Evaluation of the recovery rate and prevention of hospitalization among covid-19 outpatients: a randomized clinical trial comparing N-acetylcysteine with Bromhexine

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Abstract

Objectives: Due to the referral of COVID-19 patients to outpatient centers in the early stages, the aim of the present study is to compare the effect of N-acetylcysteine and Bromhexine on the recovery rate and prevention of hospitalization in outpatients with COVID-19

Methodology: This study was conducted from April 2022 to September 2022. First, PCR-confirmed COVID-19 patients were divided into tree groups, one of these groups received N-acetylcysteine while the other received bromhexine and One of these groups did not receive any medication. The patients were followed up on the seventh and fourteenth days of the disease in terms of the duration of changes in oxygen saturation and recovery. The hospitalization and death of the patients were also evaluated after one month.

Results: Out of 225 studied patients, oxygen saturation was increased by 1.33% in the third visit of the patients who received N-acetylcysteine compared to their first visit. This percentage was 1.19% in the patients who received bromhexine.29.77% of the patients were admitted to the hospital and 70.23% of them had no history of hospitalization within 14 day and their mortality rate was 9.33% in control group and it was zero in both groups of patients who received drug.

Conclusions: The results of this study showed that early initiation of Bromhexine and N-acetylcysteine can effectively reduce the hospitalization rate and mortality and shorten the duration of hospitalization.

Clinical trial code: IRCT20220302054167N1 and ethics code: IR.UMSHA.REC.1400.957

1. Introduction

Background: Since the emergence of the coronavirus infection in Wuhan, China, in December 2019, this virus has spread throughout the globe. Effective combat against this virus has become a global emergency. The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a single-stranded seropositive RNA virus [1] and one of the subspecies of the coronavirus family. This virous is the cause of Coronavirus disease -2019 (COVID-19). Its symptoms vary from mild ones (such as fever, muscle pain, weakness, and lethargy, cough, and loss of smell and taste) to severe cases with extensive lung involvement and acute respiratory distress syndrome leading to hospitalization, intubation, and even death [2]. COVID-19 has led to more than 5 million deaths, making medical staff, especially doctors and researchers seek efficient ways to treat, control, and even eradicate this disease. In this context, more effective treatment in the early stages can prevent the progression and deterioration of the physical conditions of the COVID-19 patients, while declining the rate of referrals and even hospitalizations and mortalities.

Objectives: The patient's symptoms usually appear a few days after exposure to the infected person. In some people with underlying diseases. COVID-19 symptoms can intensify in a few days, resulting in lung complications appearing as frosted glass in the lung CT scan [3]. Such a situation declines the oxygen

content in the blood of the patient. The production of cytokines and chemokines is one of the primary immune responses during viral infection. large amounts of IL-8, a potent chemoattractant for neutrophils, have been reported in SARS patients [4,5]. In severe COVID-19 patients, the rise in the number of neutrophils is associated with the disease severity [6]. The production of high levels of proinflammatory cytokines leads to "cytokine storm" [2,7]. When the patient is admitted to the hospital, the disease is most likely to have advanced to the second or third stage, with respiratory problems and multiple organ failure. Therefore, from the second step onwards, we should look beyond the virus and focus on the cytokine storm and the free radical storm as pathogenic agents [8].

N-acetylcysteine (NAC) has been long employed to treat paracetamol (acetaminophen) poisoning caused [9] and as a mucolytic in chronic lung diseases. N-acetylcysteine is also an antioxidant and can reduce the oxidative stress [7] As a prodrug, acetylcysteine is transformed into L-cysteine [10], which is the precursor of the biological antioxidant, glutathione. Therefore, the administration of N-acetylcysteine renews glutathione sources. N-acetylcysteine also has some anti-inflammatory effects through inhibiting NF-κB by activating nuclear factor kappa kinase regeneration and thus modulating cytokine synthesis. Replication of RNA viruses requires the support of an active NF-κB pathway in the host cells. Concerning human coronaviruses (HCoV-229E), suppression of NF-kB significantly reduces the replication rate. Thus, drugs capable of inhibiting NF-κB activation can decrement viral replication [2, 11]. Moreover, NAC has shown protective mechanisms against a variety of COVID-19-associated conditions, including cardiovascular diseases [12]. Regarding cardiac injury and thrombosis as the potentially fatal complications of COVID-19, intravenous NAC has exhibited vasodilator, anti-inflammatory, and antiaggregatory effects of nitroglycerin which can be beneficial in the improvement of the outcomes, such as acute myocardial infarction, unstable angina, and acute pulmonary edema [13].

Bromhexine has been used as an expectorant and thinner of mucous secretion in bronchitis, asthma, bronchiectasis, and inflammation of the sinuses with the accumulation of thick and sticky mucous secretions in the respiratory tracts. The present research is thus aimed at comparing the effect of N-acetylcysteine and Bromhexine on the recovery and hospitalization prevention in outpatients with COVID-19.

2. Methods

2.1. Study design and setting: This randomized clinical trial study (with a clinical trial code: IRCT20220302054167N1 and ethics code: IR.UMSHA.REC.1400.957) was carried out on 225 patients in Dibaj clinic in Iran from April 2022 to September 2022. The COVID-19 diagnosis was based on the symptoms of the patients (cough, fever, weakness and lethargy, muscle pains, runny nose, and sore throat). Moreover, nasal and/or pharynx samples were collected for RT-PCR test to diagnose COVID-19 at the health service center. The PCR-positive patients were enrolled. Noteworthy, patients were included in the study if there was no need for referral and no evidence of organ involvement, including lung. The blood oxygen saturation of the patients was measured by a pulse oximeter. The total sample volume (225 people in this study) was then randomly assigned to tree groups (A and B and C). Group A received

oral N-acetylcysteine 600 mg once a day for 5 days while the group B received 8 mg bromhexine tablets three times a day for 5 days and the group C didn't received any drug (control group). At the same time, all patients took naproxen 250 mg twice a day for 5 days, famotidine 20 mg once a day for 10 days, vitamin D 50,000 per week for 4 weeks, and vitamin C 1000 mg daily. The patient's blood oxygen saturation was assessed by pulse oximeter on the 7th and 14th day of the disease. The patients were followed up in terms of hospitalization for one month, the number of days of hospitalization, and even death. The results of examinations and patients' characteristics were also recorded in a checklist especially designed for this purpose.

2.2. Participants:

Adult patients from 18 to 80 years of age referring to Dibaj clinic, with symptoms of COVID-19 and positive RT-PCR test, SPo2 > 92%, and no underlying disease and respiratory distress were included in this research.

2.3. Sampling method:

six-block randomization method was used. To this end, sheets of paper were prepared. The letter "A" was written on two sheets, while the other two sheets were labeled by letter "B" and the other two sheets were labeled by letter "C". The sheets were shuffled and put in a desk drawer. One of these sheets was randomly pulled out upon visiting an eligible patient, assigning him/her to group "A", "B" or "C" who received NAC or bromhexine or the patients that did not receive any drug. It should be noted that a specific sheet was not returned to the drawer until all six sheets were draw once. This random assignment process continued for the next six patients until reaching the desired sample size (225 patients).

2.4. Sample size and its calculation method:

According to Suter et al. [14], the mean (standard deviation) of FIO2 pressure on the third day post treatment was 0.29 (0.09) and 0.35 (0.11) in the NAC group and the control group, respectively. Accordingly, the sample size was calculated at 95% confidence level and 80% test power. The sample size of each group was 46 people giving rise to a total sample size of 92.

$$\text{the } = \frac{(Z_{1-\alpha/2}+Z_{1-\beta})^2\times(\sigma_1^2+\sigma_2^2)}{(\mu_1-\mu_2)^2} = \frac{(1.96+0.842)^2\times(0.09^2+0.11^2)}{(0.29-0.35)^2} = 46$$

P value <0.05

2.5. Exclusion criteria:

The patients with the following conditions were excluded: patients under study with other treatment methods, patients with underlying conditions (cardiac, diabetes, and hypertension), pregnancy and breastfeeding, patients receiving nitroglycerin, evidence of pulmonary involvement and the need for hospitalization or referral to an infectious disease specialist, and complications with the use of N-acetylcysteine and bromhexine such as the history of allergy and anaphylactic shock.

2.6. Data analysis method

The independent t-test was used to compare quantitative variables and chi-square test was used to compare qualitative variables. If necessary, Poisson regression model was used to analyze the results. All statistical analyzes were performed at the 95% confidence level using Stata software, version 16.

3. Results

In this study, 225 patients were referred to the Dibaj health care service center. All of them were included in the study after their positive PCR result for COVID-19. The patients were classified into two groups using a six-block randomized method. Seventy-five patients received NAC while the other 75 patients were treated by bromhexine and 75 patients didn't received any drug(control group). Considering the sex of the subjects, 110 (48.9%) of them were women and the remaining 115 (51.1%) patients were men. The mean age of the patients was 45.31 ± 14.884 years with respective the minimum and maximum age of 18 and 80 years (Table 1).

Age	Number of patients	Percentage of patients
20>age	8	3.55%
21-30	33	14.66%
31-40	54	24%
41-50	48	21.33%
51-60	42	18.66%
61-70	32	14.22%
70<age	8	3.55%

Table 1. Age distribution of patients with COVID_19 participating in study 2022

Out of 225 patients investigated in this study, 14 (6.22%),56 (24.88%), 78 (34.66%), 56 (24.88%), 19 (8.44%), and 2 (0.88%) case referred the clinic 1, 2, 3, 4, 5, and 6 days after the emergence of the symptoms, respectively.

The average time passed from the emergence of symptoms to the first visit to Dibaj Clinic was 3.24 ± 1.026 days. Out of 225 studied patients, 67 (29.77%) cases were hospitalized while the remaining 158 (70.22%) cases had no history of hospitalization within one month. Among the 75 patients in the NAC group, 11 (14.66%) were hospitalized and 64 (85.33%) recovered at home without referring to the hospital. In the bromhexine group, 6 (8%) were hospitalized while the remaining 69 (92%) were treated at home and did not need to be hospitalized. Among the 75 patients who did not receive any medication 50(66.66%) were hospitalized and 25(33.33%) were treated at home and did not need to be hospitalized . The average hospitalization time of A and B and C groups was 5.8 and 5 and 9.63 days, respectively (Figure 1)

In general, the average recovery time of the patients (standard deviation) from the symptom appearance to the end of the symptoms was 12.18 (6.78) days, with respective minimum and the maximum recovery periods of 3 and 40 days after the emergence of symptoms. The mean duration of complete recovery of symptoms in NAC and bromhexine groups was 12.65 ± 0.90 and 10.76±0.64 (P=0.0935), respectively, showing no statistically significant difference but in control group was 15.04±8.557(p=0.0001) showing statistically significant difference.

The average oxygen saturation of all tree groups was 94.52 ± 2.502% on the first day of the visit. On the seventh and fourteenth day of the disease, it was 93.01±6.862% and 92.91±12.55%, respectively. In the NAC group, the average oxygen saturation was 94.47%, 95.43% and 95.73% in the first, second, and third visit, respectively. While in the bromhexine group, the average oxygen saturation on the first, second and third visits was 94.80%, 95.43%, and 95.93%, respectively. While in the group patients didn't receive any drug, the average oxygen saturation was 94.21%, 89.31% and 87.21% in the first, second, and third visit, respectively. While the average oxygen saturation in the first visit in the NAC and Bromhexine groups was respectively 94.47% and 94.80%. ($p = 0.393$); There is no significant difference in the average oxygen concentration on the first day of disease in the three studied groups.

On the second visit, oxygen saturation in the NAC and Bromhexine groups was 94.65% and 95.43%, respectively. There is a significant difference in the average oxygen concentration in the studied groups on the seventh day

($p < 0.001$). The average oxygen concentration on the seventh day was not significantly different for Bromhexine and NAC groups, but these two groups' oxygen concentration on the seventh day was significantly higher than the control group.

On the third visit, the oxygen saturation in the NAC (95.73%) and Bromhexine (95.93%) group was not significantly different. The average oxygen concentration on the 14th day has a significant difference in the studied groups

($p < 0.001$). The average oxygen concentration on the seventh day was not significantly different for Bromhexine and NAC groups, but these two groups' oxygen concentration on the seventh day was significantly higher than the control group.

The oxygen saturation of the first visit increased compared to the second visit and showed a 0.19% increment in the NAC group but this enhancement was 0.66% in the bromhexine group and in the control group 5.2% decrease that respectively showing a statistically significant difference ($p<0.001$). On the third visit, this increase was 1.33% and 1.19% in the NAC and Bromhexine groups respectively but in the control group was 7.43% decrease showing a statistically significant difference ($p<0.001$). (Figure 2)

No mortality was observed in the two groups A and B but in group C , 7 cases of death were recorded (9.33%). Out of 225 patients studied, 117 patients (78%) reported no complications after taking the drugs, while 33 complained about mild complications that did not require drug discontinuation or intervention. Among the patients who received NAC, 7 cases (4.6%) reported a decrease in blood pressure after taking the drug, and 8 patients (5.3%) reported stomach pain, which was resolved by changing the time of taking the drug. Of the 75 patients in the bromhexine group, 18 (12%) reported drowsiness. The patients who developed complications did not have any problem continuing the study due to the mildness of the complication.

In this study, 14 out of 67 hospitalized patients (1 from the Bromhexine group and 6 from the N-acetylcysteine group and 7 from control group) were excluded from the study due to being hospitalized before the end of the intended treatment period, they were, however, followed up for one month.

None of the patients included in this study had a history of COVID-19 vaccination.

4. Discussion

In this study, 225 patients were examined after RT- PCR confirmation of COVID-19. The patients were grouped into tree classes (NAC and Bromhexine and control groups) using the six-block randomized method. The majority of patients were men (51.1%), which is different from the study conducted by Hesni, E. in Kermanshah, where the majority of patients (74.53%) were men [15]. The largest number of patients were in the age range of 31-40 years.

In our study, the average age of patients admitted to the hospital was 58.64 years. Out of these 17 patients, 58.8% were over 60 years old while 45.31% were under 60 years old.

The highest and lowest hospitalization age was 80 and 23, respectively. The highest number of hospitalized patients was over 60 years old. Considering the underlying diseases in this age group and also the high risk of these people, it is essential to diagnose and start the necessary medicines and take the necessary care in time.

In this study, out of 225 patients studied, 67 people (29.77%) were admitted to the hospital in one month. Of the 75 patients in the NAC group, 11 (14.66%) were hospitalized while this rate was 6 (8%) in the

Bromhexine group and 50(66.66%) in control group.

In this study, the average duration of hospitalization time of A and B and C groups was 5.8 and 5 and 9.63 days .It can be concluded that Bromhexine has reduced the duration of hospitalization compared to NAC and control group . In the research conducted in Kermanshah by Hasni et al. on hospitalized COVID-19 patients, the mean duration of hospitalization was 4 days, showing a 1.8 day difference compared to the present work [15]. Izquierdo1 et al. reported no significant differences in the mean duration of hospitalization, admission to the intensive care unit or use of invasive mechanical ventilation upon using NAC [16]. The study by Ansarin et al. in Tabriz on hospitalized COVID-19 patients showed that early application of oral Bromhexine declines ICU transfer, intubation, and mortality rate in COVID-19 patients [17]. In the current study, patients of the Bromhexine group were hospitalized for fewer days. Moreover, the average recovery time of patients from the onset of symptoms to the end of symptoms was 10.75 days.

Furthermore, in this study, the mean oxygen saturation of tree groups on the first, seventh, and fourteenth day of the visit was 94.52%, 93.01%, and 92.91%, respectively. The oxygen saturation of the first visit increased compared to the second visit and showed a 0.19% increment in the NAC group but this enhancement was 0.66% in the bromhexine group and in the control group 5.2% decrease. On the third visit, this increase was 1.33% and 1.19% in the NAC and Bromhexine groups respectively but in the control group was 7.43% decrease showing a statistically significant difference .

According to the latest statistics of the Corona Center of John Hopkins University, the COVID-19-induced mortality rate of Iran is 1.9% [18]. Hesni et al. reported that out of 27,256 patients studied, 2646 (9.71%) died during hospitalization [15]. Ansarin et al. also reported a significant decrement in mortality rate (0 vs. 5, P = 0.027) of the bromhexine group compared to the standard group [17]. In the study of Taher et al., although the clinical condition of patients who underwent NAC had better results, no difference was found in the mortality of hospitalized patients compared to the placebo group [19]. In the current study, no mortality was reported in both group A and B but in control group the mortality rate was 9.3%, implying the significant effect of the early initiation of Bromhexine and NAC drugs a on reducing the death rate of patients compared to Hesni and Ansarin and Taher studies and our control group [15,17,19].

5. Conclusion

Among the patients receiving N-acetylcysteine and bromhexine, fewer patients were hospitalized in the bromhexine group and their hospitalization duration was shorter, and both groups receiving the drug compared to the control group in two significant reductions in the number of days of hospitalization and the number of The recovery days of the covid patients were higher than the control group. Also, this study showed a significant reduction in the mortality of patients in both groups receiving the drug compared to the control group.

Given the availability and affordability of both treatments, as well as their mild side effects, early initiation of bromhexine and N-acetylcysteine may be beneficial for patients depending on their needs.

However, more studies are still needed to prove their benefits

Declarations

6.1. Ethics approval and consent to participate:

This study was approved by the Research Ethics Committees of Hamadan University of Medical Scienece with the ethics code: IR.UMSHA.REC.1400.957 and this study was approved by the judges of the International Center for Registration of Clinical Trials of Iran, a member of the international centers approved by the World Health Organization and with the code: IRCT20220302054167N1 Confirmed. Informed consent was obtained from all participating patients/their legal guardians in this study after fully explaining the study method, side effects of drugs and other necessary matters. All patients were first examined in terms of drug allergy history, and then the study was fully explained to the patients, and the questions and doubts of the patients were fully answered, and it was also explained to the patients that for any reason, they wanted to continue participating in the study. do not have, they can withdraw, and this study will not interfere with their treatment. Also, all patients are assured that all their information is confidential and only collective information of the entire study is available. All methods were carried out in accordance with relevant guidelines and regulations.

6.2. Consent for publication

Not applicable.

6.3. Availability of data and materials

All data generated or analyzed during this study are included in this published article.

6.4. Competing interests:

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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6.6. Authors' contributions:

A. Eslami-Ghayour and S. Nazari: designed and wrote the manuscript text

A. Eslami-Ghayour: Data collection and responding to patients

F.Keramat: Scientific advisor

F.Shahbazi: Statistics Consultant

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7. Registration:

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Figures

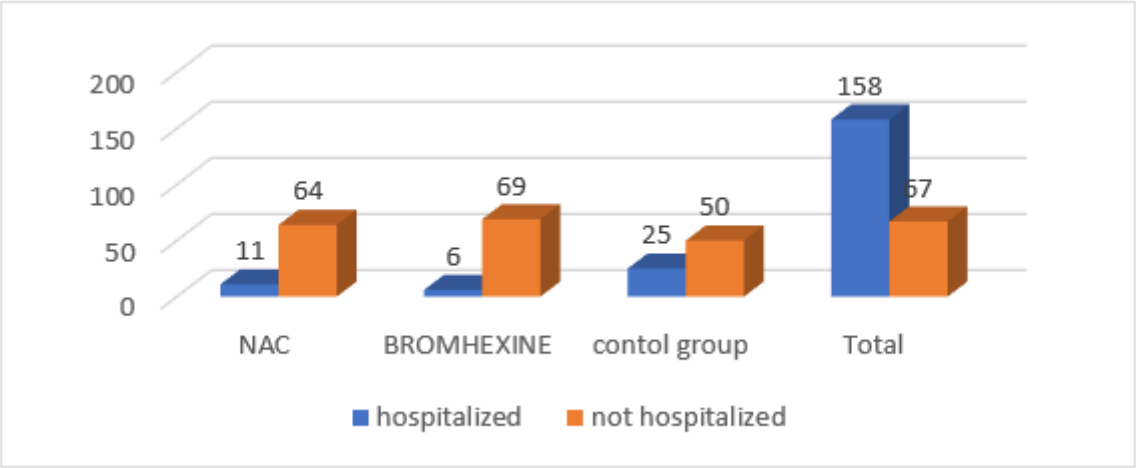

Figure 1

Frequency distribution of hospitalization status of patients visiting the clinic

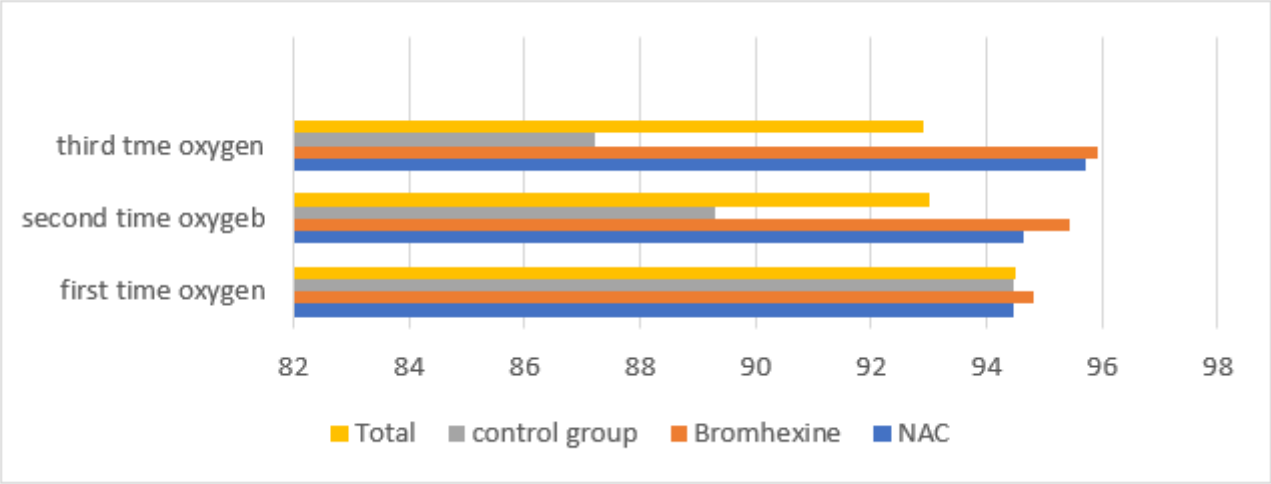

Figure 2

Distribution chart of the oxygen saturation of the two treatment groups in three different time of visits