Low Molecular Weight Heparin Protects Lung, Renal and Microcirculation Function in Patients with Covid-19 Pneumonia

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Research

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Abstract

Background

Coronavirus disease 2019 (Covid-19) remains a serious health threat worldwide. It is crucial to explore effective treatment measures that reduce mortality. Our aim was to investigate whether low molecular weight heparin (LMWH) can reduce organ injury in patients with Covid-19 pneumonia.

Methods

A retrospective study was conducted at the Shanghai Public Health Clinical Center. We initiated a LMWH protocol from January 18th 2020. LMWH was injected subcutaneously at 4100U per day until the D-dimer(DD) level returned to normal, or 5-7 days after admission, whichever occurred first. Admitted patients who received LMWH between January 18th and February 17th 2020 were assigned to the LMWH group. Patients admitted between January 18th and February 17th who did not receive LMWH anticoagulant therapy were the control group. All patients in both groups were aged >18 years, were not pregnant, had no tumors and were in accordance with the following inclusion criteria: 1) DD increased on admission; 2) Body mass index(BMI) >30; 3) History of diabetes. The exclusion criteria were: 1) Platelets <$30x10^9$/L or fibrinogen <150 mg/dL; 2) Pregnancy and lactation; 3) Presence of blood system diseases; 4) Immunosuppression; 5) Diseases with a potential risk of bleeding; 6) Receiving anticoagulant drugs or antiplatelet drugs during treatment. General clinical information, indicators for renal function, arterial blood gas analyses and blood lactic acid content were recorded in the two groups 0 (Day 0), 3 (Day 3), 7 (Day 7), and 11 (Day 11) and 15 (Day 15) days after admission.

Results

There were 48 patients in the LMWH group and 74 patients in the control group. General information, including age, gender, co-existing diseases and onset-to-admission time in both groups was similar. Compared to the control group, LMWH treatment improved the estimated glomerular filtration rate (eGFR) reduced the serum creatinine level (Scr), blood urea nitrogen (BUN)arterial blood carbon dioxide partial pressure (PaCO2) and arterial blood lactic acid content. However, LMWH treatment reduced arterial oxygen partial pressure (PaO2) and arterial oxygen saturation (SaO2).

Conclusion

LMWH might be beneficial to improve renal function, CO2 discharge and microcirculation during the early phase of Covid-19 patients . Further randomized controlled trials(RCTs) are warranted in order to further investigate this issue.

Trial registration

ChiCTR, ChiCTR2000034796. Registered 19 July 2020 - Retrospectively registered, http:// www. chictr.org.cn/listbycreater.aspx.

Introduction

The novel coronavirus designated Severe Acute Respiratory Syndrome-related coronavirus 2 (SARS-CoV-2) has caused a global outbreak of respiratory illness termed Coronavirus disease 2019 (Covid-19), starting in December 2019 and still spreading rapidly. By October 3rd 2020, SARS-CoV-2 had affected more than 200 countries, resulting in more than 34 million confirmed cases, with 1 million confirmed deaths. The main clinical manifestation of Covid-19 pneumonia is respiratory function deterioration. Severe patients may have multiple organ injury. It is reported that the mortality rate of these patients is as high as 66% [1].

Several therapeutic agents have been evaluated for the treatment of Covid-19, but thus far none have been shown to be effective. Coagulation dysfunction is one of the important causes of death in patients with severe Covid-19. Studies have shown that 71% of the patients who die meet the diagnostic criteria for disseminated intravascular coagulation (DIC) of the International Society of Thrombosis and Hemostasis (ISTH)[2]. The potential of low molecular weight heparin(LMWH) for Covid-19 has already gained the attention of some scholars[3–4]. The ISTH recommends prophylactic anticoagulation for inpatients with Covid-19, based on a study of inpatients with moderate to severe Covid-19 disease[5]. However, these recommendations are based on general thromboprophylaxis and are not specific to Covid-19. There is still no evidence of a protective effect of LMWH on organ function and microcirculation in Covid-19 pneumonia.

The novel Coronavirus Pneumonia Expert Group in Shanghai has been actively carrying out anticoagulation therapy for Covid-19 patients since the outbreak of the epidemic in Shanghai. We gave 4100U LMWH subcutaneously for qd until the D-dimer(DD) level returned to normal, or 5–7 days after admission, whichever occurred first. In this retrospective study, we investigate the effects of LMWH on kidney / lung function and arterial blood lactic acid content in patients diagnosed with Covid-19 pneumonia on admission. The results reveal that LMWH can decrease blood lactic acid content and improve the function of lungs and kidneys. This is the first report that LMWH can improve lung, renal and microcirculation function in Covid-19 patients.

Methods

Study Design

The study was a retrospective clinical study to investigate the effect of LMWH on kidneys, lungs and microcirculation in patients with Covid-19. It was approved by the institutional ethics board of the Ruijin Hospital, Shanghai Jiaotong University School of Medicine and has been retrospectively registered in the Chinese Clinical Trail Registry (ChiCTR2000034796).

The study was conducted at the Shanghai Public Health Clinical Center. Since January 18th 2020, we began to use the LMWH protocol in the treatment of Covid-19 patients with increased DD, body mass index(BMI) > 30, or a history of diabetes. LMWH was injected subcutaneously at 4100U per day until the DD level returned to normal, or 5-7 days after admission.

We screened patients admitted from January 18th to February 17th 2020. The inclusion criteria were: 1) Age >18 years; 2) No other trial drug treatment used within the time frame of the study; 3) In accordance with any of the following: DD increased on admission; BMI >30; History of diabetes. The exclusion criteria were: 1) Platelets <30×10^9/L or fibrinogen <150 mg/dL; 2) Pregnancy and lactation; 3) Presence of blood system diseases; 4) Immunosuppression; 5) Serious brain injury, cerebrovascular malformation, bronchiectasis, peptic ulcer, liver cirrhosis, hemorrhoids or other diseases with potential bleeding risk; 6) Receiving anticoagulant drugs or antiplatelet drugs during treatment; 7) <24 hours since severe trauma or surgery.

The diagnosis and severity classifications followed the guidelines of the National Health and Family Planning Commission of the People's Republic of China[6]. The specific diagnostic criteria for mild, moderate, severe, and critical types of disease are shown in Table 1.

We retrospectively screened the patients admitted during the two previous months (between January 18th and February 17th 2020). Patients who met the above criteria and received the LMWH regimen were included as the LMWH group, and those who did not receive the LMWH regimen were assigned to the control group.

Treatment protocol

All patients were treated according the guidelines of the National Health and Family Planning Commission of the People's Republic of China and the Shanghai Expert Consensus on comprehensive treatment of Covid-19[7]. The main associated therapies within the first few weeks after admission included antiviral therapy, antibiotics and glucocorticoids. The two groups did not differ with respect to these treatments. The LMWH protocol consisted of a subcutaneous injection of 4100U LMWH per day from admission until DD returned to normal, or 5-7 days from the time of admission. DIC indicators were monitored during LMWH use.

Data collection

The information and data from the two groups were collected from electronic medical records and reviewed by two trained physicians. Information about age, gender, co-existing diseases (chronic heart disease, diabetes, chronic lung disease, hypertension and other chronic diseases), onset-to-admission time and disease severity on admission was obtained. Data at days 0, 3, 7,11 and 15 after admission were collected in the two groups.

Indicators of kidney function including serum creatinine (Scr), blood urea nitrogen (BUN), and estimated glomerular filtration rate (eGFR) were recorded. Data on the microcirculation indicator, arterial blood lactic acid content, were collected. Indicators of lung function including arterial partial pressure of carbon dioxide ($PaCO_2$), arterial partial pressure of oxygen (PaO_2) and arterial oxygen saturation (SaO_2) were also collected.

Statistical Analysis

Continuous variables were presented as mean and standard deviation and compared using t-tests. Categorical variables were presented as frequencies / percentages and compared using Fisher's exact test. The generalized estimating equation (GEE) approach was applied to investigate the effect of LMWH on arterial blood lactic acid content and indicators of renal and arterial blood-gas analysis longitudinally over time, adjusted for disease severity[8]. All statistical analyses were performed using SAS v. 9.2 (SAS Institute Inc., USA). Two-sided P values of less than 0.05 were considered statistically significant.

Results

Patient characteristics

We retrospectively screened patients admitted from January 18th to February 17th 2020. 48 patients met the inclusion criteria for the LMWH group and 74 patients were included in the control group.

Characteristics of patients in the LMWH and control groups are described in Table 2. Among the patients in the LMWH group, 32 (66.7%) were male and 16 (33.3%) female. There was no significant difference in gender composition compared to the control group (37 (50.0%) male vs 37 (50.0%) female). Patients in the LMWH group showed no significant difference in age compared to the controls (60.67 ± 14.53 vs 48.26 ± 15.52; $P=0.081$). When basic diseases were considered, the results showed no significant differences between the two groups in prevalence of diabetes (16.7% vs 9.6%; $P = 0.248$), hypertension (37.5% vs 20.27%; $P = 0.400$), heart disease (14.6% vs 9.5%; $P = 0.386$), lung disease (2.08% vs 4.05%; $P = 0.138$), and others (16.67% vs 6.76%; $P = 0.945$). The onset-to-admission time in the LMWH group showed no significant difference compared with the control group (5.125 ± 4.165 vs 4.338 ± 3.393; $P=0.208$). We then compared disease severity between the two groups. In the LMWH group, 28 (58.3%) were moderate type patients, 9 (18.8%) were severe and 11 (22.9%) were critical. 74 (100%) patients in the control group were moderate type. There were significant differences in disease severity between the two groups ($p<0.05$). Then we compared the blood gas analysis, plasma lactic acid content and renal function index between the two groups on the day of admission, the results showed that there was no difference between the two groups except that $PaCO_2$ in the control group was higher than that in the LMWH group (Table 3). In order to accurately judge the effect of LMWH on microcirculation and organ function of Covid-19 patients, we therefore used the generalized estimating equation (GEE) to exclude interference from different of disease severity and $PaCO_2$ between the two groups.

Effect of LWMH on microcirculation and organ function in Covid-19 patients

The generalized estimation equation was used to analyze the effect of LMWH anticoagulant therapy on microcirculation, renal function and lung function. The parameters of the equation and the statistical results are described in Table 4.

We studied the effect of LMWH on microcirculation by observing the lactic acid content in arterial blood. The results showed that, compared with the control group, patients in the LMWH group had significantly lower arterial blood lactic acid content (Estimated value = 4.4458, P = 0.0343). Then we observed the effect of LMWH anticoagulant therapy on renal function. Analysis of the data showed that LMWH reduced the serum creatinine (Estimate=6.7342, p=0.0485) and the BUN (Estimate=-5.5513, p=0.2426) levels. The estimated glomerular filtration rate showed a trend towards a decrease (Estimate=0.1500, p=0.6189) in the LMWH group, but it was not statistically significant. We also analyzed the effect of LMWH on lung function. Results from blood gas analysis showed that the PaCO2 decreased (Estimate=5.4832, p=0.0117) in the LMWH group compared with the controls. PaO2 (Estimate=5.9151， p=0.0062) and SpO2 (Estimate =3.6902，p=0.0073) were decreased at the same time.

Discussion

Covid-19 is an illness caused by infection with the new coronavirus (SARS-CoV-2) that is associated with a systemic inflammatory response and activation of coagulation. The virus accesses host cells via the protein angiotensin-converting enzyme 2 (ACE2)[9]. Many studies have shown that the virus mainly targets vascular endothelial cells, leading to endothelial dysfunction and hypercoagulability[10]. Increased fibrinogen and factor VIII, activated coagulation, direct viral endothelial infection, increased platelet-vessel wall interaction and hypoxia play roles in the development of thrombotic complications. Coagulation disorders, including disseminated intravascular coagulation (DIC), are prominent problems in Covid-19 patients and a frequent cause of death.

The results of a multicenter retrospective study involving 1099 patients with Covid-19 showed that the incidence of DIC in critically ill patients was significantly higher than that in non-critical patients[11]. A retrospective analysis of 99 patients with Covid-19 in Jinyintan Hospital showed that 36% of the patients had increased DD levels[12]. Professor Peng Zhiyong of Central South Hospital performed a retrospective analysis of 138 patients with Covid-19, and also confirmed that DD levels of dying patients had increased at the time of admission[13]. Professor Tang Ning et al. published a retrospective analysis of the conventional coagulation indices of 183 patients with Covid-19[2]. They found that plasma fibrinogen degradation products(FDP) and DD levels in dying patients were significantly higher than those of surviving patients. Preliminary evidence suggests that LMWH has both anticoagulant and anti-inflammatory effects[14]. Recent findings that heparin interacts with the receptor binding domain of the SARS-CoV-2 spike protein S1 suggest that it has the potential to prevent viral adhesion[15]. A retrospective study including 449 patients with severe Covid-19 infection showed a lower mortality in patients with Covid-19-associated coagulopathy who received prophylactic heparin than in patients not receiving anticoagulant treatment. Of particular note, in patients with increased concentrations of D-dimer (6 times the upper limit of normal), mortality was lower in those receiving heparin[3]. However, the protective effect of LWMH on microcirculation and multiple organs in patients with Covid-19 is still not appreciated.

Pulmonary microvascular coagulation in Covid-19 results in pulmonary embolism with occlusion and micro-thrombosis in pulmonary small vessels. A review of 10 autopsies of Covid-19 patients (5 men, 5 women) found evidence of microthrombi in lung tissue[16]. A case series of post-mortem autopsies found that pulmonary embolism(PE) was the direct cause of death in 4 (33%)[17]. Treatment with LMWH within the initial 7-day onset of acute respiratory distress syndrome (ARDS) significantly improved the PaO2/FiO2 ratio and reduced the risk of 7-day mortality by 48% and the risk of 28-day mortality by 37%, particularly in the subgroup receiving high-dose LMWH of ≥ 5000U/day [18]. However, the largest available study evaluating anticoagulation was an analysis of 2,773 patients with COVID-19 in the Mount Sinai Health System found that patients who received anticoagulation were signififficantly more likely to require invasive mechanical ventilation [19].Our results showed that LMWH therapy could reduce PCO2, which was considered to be related to reduction of pulmonary vascular thrombosis and improvement in alveolar-capillary gas exchange. Additionally, our results show that anticoagulant therapy reduces arterial oxygen partial pressure and oxygen saturation, which may be related to increased tissue oxygen utilization after improvement of microcirculation, and thus decreased intravascular oxygen content.

Studies in many countries have shown that more than 20% of critically ill or dying Covid-19 patients have acute kidney injury (AKI)[20–22]. AKI is considered a negative prognostic factor regarding survival of Covid-19 patients. The pathophysiologic mechanisms leading to AKI in Covid-19 may include direct cytopathic effects of the virus on kidney tubular and endothelial cells, indirect damage caused by virus-induced cytokine release and kidney hypoperfusion due to a restrictive fluid strategy[23]. Segmental fibrin thrombus formation was found in the glomerular capillary loops in a recent post-mortem histopathologic analysis of patients with Covid-19[24]. Researchers also reported that 2 Covid-19 patients developed renal dysfunction due to renal infarction[25]. It has not been clear whether LMWH can protect kidney function in patients with Covid-19. Our study shows that LMWH anticoagulation can indeed improve renal function.

Endothelial dysfunction with vascular microthrombosis and capillary occlusion lead to damage of capillary blood flow, but the microvascular evaluation remains a problematic issue in COVID-19 patiants. In a clinical observation study of COVID-19 patients in Wuhan, Yang X et al. found that non-survivors had higher lactic acid concentration(1.9(1.4–3.2)mmol/L) than survivors (1.6(1.3–1.6)mmol/L)[26]. Our study for the first time found that LMWH can reduce the plasma lactic acid concentration in patients with covid-19, which may be related to the improvement of microcirculation, and is consistent with the result that LMWH can reduce the mortality of covid-19patiants found by N Tang et al.[3].

Limitation of this study

The relatively small sample of patients limited the power of the study. Due to the difference of severity between the two groups, we used the generalized estimation equation (GEE) method to exclude the influence of disease severity on the results.

Conclusion

This preliminary retrospective study showed that LMWH anticoagulant therapy in the early stage of Covid-19 can improve renal function, carbon dioxide discharge and microcirculation function. The results of this study provide supportive evidence for the application of LMWH in the treatment of Covid-19 patients.

List Of Abbreviations

Covid-19 Coronavirus disease 2019

LMWH Low molecular weight heparin

DD D-dimer

BMI Body Mass Index

eGFR Estimated glomerular filtration rate

Scr Serum creatinine

BUN Blood urea nitrogen

PaCO2 Arterial blood carbon dioxide partial pressure

PaO2 Arterial oxygen partial pressure

SaO2 Arterial oxygen saturation

RCT Randomized controlled trial

SARS-CoV-2 Severe Acute Respiratory Syndrome-related coronavirus 2

DIC Disseminated intravascular coagulation

ISTH International Society of Thrombosis and Hemostasis

GEE Generalized estimating equation

ACE2 Angiotensin-converting enzyme 2

FDP Fibrinogen degradation products

PE Pulmonary embolism

ARDS Acute respiratory distress syndrome

AKI Acute kidney injury

Declarations

Ethical Approval and Consent to participate

This study was approved by the institutional ethics board of Ruijin Hospital, Shanghai Jiaotong University school of medicine(2020305). The oral consent was obtained from each participated patient.

Consent for publication

All the authors approved the publication.

Availability of supporting data

All data are fully available without restriction.

Competing interests

The authors declare that they have no competing interests.

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Author contribution

LM conceived the hypothesis and wrote the manuscript. YGZ contributed to data collection. YGZ and LLX contributed intellectual input. JL contribute statistical analysis. TYZ and EQM conceived hypothesis, and reviewed the manuscript. All authors read and approved the final manuscript.

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Tables

Table 1.
Disease severity classification criteria of COVID-19 pneumonia

Severity classification	**Criterion**
Mild	The clinical symptoms were mild and no signs of pneumonia were found in lung imaging.
Moderate	The patient had symptoms of fever and respiratory infection, and the lung imaging showed pneumonia.
Severe	Adults meet any of the following criteria: 1. Short of breath, RR ≥ 30 times / min; 2. In resting state, oxygen saturation ≤ 93%; 3. PaO_2 / FiO_2 ≤ 300mmHg（lmmHg=O.133kPa） Children meet any of the following criteria: 1. Short of breath (5 years old, RR ≥ 30 times / min), except for fever and crying; 2. In resting state, oxygen saturation ≤ 92%; 3. Assisted breathing (groaning, flapping of nasal wing, triple concave sign), cyanosis and intermittent apnea; 4. Drowsiness and convulsion; 5. Refuse to eat or feeding difficulties, dehydration sign PaO_2 / FiO_2 should be corrected according to the following formula: PaO_2 / FiO_2 × [atmospheric pressure (mmHg) / 760] in high altitude area (altitude over 1000m). If lung imaging shows obvious progress of lesions within 24-48 hours, severe management should be adopted.
Critical	One of the following conditions is met: 1. Respiratory failure and need mechanical ventilation; 2. Shock; 3. Patients with other organ failure need ICU monitoring and treatment.

Remark: RR, Respiratory Rate.

Table 2.
Baseline characteristics of COVID-19 patients

Variable		Control group (n=74)	LWMH Group (n=48)	*P* value
Gender	Male	37(50.0%)	32(66.7%)	0.159
	Female	37(50.0%)	16(33.3%)	
Age(years)		48.260+15.518	60.667+14.531	0.081
Basic diseases	Diabetes	7(9.6%)	8(16.7%)	0.248
	Hypertension	15(20.27%)	18(37.5%)	0.400
	Heart disease	7(9.5%)	7(14.6%)	0.386
	Lung disease	3(4.05%)	1(2.08%)	0.138
	Kidney disease	0	0	
	Others	5(6.76%)	8(16.67%)	0.945
Onset-admission time(days)		4.338+3.393	5.125+4.165	0.208
Severity	Moderate	74(100%)	28(58.3%)	0.000*
	severe	0	9(18.8%)	
	critical	0	11(22.9%)	

*Remark: Onset-admission time: Interval from onset to admission; *, P < 0.05.*

Table 3.
Organ function data of COVID-19 patients before LWMH treatment

Variable	Control group (n=74)	LWMH Group (n=48)	*P* value
Lactic acid (mmol/L)	2.0386+1.1841	2.2133+1.0262	0.435
PaCO2 (mmHg)	5.3318+0.5468	5.0676+0.7385	0.036*
PaO2 (mmHg)	14.0057+4.8761	13.4338+5.7332	0.582
SaO2 (%)	97.0969+3.5725	96.2024+4.2127	0.241
eGFR (mL/min)	106.9940+25.595	98.1160+27.3812	0.071
Scr (μmol/L)	68.6618+24.9168	79.9923+52.85353	0.114
BUN (mmol/L)	4.9111+1.9168	6.2367+6.0781	0.083

*Remark: PaCO2, arterial partial pressure of carbon dioxide; PaO2, arterial partial pressure of oxygen; SaO2, Arterial Oxygen Saturation; eGFR, estimated glomerular filtration rate ; Scr, Serum creatinine ; BUN,blood urea nitrogen ; * , $P < 0.05$.*

Table 4.
Parameters and P values of generalized estimation equation for the effect of LMWH treatment on covid-19patients

	Group	Estimate	Standard Error	95% Confidence Limits		Z	Pr>|Z|
Lactic acid (mmol/L)	Control	4.4458	2.1005	0.3289	8.5626	2.12	0.0343*****
	LMWH	0.0000	0.0000	0.0000	0.0000	.	.
PaCO2(mmHg)	Control	5.4832	2.1738	1.2226	9.7438	2.52	0.0117*****
	LMWH	0.0000	0.0000	0.0000	0.0000	.	.
PaO2(mmHg)	Control	5.9151	2.1632	1.6754	10.1548	2.73	0.0062*****
	LMWH	0.0000	0.0000	0.0000	0.0000	.	.
SaO2(%)	Control	3.6902	1.3763	0.9926	6.3877	2.68	0.0073*****
	LMWH	0.0000	0.0000	0.0000	0.0000	.	.
eGFR(mL/min)	Control	-5.5513	4.7505	-14.8621	3.7596	-1.17	0.2426
	LMWH	0.0000	0.0000	0.0000	0.0000	.	.
Scr(μmol/L)	Control	6.7342	3.4127	0.0454	13.4229	1.97	0.0485*****
	LMWH	0.0000	0.0000	0.0000	0.0000	.	.
BUN(mmol/L)	Control	0.1500	0.3015	-0.4409	0.7409	0.50	0.6189
	LMWH	0.0000	0.0000	0.0000	0.0000	.	.

*Remark: PaCO2, arterial partial pressure of carbon dioxide; PaO2, arterial partial pressure of oxygen; SaO2, Arterial Oxygen Saturation; eGFR,estimated glomerular filtration rate ; Scr, Serum creatinine ;BUN,blood urea nitrogen ; *, $P < 0.05$.*