$). The mean age of pa-

Table 1: Comparing the baseline characteristics of studied cases between intervention (n = 50) and control (n = 50) groups

Variable	Intervention	Control	P-value
Age (year)	50.56 ± 12.23	57.1 ± 14.1	0.04
Gender			
Male	25 (50.00)	19 (38.00)	0.20
Female	25 (50.00)	31 (62.00)	
Sign and symptom			
Fever	25 (50.00)	19 (38.00)	0.20
Chill	23 (46.00)	15 (30.00)	0.09
Myalgia	21 (42.00)	19 (38.00)	0.50
Rhinorrhea	2 (4.00)	2 (4.00)	0.60
Cough	33 (66.00)	26 (52.00)	0.10
Dyspnea	33 (66.00)	30 (60.00)	0.50
Sore throat	1 (2.00)	-	0.50
Chest pain	4 (8.00)	4 (8.00)	0.60
Underlying disease			
Diabetes mellitus	3 (6.00)	4 (16.00)	0.08
Cardiac disorders	6 (12.00)	8 (16.00)	
Complications			
Gastrointestinal	24 (12)	20 (1)	0.60
Disease severity			
TSS	5.4 ± 2.0	5.6 ± 1.7	0.80

Data are presented as mean ± standard deviation or frequency (%). TSS: total severity score.

Table 2: Comparing the laboratory findings between intervention (n = 50) and control (n = 50) groups

Parameter	Intervention	Control	P-value
LDH (U/I)	493 ± 181	469 ± 163.1	0.517
FERRITIN (mcg/l)	264.2 ± 228	316.2 ± 231	0.337
ESR (mm/h)	31.9 ± 19.3	28.2 ± 20.1	0.361
CRP (U/I)	33.1 ± 21.5	26.2 ± 23.8	0.137
Hb (g/dl)	12.5 ± 1.5	12.5 ± 1.9	0.972
WBC (cells/mm^3)	6000 ± 2600	8000 ± 4400	0.008
PMN (cells/mm^3)	4600 ± 2200	7600 ± 1100	0.000
LYMPH (cells/mm^3)	1300 ± 1200	1800 ± 1100	0.000
PLT (cells/mm^3)	178.1 ± 47.9	211 ± 66.3	0.007
ALT (U/L)	34.3 ± 27.7	66.3 ± 19.2	0.098
AST (U/I)	39.4 ± 22.9	70.7 ± 27.6	0.254
ALK-P (U/I)	201.2 ± 62.3	215 ± 114	0.470
Cr (mg/dL)	1.1 ± 0.8	1.2 ± 0.8	0.420
BUN (mg/dL)	16.8 ± 507	21.9 ± 16	0.041

Data are presented as mean ± standard deviation. LDH: Lactate dehydrogenase;
ESR: erythrocyte sedimentation rate; CRP: c-reactive protein; HB: hemoglobin; WBC: white blood cell count;
PMN: polymorphonuclear neutrophils; LYMPH: lymphocytes; PLT: platelets; ALT: alanine transaminase; AST: aspartate transaminase;
ALK-P: alkaline phosphatase; CR: creatinine; BUN: blood urea nitrogen.

tients was 50.56 ± 12.23 and 57.1±14.1 years in intervention and control groups, respectively (p = 0.02). The most common signs and symptoms were cough and dyspnea in both groups. Tables 1 and 2 compare the baseline characteristics and presenting laboratory findings between two groups. The two groups were similar regarding distribution of underlying diseases (p = 0.08), the severity of COVID-19 at the time of admission (p = 0.80), signs and symptoms (p > 0.05), and essential laboratory profile (p > 0.05).

3.2. Outcomes

The length of hospital stay in the control and intervention groups was 7.7 ± 4.09 days and 4.7±1.6 days, respectively (p = 0.02). None of our patients needed ICU or mechanical ventilation or expired during our study. Two patients from our control group required re-admission 14 days after discharge. One patient in the sofosbuvir group experienced nausea, so the medication was discontinued.

4. Discussion

We intended to evaluate the safety and efficacy of sofosbuvir in cases with moderate COVID-19. We concluded that sofosbuvir may decrease the length of hospital stay (LOHS) but has no significant effect on the rate of Intensive care unit (ICU) need and mortality. Eslami et al. study revealed that sofosbuvir/daclatasvir could decrease LOHS, ICU admission rate, and mortality in patients with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (20). On the other hand, Abbaspour Kasgari et al. did not report any reduction in LOHS with sofosbuvir/daclatasvir/ribavirin administration. Limitations of their study include a small sample size (48 patients) (21).

Moreover, Sayad et al. reported that sofosbuvir/velpatasvir did not improve mortality, ICU admission, and LOHS. The limitation of their study is lining up moderate and severe patients in one arm. They revealed that the severity can dramatically change the response to treatments (22). Sofosbuvir in mild COVID-19 could improve neither hospital admission rate nor lead to symptom alleviation (17).

Our study demonstrated that sofosbuvir could significantly reduce LOHS, but it has no significant effect on ICU admission and mortality rate. We suggest initiating treatment with sofosbuvir in moderate COVID-19 to prevent exacerbation to severe infection. In this study, we answered if sofosbuvir alone is effective for COVID-19 by focusing on moderate cases. More studies are required to determine the ideal time for starting this drug to achieve the most in terms of reaching clinical recovery sooner.

5. Limitations

This study has some limitations. We missed the opportunity to compare laboratory findings, especially inflammatory markers, before and after administering sofosbuvir due to the lack of consistency in available data. Besides, we missed the opportunity of strengthening our methodology by using placebos and blinding; ethical issues and concern for patients' survival were the most important barriers.

6. Conclusion

It seems that, Sofosbuvir can decrease the length of hospital stay in cases with moderate COVID-19 without having a significant effect on the rate of ICU need and mortality.

7. Declarations

7.1. Acknowledgments

We would like to thank Dr. Laya Ohadi who helped us during this study and also the medical staff of the hospital's COVID-19 ward who facilitated the interventions of the study.

7.2. Data availability

The data used in this study is available from the first author on reasonable request.

7.3. Authors' contributions

All authors met the four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors.
Writing the first draft: RM
Revise: FA, MH
Data collection: AK, EZ, SN
Data analysis: FG, AF
Data interpretation: FG, GP
Design: FA

7.4. Funding and supports

No additional funding for the execution of the present study was received

7.5. Conflict of interest

The authors declare they have no conflict of interests

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