Bromhexine Hydrochloride Prophylaxis of COVID-19 for Medical Personnel:

A Randomized Open-Label Study

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NOTE: This preprint reports new research that has not been certified by peer review and should not be used to guide clinical practice.
ABSTRACT

Background: Bromhexine hydrochloride has been suggested as a TMPRSS2 protease blocker that precludes the penetration of the SARS-CoV-2 into cells. We aimed to assess the preventive potential of regular bromhexine hydrochloride intake for COVID-19 risk reduction in medical staff actively involved in the evaluation and treatment of patients with confirmed or suspected SARS-CoV-2 infection.

Methods: In a single-center randomized open-label study medical staff managing patients with suspected and confirmed COVID-19 were enrolled and followed-up for 8 weeks. The study began at the initiation of COVID-19 management in the clinic. We enrolled 50 participants without a history of SARS-CoV-2 infection: 25 were assigned to bromhexine hydrochloride treatment (8 mg 3 times per day), and 25 were controls. The composite primary endpoint was a positive nasopharyngeal swab polymerase chain reaction (PCR) test to SARS-CoV-2 or the signs of clinical infection within 28 days and at week 8. Secondary endpoints included the symptomatic infection rate and positive nasopharyngeal swab (PCR) tests.

Results: The rate of the combined primary endpoint did not differ significantly between the active treatment group (2/25 [8%]) and control group (7/25 [28%]); P = 0.07. A fewer number of participants developed symptomatic infection (confirmed COVID-19) in the treatment group compared to controls (0/25 vs 5/25; P = 0.02).

Conclusion: Bromhexine hydrochloride prophylaxis was associated with a reduced rate of symptomatic COVID-19. However, the prophylactic treatment was not associated with a lower combined primary endpoint rate, a positive swab PCR test and/or COVID-19. (ClinicalTrials.gov number, NCT04405999)

Keywords: COVID-19; SARS-CoV-2; prophylaxis; bromhexine hydrochloride; medical staff
INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of respiratory disease, COVID-19.\(^1\) The fast SARS-CoV-2 distribution resulted in the pandemic, and the number of infected subjects keeps growing.\(^2\) Current strategies for threat reduction include non-pharmacologic prophylactic measures, such as social distancing, masks and hand sanitizers,\(^2\) as well as antiviral and anti-cytokine agents.\(^3, 4\) In recent trials, pharmacologic preventive drugs, such as anti-malaria and antibiotic medications, have failed to prevent infection, while effective prevention is urgently required.\(^5, 6\)

The SARS-CoV has been shown to utilize endosomal cysteine proteases cathepsin B and L (CatB/L) and the transmembrane protease serine type 2 (TMPRSS2) for binding of the S-protein.\(^7\) It has been suggested that the SARS-CoV-2 penetrates alveolar cells using the same mechanism.\(^8\) The viral S-protein is attached to angiotensin-converting enzyme 2 (ACE2) of pneumocytes. Then it adheres to TMPRSS2 in S1 and S2-subunits,\(^2, 7, 8, 9, 10, 11, 12\) providing the possibility for the virus to enter the cell. According to this mechanistic perspective, the protease TMPRSS2 can be targeted for preventing the penetration of the SARS-CoV-2 into cells.\(^7, 13, 14\)

Two medications that have been shown to block the TMPRSS2 in vitro, camostat mesylate and bromhexine hydrochloride; both block the ability of the protease to activate a zymogen precursor of tissue plasminogen activator. Importantly, previous studies have demonstrated that TMPRSS2 is blocked by a significantly lower concentration of bromhexine hydrochloride than required to inactivate other proteases in the cell culture.\(^8, 13\)

Therefore, bromhexine hydrochloride is thought to prevent the penetration of the SARS-CoV-2 into cells. If this would be confirmed in clinical settings, the drug might be used as a prophylactic medication in subjects with a high risk of infection, including medical staff.

We aimed to assess the preventive potential of regular bromhexine hydrochloride intake for reduction of the risk of COVID-19 in medical staff actively involved in the evaluation and treatment of patients with confirmed or suspected SARS-CoV-2 infection.
METHODS

Study design

We conducted a single-centre randomized, open-label study to evaluate 8-week prophylaxis with bromhexine hydrochloride during the period of regular exposure to Covid-19 (ClinicalTrials.gov number, NCT04405999). We randomly assigned health care providers in a 1:1 ratio either to bromhexine hydrochloride or to a control group.

Study enrollment started on May 13, 2020, when the Almazov Centre began the COVID-19 treatment program, and lasted two weeks while new medical staff was involved in infection management. The study terminated on August 9, 2020 due to the termination of infected patients’ admission to the hospital. The study was approved by the Almazov National Medical Research Centre ethics committee (protocol #0105-20-02С from May 12, 2020) and conducted in accordance with the Declaration of Helsinki.

Participants

We included participants over 18 years who were employed within the emergency departments where patients with confirmed/suspected COVID-19 were admitted, intensive care units, and clinical departments. All participants were obliged to wear personal protective equipment (PPE) as prescribed by WHO recommendations and local instructions. The PPE included respirators class FFP2 or FFP3, full skin covering, and protective eyeglasses. Blood tests for SARS-CoV-2 antibodies were taken at baseline (serologic qualitative assessment of IgM and IgG, ELISA-BEST, Vektor-Best, Novosibirsk, Russia).

Participants were excluded if they had symptoms of respiratory infection within the last 2 months or a history of COVID-19, or a positive nasopharyngeal swab polymerase chain reaction (PCR) test to SARS-CoV-2 before the day of randomization, a confirmed direct contact to a subject positive for SARS-CoV-2 within the last 14 days or had a positive serologic test (either IgM or IgG). The additional exclusion criteria were a history of gastric ulcer or other contraindications to bromhexine hydrochloride, pregnancy, and any severe chronic disease.
Setting
Recruitment was performed via the institution’s electronic communication systems and via personal contacts with healthcare providers. The participants provided a scanned copy of signed consent. We performed follow-up phone calls and sent e-mail surveys on days 7, 14, 21, 28, and at week 8. A survey asked about any follow-up testing, illness, or hospitalizations. Participants who did not respond to follow-up surveys were actively contacted by text messages, and telephone calls.

Interventions
The study statisticians adjusted a software for randomization using the minimization method weighing the following factors: age (categories: 18-45, 45-64, 65-74, 75-79 years), the type of anticipated contacts with SARS-CoV-2 (confirmed SARS-CoV-2 infection cases within the “red” zone, working closely with colleagues who had proven contacts with SARS-CoV-2 patients). A study coordinator sequentially assigned participants. The assignments were open to investigators and participants.

Bromhexine hydrochloride was dispensed and shipped to participants by the study coordinator. The dosing regimen for bromhexine hydrochloride was 8 mg 3 times per day starting from the day before the first contact with COVID-19 (first day of work in an infection department). The dosing regimen was based on previous reports.8, 15

The control group was not prescribed any additional drug or placebo.

Outcomes
The composite primary endpoint was prespecified as a positive nasopharyngeal swab SARS-CoV-2 PCR test or the presence of clinical symptoms of infection within 28 days and during the weeks 5 - 8 after the last contact to subjects with COVID-19. COVID-19–related symptoms were assessed based on the U.S. Council for State and Territorial Epidemiologists Criteria for confirmed cases (positive nasopharyngeal swab PCR test), probable cases (the presence of cough, shortness of breath, or difficult breathing, or the presence of two or more symptoms of
fever, chills, rigors, myalgia, headache, sore throat, and new olfactory and taste disorders), and possible cases (the presence of one or more compatible symptoms, which could include diarrhea). Secondary endpoints included: time from the first contact with a person with suspected/confirmed COVID-19 to the appearance of respiratory infection symptoms; the number of days before first positive SARS-CoV-2 test; the number of asymptomatic participants with a positive nasopharyngeal swab test; the number of mild, moderate and severe COVID-19 cases; adverse events possibly related to bromhexine hydrochloride.

According to the study protocol, nasopharyngeal swab SARS-CoV-2 PCR tests were performed every 7 days, and additional tests were performed in a case of infection. The PCR was performed by qualitative analysis (DNA-technology, Moscow, Russia).

Outcomes were measured at 7, 14, 28 days after study enrollment, and then at 8 weeks. Outcome data including PCR, COVID-19–related symptoms, adherence to the study drug and side effects were collected through participants’ reports.

Sample size

Considering the high incidence of COVID-19 in front-line healthcare workers (>20%), and a trend towards a higher prevalence of COVID-19 positive subjects among medical staff reported in some Russian hospitals, we had anticipated that a combined primary endpoint would develop in 20 to 50% of participants. We theoretically assumed that prophylactic administration of bromhexine hydrochloride would decrease the primary outcome by 30%. Using Fisher’s exact test with a two-sided alpha of 0.05 and 80% power, we estimated that 24 subjects would need to be enrolled in each group.

Statistical analysis

The primary and secondary endpoints were assessed with the Mann-Whitney U test. Statistical analysis was performed using STATISTICA software 13.0 (StatSoft, USA), according to the
intention-to-treat principle, with a P-value suggesting a statistically significant difference when
<0.05.

RESULTS

Participants

One hundred and fifty healthcare providers were initially invited, and 62 positive
responses were obtained. Among 62 subjects who agreed to participate, 50 persons fulfilled the
inclusion criteria (80.6%) (Figure 1).

The demographic and clinical characteristics of the participants are presented in Table 1.
Three (6%) of the participants were hypertensive, 2 participants had hypercholesterolemia.
Physicians comprised 88% of the population, and nurses 12%. The median time spent working
with the exposure to patients with confirmed/suspected COVID-19 was 7.5 hours per week.
Overall, 80% (40 out of 50) participants had a very high risk exposure (contacting with
aerosols from intubated COVID-19 patients) and 20% (10 out of 50) - a relatively lower risk
exposure (contacting with suspected/confirmed COVID-19 patients). All the participants had a
6-hour duration of the works with infection followed by breaches, used FFE respirators,
eyeglasses and skin coverings, and had direct contacts with the staff outside the “red zones”
without PPE.

Seven (14%) participants used vitamins D, C as general prevention of infection: 3
participants in the bromhexine group (3/25, 12%) and 4 participants in the control group (4/25,
16%; P>0.05). None of the participants reported any unprotected contact with COVID-19
patients outside the hospital.

There were no subject losses nor dropouts after randomization.

Primary endpoint

All participants completed all scheduled surveys. The primary end-point, a positive swab test
and/or infection symptoms, was documented in 9/50 (18%) participants: in 8 - by day 28, and in
1 - by week 8 (Table 2). The primary outcome rate did not differ significantly between the
treatment and control groups (2/25 (8%) vs 7/25 (28%), respectively) (P=0.07). Two hospitalizations for COVID-19 pneumonia were reported in the control group (2/25, 8%), and none – in the bromhexine group (0/25, P=0.16). No severe cases with intensive care unit admissions or deaths occurred.

**Secondary endpoints**

There was no difference between the groups in the time since the first contact with a person with suspected/confirmed COVID-19 to the appearance of respiratory infection clinical symptoms or an asymptomatic positive PCR test. The first positive SARS-CoV-2 PCR tests in the treatment group appeared at 2 and 3 weeks, and in the control groups the positive tests were obtained at 2, 3, 4 weeks, and during weeks 5-8 (Table 2). Both SARS-CoV-2 PCR positive participants in the bromhexine treatment group continued the intake of bromhexine hydrochloride until two consecutive negative tests.

Among 9 persons with a positive SARS-CoV-2 PCR test, 4 were asymptomatic (2/25 – in the treatment group, and 2/25 – in the control group; P>0.05). Five participants from the control group had infection symptoms: only respiratory virus infection symptoms - in 3 persons; pneumonia – in 2. All participants with respiratory symptoms were positive for SARC-Cov-2 and were compatible with confirmed COVID-19 per the U.S. case definition.

Taking together, symptomatic COVID-19 was diagnosed in the control group only: no cases in the treatment group (0/25) vs 5/25 cases in the control group, P=0.02.

**Adherence and safety**

Missed days of bromhexine intake were reported by 4 participants, the duration of termination treatment was 1-4 days. One participant who missed two days of the drug intake had a positive SARS-CoV-2 PCR test (asymptomatic case). It was impossible to assess whether missed drug intake and infection occurred on the same day.

Two participants reported adverse events possibly related to bromhexine hydrochloride treatment: a short period of hot flashes at the treatment initiation and transient cough. No cases
of treatment termination or interruption due to adverse events were reported. There were no adverse events in the control group. No statistically significant difference was found in the rates of adverse events between the groups.

**DISCUSSION**

The present study shows several important facts. The primary combined endpoint, the rate of positive nasopharyngeal swab PCR tests to SARS-CoV-2 and/or symptomatic COVID-19, was similar in both groups. However, there was a trend towards a lower rate of the positive swab PCR test in the bromhexine hydrochloride treatment group. Importantly, the rate of clinically significant SARS-CoV-2 infection was statistically lower in the treatment group (0/25 participants) compared to the control group (5/25 participants).

It should be acknowledged that the risk of symptomatic and severe COVID-19 depends on age and co-morbidity. Our study population was generally younger and healthier than in the majority of COVID-19 studies. However, in a recent study of post-exposure COVID-19 prophylaxis by hydroxychloroquine, the mean age and average health status of the participants was comparable. Thus, for prevention efficacy assessment, our group can be informative. Moreover, the fact, that the safe and cheap drug showed the risk reduction of symptomatic infection can be important for future larger studies and practical use.

We used a thorough approach for detecting asymptomatic cases performing nasopharyngeal swab PCR tests every week of follow-up using the approved methodology. Two factors increase the value of our study: good adherence, which is significantly higher, compared to generally published prevention studies, and the high survey response rate. This can be explained by the high motivation and high awareness of the medical staff.

It should be mentioned that a small number of participants used additional medications, including ACE2 inhibitors/ARA, or vitamin C, D. No statistical difference in the use of additional pharmacological treatment was documented between groups, and the number of subjects with additional medications was very small, thus we can conclude that this aspect had
no impact on the study results. It is plausible that the results may be more robust with a placebo-controlled group. Due to the organizational difficulties during a limited period for study preparation, the provision with placebo was impossible.

Although all healthcare workers had been instructed to wear protective masks and medical gloves outside the hospital, we cannot exclude that some of the participants might have been infected outside the hospital or during direct communication within the community during rest and meals. However, if bromhexine hydrochloride prevention is effective, it should be effective anywhere.

It is generally believed that the risk of infection is lower when the staff uses PPE as appropriate. Thus, further reduction of clinically significant cases can be an argument of implementation of this approach into clinical practice, even before obtaining better evidence.

In a recently published randomized study of bromhexine hydrochloride treatment in patients hospitalized with COVID-19, the authors have shown that the early administration of oral bromhexine reduces the intensive care unit transfer, intubation, and mortality rate. In another small open-label randomized study, where 18 patients with COVID-19 were included, bromhexine hydrochloride treatment has been shown associated with a trend towards the improvement in the need for oxygen therapy, and discharge rate within 20 days. Although hypothesis regarding the positive effects of bromhexine on viral penetration into the cells in non-infected subjects differs from the background presented in two latter studies, all these investigations taken together support the assumption of positive effects of the drug against the SARS-CoV-2.

Whether prophylactic use of bromhexine hydrochloride against SARS-CoV-2 infection in the general population is effective, is a separate question that should be answered in larger-scale randomized trials.

Study limitations
The study sample size may appear limited, however, it was enough to demonstrate the significant difference in secondary outcome between the groups.

Another limitation is the lack of sequential serologic testing, which we considered less informative due to a very short study period.

CONCLUSIONS

In this randomized single-centre open-label study, bromhexine hydrochloride prophylactic treatment was associated with a reduction in the rate of symptomatic COVID-19 among medical personnel. However, the primary combined outcome, the rate of a positive nasopharyngeal swab PCR test and/or COVID-19, did not reach a statically significant difference.

This study suggests that bromhexine hydrochloride may offer clinical value when taken as a prophylactic treatment.

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AUTHOR CONTRIBUTIONS

Research idea: ENM, TAL, DS. Study design: ENM, TAL, AOK, EVSh. Data collection and management: ENM, TAL, ADV, DSL, EYuV. Data interpretation and analysis: ENM, TAL, ADV, DS, DSL, AOK, EVSh. Writing article draft: ENM, TAL, AOK. Critical review and approval of the article final version: all authors.

SUPPLEMENTS
The full study protocol is available in supplements in both, original Russian version, and translated English version.

**STUDY HIGHLIGHTS**

- Bromhexine hydrochloride is a TMPRSS2 protease blocker that is thought to preclude the penetration of the SARS-CoV-2 into cells;

- Prophylactic treatment with bromhexine hydrochloride reduces the rate of clinical infection among medical workers who manage patients with COVID-19
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Table 1. Demographic and clinical characteristics of study participants

|                                | Bromhexine treatment group | Control group | Overall | P      |
|--------------------------------|----------------------------|---------------|---------|--------|
| n                              | 25                         | 25            | 50      | 1.00   |
| Age, years                     | 41.7±6.9                   | 39.5±8.2      | 40.6±7.6| 0.43   |
| Sex, n (%) of males            | 11 (44%)                   | 10 (40%)      |         | 0.78   |
| BMI                            | 25.1±3.9                   | 23.9±4.1      | 24.6±4.0| 0.76   |
| Work within the “red zone”, n (%)| 14 (56%)                   | 11 (44%)      | 25 (50%)| 0.41   |
| Co-morbidity, n                | 2                          | 1             | 3       | 0.82   |
| ACEi2 inhibitors/ARA treatment, n| 1                          | 1             | 2       | 1.00   |
| Additional pharmacological drugs, n | Vitamin D/C                | 1             | 4       | 5      | 0.16   |
| Drug non-adherence             |                            |               |         |        |
| Missed doses of bromhexine, n  | 4                          | -             | -       |        |
| Number of missed bromhexine doses, Median [IQR] | 6 [5.25; 7.5] | - | - | |
| Time spent in the “red zone”, mean±SD; Median [IQR], hours | 64.1±69.5; 40 [2; 144] | 66.6±78.2; 20 [3; 160]; 66.1±72.6; 30.0 [2; 144] | 0.97   |
| Time spent in the hospital, hours | 145.1±44.5               | 143.2±40.6    | 144.2±42.2| 0.66   |
| Participants who worked in intensive care units, n | 6                          | 6             | 12      | 1.00   |
| Participants who worked in re-purposed infectious wards or COVID-19 admission departments, n | 12                         | 14            | 28      | 0.58   |
| Participants who worked in invasive cardiology/electrophysiology departments, n | 6                          | 4             | 10      | 0.49   |
| Adverse events, n              | 2                          | 0             | 2       | 0.16   |
| Positive SARS-CoV-2 PCR test, n| 2                          | 7             | 9       | 0.07   |
| Asymptomatic                   | 2                          | 2             | 4       | 1.00   |
| Symptomatic                    | 0                          | 5             | 5       | 0.02   |
| COVID-19 moderate, n           | 0                          | 3             | 3       | 0.08   |
| COVID-19 severe with hospitalization, n | 0                          | 2             | 2       | 0.16   |
n, number of participants; BMI, body mass index; ACEi2, angiotensin 2 converting enzyme inhibitors; ARA, angiotensine receptor antagonists; AD, standard deviation; IQR, interquartile range; PCR, polymerase chain reaction.
Table 2. Timeline of positive SARS-CoV-2 tests in both groups. P>0.05 for each period of time.

|                        | Days 1-7 | Days 8-14 | Days 15-21 | Days 22-28 | Weeks 5-8 |
|------------------------|----------|-----------|------------|------------|-----------|
| **Number of participants with a positive PCR test** |           |           |            |            |           |
| Treatment group        | 0        | 1         | 1          | 0          | 0         |
| Control group          | 0        | 2         | 3          | 1          | 1         |
| **Number of participants with clinical symptoms of respiratory infection** |           |           |            |            |           |
| Treatment group        | 0        | 0         | 0          | 0          | 0         |
| Control group          | 0        | 0         | 2          | 3          | 0         |
| **Total number of participants with an outcome** | 0        | 3         | 4          | 1          | 1         |
**Figure 1.** Screening and randomization.