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Efficacy of oral indomethacin in the treatment of COVID-19 infection; a randomized clinical trial

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Abstract

Introduction: Given the anti-viral activity of indomethacin and that it may be as a potent inhibitor of coronavirus replication, the goal of this study was to assess the efficacy of oral indomethacin in the treatment of COVID-19 infection.

Objectives: We evaluated the efficacy of oral Indomethacin on pneumonia of COVID 19 infection.

Patients and Methods: This randomized clinical trial was conducted on 45 patients with moderate symptoms of coronavirus-induced pneumonia admitted to Amin and Noor hospitals. All patients were randomly divided into two groups. In the intervention and control groups, 200 mg of hydroxychloroquine tablet was administered twice daily for 5 days. Acetaminophen was also prescribed if needed. Moreover, 75 mg indomethacin in slow-release formulation was administered for 5 days in the intervention group. Then patients were assessed regarding clinical parameters.

Results: The mean age of patients in the case and control groups was 51.59±15.74 and 56.65±12.90 years old, respectively ($P=0.41$). Among 45 patients, 22 (48.9%) and 23 patients (51.1%) were male and female, respectively. The frequency of tracheal intubation in intervention and control groups was 0 (0%) and 1(4.54%), respectively ($P=0.51$). The mean recovery time in the intervention and control groups was 7±4 and 5±2, respectively ($P=0.52$). Furthermore, no patients in the two groups were re-hospitalized up to 28 days ($P>0.05$). Moreover, there was no significant difference between the two groups after intervention in terms of SpO2% ($P=02$).

Conclusion: According to these findings, oral indomethacin did not affect tracheal intubation in patients with COVID-19. Moreover, mean recovery time, re-hospitalization and SpO2 value were not influenced by indomethacin. Therefore, the use of oral indomethacin is not suggested in these patients.

Trial Registration: The trial protocol was approved by the Iranian Registry of Clinical Trials website(identifier: IRCT20200427047215N1; https://www.irct.ir/trial/47520, ethical code; IR.MUI.MED.REC.1399.045).

Introduction

Coronavirus disease 2019 (COVID-19) was first originated at China in December 2019 (1). It spread rapidly around the world, which was due to severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection (2). The majority of cases were in middle-aged and older people, however, a growing trend of COVID-19 was also observed in children in many countries around the world (3). The mortality rate of COVID-19 was lower than the Middle East respiratory syndrome (MERS) and coronaviruses severe acute respiratory syndrome (SARS) (1). Moreover, the common symptoms of this disease were fever, severe headache, cough, fatigue and myalgia (1). Indomethacin as an inexpensive non-steroidal anti-inflammatory drug (NSAID) and a non-selective inhibitor of cyclooxygenase 1 and 2 had antiviral activity against various viral pathogens. The antiviral activity of indomethacin against various human viral pathogens including human immunodeficiency virus (HIV), SARS-CoV-2, herpes virus, and hepatitis B had been seen in many studies (4).

Key point

In a randomized clinical trial, we found oral Indomethacin (75 mg as slow release) in COVID-19 pneumonia did not affect tracheal intubation, mean recovery time, re-hospitalization and SpO2 value. Therefore, the use of oral indomethacin is not suggested in these patients.

Various therapeutic drugs were investigated and developed during the current COVID-19 pandemic. NSAIDs were commonly used as analgesics or antipyretics in patients with viral pneumonia (5). Indomethacin, as an NSAID drug, was a unique medicine with anti-inflammatory and anti-viral activity (6).

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Indomethacin can be used alone or in combination with antiviral therapy like remdesivir in noncritical patients (7). NSAIDs are less frequently used due to gastrointestinal side effects, like renal and platelet dysfunction; however, indomethacin was rarely caused serious complications (8, 9). The anti-inflammatory effect of indomethacin was well recognized; since previous reports showed the anti-viral property of this drug (4).

Objectives

Given the pandemic of COVID-19 and potent antiviral activity of indomethacin (4) and while indomethacin may be as a potent inhibitor of coronavirus replication, thus the aim of this study was to assess the efficacy of oral indomethacin in the treatment of COVID-19 infection.

Patients and Methods

Study design

This randomized clinical trial was conducted on 45 patients with moderate symptoms of coronavirus-induced pneumonia admitted to Amin and Noor hospitals, Isfahan (Figure 1). Inclusion criteria were age range 18-75 years old, oxygen saturation (SPO2) levels between 85% and 90%, definitive diagnosis of COVID-19 based on reverse transcription polymerase chain reaction (RT-PCR), or chest high-resolution computed tomography, no need for intubation in the first 24 hours of hospitalization, no multiple organ failure and shock at the time of hospitalization and arterial oxygen saturation of 90% to 93% in room air with a respiratory rate of more than 30 breath/minute.

Exclusion criteria were sensitivity to indomethacin or NSAIDs, glomerular filtration rate (GFR) less than 60 CC/min, active gastrointestinal bleeding and history of urticaria and similar reactions during aspirin use.

In this step, 200 mg of hydroxychloroquine tablet was administered twice daily for five days in two groups (intervention and control groups). Acetaminophen was also prescribed if needed. Moreover, 75 mg indomethacin in slow-release formulations was administered for five days in the intervention group. The treatment plan was prescribed as soon as the initial tests were ready. The rate of readmission within 14 days of discharge, intubation time, intubation rate, and clinical improvement signs (body temperature less than 38°C, reduction of cough symptom; respiration rate less than 24 per minute and oxygen saturation more than 90% in room air) and re-hospitalization up to 28 days were extracted from medical records. The patients were assessed regarding clinical parameters every day. SpO2 was measured by pulse oximeter (C101a2 model).

Statistical analysis

Data were imported to SPSS, version 19. Chi-square and independent *t* tests were applied for analysis of data. *P* value <0.05 was considered significant.

Results

The mean age of patients in the case and control group was 51.59 ± 15.74 years and 56.65 ± 12.90 years old ($P = 0.41$). Among 45 patients, 22 (48.9%) were male.

The frequency of tracheal intubation in intervention and control groups was shown in Table 1.

As shown in Table 2, no significant difference was seen between two groups regarding frequency of tracheal intubation ($P > 0.05$). The mean recovery time in thr intervention and control groups are shown in Table 2. As shown in this table, no significant difference between two groups regarding recovery time was seen ($P > 0.05$). The mean SpO2 at the first and end of study is demonstrated

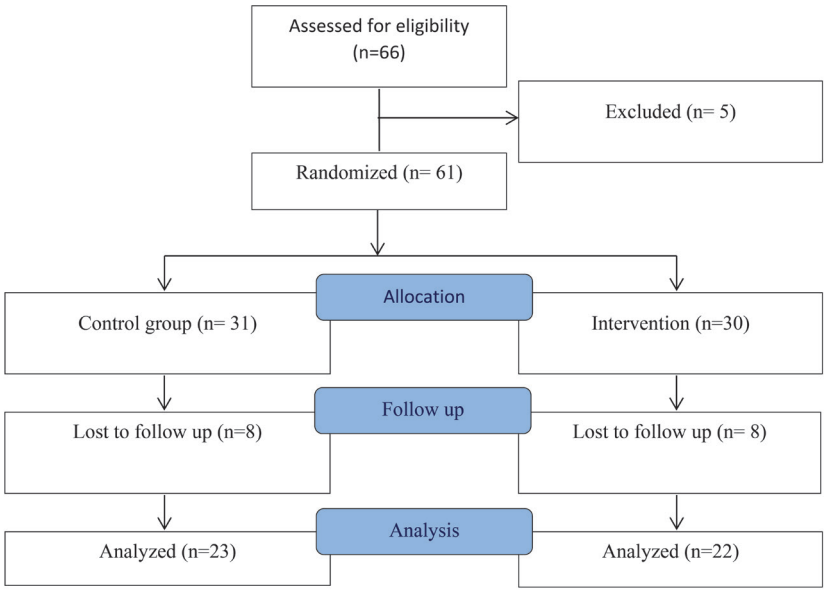

Figure 1. Consort flowchart of the study.

Table 1. The frequency of tracheal intubation in intervention and control groups

Group	Frequency (%)	*P* value
Case	0 (0)	0.51
Control	1 (4.54)	

Table 2. The mean recovery time in intervention and control groups

Group	Frequency (%)	*P* value
Case	7 ± 4	0.52
Control	5 ± 2	

Table 3. The mean SpO2 in the first and end of study

Group	In the first of study (Mean ± SD)	In the end of study (Mean ± SD)
Case	87.18±4.05	91.73±3.19
Control	88.2±3.20	92.5±2.7
P value	0.39	0.2

in Table 3. We found, no significant difference was seen between case and control groups before intervention regarding SpO2. Moreover, there was no significant difference between two groups after intervention in terms of SpO2 ($P > 0.05$). Furthermore, no patients in the two groups were re-hospitalized in the hospital up to 28 days ($P > 0.05$).

Discussion

In the current study, we assessed the efficacy of oral indomethacin in the treatment of COVID-19. We observed no significant difference in frequency of patients in two groups (case and control groups) regarding tracheal intubation, indicating no efficacy of oral indomethacin in the treatment of COVID-19. In addition, no significant difference between case and control groups in terms of recovery time and re-hospitalization was detected. Marinella assessed the effect of indomethacin and resveratrol (an antiviral medicine) in the treatment of SARS-CoV-2/COVID-19 and reported that indomethacin decreased canine coronavirus levels in dogs (6). Moreover, Marinella also demonstrated antiviral activity of resveratrol as a potent antioxidant and antiviral activity against several viruses (6). Although there was no randomized trial data regarding comparison of indomethacin and resveratrol in progression of SARS-CoV-2 infection, these agents should be considered as worthy therapeutic adjuncts (7,10). Amic et al reported that indomethacin had a potent antiviral activity against the canine CoV and SARS-CoV (4). They also reported that indomethacin acted via blocking viral RNA synthesis at cytoprotective doses (4). On the other hand, the use of this drug was associated with potent antiviral activity against the SARS CoV-2 pseudovirus.

Kanakaraj et al assessed the effect of low dose indomethacin in treatment of COVID-19 in kidney transplant recipients and demonstrated good recovery at the end of 4 weeks; therefore, it prevented more hospitalizations by attenuating or avoiding the cytokine storm (11). It seems the difference between current study and other studies was related to the degree of disease, dose of medicine during the day, and type of disease.

We did not observe any significant difference between the two groups after intervention regarding SpO2%. Ravichandran et al assessed the effect of indomethacin and paracetamol in patients with mild and moderate COVID-19. No one in indomethacin group developed desaturation, while 20 patients in the paracetamol group developed desaturation (12). The findings of this study indicated the superiority of indomethacin to paracetamol. Ravichandran et al also assessed the efficacy and safety of indomethacin in treatment of COVID-19. They administered 75 mg indomethacin (sustained release) for five days with remdesivir and observed among the patients of intervention group only one needed supplementary oxygen, whereas 28 out of 72 patients in the paracetamol group needed oxygen supplement (12). According to these findings, the administration of indomethacin along with standard medicine prevented progression of pneumonia and provided faster symptomatic relief and reduced the duration of disease. It seems that the difference between our study and the study by Ravichandran et al was related to the difference of severity of COVID-19 and standard medicine used in two studies.

Although precise mechanism of antiviral action of indomethacin was unknown, it seems that indomethacin may interrupt the viral life cycle of various herpesviruses and reduce latent infections via inhibiting the synthesis of prostaglandin (9). Indomethacin can also reduce inflammatory mediators including interleukin-6 and tumor necrosis factor as well as superoxide free radicals, which invoke cellular damage. On the other hand, blunting of cascade of cytokine storm by indomethacin can conceivably reduce inflammatory mediators (9). Raaben et al also reported that indomethacin is used as a potent anti-inflammatory drug via blocking the activity of cyclooxygenase 1 and 2 and reducing the synthesis of prostaglandin by inhibiting cyclooxygenase (4). Based on the finding of this study, indomethacin triggers a cellular antiviral defense mechanism by activating PKR (protein kinase R) in an interferon- and dsRNA (double-strand RNA(dsRNA))-independent manner (4). PRK plays a main role in the antiviral defense mechanism of the host and acts as a sensor of virus replication. Furthermore, it after activation leads to eukaryotic initiation factor-2α (eIF2α) phosphorylation and block of synthesis of protein in virally infected cells (13).

Conclusion

According to the findings of study, oral indomethacin did not affect tracheal intubation and in patients with COVID-19. Moreover, mean recovery time, re-hospitalization and SpO2 value were not influenced by

indomethacin. Therefore, the use of oral indomethacin is not suggested in these patients.

Limitations of study

The first limitation of this study is that patients with severe symptoms were not evaluated because they received various antibiotics and drugs in order to control the confounding factors. The second limitation is small sample size of the groups.

Authors' contribution

MS, SP and AD were the principal investigators of the study. MS, AD, FS, and BA were included in preparing the concept and design. AD and ZA revisited the manuscript and critically evaluated the intellectual contents. All authors participated in preparing the final draft of the manuscript, revised the manuscript and critically evaluated the intellectual contents. All authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research was conducted in accordance with the tents of the Declaration of Helsinki. The Ethics Committee of Isfahan University of Medical Sciences approved this study (IR.MUI.MED.REC.1399.045). Accordingly, written informed consent was taken from all participants before any intervention. The trial protocol was approved by the Iranian Registry of Clinical Trials (identifier: IRCT20200427047215N1; https://www.irct.ir/trial/47520). Moreover, Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors. This study was a part of internal medicine residency thesis of Zeinab Ahmadikia at this university.

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