A Randomized Clinical Trial Comparing N-acetylcysteine and Bromhexine in Outpatients with COVID-19

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Abstract

This study aimed to compare the effects of N-acetylcysteine and Bromhexine on the recovery rate and prevention of hospitalization in outpatients with COVID-19. PCR-confirmed COVID-19 patients were divided into three groups: N-acetylcysteine group, Bromhexine group, and control group. Patients were followed up on the seventh and fourteenth days of the disease, and hospitalization and mortality rates were evaluated after one month. The study found that both N-acetylcysteine and Bromhexine can effectively reduce hospitalization rates and mortality and shorten the duration of hospitalization. The third visit of patients who received N-acetylcysteine showed an increase of 1.33% in oxygen saturation compared to their first visit, and in patients who received Bromhexine, this increase was 1.19%. The mortality rate was 9.33% in the control group and zero in both groups of patients who received medication. This study provides evidence for the early initiation of N-acetylcysteine and Bromhexine in outpatients with COVID-19. Clinical trial code: IRCT20220302054167N1, ethics code: IR.UMSHA.REC.1400.957.

1. Introduction

Since its emergence in December 2019, the coronavirus disease (COVID-19) caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has become a global emergency, spread rapidly worldwide [1]. While COVID-19 can present as mild symptoms, including fever, cough, and loss of smell or taste, it can also lead to severe cases with extensive lung involvement, acute respiratory distress syndrome, hospitalization, intubation, and even death [2]. 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 [3]. 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 works by breaking down and thinning the mucous secretions in the respiratory tract, making it easier for the body to expel them. This helps to relieve symptoms such as cough, congestion, and difficulty breathing. Additionally, Bromhexine has been shown to have anti-inflammatory effects, which can help to reduce swelling and irritation in the respiratory tract [14].Bromhexine has a long history of use in respiratory tract disorders and has been widely studied for its effectiveness in treating these conditions. It is generally well-tolerated, with few side effects reported. Overall, Bromhexine is an important tool in the management of respiratory tract disorders characterized by thick and sticky mucous secretions. Its effectiveness as an expectorant and mucolytic agent makes it a valuable option for those seeking relief from respiratory symptoms [15].

In the midst of the ongoing COVID-19 pandemic, preventing hospitalization and improving recovery among outpatients is of utmost importance. To address this issue, we have conducted a randomized clinical trial comparing the efficacy of N-Acetylcysteine with Bromhexine. Our aim is to elucidate effective treatment options that can help manage the symptoms of COVID-19 and potentially reduce the burden on hospital systems.

2. Methods

2.1. Study design and setting

This randomized clinical trial (RCT) study, with a clinical trial code of IRCT20220302054167N1 and an ethics code of IR.UMSHA.REC.1400.957, was conducted on 225 patients at the Dibaj clinic in Iran between April 2022 and September 2022. The diagnosis of COVID-19 was based on the patients' presenting symptoms, which included cough, fever, weakness, lethargy, muscle pains, runny nose, and sore throat. Nasal and/or pharynx samples were collected from patients for an RT-PCR test to confirm the COVID-19 diagnosis at the health service center, and only PCR-positive patients were enrolled in the study. It is noteworthy that patients were included in the study only if there was no need for referral and no evidence of organ involvement including the lungs after Chest-CT, and they had never received the COVID-19 vaccine. To mitigate potential bias, we only included patients who visited the clinic within three days of symptom onset in this study. Blood oxygen saturation of the patients was measured using a pulse oximeter. The total sample of 225 participants was then randomly assigned to three groups (A, B, and C). Group A received oral N-acetylcysteine 600 mg twice a day for five days, while group B received 8 mg Bromhexine tablets three times a day for five days. The control group (group C) did not receive any medication. All patients took naproxen 250 mg twice a day for five days, famotidine 20 mg once a day for ten days, vitamin D 50,000 per week for four weeks, and vitamin C 1000 mg daily. Blood oxygen saturation was assessed by a pulse oximeter on the seventh and fourteenth day of the disease, and the

patients were followed up for one month in terms of hospitalization, the number of days of hospitalization, and even death. The results of examinations and patients' characteristics were also recorded in a checklist designed for this purpose.

2.2. Participants

We enrolled adult patients aged 18-80 years with symptoms suggestive of COVID-19 who presented to Dibaj Clinic within three days of symptom onset and had a positive RT-PCR test, SPo2 > 92%, and normal chest CT on their initial visit. Patients without underlying medical conditions or respiratory distress, who had not received any COVID-19 vaccine, were included in this research.

2.3. Sampling method

We employed a six-block randomization method for patient allocation. Sheets of paper were prepared, with the letters "A" written on two sheets, "B" on two sheets, and "C" on two sheets. These were shuffled and placed in a desk drawer. At the time of the patient's eligibility, one sheet was randomly drawn, and the patient was assigned to group "A", "B", "C", or no drug. Notably, a specific sheet was not returned to the drawer until all six sheets had been drawn once. This random assignment process continued for the next six patients until the desired sample size of 225 patients was achieved.

2.4. Exclusion criteria

We did not include patients who did not meet the following criteria:: those undergoing other therapies, patients with underlying conditions such as heart disease, diabetes, and hypertension, pregnant or lactating patients, patients receiving nitroglycerin, those who showed evidence of lung involvement (oxygen levels < 92%, persistent symptoms of shortness of breath and chest pain, and evidence of lung involvement seen in CT scans) requiring hospitalization or referral to a hospital, as recommended by the infectious diseases specialist at the hospital, and those who have a history of allergy or anaphylactic shock to N-acetylcysteine or Bromhexine or have experienced side effects while using them.

2.5. Data analysis method

We used the independent t-test to compare quantitative variables, the chi-square test to compare qualitative variables, and ANOVA test to compare the means of three or more groups. If necessary, we analyzed the results using a Poisson regression model. All statistical analyses were performed at a 95% confidence level using Stata software, version 16.

3. Results

The present study aimed to investigate the efficacy of N-acetylcysteine (NAC) and Bromhexine in treating COVID-19 positive patients. The study included a total of 225 patients who were referred to Dibaj Medical Center after being tested positive for COVID-19 through PCR. The patients were randomly assigned to one of three groups: 75 patients received NAC, 75 patients were treated with Bromhexine, and 75 patients

served as a control group and received no medication. Among the total sample, 110 individuals (48.9%) were female and 115 individuals (51.1%) were male. The mean age of the patients was 45.31 ± 14.884 years with a range of 18 to 80 years. Out of 225 patients, 38 (16.88%) were hospitalized, while 187 (83.11%) had no history of hospitalization within a month. In the NAC group, 11 out of 75 patients (14.66%) were admitted to the hospital, of which 5 were female with a mean age of 50.4 years and 6 were male with a mean age of 54.16 years. The remaining 64 patients (85.33%) recovered at home without hospitalization. In the Bromhexine group, 6 out of 75 patients (8%) were hospitalized, of which 4 were female with a mean age of 48.25 years and 2 were male with a mean age of 49 years. The remaining 69 patients (92%) were treated at home and did not require hospitalization. Among the 75 patients in the control group who did not receive any medication, 21 (28%) were admitted to the hospital, of which 13 were male with a mean age of 47.125 years and 8 were female with a mean age of 50.38 years. The remaining 54 patients (72%) were treated at home and did not require hospitalization. overall, The average age of hospitalization for patients was found to be 55.15 years, with a minimum age of 24 and a maximum age of 80 Out of the 38 patients who were admitted to the hospital, 58.8% were over 60 years old, while 45.31% were under 60 years old(Table 1).

Treatment group	Female	Male	Total	Mean age		Mean Hospitalization time(days)	
				Female	Male	Female	Male
NAC	36	39	75	50.4	54.16	6.77	8
Bromhexine	27	48	75	48.25	49	5.3	5.25
Control	47	28	75	50.38	47.125	9.875	11.07

Table 1. Comparison of Treatment Outcomes for COVID-19 Patients: A Gender-Based Analysis

In the NAC group, 4(4.4%) out of 11 hospitalized patients required ICU admission, whereas 1(2.4%) out of 6 hospitalized patients in the Bromhexine group required ICU admission. Among the control group, 11(10.2%) out of 21 hospitalized patients required ICU admission. The mean hospitalization time was 5.8, 5, and 9.63 days for groups A, B, and C, respectively. In the Bromhexine group, the mean hospitalization time was 5.25 days in males and 5.3 days in females. In the NAC group, the mean hospitalization time was 5.4 days in females and 8 days in males. In the control group, the mean hospitalization time was 11.07 days in males and 9.875 days in females respectively and the difference between these three groups is statistically significant (p=0.766).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 (Table 2).

Treatment Group	number of Patients	Hospitalized (%)	ICU Admission (%)	Mean Hospitalization Time (days)	Mean Recovery Time (days)
N-acetylcysteine (NAC)	75	11(14.66%)	4(36.36%)	6.7±3.3	12.65±0.90
Bromhexine	75	6(8%)	1(16.67%)	5.3±0.47	10.76±67
Control	75	21(28%)	11(52.38%)	10.47±2.29	15.04±8.557
p-value	-	0.003	0.095	<0.001	<0.001
Total	225	38(16.88%)	16(42.11%)	7.8±4.2	12.18±6.78

Table2. Comparison of hospitalization rates, ICU admissions, mean hospitalization duration, and mean recovery time among COVID-19 positive patients treated with N-acetylcysteine, Bromhexine, and no medication in a 2022 study.

The average oxygen saturation of all three 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. The ANOVA test results are as follows: On the first day of the visit, there was no significant difference in the average oxygen concentration between the three groups (p = 0.393).On the seventh day of the disease, there was a significant difference in the average oxygen concentration between the three groups (p < 0.001). The oxygen concentration in the NAC and Bromhexine groups was significantly higher than the control group . On the fourteenth day of the disease, there was a significant difference in the average oxygen concentration between the three groups (p < 0.001). The oxygen concentration in the NAC and Bromhexine groups was significantly higher than the control group.

Additionally, there was a significant difference in the oxygen saturation levels between the first and second visit in all three groups (NAC, Bromhexine, and control). The oxygen saturation levels increased from the first visit to the second visit in the NAC and Bromhexine groups, while in the control group, it decreased. The differences were statistically significant (P<0.001). Similarly, there was a significant difference in the oxygen saturation levels between the second and third visit in all three groups. The oxygen saturation levels increased from the second visit to the third visit in the NAC and Bromhexine groups, while in the control group, it decreased. The differences were statistically significant (p < 0.001) (figure2).

In this study, mortality rate was ziro in Groups A and B, while seven deaths (9.33%) were recorded in Group C. Among the fatalities, there were 4 men and 2 women with a mean age of 63 years. Out of the 225 patients studied, 117 (78%) reported no complications after taking the drugs, while 33 reported mild complications that did not require drug discontinuation or intervention. In the N-acetylcysteine group, 7 cases (9.33%) reported a decrease in blood pressure after taking the drug, and 8 patients (10.66%) had stomach pain and among the 75 patients in the Bromhexine group, 18 (24%) had drowsiness, which resolved upon changing the time of taking the drug. The patients who developed complications did not experience any problems continuing the study due to the mildness of the complications. No patients were withdrawn from the study because of adverse effects.

4. Discussion

In this study, the efficacy of N-acetylcysteine (NAC) and Bromhexine in treating COVID-19 positive patients was investigated, and the results were compared with a control group that received no medication.

The study included a total of 225 patients, randomly assigned to three groups. The study results indicate that the hospitalization rate was lower in both the NAC and Bromhexine groups compared to the control group, and the rate of admittion in icu was reduced. Although the difference was not statistically significant, the mean hospitalization time was shorter in the treatment groups compared to the control group. Furthermore, our study, along with the research carried out by Izquierdo JL et al., indicates that N-acetylcysteine (NAC) exhibits promising outcomes in mitigating patient mortality and reducing intensive care unit admission in the treatment of Covid-19{16}. Similarly, the study conducted by Taher et al. supports the beneficial effect of NAC in treating Covid-19 patients [19]. Moreover, the investigation conducted by Du Preez HN et al. produced results consistent with our study, demonstrating positive outcomes with the use of NAC [20]. Although these studies provide encouraging findings, it is important to continue exploring and validating the efficacy of NAC as a treatment for Covid-19. In a study conducted by Ansarian et al., which is similar to our research, it was concluded that Bromhexine has helpful significant improvements in clinical outcomes and even mortality rates [17]. In another study written by Tolouian et al., the use of Bromhexine was found to aid in the recovery of COVID-19 patients, but unlike our study, it did not have an effect on mortality [21]. In our study, we observed that in all groups, the hospitalization and mortality rates were higher in men and among the elderly population. These findings are consistent with the study conducted by Hesni et al. in Kermanshah.[15] Furthermore, the average recovery time of the patients in the NAC and Bromhexine groups was comparable, and both groups had a shorter recovery time compared to the control group. However, the difference in recovery time was not statistically significant between the treatment groups. In study written by Tolouian et al., the use of Bromhexine was found to helpful decreasing the duration of hospitalization [21].In terms of oxygen saturation levels, the results showed that the average oxygen saturation in the treatment groups was higher compared to the control group, particularly on the seventh day of the disease. The average oxygen saturation levels were also comparable between the NAC and Bromhexine groups. The mortality rate among patients in groups A and B who received the medication was zero, which aligns with findings

from previous studies, such as Ansarian's research [17]. However, the mortality rate in the control group was significantly higher compared to the figures reported by Johns Hopkins Coronavirus Resource Center. One possible explanation for this discrepancy is that we only included patients who had not received the COVID-19 vaccine, which is a known risk factor [18]. Overall, the results of this study suggest that NAC and Bromhexine may be effective in treating COVID-19 positive patients, with a lower hospitalization rate, shorter hospitalization time, and improved oxygen saturation levels. However, further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings.

5. Conclusion

The present study aimed to investigate the effectiveness of N-acetylcysteine (NAC) and Bromhexine in the treatment of patients with positive COVID-19. The study findings indicate that both NAC and Bromhexine groups showed a lower rate of hospitalization compared to the control group. Furthermore, a smaller percentage of patients required hospitalization in the ICU in the treatment groups. The average hospitalization time in the treatment groups was also shorter compared to the control group. Additionally, the mean time of symptom improvement was shorter in the NAC and Bromhexine group compared to the control group. However, no statistically significant difference was observed between NAC and Bromhexine in terms of hospitalization or symptom recovery time. Notably, the mortality rate was significantly lower in patients who received the NAC or Bromhexine.

In conclusion, the results of this study suggest that NAC and Bromhexine may be effective in treating COVID-19-positive patients, in lower hospitalization rates, shorter hospital stays, faster recovery times, and reduced mortality compared to the control group. Nevertheless, it is essential to continue exploring and validating the efficacy of NAC and Bromhexine as a treatment for COVID-19, as these findings provide encouraging but preliminary evidence.

6. Limitation

1. The study was conducted in a single clinic in Iran with a specific population, and the findings may not be generalizable to other populations or settings.

2. The study excluded patients with underlying medical conditions, those requiring hospitalization, and those who had received the COVID-19 vaccine, which limits the generalizability of the findings to these specific patient groups.

7. Declarations

7.1. Ethics approval and consent to participate:

This study was approved by the Research Ethics Committees of Hamadan University of Medical Science, with the ethics code IR.UMSHA.REC.1400.957. Additionally, it 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, with the code IRCT20220302054167N1 confirmed. Informed consent was obtained from all participating patients or their legal guardians in this study after fully explaining the study methods, drug side effects, and other necessary matters. Prior to participation, all patients were screened for drug allergy history. The study was fully explained to the patients, and all their questions and doubts were addressed. It was also emphasized to the patients that they could withdraw from the study at any time without affecting their treatment. All patients were assured that their personal information would remain confidential and that only collective information from the entire study would be available. Finally, all methods were carried out in accordance with relevant guidelines and regulations.

7.2. Consent for publication

Not applicable.

7.3. Availability of data and materials

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

7.4. 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.

7.6. Authors' contributions:

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

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

 F.Keramat: Scientific advisor

F.Shahbazi: Statistics Consultant

Arash Eslami-Ghayour: Data analysis and editor

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8. Registration:

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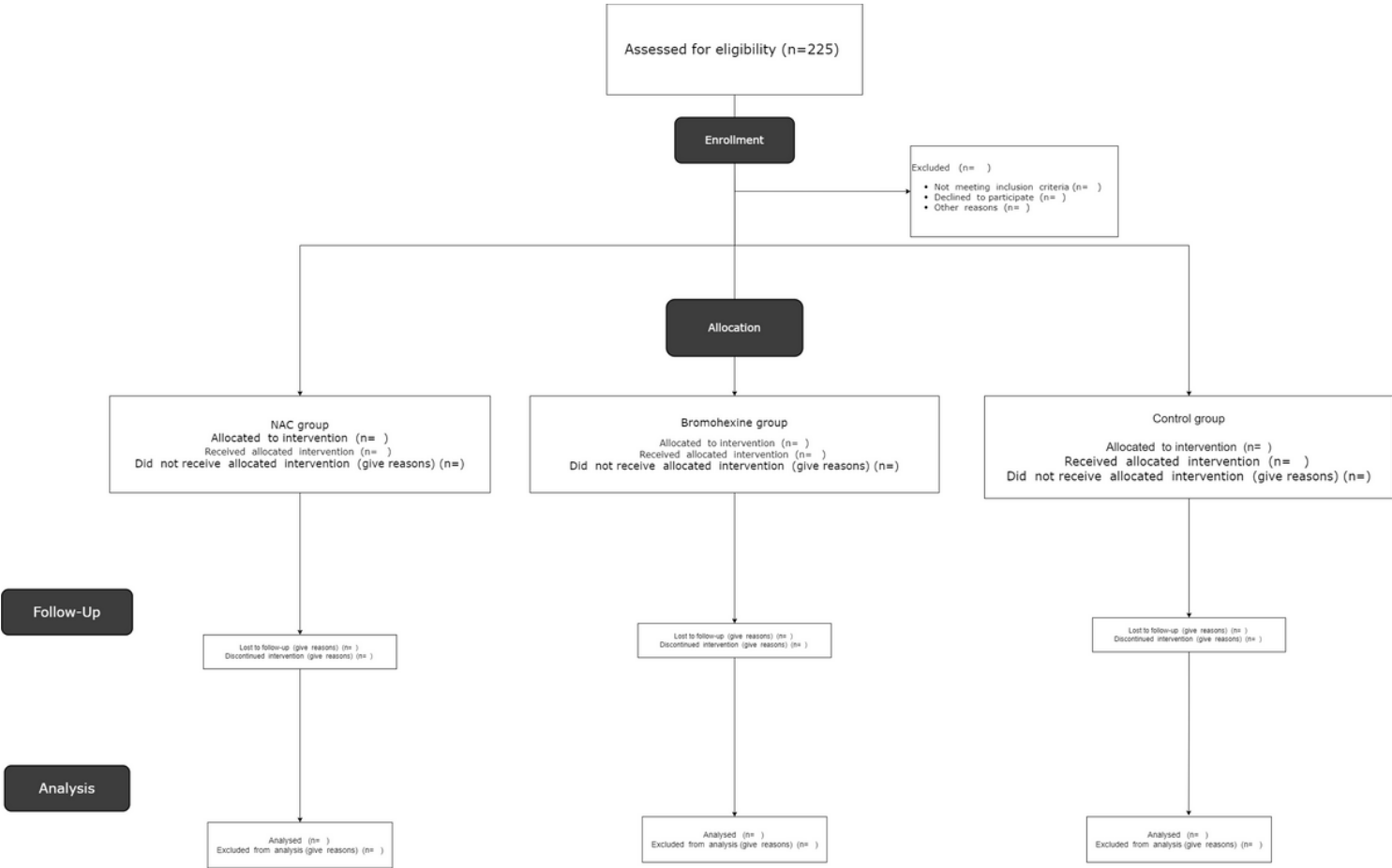
Figures

Figure 1

Consort diagram for a randomized clinical trial study comparing the effects of two drugs, NAC and Bromhexine, on outpatients with COVID-19, including a control group.
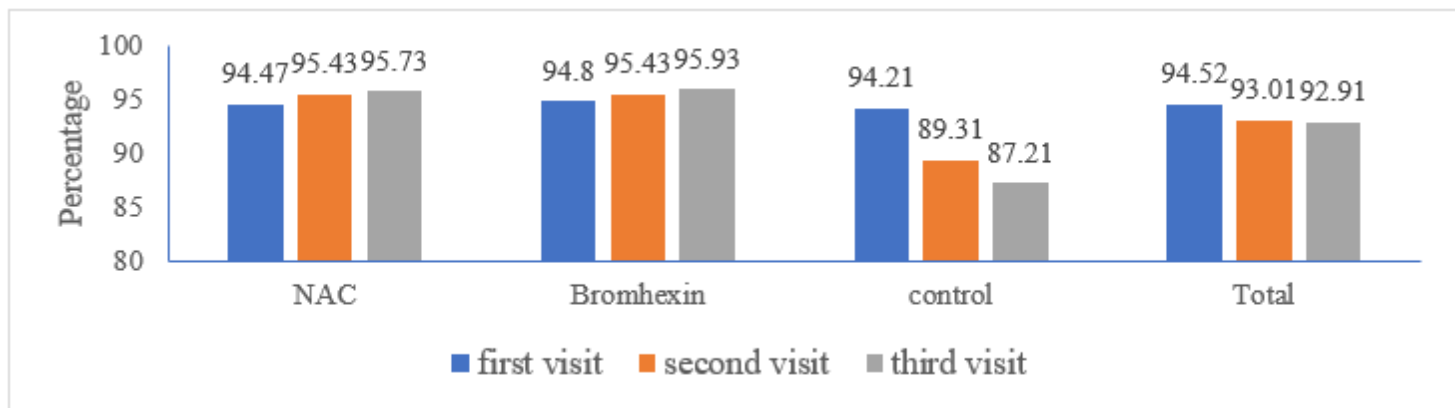
Figure 2

Comparison of Average Oxygen Saturation among NAC, Bromhexine, and Control Groups over Three Visits