Journal of Research in Clinical Medicine

J Res Clin Med, 2023, 11: 24
doi: 10.34172/jrcm.2023.33431
https://jrcm.tbzmed.ac.ir

TUOMS PRESS

Original Article

Prospective, randomized single-blind, multicenter comparison of the analgesic efficacy of flurbiprofen/thiocolchicoside and ibuprofen in myalgia complaints in SARS-CoV-2 patients

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Article info

Article History:
Received: January 28, 2023
Accepted: April 20, 2023
e-Published: October 25, 2023

Keywords:
Analgesia, Myalgia, Pain, SARS-CoV-2

Abstract

Introduction: Myalgia is a common symptom in patients with COVID-19. NSAIDs perform pain suppression mechanisms by suppressing prostaglandin synthesis through inhibition of cyclooxygenase enzyme (COX). Thiocolchicoside activates GABA and Glycine receptors at the spinal level and exerts a myorelaxant effect. The aim of this study is to compare the analgesic efficacy of two drugs, the active ingredients of which are ibuprofen and flurbiprofen/thiocolchicoside.

Method: The study was designed according to a multicenter, prospective, randomized, controlled clinical trial model. A power analysis was performed based on the study of Derosa et al. including patients with myalgia complaints(11). By accepting 80% power and 5% type-1 error, the number of patients to be included in each group was calculated as at least 68. We planned to include 100 patients in each group, taking into account data losses and patients who may drop out of the study during follow-up (n = 200).

Results: According to the results of the study, the difference between baseline and 2nd day NRS and the difference between baseline and 3rd day NRS were found to be statistically significantly higher in the group using ibuprofen 800 mg retard TB ($P < 0.05$).

Conclusion: In the treatment and follow-up of patients with COVID-19 and myalgia complaints, ibuprofen 800 mg retard tb can be preferred primarily because its effectiveness is superior and no side effects are observed.

Introduction

Pain is a common symptom caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).[1] Acute pain can be classified as localized pain (sore throat or pharyngalgia), distant pain (headache), and general discomfort (body pain, limb or muscle and joint pain) in respiratory tract infection.[2] In addition, pain associated with coronavirus disease 2019 (COVID-19) may occur as a result of the neurotropic properties of SARS-CoV-2 or an autoimmune response to the virus. Despite several proposed factors involved in the disease pathophysiology, the exact underlying mechanism promoting the various persistent pain syndromes associated with COVID-19 are yet to be determined.[2-4] however, muscle injury or fascia play a crucial role in pain development.[5] Myalgia, reflecting the hyperinflammatory responses,[5] is a common symptom in patients with COVID-19 and other viral upper respiratory tract infections. Myalgia may be diagnosed as the first symptom in one-third of patients.[6] In individuals with COVID-19 infection, myalgia may last long continue more than in patients with other viral infections.[7] it is suspected that cytokines stimulate the prostaglandin E2 (PGE2) production, which in turn mediates pain through peripheral receptors.[8] In the acute phase, anti-inflammatory agents and muscle relaxants such as non-steroidal anti-inflammatory drugs (NSAIDs) are recommended to relieve pain and reduce edema.[5] NSAIDs lead to pain relief by suppressing PGs synthesis through inhibition of cyclooxygenase enzyme (COX).[9] In addition, it has been well-established that thiocolchicoside through activation of GABA and glycine receptors at the spinal level can exert a myorelaxant effect.[10]

The aim of this study is to compare the analgesic efficacy of two pain relief agents, in which the active ingredients

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consisting of ibuprofen and flurbiprofen/thiocolchicoside, to evaluate anti-analgesic effects on COVID-19 patients.

Methods

Study design and setting

The study was designed according to a multicenter, prospective, randomized, controlled clinical trial model, conducted on SARS-CoV-2 positive patients admitted to the emergency departments (EDs) of two tertiary hospitals. Ethical approval was obtained from the local ethics committee for the research. All patients participating in the study were informed and their written consent was obtained. This study complies with the principles of Good Clinical Practice of the Declaration of Helsinki. A detailed informed consent form was also signed by each patient before inclusion in the study. The study was carried out according to the CONSORT directive.

Patient selection

Patients with a confirmed SARS-CoV-2 through polymerase chain reaction (PCR) test, presenting with the complaint of myalgia were included in the study. The participants were aged between 18-65 years old, hemodynamically stable, had no comorbidities, a numeric rating scala (NRS) score of $4 \leq$, and no history of adverse reactions caused by the drugs were included.

The patients who were pregnant, lactating, patients with a history of allergic reaction to drug used in the study, the patients with comorbidity such as hypertension, kidney failure, liver disease, chronic obstructive pulmonary disease, heart failure, diabetes, etc), patients who had used analgesic drugs in the last 6 hours, those with hearing impairment, and patients with underlying neurological and psychiatric disorders were excluded from the study.

Sampling size

The sample size was calculated by using G-Power 3.1 software. A power analysis was performed based on the study of Derosa et al.[11] By accepting 80% power and 5% type-1 error, the number of patients to be included in each group was calculated as at least 68. We planned to include 100 patients in each group, taking into account data missing and patients who may fail to follow-up (n = 200).

Randomization

Randomization was carried out by the principal investigator. The randomization table was created on the website https://www.randomizer.org/. Patients were assigned to groups in a ratio of 1:1. For the patients accepted to participate in the study, the predetermined drugs were given to the patients as tuberculosis (TB) at discharge. The relevant drugs were numbered in equal groups (treatment no. 1 and treatment no. 2), and the randomly selected drug was explained to the physician responsible for patient care, who was outside the researcher group working in the outpatient clinic and was given by hand on the way to the patients. The data obtained from the patients was recorded on the case report form. The physicians in the study did not know which drug was given to the patient until the end of the study.

Treatment protocol and grouping

The treatment protocol was administered to all patients included in the study, as a standard, 50 mg dexketoprofen trometamol (Arveles® 50 mg/2 mL ampoule, Ufsa, Pharmaceutical Ind. Trade. Co. Ltd. Turkey) in 150 mL 0.9% NaCl, intravenously 10 minutes. It was given as a rapid infusion upon the admission (t = 0)

During the discharge of the patients, drugs in the form of TB, were given to the patients as treatment No. 1 or 2. The patients were advised to use it b.i.d with 12 hours interval.

Information was given about the use of NRS in pain level measurement and the NRS scale. The NRS is a scale of 0-10 cm, and patients who expressed the pain severity from 0 to 10, which was recorded daily.

Group 1; flurbiprofen + thiocolchicoside (Majezik Duo®100 mg/8 mg film-coated tb, Sanovel İlaç San. ve Tic. A.Ş., Istanbul, Turkey), Group 2; ibuprofene 800 mg (Brufen Retard® 800 mg slow release film tube, Abbott Laboratories İTH. İHR. VE TİC. LTD. ŞTİ, İstanbul, Turkey).

Statistical analysis

IBM SPSS Statistics, version 20.0 (Armonk, NY: IBM Corp) was used for statistical analysis. Distribution analysis of continuous data was performed with the Shapiro-Wilk test. Frequency (n) and percentage (%) were given for categorical variables, and median and interquartile range for variables that did not show normal distribution. Pearson chi-square and Fisher's exact tests were used to compare categorical data in the study. Data that did not fit the normal distribution were compared with the Mann-Whitney U test. The $P < 0.05$ level was used for statistical significance.

Results

A total of 198 patients were included in the study, which was assigned into two groups consisting of 98 and 100 patients, respectively. In the first group with 98 patients, two patients were excluded from the study because of inappropriate utilizaion of the given drugs. The patient distributions and treatment groups in the study are given as CONSORT flow diagram (Figure 1). Out of all participants, 60.1% of the patients were female and the mean age was 35.6 ± 12.0 years old.

According to the demographic and physical characteristics, symptom onset time, analgesic use, and time to take analgesics between the two groups have been brought in Table 1, it was found that the NRS score

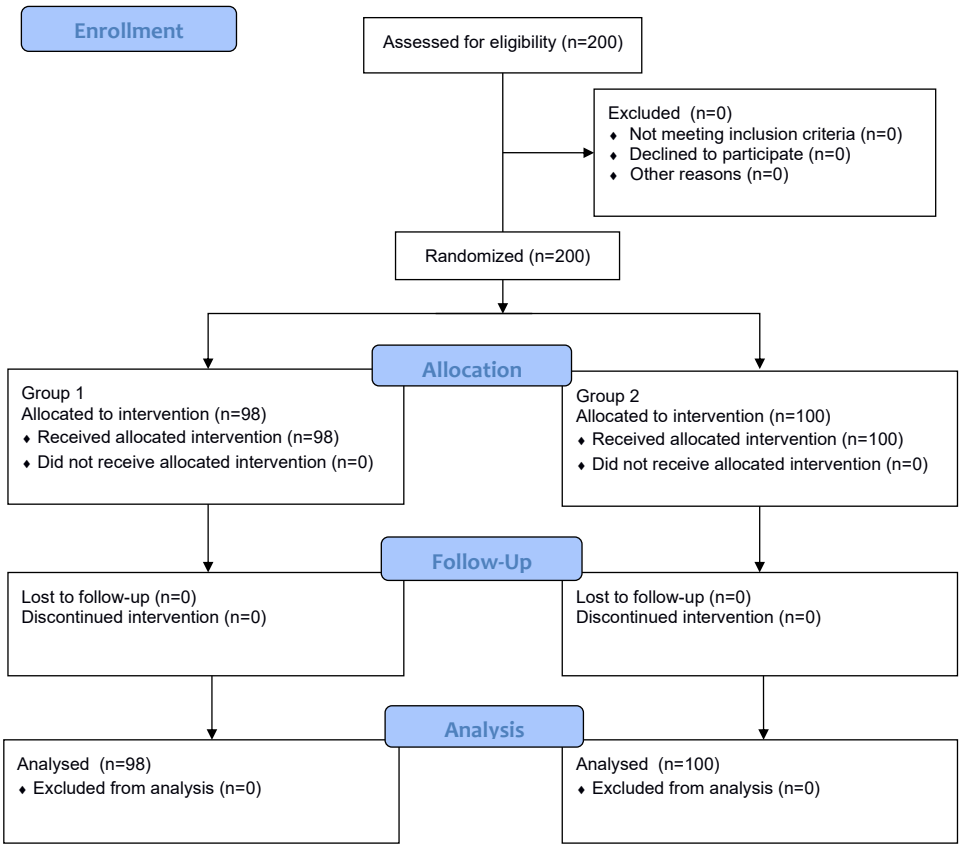

Figure 1. Distribution pattern of treatment groups

was significantly higher in group 2 and was statistically significant ($P=0.002$). Other NRS scores did not show statistically significant difference ($P>0.05$).

In Table 2, the differences in pain scores at baseline and at follow-up are evaluated. According to these results, the difference between baseline and 2nd day NRS and baseline and 3rd day NRS differences were found to be statistically higher in the group 2 ($P<0.05$). However, there was no significant difference between the two groups in terms of baseline and day 1 NRS difference ($P>0.05$).

Discussion

Available data show that pain is a common symptom. which has been often described as a clinical feature of COVID-19.[4,12] The main pain syndromes associated with the acute phase of this disease are headache, myalgia, arthralgia, and neuropathic pain.[13] It can be also assumed that the myalgia is not a significant predictor of the severity of COVID-19 infction.[6,13]

In this study, the efficacy of ibuprofen 800 mg retard tb and flurbiprofen/thiocolchicoside 100/8 mg tb forms were compared in patients who had COVID-19 infection, and referred to the ED with the complaint of myalgia and were planned to be discharged. This multicenter, prospective, randomized controlled clinical trials the first study, comparing two distinct forms of tb in COVID-19 patients with myalgia. Although, the efficacy of both drugs used in the study on myalgia symptoms was significantly high, only the difference between NRS scores of day 0 and day 3 was statistically significant in favor of ibuprofen 800 mg retard tablet. None of the patients experienced clinical worsening and readmission.

In a few studies that assessed the myalgia, it has been also reported that myalgia is prominent almost in ≥50% of the patients.[12,13]

there are limited studies regarding the ibuprofen and flurbiprofen active ingredients application,[14-18] for example, the combination of oral ibuprofen and flurbiprofen spray were used in the management of pain after tonsillectomy, and a statistically significant relief was observed in the group with flurbiprofen spray.[14]

In a multi-clinical study, 195 patients with osteoarthritis were received 80 mg/day flurbiprofen or 1600 mg/day ibuprofen for six weeks, and subsequently, the improvement in the pain levels of the patients was compared. The results did not show a statistically significant difference between the two groups.[15] In another study involving 208 patients with rheumatoid arthritis (RA), 120 mg flurbiprofen and 2400 mg ibuprofen were used daily for 6 weeks. Furthermore, pain and tenderness in addition to other symptoms of RA were evaluated. No statistically significant difference was also found between the two drugs.[16]

Studies on the pain control of primary dysmenorrhea using multiple NSAIDs, including ibuprofen and flurbiprofen, were presented as a meta-analysis, and it was

Table 1. Demographics and pain scales

Variables	Group 1		Group 2		*P* value
	Median (25-75%)	n (%)	Median (25-75%)	n (%)	
Age (year)[b]	31 (26-42)		34.5 (26-42.5)		0.521
Gender[a]					
Male [b]		41 (41.8)		38 (38)	0.581
Female [b]		57 (58.2)		62 (62)	
Height [b]	168 (162-177)		167 (162-175)		0.601
Weight [b]	68 (59-82)		69.5 (60-79.5)		0.982
Symptom start time [b]	48 (20-48)		48 (24-72)		0.400
Analgesic use[a]		34 (34.7)		47 (47)	0.078
Analgesic use timing[b]	12 (10-16)		12 (8-14)		0.204
NRS-0 [b]	6 (5-7)		7 (6-8)		0.002
NRS-1 [b]	4 (3-5)		4 (3-6)		0.061
NRS-2 [b]	3 (1-4)		3 (2-5)		0.468
NRS-3 [b]	2 (0-3)		1 (0-3)		0.962

[a] Pearson Chi-square test. [b] Mann Whitney-U test
NRS: Numeric Rating Scale

reported that the flurbiprofen group's efficacy on pain control was superior to the other NSAID groups.[17] They reviewed 14 studies on the symptomatic treatment of RA in which patients used orally 200 mg flurbiprofen, 4000 mg aspirin, 150 mg indomethacin, 750 mg naproxen, and 1800 mg ibuprofen. As a result of this study, it was reported that the group using flurbiprofen was statistically relieved more effectively than the other NSAID groups.[18] In our study, although the daily dose of the flurbiprofen group was higher and there was 8 mg thiocolchicoside in the active ingredient of the drug, the decrease in the pain levels of the patients was statistically more significant in the ibuprofen group.

In two studies, it has been revealed that the pain complaints are more common among women , which may be due to genetic, hormonal, and psychosocial factors.[19,20] In line with this report, most of the patients included randomly to our study were also women.

Also, Akarsu and his colleagues indicated that myalgia is more common in women, the average onset of symptoms is 48 hours, and the severity of pain is moderate to severe,[13] which were similar to the findings of our study.

Limitations of this study

Our study has also several limitations. The first one is that although the study was a multicenter, randomized controlled clinical trial, it could not be double-blind. In both groups, the practitioners and patients did not know the drugs given during the discharge of the patients. However, the study could not be designed as double-blind because the patients could see the drug's name when they used the drugs at home. Our second limitation is referred to the patients with co-morbidities were not included in the study. While medications are administered through telephone inquiries regarding patient adherence, it is important to acknowledge another inherent limitation of our study, which pertains to patients' autonomous discretion in the utilization of prescribed medications. In addition, the fact that the median of the initial pain score of group 2 patients was higher can be considered as a limitation.

Table 2. Follow-up differences in pain scales

	Group 1	Group 2	*P* value[a]
	Median (25-75%)	Median (25-75%)	
NRS difference 0-1	2.0 (1.0-3.0)	2.0 (1.0-3.0)	0.086
NRS difference 0-2	3.0 (2.0-4.0)	4.0 (2.5-5.0)	0.034
NRS difference 0-3	4.0 (3.0-5.0)	5.0 (4.0-6.0)	0.001

[a] Mann Whitney-U test.
NRS: Numeric Rating Scale.

Conclusion

In the treatment and follow-up of patients with COVID-19 and myalgia complaints, ibuprofen 800 mg retard tb can be preferred primarily because its effectiveness is superior and no side effects are observed.

Acknowledgments
All authors would like to thank all the patients for their willingness to participate in the study and their patience.

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Competing Interests
The authors declare no competing interests.

Ethical Approval
This study was approved by the Atatürk University Faculty of Medicine Ethics Committee (Date: 28 April 2022, no: 4/27-Ethic Number: B.30.2.ATA.0.01.OO/354).

Study Highlights

What is current knowledge?
- There are no studies on the analgesic efficacy of ibuprofen and flurbiprofen on Covid-19 myalgia.

What is new here?
- Ibuprofen 800 mg retard tablet has a more effective analgesic effect than flurbiprofen in Covid 19 myalgia.

Funding
The author did not receive any type of commercial support for this study.

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