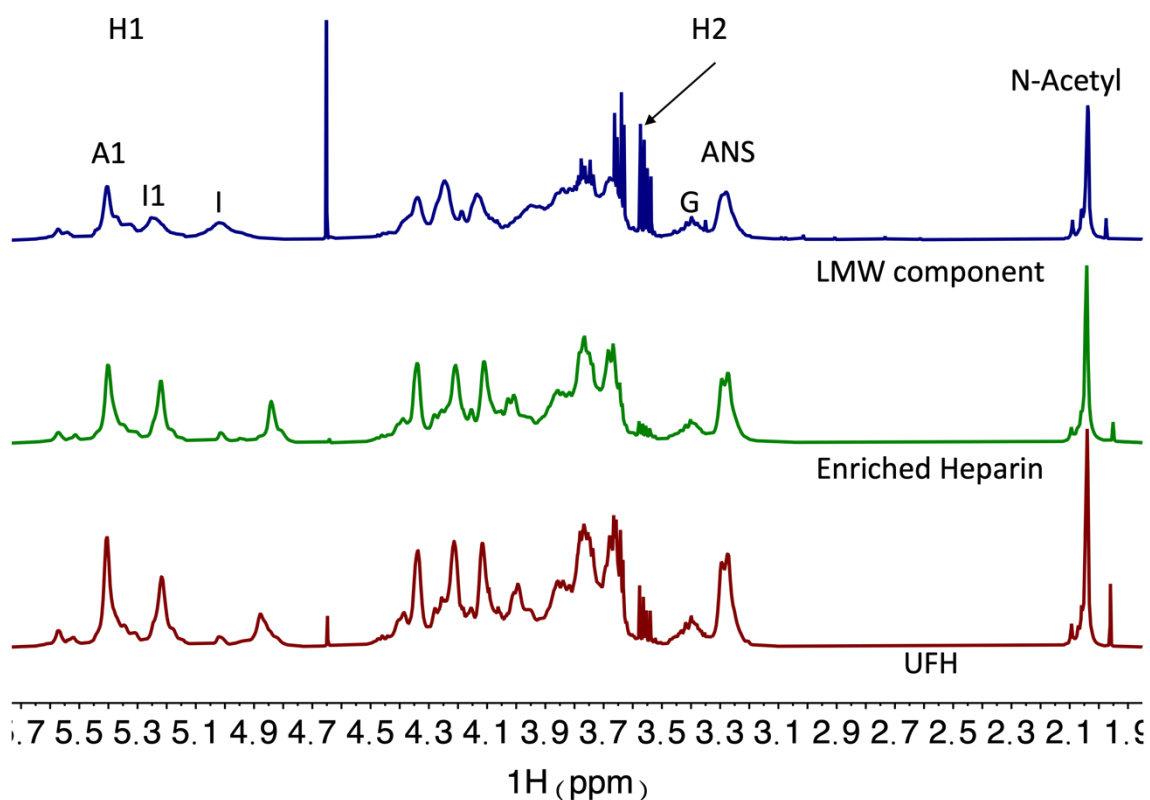


Nebulized enriched heparin improves respiratory parameters in patients with COVID-19: a phase I/II randomized and triple-blind clinical trial.

This supplement contains the following items:

1. Supplementary results (Page 2-6)



Supplementary Figure 1. ^1H NMR spectra of heparin samples. ANS, sulfoamino-D-glucopyranose; A1, 6-O-sulfo-2-sulfoamino-D-glucopyranose; N-Acetyl, acetyl group of 2-deoxy-2-acetylamino-D-glucopyranose; I1, 2-O-sulfo-iduronic acid; G, glucuronic acid; I, iduronic acid. Signals due to the low-molecular-weight formulation components are highlighted by an arrow.

Supplementary Table 1. Symptoms.

Symptoms	Incidence	D0	D7	P value [#]
Fever				
Placebo	11 (79%)	1 (7.1)	0 (0.0)	0.9999
Heparin	7 (54%)	2 (15.4)	0 (0.0)	0.5000
P value*	0.2365	0.5956	0.9999	
Dry cough				
Placebo	14 (100%)	8 (57.1)	1 (7.1)	0.0156
Heparin	12 (92%)	8 (61.5)	1 (7.7)	0.0150
P value*	0.4815	0.9999	0.9999	
Asthenia				
Placebo	12 (86%)	2 (14.3)	1 (7.1)	0.9999
Heparin	8 (62%)	4 (30.8)	0 (0.0)	0.1250
P value*	0.2087	0.3845	0.9999	
Myalgia				
Placebo	13 (93%)	4 (28.6)	0 (0.0)	0.1250
Heparin	7 (54%)	3 (23.1)	0 (0.0)	0.2500
P value*	0.0329	0.9999	0.9999	
Odynophagia				
Placebo	2 (14%)	0 (0.0)	0 (0.0)	0.9999
Heparin	1 (8%)	0 (0.0)	0 (0.0)	0.9999
P value*	0.9999	0.9999	0.9999	
Diarrhea				
Placebo	5 (36%)	1 (7.1)	0 (0.0)	0.9999
Heparin	4 (31%)	1 (7.7)	0 (0.0)	0.9999
P value*	0.9999	0.9999	0.9999	
Cephalalgia				
Placebo	4 (29%)	0 (0.0)	0 (0.0)	0.9999
Heparin	8 (62%)	5 (38.5)	1 (7.7)	0.1250
P value*	0.1283	0.0159	0.4815	
Anosmia				
Placebo	4 (29%)	0 (0.0)	0 (0.0)	0.9999
Heparin	4 (31%)	0 (0.0)	0 (0.0)	0.9999
P value*	0.9999	0.9999	0.9999	
Ageusia				
Placebo	4 (29%)	0 (0.0)	0 (0.0)	0.9999
Heparin	4 (31%)	0 (0.0)	0 (0.0)	0.9999
P value*	0.9999	0.9999	0.9999	
Dyspnea				
Placebo	12 (86%)	7 (50.0)	1 (7.1)	0.0310
Heparin	8 (62%)	7 (53.8)	0 (0.0)	0.0150
P value*	0.2087	0.9999	0.9999	
Chest pain				
Placebo	0 (0%)	0 (0.0)	0 (0.0)	0.9999
Heparin	4 (31%)	0 (0.0)	2 (15.4)	0.5000
P value*	0.0407	0.9999	0.2222	
Hyporexia				
Placebo	6 (43%)	3 (21.4)	0 (0.0)	0.2500
Heparin	8 (62%)	2 (15.4)	0 (0.0)	0.5000
P value*	0.4495	0.9999	0.9999	
Bleeding				
Placebo	0 (0%)	0 (0.0)	0 (0.0)	0.9999
Heparin	0 (0%)	0 (0.0)	0 (0.0)	0.9999
P value*	0.9999	0.9999	0.9999	

Placebo n=14; Heparin n=13.

Results expressed as n (%).

[#] McNemar test.

* Fisher's exact test

Supplementary Table 2. Laboratory tests (continuation).

Analyses / Groups	D0	D2	D5	D7	P value
Albumin, g/dL					
Placebo	3.3 (0.2)	3.2 (0.8)	3.1 (0.7)	3.2 (0.6)	0.9202 ^{##}
Heparin	3.3 (0.4)	3.4 (0.6)	3.4 (0.2)	3.6 (0.5)	0.3735 ^{##}
P value ^{**}	0.9673	0.8371	0.5278	0.3263	
Globulin, g/dL					
Placebo	2.0 (0.2)	1.9 (0.1)	2.0 (0.2)	2.0 (0.1)	0.8058 ^{##}
Heparin	1.9 (0.1)	2.0 (0.1)	1.9 (0.2)	1.9 (0.2)	0.8154 ^{##}
P value ^{**}	0.7982	0.2368	0.4441	0.7905	
Hematocrit, %					
Placebo	39.4 (5.4)	39.3 (5.3)	40.5 (5.2)	40.4 (4.5)	0.9050 [#]
Heparin	39.3 (7.9)	39.8 (9.6)	39.8 (7.6)	41.8 (8.2)	0.8703 [#]
P value [*]	0.9632	0.8734	0.7898	0.5979	
MCV, fL					
Placebo	88.2 (4)	88.1 (4.3)	88 (4.3)	88.3 (3.9)	0.9984 [#]
Heparin	85.5 (8.3)	85.3 (7.5)	85.7 (7.9)	85.2 (7.1)	0.9983 [#]
P value [*]	0.2873	0.2317	0.3820	0.1851	
RDW, %					
Placebo	13.5 (1.2)	13.5 (1)	13.5 (1)	13.5 (0.8)	0.9897 ^{##}
Heparin	14.4 (3.7)	14.5 (3.5)	14.6 (3.2)	15.4 (5)	0.3846 ^{##}
P value ^{**}	0.8017	0.9698	0.6601	0.1635	

Placebo n=14; Heparin n=13.

Results expressed as mean (standard deviation) on parametric analysis.

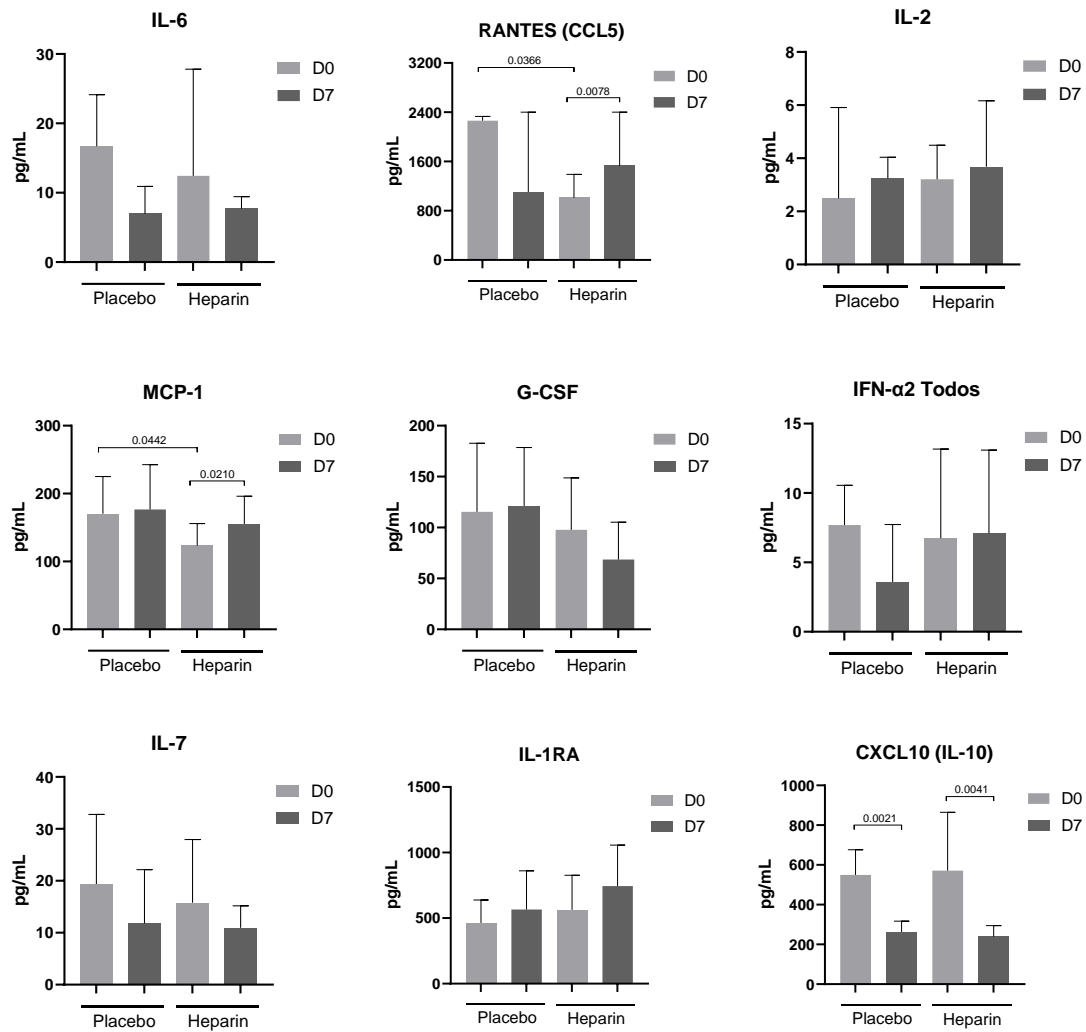
Results expressed as median (IQR) on nonparametric analysis.

* Unpaired t test.

** Mann-Whitney test.

One-way ANOVA.

Kruskal-Wallis test.



Supplementary Figure 2. Inflammatory markers. Serum cytokines from placebo and enriched heparin patients were evaluated.



Supplementary Figure 3. Representative tomographic results of the pattern of lung involvement. Patient 7 – A: Pre-treatment score 3; B: Post-treatment with score 1; Patient 12 – C: Pre-treatment score 2; D: Post-treatment with score 1; Patient 23 – E: Pre-treatment score 3; F: Post-treatment with score 1.