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Research Article

Is there a Place to Sulodexide in Critically Ill COVID-19 Patients? A Prospective Interventional Clinical Trial

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Received: March 25, 2023; **Published:** June 19, 2023

Abstract

Introduction: Actually, endotheliitis is considered to be prominent in hypoxemic COVID-19 patients. Sulodexide (glycosaminoglycan with endothelial protective, vascular anti-inflammatory and antithrombotic activities) was identified to be helpful in this cases. The aim of this study was to evaluate the effect of sulodexide supplementation in severe SARS-CoV-2 pneumonia and to determine its impact on prognosis.

Methods: A two-arm interventional clinical study in the Intensive Care Unit (ICU) from April 2021 to December 2021, approved by the Ethics Committee. Consenting COVID-19 patients over the age of 18 are included. Two groups were identified: Group 1 (G1) the intervention group and group 2 (G2) the control group. Consenting COVID- 19 patients over 18 years were included. Two groups were identified: Group 1 (G1) interventional group and group 2 (G2) control. Sulodexide (500 LSU) was given for 21 days from the first day of ICU admission to discharge. There are no conflicts of interest to declare. Epidemiological and evolving data were analyzed. The study was conducted anonymously. No conflict of interest to be declared.

Results: A total of 149 patients with severe SARS-CoV-2 pneumonia were included during the study period. Seventy patients agreed to participate in the clinical study (G1). The rest were defined as the control group. On admission, the two groups were comparable in terms of demographic characteristics, clinical presentation, and initial severity. Comparison of outcome parameters showed that group 1 patients had fewer thromboembolic complications (23.1% vs. 39.6%, p = 0.016), required invasive mechanical ventilation (16.8% vs. 36%), with lower mortality (19% vs 36%, p = 0.047). In G2, cardiovascular complications were found in hospital (37% vs 12%). Multivariate analysis showed that sulodexide use was an independent protective factor against thromboembolic events. There were no significant differences in terms of bleeding complications' occurrence, hemodynamic instability, incidence of healthcare-associated infections, barotrauma complications and length of ICU stay. Multivariate analysis showed that sulodexide use was an independent protective factor against thromboembolic events (OR=0,57; IC a` 95% [0.6-0.8]; p = 0,04). Follow-up of patients after three months of discharge, showed no differences in terms of cardiovascular complications, or post-COVID effects.

Conclusion: In this study, sulodexide appeared to reduce the risk of thromboembolism and cardiovascular complications in severely ill COVID-19 patients without affecting the bottom line. This benefit, if identified, could improve clinical outcomes and reduce the need for hospital care to assess for COVID19. Further prospective, multicentre studies with endothelial function studies are needed to confirm this contribution.

Keywords: COVID-19; Sulodexide; Acute Respiratory Distress; Intensive Care Unit; Outcome

Abbreviations

ARDS: Acute Respiratory Distress Syndrome; APACHE: Acute Physiology and Chronic Health Evaluation; BMI: Body Mass Index; ICU: Intensive Care Unit; ORs: Odds Ratios; RT-PCR: Reverse-Transcriptase Polymerase Chain Reaction; SAPS II: Simplified Acute Physiology Score

Introduction

Since December 2019, high worldwide morbidity and mortality in severe acute respiratory distress syndrome (ARDS) related to coronavirus 2 (SARS-CoV-2) infection have been reported. Actually, many studies have demonstrated that severe forms were induced by vascular endothelial-dependent systemic complications [1]. A Tunisian multicenter trial conducted by the Tunisian society of cardiology and cardiovascular surgery had showed that prescription of Sulodexide in patients with long COVID-19 may be a good alternative to improve symptoms associated to endothelial dysfunction [2]. Based on this positive results, we assessed whether sulodexide's pleiotropic properties with endothelium restoration, anti-inflammatory and antithrombotic properties can reduce severity of COVID-19 critically ill patients. This benefit, if found, could improve clinical outcomes and reduce global mortality.

Materials and Methods

We performed a prospective controlled trial with a parallel-group design in consecutive hypoxic confirmed COVID-19 patients admitted to intensive care unit. The recruiting period ranged from April 26th to December 31st, 2021. Consenting COVID-19 patients over 18 years old who did agree to receive sulodexide signed an informed consent. It assessed patient's ability to understand relevant medical information and alternatives implications treatment to make an independent and voluntary decision. It globally included diagnosis severity, eventual benefits and risks of Sulodexide. Inclusion, exclusion and elimination criteria are defined in the table 1. Two groups were identified: Group 1 (G1) receiving treatment and group 2 (G2) control. Sulodexide was administered on the first day of ICU hospitalisation. The posology was daily intravenously 500 LSU with oral relay at discharge for a total of twenty one days. Were included patient's demographics and clinical characteristics, need to mechanical ventilation, Occurrence of thrombo-embolic events and outcomes. All patients received an evaluative follow-up at three months. Primary endpoint was intrahospital mortality. Secondary endpoints were need to invasive ventilation, presence of thromboembolic events confirmed by ultrasound or computed tomography thoracic scan, major bleeding events and length of hospital stay. Data were collected using SPSS software version 23. Results were summarized as odds ratios (ORs) and 95% confidence intervals (CIs). A two-tailed p-value of 0.05 was considered statistically significant. The area under the receiver operating characteristic curve was used to assess the ability of the model to discriminate patients. Calculate goodness-of-fit (Hosmer Lemeshow) to assess relevance for logistic regression. Our study was conducted anonymously. Our study was Informed and approved by the Clinical Research Ethics Committee in accordance with the principles of the Declaration of Helsinki. Approval of local ethics committee as well as registration of protocol in an international website (Clinical Trials). We declare absence of any conflict of interest or financial, professional or personal competition that could influence performance or presentation of results described in our work.

Inclusion criteria	Non inclusion criteria	Exclusion criteria
Age> 18years	A negative RT-PCR SARS-CoV-2	Withdrawal of informed consent
Male or female	Known pregnancy	Lost to follow-up
Sign informed consent	History of thrombo-embolic event in the previous 6 months	
Severe acute respiratory syndrome	Chronic use of sulodexide	
A positif RT-PCR SARS-CoV- 2	Known allergy to sulodexide or its component products	

Table 1: *Inclusion, non inclusion and exclusion criteria.*
RT-PCR: Reverse-Transcriptase Polymerase Chain Reaction.

Results

Of 169 patients randomised, 20 were excluded. A total of 149 patients were enrolled for final data: 72 patients (48.3%) in sulodexide group and (51.69%) in control group (Figure 1).

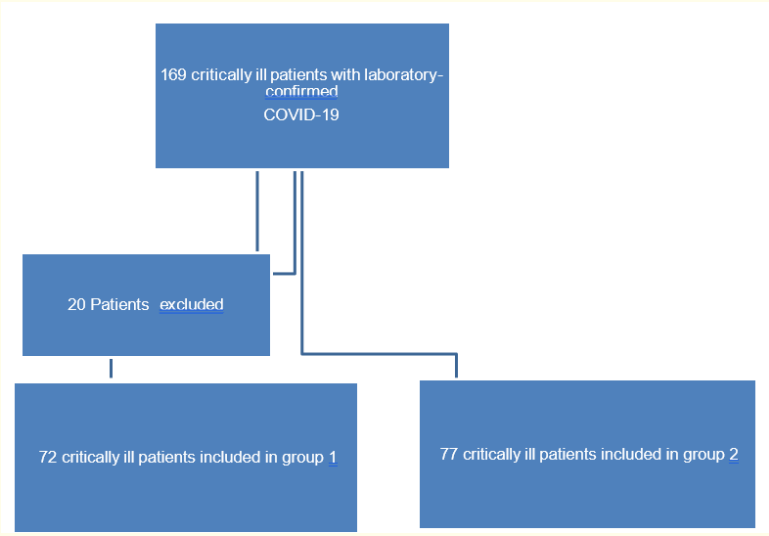

Figure 1: *Flowchart of the study and included patients with critical COVID-2019.*

Demographics, clinical characteristics and medical history were similar in both groups (Table 2). Also, co- administered medications (oxygenating devices, antibiotics, anticoagulation modalities and vitamin therapies) were similarly distributed (Table 3).

Main Characteristic	All Patients (n = 149)	G1	G2	P
Age, (years, mean ± SD)	52 ± 11	51 ± 11	52 ± 10	0.63
Male gender, n (%)	84,56	43,54	41,53	0.26
APACHE II (mean ± SD)	7 ± 5	7 ± 5	7 ± 4	0.07
SAPSII (mean ± SD)	22 ± 8	21 ± 7	22 ± 9	0.97
Comorbidities, n (%)	73	76	70	0.24
Diabetes	51	22	29	0.41
BMI, kg/m^2 (mean ± SD)	41	47	35	0.09
Hypertension	37	17	20	0.53
Vaccinated patients n (%)	8(5)	4(5)	4(5)	0.90
Duration of symptoms (days, median (IQR))	11(5-30)	11(5-21)	11(5-30)	0.75
PaO_2/fiO_2 ratio (mean ± SD)	120 ± 23	116 ± 52	140 ± 77	0.32
Mild to moderate ARDS, n (%)	80(53)	33(45)	47(61)	0.42
Severe ARDS, n (%)	66(44)	39(54)	27(35)	0.35
Lesion extent on computed tomography >75%, n (%)	101(68)	51(72)	55(65)	0.15
Presence of pulmonary embolism on ICU admission, n (%)	8(5)	5(7)	3(4)	0.44

Table 2: *Demographic and clinical characteristics and comorbidities of patients.*
SD: Standard Deviation; APACHE: Acute Physiology and Chronic Health Evaluation, Simplified Acute Physiology Score (SAPS) II; IQR: Interquartile Range; ARDS: Acute Respiratory Distress Syndrome; BMI Body Mass Index; ICU: Intensive Care Unit.

Parameters	All Patients (n = 149)	G1 (n = 72)	G2 (n = 77)	P
Non-invasive mechanical ventilation with HFNC n(%)	129 (86)	56(78)	63(82)	0.9
Prone position n(%)	88(59)	50(69)	33(50)	0.15
Glucocorticoids n(%)	139(93)	69(95)	70(90)	0.19
Antibiotics n(%)	100(65)	47(65)	53(66)	0.52
Anticoagulation modality				
Prophylactic n(%)	54(36)	24(33)	30(39)	0.07
Over intermediate (LMWH or increased weight -based dosing) n(%)	21(14)	15(21)	6(8)	0.07
Therapeutic(n,%)	75(50)	33(46)	42(53)	0.09
Vitaminotherapy n(%)	149(100)	72(100)	77(100)	0.8

Table 3: *Therapeutic strategy on ICU admission.*
HFNC: High Flow Nasal Cannula; LMWH: Low-Molecular-Weight Heparin.

Comparison of outcome parameters showed that group 1 patients had fewer thromboembolic complications (23.1% vs 39.6%, p0.016) and required invasive mechanical ventilation (16.8% vs 21.3%, p0.016), G1 mortality was lower (19% vs. G2 cardiovascular complications (37% vs. 12% p < 0.03) (Figure 2). No significant differences were noted between the two groups in terms of occurrence of bleeding complications, haemodynamic instability, incidence of healthcare-associated infections, barotrauma complications and length of ICU (Table 4). Sulodexide use is an independent protective factor against thromboembolic events in multivariate analysis (OR = 0,57, CI 95% [0.6-0.8]; p = 0,04). Follow-up examinations three months after patient discharge showed no difference in terms of cardiovascular complications or post-COVID effects.

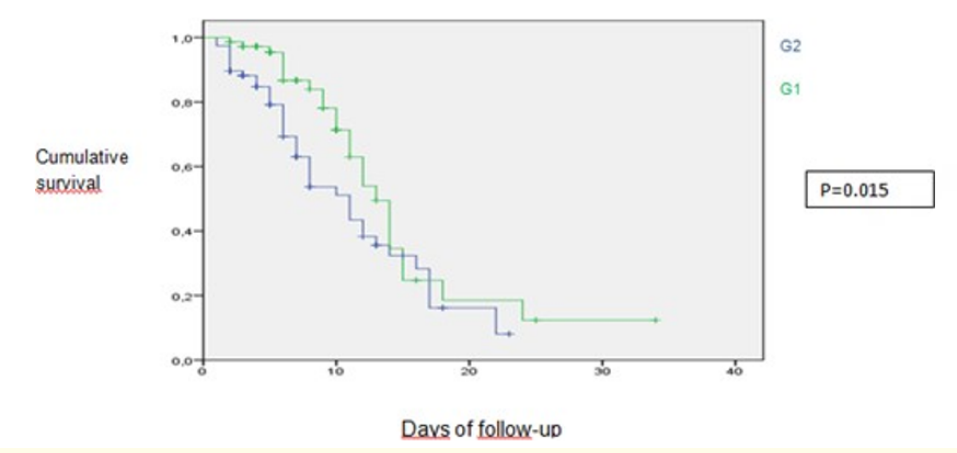

Figure 2: *Survival analysis in both groups.*

Parameters	All patients (n = 149)	G1 (n = 72)	G2 (n = 77)	P-value
Occurrence of TEC (n,%)	22,15	5,7	17,23	0.010
PE(n,%)	20,13	5,7	15,19	0.02
DVT(n,%)	2,1	0	2,2	$<10^{-3}$
Cardiovascular complications (n,%)	38,25	9,12	29,37	$<10^{-3}$
Coronary ischemia (n,%)	9,6	1,1	8,10	0,04
Ischemic stroke (n,%)	5,3	0	5,6	0,02
Limb ischemia (n,%)	2,1	0	2,2	$<10^{-3}$
Invasive ventilation (n,%)	60,40	22,30	38,49	0,015
Healthcare-associated infection (n,%)	68,46	33,46	35,45	0,54
Renal failure (n,%)	28,19	5,7	23,30	$<10^{-3}$
Shock (n,%)	37,24	16,22	21,28	0,30
Mortality (n,%)	60,40	22,30	38,49	0.015

Table 4: *Comparison of the evolving parameters of the two groups.*
TEC: Thromboembolic Complications; PE: Pulmonary Embolism; DVT: Deep Vein Thrombosis.

Discussion

Our study demonstrate that sulodexide was associated with a significantly lower risk of in-hospital all-cause mortality with decreased thromboembolic events and need to oro-tracheal intubation. There was no clear difference in rates of occurrence of septic shock or renal failure. No other secondary outcomes, such as Hemorrhagic event or abdominal discomfort were reported.

In fact, Sulodexide is a highly purified mixture of glycosaminoglycans (GAG) with anticoagulant and antithrombotic properties used in the prophylaxis and treatment of thromboembolic diseases. The pharmacological effects of sulodexide are significantly different from those of other. It is a glycosaminoglycan characterized by a prolonged half-life and a reduced effect on overall coagulation and bleeding parameters. Sulodexide is able to potentiate the antiprotease activities of both antithrombin III and heparin cofactor I [3]. As a precursor for the synthesis of GAGs, sulodexide can restore damaged endothelial glycocalyx and prevent further degradation [4]. This antithrombotic and antithrombin action has important pharmacological implications, making sulodexide a suitable drug for the prevention and treatment of arterial and venous peripheral diseases.

The clinical progression of COVID-19 shows a biphasic pattern. The first phase corresponds to viral replication and is characterized by upper respiratory symptoms, after which recovery begins in 80% of patients. The second phase is associated with a severe inflammatory response and is characterised by symptom persistence, onset of breathing difficulty and chest pain. These symptoms can quickly progress to full-blown acute respiratory distress syndrome (ARDS), requiring supplemental oxygen or requiring hospitalization [5]. Our trial focused on the second stage of the disease. The severe forms of coronavirus disease 2019 are associated with a particularly high incidence of venous and arterial thrombotic events contributing to subsequent multi-organ failures [6]. Accumulating evidence points toward an important role of endothelial dysfunction in the pathogenesis of COVID-19. In fact, endothelial dysfunction unbalances the vascular equilibrium to favor vasoconstriction, with subsequent organ ischemia, inflammation and tissue edema leading to a pro-coagulant state and compromising oxygen exchange. The endothelial surface layer on the lungs plays a critical role in the host immune response to the virus, both as an effector and as a target organ [7]. There is evidence of endothelial viral inclusion and diffuse endothelial inflammation, triggering a systemic release of inflammatory cytokines. This response produces an imbalance between the excessive formation of reactive

oxygen species and the antioxidant defence capacity. The inner surface of all vascular endothelium is coated by the glycocalyx which plays an important role in microvascular and endothelial stability [8].

Synergistic activity of sulodexide's pleiotropic effects on different biological targets may play an essential role in limiting disease progression, thus resulting in a reduced need for supplemental oxygen and hospital care as was observed in a Mexican study. It showed that use of this drug in mildly to moderately COVID-19 patients, in early stage, may reduce need for oxygen and hospitalization in intensive care unit [5]. No systematic reviews or meta-analyses have performed previously in ill critical patients COVID-19. Sulodexide in patients with long COVID-19 may be a good intervention to ameliorate chest pain, palpitations, fatigue and neuro-cognitive difficulties associated to endothelial dysfunction [2].

In our study, we found that Sulodexide was safe. It can be used with no significant risk of side effects. Sulodexide may be a real solution in prevention COVID-19 induced cardio-vascular complications. Sulodexide might be better known for its antithrombotic effect similar to that of low molecular weight heparin and has been proposed as an option for targeting thromboembolic risk in COVID-19 patients. Its endothelial protective properties may add a benefit of equal or greater importance in the early stages of the disease [8]. Additionally, Antithrombotic and profibrinolytic effects sulodexide may also be efficient against the accent procoagulant state caused by SARS-CoV-2, without majoring bleeding risk. This antithrombotic and antithrombin activities are great pharmacologic interest and classified sulodexide as a suitable drug for the prophylaxis and treatment of arterial and venous peripheral vascular diseases [9]. Strengths of our study were his controlled, and prospective design, without need for biological exam. Lack of controlled data regarding endothelial function evaluation in critical ill COVID-19 could be one of the study limitations.

Endothelial dysfunction is warranted to better understand the pathophysiology underlying of severe acute respiratory distress syndrome related to coronavirus 2 infection and to guide therapeutic intervention. Randomized studies are requested to study the effect of treatment with action on the endothelium function such as beta-blockers, ACE inhibitors, ARBs and statins on critical ill patients COVID-19 symptoms.

Conclusion

In summary, when used in severe COVID-19 patients, the synergic activity of sulodexide's pleiotropic effects on different biological targets can play an essential role in limiting disease progression, resulting in a decreased need for invasive ventilation and mortality, as observed in this trial. These findings justify further multicentre confirmatory studies.

Conflict of Interest

This is to certify that I Khaoula Ben Ismail and the author of the article: Is there a place to Sulodexide in critically ill COVID-19 patients? A prospective interventional clinical trial certify that there is no conflict of interest regarding the publication of this manuscript.

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Volume 7 Issue 4 April 2023