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ARTICLE

Bromhexine Hydrochloride Tablets for the Treatment of Moderate COVID-19: An Open-Label Randomized Controlled Pilot Study

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This open-label randomized controlled pilot study aimed to test the study feasibility of bromhexine hydrochloride (BRH) tablets for the treatment of mild or moderate coronavirus disease 2019 (COVID-19) and to explore its clinical efficacy and safety. Patients with mild or moderate COVID-19 were randomly divided into the BRH group or the control group at a 2:1 ratio. Routine treatment according to China's Novel Coronavirus Pneumonia Diagnosis and Treatment Plan was performed in both groups, whereas patients in the BRH group were additionally given oral BRH (32 mg t.i.d.) for 14 consecutive days. The efficacy and safety of BRH were evaluated. A total of 18 patients with moderate COVID-19 were randomized into the BRH group ($n = 12$) or the control group ($n = 6$). There were suggestions of BRH advantage over placebo in improved chest computed tomography, need for oxygen therapy, and discharge rate within 20 days. However, none of these findings were statistically significant. BRH tablets may potentially have a beneficial effect in patients with COVID-19, especially for those with lung or hepatic injury. A further definitive large-scale clinical trial is feasible and necessary.

Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?
☑ Bromhexine hydrochloride (BRH) is capable of inhibiting transmembrane protease serine 2 (TMPRSS2) and TMPRSS2-specific viral entry and is theoretically regarded to be effective against severe acute respiratory syndrome-coronavirus 2.

WHAT QUESTION DID THIS STUDY ADDRESS?
☑ This open-label randomized controlled pilot study evaluated the study feasibility of BRH tablets for the treatment of coronavirus disease 2019 (COVID-19) and to explore its clinical efficacy and safety.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?
☑ The study of BRH tablets for the treatment of COVID-19 is feasible and necessary.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?
☑ BRH tablets may potentially have a beneficial effect against COVID-19, especially for patients with lung and hepatic injury. A further large-scale clinical trial is warranted to confirm our findings.

The epidemic novel coronavirus disease 2019 (COVID-19) has now rapidly spread from China to around the world.[1,2] Among all infected patients, 80% of patients have been categorized as having moderate disease; and the overall fatality rate is ~ 2.3%, with the elderly experiencing a higher rate.[3] Asymptomatic carriers are also contagious, which contributes to the growing epidemic status. There is an urgent need for effective treatment to not only relieve the symptomatic patients but to curb viral transmission.

The novel coronavirus mainly invades the human body through angiotensin-converting enzyme 2/transmembrane protease serine 2 (TMPRSS2).[4] Previous studies on severe acute respiratory syndrome, Middle East respiratory syndrome, and other respiratory viruses have revealed that TMPRSS2 participates in the process of host cell entry, maturation, and release of the virus, which enhance the viral infectivity.[5–7] Therefore, inhibition of TMPRSS2 may be a promising therapeutic approach for COVID-19.[4] The

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latest prophylactic and treatment option for severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) infection proposed by researchers from the Netherlands, the United States, Indonesia, South Africa, and Italy is the use of a TMPRSS2 inhibitor.[8]

Bromhexine hydrochloride (BRH), a widely used mucolytic agent, has a specific inhibitory effect on TMPRSS2.[9] The half-maximal inhibitory concentration value of BRH toward TMPRSS2 is merely 0.75 μM.[9] BRH at a dosage that selectively inhibits TMPRSS2 and TMPRSS2-specific viral entry is regarded to be effective against SARS-CoV-2.[8] Therefore, the aim of this study was to conduct a clinical pilot study to test the study feasibility of BRH tablets for the treatment of moderate COVID-19 and to explore its clinical efficacy and safety.

METHODS

Study design and participants

This study was an open-label randomized controlled pilot study conducted at The Second Affiliated Hospital of Wenzhou Medical University, Zhejiang, China. The study was approved by the hospital's ethics committee (LCKY2020-07), and informed consent was obtained from all enrolled patients. This study was registered on Clinicaltrials.gov (No. NCT04273763).

The clinical diagnosis for type of COVID-19 was defined as mild, moderate, and severe (or critical) types, according to National Health Commission of People's Republic of China the Diagnosis and Treatment Plan (5th Edition) for the novel coronavirus disease. Mild type was diagnosed when clinical symptoms were mild and there were no pneumonia manifestations on chest radiograph. Moderate type was diagnosed with fever, respiratory, and other symptoms onset, and with pneumonia manifestations on chest radiograph. The severe (or critical) type was defined if any of the following is fulfilled: (1) respiratory distress ≥ 30 times/minute; (2) oxygen saturation ≤ 93% in resting state; (3) oxygenation index ≤ 300 mmHg (1 mmHg = 0.133 kPa); (4) respiratory failure occurs and requires mechanical ventilation; (5) shock appears; and (6) combined with other organ failures, intensive care unit monitoring and treatment are required.

Hospitalized patients with COVID-19 were included if they fulfilled the following criteria: (1) age ≥ 18 years but ≤ 80 years; (2) confirmed or clinically suspected mild or moderate coronavirus pneumonia (COVID-19), based on China's Novel Coronavirus Pneumonia Diagnosis and Treatment Plan (Provisional 5th Edition); and (3) signed informed consent.

The exclusion criteria were as follows: (1) alanine aminotransferase ≥ 5 × the upper limit of normal (ULN), total bilirubin level ≥ 3× ULN, or creatinine ≥ 1.5 × ULN; (2) severe liver disease; (3) severe or critical cases; (4) history of severe gastrointestinal diseases, such as gastric ulcers or bleeding; (5) lactose intolerance; (6) allergic to BRH or ingredients, including starch, lactose, and magnesium stearate; and (7) pregnant or breastfeeding women.

Patients meeting the following criteria were withdrawn from the study: (1) progression to severe or critical status; (2) development of dyspnea, shock, or other organ dysfunction and requirement of mechanical ventilation or intensive care unit admission; (3) the patient requested to be withdrawn; and (4) development of complications or serious adverse events (AEs), as assessed by the investigator.

Procedures

The patients were randomized based on the Interactive Web Response System. All patients were divided into the treatment group (BRH group) or the control group (control group) at a 2:1 ratio. All participants were treated with antiviral drugs, including arbidol hydrochloride granules (0.1 g–0.2 g t.i.d.) and recombinant human interferon α2b spray (0.083 mL t.i.d.), on the doctors' discretion according to China's Novel Coronavirus Pneumonia Diagnosis and Treatment Plan.

Patients in the treatment group received BRH tablets (32 mg t.i.d.) after meals for 14 consecutive days. Treatment was discontinued once the patient met the discharge criteria. The BRH tablets were manufactured by Wanbangde Pharmaceutical Group of China (Lot No. BYSXPM190802).

The dosage of BRH tablets was evaluated by the following calculation: it was assumed that the effective target (lung tissue) concentration of Bromhexine was 279 ng/mL, which was equal to half-maximal inhibitory concentration 0.75 μM[9] (the inhibition of Bromhexine on TMPRSS2 protease) multiplied by the molecular weight of Bromhexine (373 g/mol). The concentration of lung tissue was 2.4–5.9 times of the plasma concentration.[10] Therefore, the effective plasma concentration was estimated as 49–116 ng/mL. Because the pharmacokinetic parameters of BRH were proportional to an oral dose of 8–32 mg, we estimated the peak plasma concentration (C_{max}) of 32 mg BRH tablets, which was 90 ng/mL, according to C_{max} = 22.50 ± 7.50 μg/L of 8 mg BRH.[11]

At baseline, the demographic data, including age, sex, comorbidities, height, and body weight, were collected. The clinical characteristics, including vital signs and laboratory results, were recorded. Chest computed tomography (CT) images and SARS-CoV-2 nucleic acid testing were performed.

Outcomes

The study objective was to evaluate the efficacy and safety of BRH at a dose of 32 mg three times per day in patients with moderate COVID-19. The primary and secondary outcomes were assessed during the study period of 14 days.

The primary end points were the time to clinical recovery and the deterioration rate after initiation of medications. Clinical recovery was defined as clinical symptoms (fever and respiratory symptoms) returning to normal over 48 hours. Disease deterioration was defined as the presence of respiratory distress, respiratory rate ≥ 30 times/minute, oxygen saturation ≤ 93% in the resting state, and oxygenation index ≤ 300 mmHg.

The secondary outcomes assessed the virologic clearance during the study period (SARS-CoV-2-negative conversion within 20 days, rate of SARS-CoV-2-negative conversion), clinical follow-up (clinical remission rate, time to fever remission, rate of significant improvement in chest CT, percentage of patients requiring oxygen therapy, and discharge rate within 20 days), and the occurrence of side effects. Deteriorated patients who progressed to severe or critical condition were withdrawn from the study.

Chest CT was blindly interpreted at the baseline (7 days before randomization) and after randomization (7 days ± 1 day) by two experienced radiologists. A semiquantitative scoring system was used to quantitatively assess the pulmonary improvement, and the cases were divided into the following five categories: no improvement (< 10% absorption), mild improvement (10–30% absorption), improvement (30–60% absorption), remarkable improvement (60–90% absorption), and complete improvement (> 90% absorption).

All AEs reported during the study were recorded and graded according to the Common Terminology Criteria for Adverse Events, version 5.0. Assessments of laboratory parameters, physical condition, chest images, and nucleic acid test results were performed at baseline, during the study period, and at the 3-week follow-up. Assessments were also conducted at the end of the study period or the time of withdrawal, as appropriate.

Sample size

The sample size of this study was estimated using a two-sided one-sample *t*-test. According to the mean duration of recovery (18.7 days, SD = 7.5) among the most recent 30 cured patients with COVID-19 in the Second Affiliated Hospital and Yuying Children's Hospital of Wenzhou Medical University, given 80% power and type I error of 0.05, the mean duration of recovery was assumed to be shortened by 5 days, 2.5 days, and 1 day after treatment of BRH. Using PASS 15, the sample size was estimated to 16, 34, and 54 patients in total, accordingly. Considering an expected dropout rate of 20%, the sample size should attain 20, 43, and 68 patients for 3 sections.

Statistical analysis

In this study, demographic and baseline characteristics as well as efficacy and safety measurements were summarized using descriptive statistics. Continuous variables were summarized as medians and interquartile ranges, whereas categorical variables were expressed as the counts and percentages of patients in each category. No imputation was made for missing data. The Kruskal–Wallis rank sum test was used to determine the significance among the continuous variables, and Fisher's Exact test or the χ^2 test was used to determine the association among categorical data. All statistical tests were two-sided, and a *P* value of < 0.05 was considered statistically significant. All analyses were performed with R software (version 3.6.3; www.r-project.org).

RESULTS

Demographics and clinical characteristics

Of the 23 patients with moderate COVID-19, 18 patients met the inclusion criteria and were enrolled in this study (**Figure 1**). The number of patients finally included was less than expected due to the successful containment of disease in China. Of these 18 patients, 12 patients received BRH and 6 were in the control group. A total of 9 patients, 8 from the BRH group and 1 from the control group, had treatment duration of < 14 days because of early cessation with disease recovery. None of the 18 patients withdrew from the study.

The baseline demographics and clinical characteristics are presented in **Table 1**. Overall, 14 (77.8%) patients were men, with a median age of 52 years. No significant difference was observed between the BRH and the control groups with regard to age, sex, body mass index, comorbidities, duration of treatment, other medications, and laboratory results. All patients received antiviral drugs, including arbidol hydrochloride granules and recombinant human interferon α2b spray. The results of the baseline routine blood test, blood gas analysis, and biochemical tests, including blood glucose levels as well as liver and kidney function, did not differ between groups (**Table 1**).

Efficacy

There were no significant differences in the primary and secondary outcomes between the BRH group and the control group. The median (interquartile) time from onset to recovery for all patients was 15.0 days (13.0–22.0 days). All patients in both groups achieved clinical remission and negative SARS-CoV-2 results. The overall time to fever remission was 11.0 days (9.0–12.0 days), with 10.5 days (9.3–11.0 days) for the BRH group and 11.5 days(9.5–12.0 days)

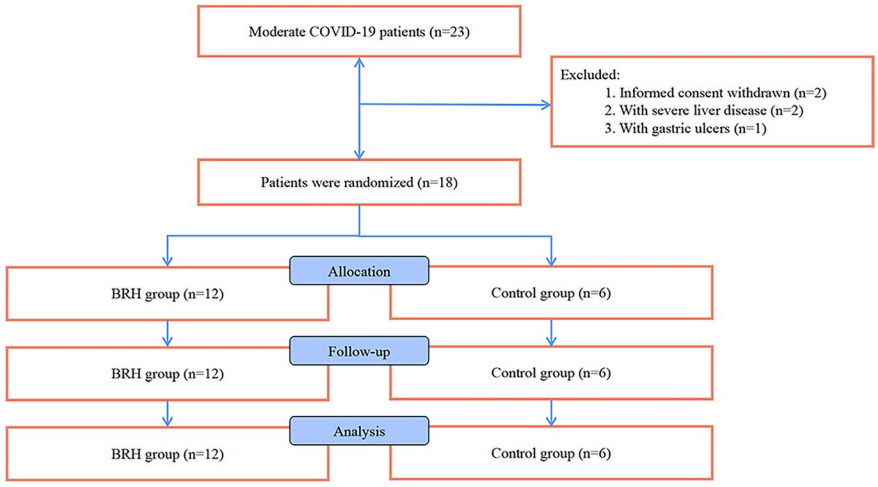

Figure 1 Consort diagram of the study. BRH, bromhexine hydrochloride; COVID-19, coronavirus disease 2019.

Table 1 Demographics and clinical characteristics of the study population

Parameters	BRH group (*n* = 12)	Control group (*n* = 6)
Age, years [IQR]	53 [50–62]	47 [32–51]
Sex, n (%)		
Female	2 (16.7)	2 (33.3)
Male	10 (83.3)	4 (66.7)
Height, cm – median [IQR]	168 [165–170]	163.50 [159–173]
Weight, kg – median [IQR]	61.5 [57.8–73.5]	70.5 [64.5–75.0]
Body mass index, kg/m^2 – median [IQR]	23.2 [21.2–24.8]	24.67 [24.6–25.0]
Comorbidities – *n* (%)		
Hypertension	4 (33.3)	2 (33.3)
Gout	1 (8.3)	1 (16.7)
Diabetes	2 (16.7)	0 (0)
Thyroid nodules	1 (8.3)	0 (0)
Hearing loss	1 (8.3)	0 (0)
Hyperthyroidism	1 (8.3)	0 (0)
Duration of treatment, days – mean ± SD	12.2 ± 2.0	13.5 ± 1.2
Medications – *n* (%)		
Glucocorticoids	2 (16.7)	2 (33.3)
Antiviral drugs	12 (100)	6 (100)
Interferon	10 (83.3)	4 (66.7)
Expectorants	10 (83.3)	6 (100)
Traditional Chinese medicine	11 (91.7)	5 (83.3)
Others	12 (100)	6 (100)
Laboratory results		
RBC, *10^{12}/L	4.4 [4.1–4.7]	4.3 [4.1–4.4]
WBC	5.6 [5.2–6.3]	5.4 [4.7–6.4]
< 4*10^9/L – *n* (%)	1 (8.3)	1 (16.7)
PLT	259.5 [175.8–296.5]	304.5 [231.8–321.0]
> 100*10^9/L – *n* (%)	12 (100.0)	6 (100.0)
NET, % – median [IQR]	0.7 [0.6–0.7]	0.7 [0.6–0.7]
LM, % – median [IQR]	0.3 [0.2–0.3]	0.2 [0.2–0.3]
EO, % – median [IQR]	0.0 [0.0–0.0]	0.0 [0.00–0.0]
BA, % – median [IQR]	0.0 [0.0–0.0]	0.0 [0.0–0.0]
CRP, mg/L – median [IQR]	8.5 [3.4–21.9]	5.8 [1.4–40.2]
> 8 mg/L – *n* (%)	6 (50.0)	3 (50.0)
ALT, IU/L – median [IQR]	29.0 [23.5–35.5]	34.0 [31.5–74.0]
> 69 IU/L – *n* (%)	0 (0.0)	0 (0.0)
TBIL, μmol/L – median [IQR]	10.3 [8.5–13.0]	7.9 [6.75–10.7]
≤ 21 μmol/L – *n* (%)	12 (100.0)	6 (100.0)
BUN, mmol/L – median [IQR]	4.2 [3.5–4.6]	3.8 [3.6–4.1]
> 8.2 mmol/L – *n* (%)	12 (100.0)	6 (100.0)
Glucose, mmol/L – median [IQR]	5.1 [4.7–5.4]	5.0 [4.7–6.7]
ESR, mm/hour – median [IQR]	0.3 [0.1–0.4]	0.2 [0.2–0.3]

ALT, alanine aminotransferase; BA, basophil; BRH, bromhexine hydrochloride; BUN, blood urea nitrogen; Cr, creatine; CRP, C-reactive protein; EO, eosinophil; ESR, erythrocyte sedimentation rate; IQR, interquartile range; LM, lymphocyte; NET, neutrophil; PLT, platelet; RBC, red blood cell; TBIL, total bilirubin; WBC, white blood cell.

for the control group (P = 0.70). No patient in either group deteriorated during the observation period. The BRH group had a greater rate of remarkable/complete improvement by CT imaging (66.7% vs. 33.3%, P = 0.62), a lower percentage of patients requiring oxygen therapy (16.7% vs. 33.3%, P = 0.11), and higher discharge rate within 20 days (83.3% vs. 33.3%, P = 0.12; **Table 2**). The chest CT images before and after randomization for all cases in both groups are displayed in **Figures 2 and 3**. All the 18 patients in this study received concomitant medication, and the specific drugs are listed in **Table 3**.

Adverse events

For the overall study cohort, a total of 13 patients (72.2%) experienced AEs during the study period, including liver injury (38.9%), gingivitis (11.1%), insomnia (11.1%), headache (5.6%), and elevated white blood cells in urine (5.6%). However, all AEs were graded as 1 (headache and elevated white blood cells in urine) or 2 (insomnia, gingivitis, and liver dysfunction), and no patient suspended the treatment because of severe AEs. The most commonly experienced AE was liver injury, which happened in 3 patients (25.0%) and 4 patients (66.7%) in the BRH group and the control group, respectively. No significant difference of all kinds of AEs was observed between the BRH group and the control group. Of note, 9 of 13 of the AEs were defined as not related, and 4 AEs were defined as possibly not related to the treatment. At the end of the 14-day study observation period, 6 patients were fully recovered, 1 was in ongoing recovery, and 6 were still unrelieved (**Table 4**).

Follow-up

Follow-up was conducted 1 week following the end of treatment. None of the subjects had any symptoms, such as fever and cough. Laboratory measurements, including routine blood, C-reactive protein, and biochemical tests, were reassessed, and the results showed that the liver function of two patients in the control group was still abnormal, indicating an incomplete recovery of AEs. Re-examination of the viral nucleic acids showed negative results for all patients.

DISCUSSION

To the best of our knowledge, this pilot study is the first to assess the efficacy and safety of BRH for the treatment of patients with COVID-19. The primary end points and the secondary outcomes did not reach significant difference between the two groups. However, the proportion of remarkable/complete improvement in patients who had chest CTs and the discharge rate within 20 days in the BRH group were 2-fold higher than the control group in value. In addition, the rate of hepatic injury in the BRH group was twofold lower than the control group. These results may suggest that BRH tablets at a dose of 32 mg t.i.d. help to alleviate hepatic or lung injury induced by SARS-CoV-2. No Bromhexine-related adverse drug reactions were found in this study, which indicated 32 mg t.i.d. oral BRH could be safe. A further definitive large-scale clinical trial is feasible and necessary to evaluate its effects and safety.

The lungs are the major target of the virus causing COVID-19.[12] The chest CT imaging results displayed that

Table 2 Efficacy

	BRH group (*n* = 12)	Control group (*n* = 6)	*P* value
Primary outcome			
Time to recovery, days – median [IQR]	16.0 [14.5–20.5]	15.5 [13.5–25.0]	1
Secondary outcome			
Clinical remission rate – *n* (%)	12 (100)	6 (100)	–
Time to fever remission, days – median [IQR]	10.5 [9.3–11.0]	11.5 [9.5–12.0]	0.70
SARS-CoV-2-negative conversion within 20 days – *n* (%)	11 (91.7)	6 (100.0)	–
Rate of SARS-CoV-2-negative conversion – *n* (%)	12 (100)	6 (100)	–
Remarkable/complete improvement in chest CT – *n* (%)	8 (66.7)	2 (33.3)	0.62
Percentage of patients requiring oxygen therapy – *n* (%)	2 (16.7)	2 (33.3)	0.11
Discharge rate within 20 days – *n* (%)	10 (83.3)	2 (33.3)	0.12

BRH, bromhexine hydrochloride; CT, computed tomography; IQR, interquartile range; SARS-CoV-2, severe acute respiratory syndrome-coronavirus 2.

the pneumonia was predominantly bilateral (72.9%).[13] COVID-19 infection is enhanced by TMPRSS2.[14] BRH inhibits TMPRSS2 and may therefore have a protective effect against COVID-19-induced acute lung injury. In this pilot study, patients receiving BRH were less likely to require oxygen therapy compared with those in the control group, although no significant difference was found. This result indicates that BRH might improve lung ventilation through its inhibitory effect on TMPRSS2, and this concept has been confirmed in previous animal studies. In respiratory influenza virus-infected mice, TMPRSS2 was a host cell factor essential for viral spread, and knockout of TMPRSS2 expression inhibited viral replication.[15–17] The roles of TMPRSS2 during SARS-related and MERS-related coronavirus infections also have been identified recently.[18]

BRH is a frequently used medication for the treatment of respiratory diseases. The dose and duration of BRH applied in the current study (32 mg 3 times per day for 14 consecutive days) was established based on the European drug instructions and the results from preliminary studies.[9,19]

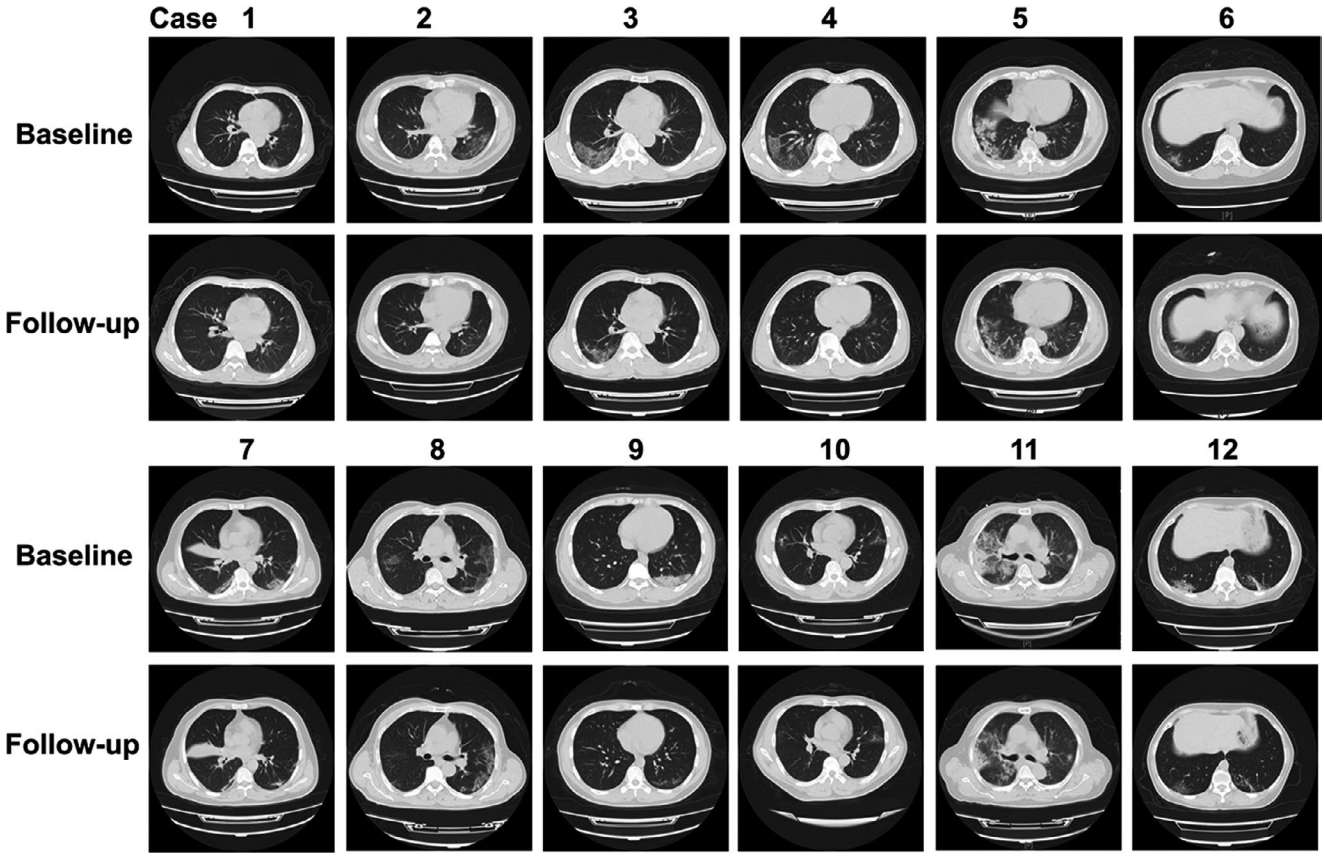

Figure 2 Chest computed tomography images before and after randomization (day 0) in the bromhexine hydrochloride group (*n* = 12). *Baseline: 7 days before the randomization (median [range]: –1.5 [–4 to –1] days); follow-up: 7 days ± 1 day after randomization (median [range]: 6 [6 to 8] days).

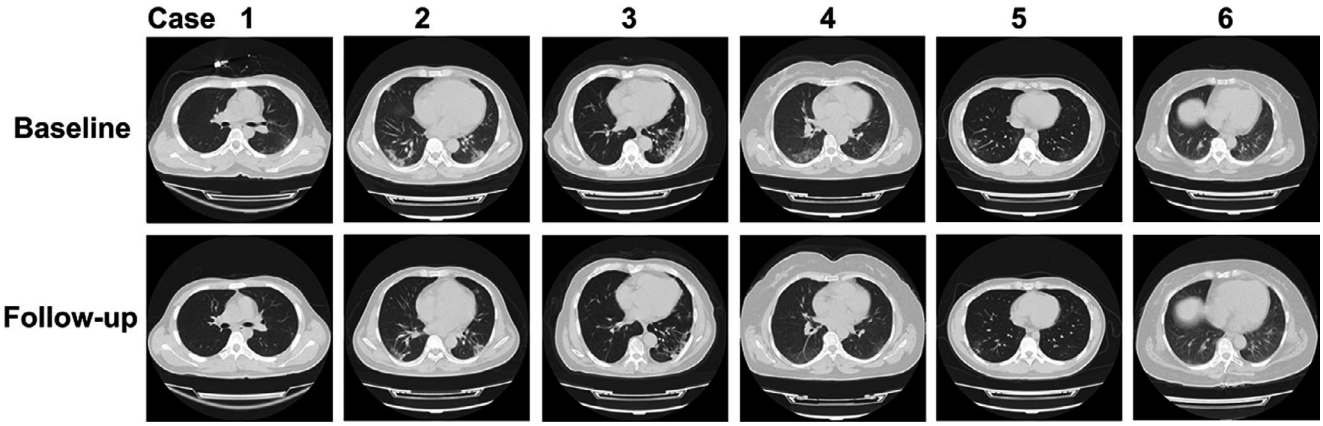

Figure 3 Chest computed tomography images before and after randomization (day 0) in the control group (n = 6). **Baseline: 7 days before the randomization (median [range]: –1 [–2 to –1] days); follow-up: 7 days ± 1 day after randomization (median [range]: 6 [6 to 8] days).

As stated in the drug instructions, a dose of BRH at 96 mg per day is the maximum dose for adults, which ensures a strong inhibition of TMPRSS2. Previously reported side effects include mild gastrointestinal disturbances and allergic reactions, which are rare. In the current study, however, gastrointestinal AEs were not common, but mild or moderate AEs including insomnia, gingivitis, headache, and an elevated white blood cell count in urine were recorded; these AEs were mostly determined as not related to BRH.

Recent research demonstrated that the clinical characteristics of COVID-19 in China has underlying impact to hepatic injury on mild and severe cases,[20–22] which were reflected by the increase of alanine transaminase and aspartate transaminase levels.[23,24] It is consistent to our findings, where applying the BRH seemed to prevent the chance of suffering hepatic injury, compared with the control group. Although the results did not reach statistical significance due to the limited sample size, it could still provide a signal for future studies that BRH has potential beneficial effect to patients with COVID-19 through antiviral mechanisms. As expected, this clinical study is the first preliminary research exploring the efficacy and safety of BRH tablets for the treatment of COVID-19. Nevertheless, there are several limitations that must be addressed. First, the open label nature is a limitation, because the CT images was read blindly whereas the other end points could be affected by the caregiver's decision of drug allocation, such as the use of oxygen therapy. Second, an initial loading dose might enhance the inhibition of the virus. However, we did not design the loading dose because of limited evidence.

In conclusion, our results demonstrate that BRH tablets may potentially have a beneficial effect in patients with COVID-19, especially for those with lung or hepatic injury. A further definitive large-scale clinical trial is feasible and necessary.

Table 3 Concomitant medication

	BRH group (n = 12)	Control group (n = 6)
Corticosteroids[a] – n (%)	2 (16.7%)	2 (33.3%)
Antiviral drugs[b] – n (%)	12 (100.0%)	6 (100.0%)
Interferon[c] – n (%)	10 (83.3%)	4 (66.7%)
Antitussive therapy[d] – n (%)	10 (83.3%)	6 (100.0%)
Chinese herbal medicines[e] – n (%)	11 (91.7%)	5 (83.3%)
Other medication[f] – n (%)	12 (100.0%)	6 (100.0%)

BRH, bromhexine hydrochloride.
[a]The used corticosteroids included methylprednisolone and budesonide suspension for inhalation.
[b]The antiviral drugs included arbidol hydrochloride granules and hydroxychloroquine sulfate tablets.
[c]Recombinant human interferon α2b spray was applied as interferon.
[d]The interferon included erdosteine capsules and acetylcysteine tablets.
[e]Chinese herbal medicine followed Zhinan - the Chinese herbal medication section according to the different severity of patients.
[f]Other medicines used included vitamin C tablets, potassium chloride sustained-release tablets.

Table 4 Adverse events

	BRH group (n = 12)	Control group (n = 6)
Hepatic injury[a] – n (%)	3 (25.0)	4 (66.7)
Grade 1 – n (%)	3 (100)	3 (75)
Grade 2 – n (%)	0 (0)	1 (25)
Insomnia – n (%)	1 (8.3)	1 (16.7)
Gingivitis – n (%)	2 (16.7)	0 (0)
Headache – n (%)	0 (0)	1 (16.7)
Elevated WBCs in urine[b] – n (%)	0 (0)	1 (16.7)
Grade 1 – n (%)	0 (0)	1 (100)

BRH, bromhexine hydrochloride; WBC, White blood cell.
The severity of the hepatic injury and elevated WBCs in urine are presented by grades according to Common Terminology Criteria for Adverse Events version 4.0 (CTCAE).
[a]A total of seven patients was diagnosed as having liver injury. In the BRH group, three patients suffered increase in alanine aminotransferase (ALT; the upper bound of normal range is 69 IU/L), where the absolute values were 127 IU/L, 88 IU/L, and 141 IU/L accordingly. In the control group, three patients suffered increase in ALT, where the absolute values were 89 IU/L, 237 IU/L, and 95 IU/L accordingly; and one patient had an increase from the upper bound of normal range (46 IU/L) in aspartate transaminase to 77 IU/L.
[b]Patient #16 reached a high level of WBC in urine at 71.46/hp, where the normal range is 0/hp to 3/hp.

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Conflict of Interest. The authors declared no competing interests for this work.

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