Evaluation of the Efficacy and Safety of Oral N-acetylcysteine in Patients With COVID-19 Receiving the Routine Antiviral and Hydroxychloroquine Protocol: A Randomized Controlled Clinical Trial

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Abstract

ABSTRACT The current absence of gold-standard or all-aspect favorable therapies for COVID-19 renders a focus on multipotential drugs proposed to prevent or treat this infection or ameliorate its signs and symptoms vitally important. The present well-designed randomized controlled trial sought to evaluate the efficacy and safety of N-acetylcysteine as adjuvant therapy in hospitalized Iranian patients with COVID-19. Four different diets in 60 patients include; Kaletra (lopinavir/ritonavir) + hydroxychloroquine with/without N-acetylcysteine (600 mg TDS) and atazanavir/ritonavir + hydroxychloroquine with/without N-acetylcysteine (600 mg TDS), were administered in the study. At the end of the study, a further decrease in C-reactive protein was observed in groups with N-acetylcysteine (P =0.008), and no death occurred in the atazanavir/ritonavir + hydroxychloroquine + N-acetylcysteine group, showing that the combination of these drugs may reduce mortality. A significant rise in O2 saturation was observed in atazanavir/ritonavir+hydroxychloroquine+N-acetylcysteine group (P <0.05). Accordingly, oral or intravenous N-acetylcysteine, may enhance O2 saturation, blunt the inflammation trend (by reducing C-reactive protein), and reduce mortality in hospitalized patients with COVID-19. The N-acetylcysteine could be more effective as prophylactic or adjuvant therapy in stable and non-severe cases of COVID-19 with a particularly positive role in the augmentation of O2 saturation and faster reduction of the CRP level and inflammation.

INTRODUCTION

Background: The first case of severe acute respiratory coronavirus syndrome (SARS-CoV-2) was reported in late November 2019 in Wuhan, China. By then, many patients had been admitted to the hospital for acute pneumonia of unknown origin. On March 11, the World Health Organization (WHO) announced the outbreak of COVID-19 and declared it to be an epidemic (1, 2). The virus is transmitted through respiratory droplets or aerosols (3). One of the theories concerning the coronavirus pathogenesis is that the virus binds to host cells through angiotensin-converting enzyme 2 (ACE2). ACE2 is expressed by the epithelial cells of the lung, intestine, kidney, and blood vessels (4). Diabetes, ACE inhibitors, and angiotensin II receptor blockers (ARBs), which are used for hypertension control, increase ACE2 expression and COVID-19 risk (4). The symptoms of COVID-19 include dry coughs; malaise; fever; dyspnea; multiorgan failure; acute respiratory distress syndrome (ARDS) requiring mechanical ventilation and oxygen therapy in the intensive care unit (ICU); coagulopathy with thrombosis; systemic manifestations such as sepsis, septic shocks, and multiorgan dysfunction syndrome; and mucocutaneous involvement (5, 6). Therefore, COVID-19 is considered a disease with a thousand faces (7, 8).

Diversity in the clinical manifestations of COVID-19 is related to the interaction between the coronavirus and the immune system (6, 9). Inflammatory responses, cytokine storms, and chemokines are critical issues allied to the complications of COVID-19 (10, 11). About 33% of the patients with COVID-19 require ICU admission, with a mortality rate of 20% reported in some investigations (12, 13). Additionally, a mortality rate of 49.0% has been reported among critical patients with comorbid cardiovascular diseases, hypertension, diabetes, chronic respiratory diseases, or cancer (12). Polymerase chain reaction (PCR) tests of the upper respiratory tract samples, lung computed tomography (CT) scans, and blood tests are accepted by the WHO for the diagnosis of COVID-19 (3, 14). N-acetylcysteine (NAC) is a multipotential drug suggested by the literature for the prevention and treatment of COVID-19 (1, 15-24). NAC is antioxidant glutathione with a wide variety of use in different medical conditions, including loosening thick mucus and treating a wide range of diseases such as acetaminophen overdose, pulmonary disorders, cystic fibrosis, idiopathic pulmonary fibrosis, ARDS, bronchitis, chronic obstructive pulmonary disease, and pneumonia (6, 24). Evidence indicates the important roles of NAC in the prevention and treatment of COVID-19 by regulating oxidative and apoptotic responses, boosting the immune system, reducing cytokines and interleukins in the wake of COVID-19 infection, suppressing viral replication (especially via the mucolytic properties of NAC, diluting the viral load in the respiratory system), preventing and alleviating pulmonary disorders, augmenting oxygenation, supporting the therapeutic course of patients with sepsis hospitalized in the ICU, diminishing comorbidities, decreasing the likelihood of non-pulmonary end-organ damage or failure and liver failure, and facilitating oxygenation and circulation (24-26). COVID-19 can manifest itself through neurological disorders such as Guillain–Barre syndrome, seizure, headache, and stroke (27). NAC is capable of exerting protective effects on the nervous system and helps prevent or treat these manifestations (5). Liver failure can develop in patients with COVID-19 for several reasons, including metabolic acidosis and complications induced by certain drugs such as remdesivir, which is one of the most commonly used drugs in these patients. In this regard, one of the most well-known effects of NAC is the prevention and treatment of hepatotoxicity (28-30).

A Gap of Knowledge:

Despite numerous studies on COVID-19, no gold-standard treatment for this disease has been found yet, hence the current use of supportive therapies. The best way to manage the disease is through prevention, with vaccination already underway around the world; nonetheless, many cases of COVID-19–related infection and death are still reported.

Most COVID-19 supportive drugs modulate the immune system to regulate inflammatory storms (5). Many of the immune modulators have immunosuppressive properties that may not work properly in viral disorders (5). NAC is one of the few immune modulators without immunosuppressive properties (31). However, all the articles suggesting the use of NAC in the treatment of COVID-19 recommend further well-designed randomized controlled clinical trials (RCTs).

Aim:

This double-blind (secondary assessor- and analyst-blinded) RCT was designed to evaluate the effects of oral NAC on the treatment of hospitalized patients with COVID-19.

Although it seems that NAC confers significant benefits in patients with mild COVID-19 before hospitalization, the present study focused solely on inpatients. The current study is one of the well-designed RCTs to evaluate the efficacy and safety of NAC as adjuvant therapy in hospitalized patients with COVID-19.

METHODS

Design and Settings

The present double-blind RCT was performed in Rasool Akram Medical Complex, Tehran, Iran, on 60 patients with COVID-19. The diagnosis of COVID-19 was established according to the opinion of the treating physician, based on clinical signs and PCR or paraclinical or laboratory findings.

Sampling and Allocation

The sampling convenience method was employed. Eligible participants were classified by stratified blocked randomization and based on diet therapy (4 regimens). Thereafter, they were randomly assigned to either the intervention group or the routine treatment regimen group. Randomization was done separately within each group. The size of the blocks was 4; in other words, 2 allocations to the intervention group and 2 allocations to the routine treatment group were considered.

Eligibility Criteria

The indication for hospitalization according to the national protocol was as follows: fever above 39° or being toxic in the examination, respiratory distress, the use of respiratory muscle relaxants, the use of suprasternal or intercostal retraction, a respiratory rate greater than 30 per minute, a heart rate higher than 120 beats per minute, a peripheral blood O_2 saturation level less than 93%, having an underlying disease (eg, diabetes, hypertension, heart failure, immune system disorders, renal or hepatic impairment, a history of asthma or chronic obstructive pulmonary disease, and smoking), age over 50 years in the case of being symptomatic, and the involvement of one-third of 3 to 5 pulmonary lobes. The exclusion criteria were composed of being a child, having unstable vital signs, being either intubated or needing intubation, being admitted to the ICU, having decreased levels of consciousness, having a respiratory rate greater than 24, having a blood pressure level below 90/60 mm Hg, exhibiting multi-lobular infiltration on CT scans or chest X-rays, having permanent hypoxia, being pregnant or lactating, and having previous allergies to NAC or glutathione-based drugs. The withdrawal criteria were comprised of drug intolerance, severe complications probably related to NAC during treatment, and unwillingness to continue collaboration with the study at any point and for any reason.

Interventions and Follow-up

Two 30-person diets, comprising 15 single diets of Kaletra (lopinavir/ritonavir) + hydroxychloroquine (HCQ) with/without NAC (600 mg TDS) and atazanavir/ritonavir + HCQ with/without NAC (600 mg TDS), were administered in the study. Sixty patients completed the study. (15 patient: Kaletra + HCQ / 15 patient: Kaletra + HCQ + NAC / 15 patient: atazanavir/ritonavir + HCQ / 15 patient: atazanavir/ritonavir + HCQ + NAC) The control and intervention groups received the national protocol treatment, and NAC was added to the treatment of the intervention group. Since the eligible patients had no contraindications for NAC, the protocol was 600 mg orally every 8 hours for 14 days.

Blinding

The secondary assessor and the data analyst were blinded to the treatment regimens.

Paraclinical Data

Laboratory parameters were evaluated by using the peripheral blood samples of the patients. Additionally, lactate dehydrogenase (LDH), tumor necrosis factor-α, interleukin-6, complete blood count (CBC), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) tests were performed daily for the patients, and the course of laboratory changes was monitored. Radiological examinations of lungs were performed by CT scanning twice: at admission and discharge, and differences in radiological findings were recorded and compared. In the patients with minor underlying problems or gastrointestinal intolerance, 600 mg of oral tablets every 12 or 24 hours were given.

Response to Treatment Criteria

- Time of improvement in symptoms such as coughs, shortness of breath, and lethargy
- Improvements in O_2 saturation without changes in the treatment protocol and reductions in the need for O_2
- Duration of hospitalization according to the course of symptom improvement
- Re-admission after discharge
- Serial evaluations of laboratory parameters, consisting of LDH, tumor necrosis factor-α, interleukin-6, CBC, ESR, and CRP, and comparison of parameters at hospitalization, during hospitalization, and at

discharge
- Investigation of changes in anti-inflammatory parameters
- Examination of radiological changes at the beginning of hospitalization and during hospitalization
- Need for ICU admission during hospitalization

Primary and Secondary Outcomes

The primary outcomes of the study were the efficacy and side effects of NAC, and the secondary outcomes were drug tolerance and treatment satisfaction. The effectiveness of treatment was evaluated according to the duration of hospitalization; improvement in O_2saturation, laboratory and paraclinical findings, and clinical symptoms; and the assessment of complications based on a questionnaire.

Ethical Considerations

The research adhered to the tenets of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Iran University of Medical Sciences (ethical code # IR.IUMS.REC.1399.206 registered on August 16, 2020), and the study protocol was registered in the Iranian Registry of Clinical Trials (#IRCT20200623047897N1; https://en.irct.ir/trial/49277). Written informed consent was obtained from all the patients.

RESULTS

In this study, the mean age of the patients was 57.82 ± 18.23 years, and the mean hospitalization duration was 10.13 ± 6.07 days. In respect of sex, 31 patients (51.7%) were female, without any significant differences between the groups. Table 1 and Table 2 present the clinical and paraclinical characteristics of the study population at admission and discharge showing that CRP (F =9.102, P =0.008), alkaline phosphatase (ALP) (F =7.650, P =0.001), and diff_segment (F =5.156, P =0.007) at discharge were different between the 4 groups in such a way that the atazanavir/ritonavir + HCQ + NAC group had the lowest value concerning CRP. Regarding ALP at discharge, the Kaletra + HCQ + NAC group had the highest value. Furthermore, diff_segment had the highest value in the atazanavir/ritonavir + HCQ + NAC group.

According to the χ^2 test, 6 patients in the Kaletra + HCQ group received intravenous immune globulin (IVIG), while the atazanavir/ritonavir + HCQ + NAC group did not receive any IVIG, with the difference constituting statistical significance (P =0.015). Given that the patients were randomly divided into 4 groups, the groups were different with respect to fatigue and anorexia, cardiovascular diseases, and hypertension (Table 3). Regarding binary variables, most cases of fever were reported in the atazanavir/ritonavir + HCQ + NAC group (n =12), most cases of cough in the atazanavir/ritonavir + HCQ + NAC group (n =13) most cases of dyspnea in the atazanavir/ritonavir + HCQ + NAC group (n =13), and most cases of fatigue in the atazanavir/ritonavir + HCQ + NAC group (n =13) and the atazanavir/ritonavir + HCQ group (n =13). Additionally, 12 cases of body aches were reported in the atazanavir/ritonavir + HCQ group, 4 cases of diarrhea in the Kaletra + HCQ group, 7 cases of sore throat in the atazanavir/ritonavir + HCQ+ NAC group, 7 cases of chest discomfort in the Kaletra + HCQ group, 7 cases of headache in the atazanavir/ritonavir + HCQ group, 14 cases of dizziness in the Kaletra + HCQ group + NAC, only 1 case of seizure in the atazanavir/ritonavir + HCQ + NAC group, 6 cases of olfactory dysfunction in the Kaletra + HCQ + NAC group (fewest cases of olfactory dysfunction were observed in the Kaletra + HCQ + NAC group and the atazanavir/ritonavir + HCQ + NAC group), and 5 cases of taste disorders in the Kaletra + HCQ + NAC group.

The administration of dexamethasone, acetaminophen, azithromycin, ceftriaxone, interferon-β, and levofloxacin was not the same across the 4 groups. For instance, 6 patients in each of the atazanavir/ritonavir + HCQ and atazanavir/ritonavir + HCQ + NAC groups received interferon-β (P =.002), indicating that the zero mortality in the atazanavir/ritonavir + HCQ + NAC. Two patients in the Kaletra + HCQ group, 1 patient in the atazanavir/ritonavir + HCQ group, and 1 patient in the Kaletra + HCQ + NAC died; this difference, however, was not statistically significant (χ^2 =2.134, P =.896). All the patients in the atazanavir/ritonavir + HCQ + NAC group were discharged in good condition (Table 4).

According to the linear regression model, performed to predict the length of stay at the ICU, the use of IVIG, creatine phosphokinase (CPK) elevation, and ESR decrease were correlated with an increased length of stay at the ICU (Table 5). None of the used drugs had a significant difference regarding mortality (Table 6).

Apropos of improvement in O_2 saturation with the 4 types of medicine, the results showed that such improvement with atazanavir/ritonavir + HCQ + NAC (P =.001) and atazanavir/ritonavir + HCQ (P =0.008) was significant insofar as these 2 groups had a high level of O_2 saturation after treatment by comparison with the primary O_2 saturation level (before intervention) (Table 7). No statistically significant differences in this regard were observed between the 4 groups (P>0.05) (Table 8 and Fig. 2).

DISCUSSION

Evidence indicates some therapeutic effects for NAC on COVID-19 and its consequences. For instance, the oxidative-, immune-, and apoptotic-regulatory effects of NAC, as well as its special properties such as facilitation of oxygenation and circulation, can positively impact respiratory outcomes and prevent end-organ failure. Further, high-quality studies have reported the antioxidant and immunomodulatory roles of NAC in the treatment of viruses targeting the respiratory system (e.g., influenza [strains A and B] and respiratory syncytial virus) and the related acute injuries such as ARDS. Not only could NAC have a supportive role in patients hospitalized in the ICU, patients with sepsis, and patients with non-pulmonary end-organ damage or failure but also it could play a positive role in comorbidities. Moreover, NAC could be administered as a potential adjuvant therapy for COVID-19, considering patient status, indications, and contraindications (5, 32-34). Oral NAC may also be recommended as a preventive or therapeutic agent for disease-related outcomes in stable non-septic and non-intubated patients. The efficacy of IV NAC has been indicated in some moderate-to-severe or ICU-admitted cases of COVID-19 who have experienced complications like end-organ failure. There are many reports of the efficacy of NAC administration in cytokine storms, dyspnea, and ARDS related to COVID-19 (5). If indicated, the use of NAC via different administration routes varies case by case. Currently, based on studies with the highest level of evidence, it can be concluded that NAC may be most effective in stable patients when administered in the standard dose, and its preventive role (ie, to help non-infected patients or to help infected patients experience a better disease course) may be the most important aspect of this multipotential drug (35). To our knowledge, the present study is one of the best-designed RCTs to date for the evaluation of the efficacy and safety of NAC in hospitalized patients with COVID-19 infection. In summary, the findings of this RCT showed that the mean hospitalization duration (not merely in the ICU) was the shortest in the atazanavir/ritonavir + HCQ group (6.73 d) and longest in the Kaletra + HCQ + NAC group (11.87 d), with the difference between the 4 treatment groups in this regard failing to constitute statistical significance (P = 0.082). The mean length of ICU stay was the shortest in the atazanavir/ritonavir + HCQ + NAC group (1.8 d) and longest in the Kaletra + HCQ group (3.4 d), although these differences were not statistically meaningful (P =0.172). These results, albeit statistically nonsignificant, showed that the patients who received NAC had more total hospitalization days and fewer ICU hospitalization days, which means that these patients were more likely to have a stable general condition.

At hospitalization and before the commencement of the main treatment, CT scans and severity scores showed that ground glass opacification consolidation had the highest frequency (n =11) in the atazanavir/ritonavir + HCQ group and the lowest frequency (n =6) in the Kaletra + HCQ + NAC and Kaletra + HCQ groups. Bilateral opacification consolidation had the highest frequency in the atazanavir/ritonavir + group HCQ (n =8) and the lowest frequency in the Kaletra + HCQ + NAC group (n =5). Multifocal opacification consolidation exhibited the highest frequency in the atazanavir/ritonavir + HCQ group (n =7) and the lowest frequency in the Kaletra + HCQ group (n =4). None of the above was significantly different between the groups, denoting a normal distribution regarding lung involvement severity between the groups in this RCT.

At hospitalization and before the commencement of the main treatment, the 4 study groups were statistically significantly different in terms of seg_lymph_ratio, CRP, partial thromboplastin time (PTT), and LDH;

nonetheless, at the end of the study, only CRP remained statistically meaningfully different between the groups. A further decrease in CRP was observed in the NAC group at the end of the study. Concerning CRP at discharge, the atazanavir/ritonavir + HCQ + NAC group had the lowest value (5.99), whereas the Kaletra + HCQ group had the highest value (40.00); therefore, the difference between the groups in CRP was statistically significant (P =0.008). In regard to ESR at discharge, the atazanavir/ritonavir + HCQ + NAC group exhibited the lowest value (9.00), while the Kaletra + HCQ + NAC group showed the highest value (65.50); there was, however, no statistically meaningful difference between the groups vis-à-vis ESR, indicating CRP changes are a more sensitive criterion for measuring response to treatment and reducing inflammation than ESR.

Other than CRP, in terms of the comparison of laboratory findings before the treatment of the hospitalized patients and at the time of discharge, the statistically significant findings are as follows:

With respect to diff_segment at discharge, whereas the Kaletra + HCQ + NAC group had the lowest value (62.97%), the atazanavir/ritonavir + HCQ + NAC group exhibited the highest value (79.96%). Conversely, apropos of ALP at discharge, the highest and lowest values were observed in the Kaletra + HCQ + NAC group and the atazanavir/ritonavir + HCQ + NAC group, respectively, and this difference was of statistical significance (P =0.001). It could be interpreted that the antiviral regimen exerted a more significant impact on diff_segment and ALP, so the improvement trend was more pronounced in the atazanavir/ritonavir regimen than in the Kaletra (lopinavir/ritonavir) regimen. As we know, in COVID-19 course we usually have leukopenia, lymphopenia and partial increase of segmented cell percentage but a lower total segmented cell count than the normal situation.

No death occurred in the atazanavir/ritonavir + HCQ + NAC group, indicating that the combination of these drugs might reduce mortality.

In regard to O_2 saturation, the highest level was observed in the atazanavir/ritonavir + HCQ group and the atazanavir/ritonavir + HCQ + NAC group at the end of the study. Additionally, a significant increase occurred after intervention in the O_2 saturation level of the groups that received NAC (P <0.05), which can be considered the most important finding of the current study.

A redox imbalance in alveolar epithelium cells causing apoptosis, increased inflammation and, consequently, impaired gas exchange has been documented in most COVID-19 cases. Many articles have reviewed the potential positive effects of NAC as a multipotential drug in the management of COVID-19 and its associated complications (5). In addition, some original studies including case reports, case series, and trials have focused on NAC for the treatment and management of patients with COVID-19 and its associated complications such as end-organ failure (especially, acute liver failure in the cases of remdesivir-induced liver failure, elevated liver enzymes, and intrahepatic hemorrhage), ARDS, and seizure (36, 37). In these complicated cases, NAC has usually been used as an IV infusion.

In an RCT conducted in Brazil to evaluate the efficacy and safety of IV NAC in admitted severe cases of COVID-19 (oxyhemoglobin saturation <94% or respiratory rate >24 breaths/minute), IV NAC failed to significantly reduce the need for mechanical ventilation by comparison with the control group in that 20.6% of the NAC group as opposed to 23.9% of the dexterous group required mechanical ventilation. Also in that study, the duration of mechanical ventilation, the rate of ICU admission, the length of ICU stays, and the rate of mortality were not statistically significantly different between the intervention and case groups, indicating that the administration of NAC in high doses did not affect the evolution of severe COVID-19 (35). The present study enrolled solely stable, moderate-to-severe, non-ICU admitted COVID-19 patients (N =60), among whom only 11 patients ultimately needed ICU admission during their disease course regardless of their therapeutic regimen. Accordingly, the severity score of patients and the administration route of NAC (IV vs oral) were different between the current RCT and the one in Brazil. Still, the interpretation of the results of these 2 trials indicates that NAC could be more effective as prophylactic or adjuvant therapy in stable non-severe cases of COVID-19 with a particularly positive role in the augmentation of O_2 saturation and faster reduction of the CRP level and inflammation.

Aside from the therapeutic roles of NAC, not least as adjuvant therapy, the prophylactic roles of this multipotential drug in COVID-19 infection (38-40) and its related complications (41) have been discussed in many reviews (40, 42-47) and original studies (48, 49) all of which have focused mainly on the drug as an anti-inflammatory and anti-apoptotic agent.

In a very well-designed study on the treatment of COVID-19 patients with NAC, the drug in high doses failed to improve the outcomes of severe and ICU-admitted cases (35, 50). Another trial demonstrated that a combination of methylene blue, vitamin C, and N-acetyl cysteine increased the survival rate of COVID-19 patients (16). The results of a case series indicated that the oral and IV administration of glutathione, glutathione precursors (N-acetyl-cysteine), and ∝-lipoic acid might represent a novel treatment approach to blocking NF-ϰB and addressing cytokine storms and ARDS in patients with COVID-19 pneumonia (51). In a comprehensive study, a combination of copper, NAC, colchicine, and nitric oxide with candidate antiviral agents (viz. remdesivir or EIDD-2801) was used as a treatment for patients positive for SARS-CoV-2 (17). In the pandemic era of COVID-19, the authors of the present study have sought to assess the diagnostic, prognostic, and therapeutic concerns of this infection, focusing especially on dermatologic issues (52-63). They have also conducted comprehensive and systematic reviews and original articles. In their first review study, they discussed the potential drugs that could positively affect the COVID-19 course and outcome such as NAC (5). Since then, they have endeavored to conduct RCTs aimed at evaluating the efficacy and safety of multipotential drugs such as NAC. In light of the findings of the current RCT, we posit that the use of oral or IV NAC, if indicated, may boost O_2 saturation, ameliorate inflammation by lowering CRP, and lessen mortality.

CONCLUSIONS

Given the current absence of any gold-standard therapy for the treatment of COVID-19 or its associated complications, multipotential drugs with anti-inflammatory, antioxidant and anti-apoptotic properties could have promising results if indicated or used in a proper setting. We designed one of the best-designed RCTs to date to evaluate the efficacy and safety of NAC in the treatment of patients with COVID-19. The salient findings of this RCT were that at the end of the study, a further drop in C-reactive protein was detected in the NAC group (P =0.008), and no death occurred in the atazanavir/ritonavir + HCQ + NAC group, indicating that the combination of these drugs may lessen mortality. Moreover, the atazanavir/ritonavir + HCQ and atazanavir/ritonavir + HCQ + NAC groups had the highest O_2 saturation at the end of the study and a significant elevation in O_2 saturation after the start of the intervention, including NAC (P<0.05). In light of the findings of the present RCT, we can conclude that oral or intravenous NAC, if indicated, may boost O_2 saturation, blunt the inflammation trend (by reducing C-reactive protein), and decline mortality in hospitalized patients with COVID-19. The NAC could be more effective as prophylactic or adjuvant therapy in stable non-severe cases of COVID-19 with a particularly positive role in the augmentation of O2 saturation and faster reduction of the CRP level and inflammation.

Author's Contributions:

All authors contributed to the preparation of data and the finalization of this article. All the figures have been produced by the authors of this article and are personal data.

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Declaration of Conflict of Interest:

The authors declare there is no conflict of interests.

Data Availability:

The data supporting the findings of this study are available from the corresponding author upon reasonable requests.

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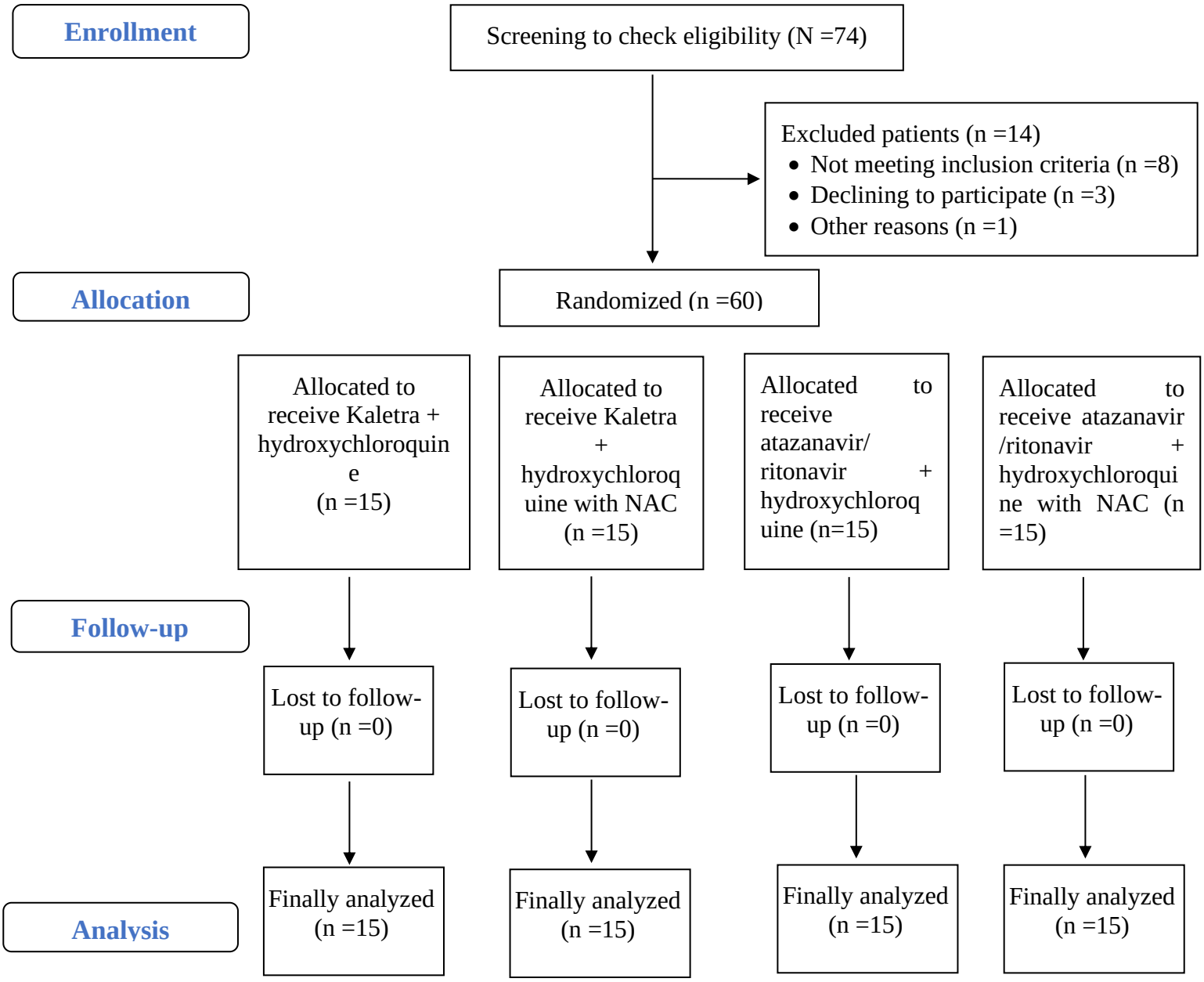
Figure 1. The flow diagram shows the flow of patients through the trial



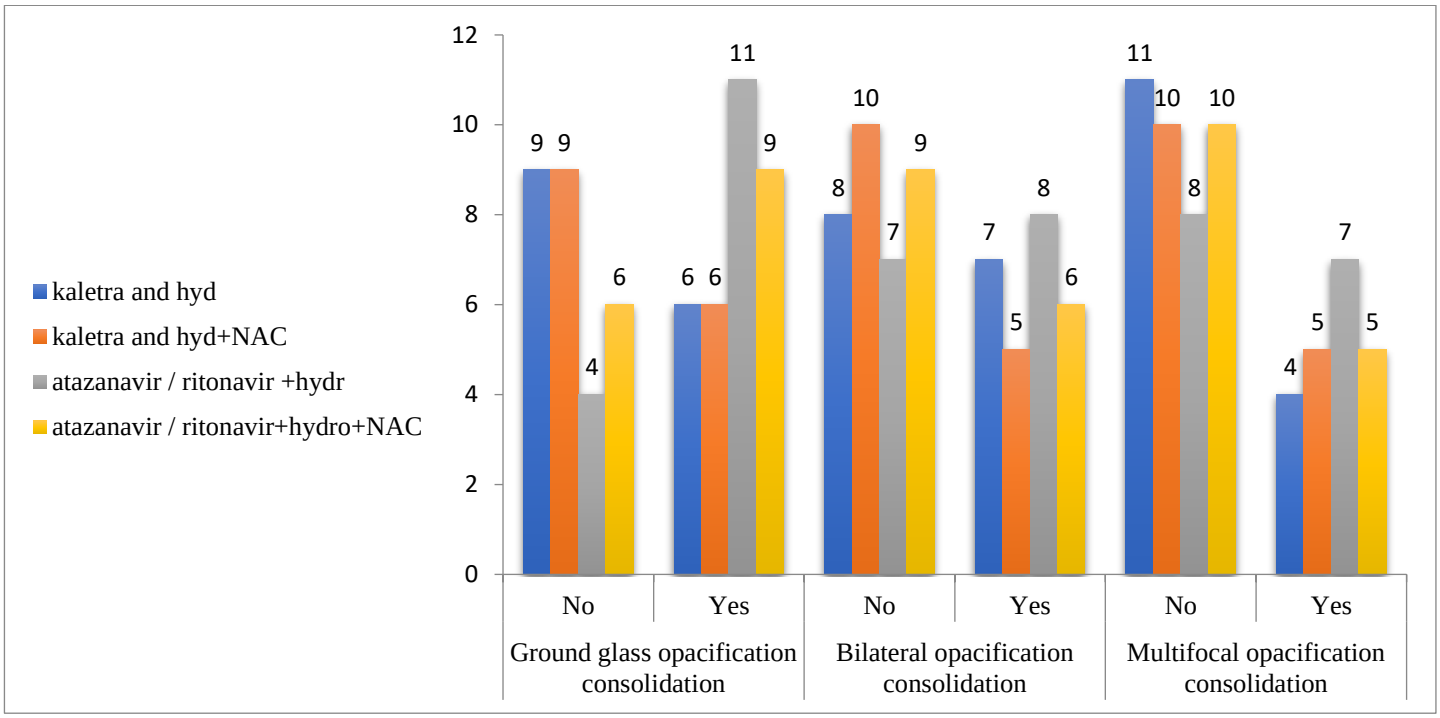


Figure 2. The image illustrates a comparison of opacification consolidation between the study groups according to the drugs administered.