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Research Article

Combination of Chinese and Western Medicine: Molnupiravir and Lianhua Qingwen in the Treatment of Novel Coronavirus Pneumonia (COVID-19)

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Abstract:

Objective: This study aimed to assess the effectiveness of Molnupiravir and Lianhua Qingwen in treating patients with novel coronavirus pneumonia (COVID-19).

Materials and Methods: We conducted a study involving 14 cases of COVID-19 infection within a unit group in Laos. During the treatment regimen, these patients received the antiviral drugs Molnupiravir and Lianhua Qingwen as prescribed. We utilized laboratory results of viral nucleic acid tests as observational parameters and statistically analyzed the data using SPSS 26.0 software (linear regression analysis). Our data analysis aimed to determine if there were significant differences in the Ct values of the N gene and ORF1ab gene of SARS-CoV-2 before and after treatment.

Results: The results indicated statistically significant differences in the N gene ($t = -7.014$, $P < 0.001$) and ORF1ab gene ($t = -7.398$, $P < 0.001$). Post-treatment, the values of the N gene and ORF1ab gene were significantly higher than their pre-treatment values, signifying that the combined utilization of Molnupiravir and Lianhua Qingwen had a substantial impact on the treatment of COVID-19.

Conclusion: Molnupiravir and Lianhua Qingwen effectively inhibited the replication of SARS-CoV-2, resulting in a marked improvement in the clinical symptoms of the patients. Laboratory test results also indicated a significant reduction in viral load. These findings provide substantial evidence supporting the efficacy of the combination of Molnupiravir and Lianhua Qingwen in the treatment of COVID-19.

Key words: novel coronavirus; Molnupiravir; Lianhua Qingdao; viral load

Introduction

Since December 2019, the world has been grappling with an outbreak of novel coronavirus pneumonia, known as Coronavirus Disease 2019 (COVID-19), originating in Wuhan, Hubei Province, China. This outbreak soon spread to numerous countries worldwide[1]. The gravity of the situation prompted the World Health Organization

(WHO) to declare the COVID-19 outbreak a Public Health Emergency of International Concern (PHEIC) on January 30, 2020. Subsequently, on March 11, 2020, WHO escalated its classification to declare COVID-19 a global pandemic[2]. As of December 2022, the disease has caused approximately 6.6 million deaths and over 651 million infections[3].

Consequently, in addition to the extensive efforts directed toward the development and promotion of antiviral vaccines, nations have been actively engaged in the development of various antiviral drugs. In November 2021, the UK Medicines and Healthcare Products Regulatory Authority (MHRA) approved the launch of the antiviral drug Molnupiravir[4]. The efficacy of Molnupiravir in reducing hospitalization

and death rates among COVID-19 patients has been demonstrated in clinical trials, with a reduction of up to 50% in risk[5].

Lianhua Qingwen is an innovative patented traditional Chinese medicine with potential efficacy against respiratory system diseases[6]. It can alleviate symptoms such as fever, cough, fatigue, muscle pain, and shortness of breath[7]. This traditional Chinese medicine is used to prevent severe acute respiratory syndrome (SARS)[8] and can inhibit and kill coronaviruses associated with SARS and Middle East respiratory syndrome[9-11]. Over the past decade, it has become a representative traditional Chinese medicine for treating respiratory infectious diseases[12].

This article aims to explore the potential efficacy of the newly approved antiviral drug Monupiravir in combination with the traditional Chinese medicine Lianhua Qingwen in the treatment of COVID-19. By investigating the combined use of these treatment methods, this study aims to help understand the effective treatment methods of COVID-19 and may provide new insights and strategies for combating the epidemic.

Materials and Methods

1 Information and Methodology

1.1 Subjects We enrolled a total of 14 COVID-19-infected patients from a specific unit group in April 2022 for this study. Among these participants, there were 12 male patients and 2 female patients, ranging in age from 27 to 57 years. In this study, we employed a random sampling method to ensure the representativeness of our sample. This approach aims to randomly select research subjects from the entire population rather than targeting specific individuals or groups. The purpose of our adoption of random sampling is to enhance the generalizability and comparability of the study results, thereby increasing the reliability and credibility of our research. The diagnosis of COVID-19 in these patients adhered to the criteria outlined in the "Diagnostic and Treatment Program for Novel Coronavirus Pneumonia (Trial Ninth Edition).[13]" It is worth noting that these patients did not have any specific records or events related to a history of infection-like illnesses. Consequently.

1.2 Methods The patients received a prescribed course of medication following the instructions for Molnupiravir and the guidance provided in the "Diagnostic and Treatment Program for Novel Coronavirus Pneumonia (Trial Ninth Edition)." During the study, we performed SARS-CoV-2 nucleic acid testing on infected patients, which included testing for the ORF1ab and N genes. Testing was conducted during two stages: the initial stage of infection (prior to treatment initiation) and during the treatment period (after completing the first course of treatment). Corresponding Ct values were recorded at both stages.

1.3 Reagents and Instruments

1.3.1 Sample Collection: For sample collection, single-use virus sampling tubes containing guanidinium salts were employed. Both nasal and pharyngeal areas were simultaneously sampled in this study[13-15].

1.3.2 In this study, a series of nucleic acid extraction devices and reagents were employed. The nucleic acid extraction apparatus used was an automatic nucleic acid extractor, and the nucleic acid extraction reagent utilized was a commercially available kit. For nucleic acid amplification, a fully automated medical PCR analysis system was utilized alongside a commercially available nucleic acid amplification reagent.

1.3.3 Procedure: We strictly adhere to the protocols provided by the experimental instruments and reagents. The procedure begins by equilibrating the nucleic acid amplification reaction solution, enzyme mixture, and ORF1ab/N reaction solution from the kit to room temperature. Subsequently, these components are briefly centrifuged with full shaking, and a reaction system with a total volume of 20 μL is prepared. Purification and nucleic acid extraction are conducted using the nucleic acid amplification instrument, employing 200 μL of the sample and nucleic acid extraction reagent. Following this, 5 μL of the purified sample is added to the reaction system, which is then briefly centrifuged with tightly fitted caps. For each batch of experiments, including 3 negative controls and 1 positive control is essential. Reverse transcription is performed at 50℃ for 10 minutes, followed by pre-denaturation at 95℃ for 5 minutes, denaturation at 95℃ for 10 seconds, and annealing/extension/detection of fluorescence at 55℃ for 40 seconds, with a total of 45 cycles.

1.3.4 Methodology: In this study, real-time fluorescence PCR was employed, with specially designed primers for the ORF1ab and N genes of SARS-CoV-2, along with TaqMan probes[16]. These were amplified using a fluorescence quantitative PCR instrument. We used the ROC curve method to determine the CT values for the ORF1ab and N genes. To ensure experiment accuracy, we incorporated endogenous ribonuclease P (RNase P) as an internal reference control[17]. This was done to monitor the experiment throughout the process and prevent false-negative results resulting from misclassification.

1.3.5 Quality Control: Each batch of experiments must adhere to the requirements outlined in Table 1 for both negative and positive controls. Additionally, the Ct value of the RNase P assay for human samples should be less than 45, ensuring the quality of the experiment[17].

target of detection	negative control	positive control
ORF1ab	No Ct value	Ct ≤ 30
N	No Ct value	Ct ≤ 30
internal reference (within the same publication)	—	Ct ≤ 30

Table 1: Negative/positive control Ct value

The instructions for the new coronavirus nucleic acid test specify that any sample with a Ct (Cycle Threshold) value of 40 or lower is reported as a positive result. In this study, we considered samples with a Ct value of 41 as negative results and included them in our statistical analysis[13].

1.4 Statistical processing

The data were analyzed statistically using SPSS 26.0 software. A linear regression analysis was conducted to examine the Ct values of the N gene and ORF1ab gene before and after treatment. The statistical results are presented in Table 2. The significance of the difference in Ct values between the N gene and ORF1ab gene before and after processing was determined based on the data analysis. A significance level of $p < 0.05$ indicates that the observed differences are statistically significant.

serial number	gender	age	Pre- treatment		Post-treatment	
			N	ORF1ab	N	ORF1ab
1	male	33	18.285	18.043	34.371	36.348
2	female	32	28.246	28.363	41.000	41.000
3	male	40	26.887	27.605	41.000	41.000
4	male	27	23.457	23.121	31.973	33.160
5	male	38	22.238	22.598	41.000	41.000
6	female	32	28.629	28.832	37.543	41.000
7	Man	39	22.137	23.371	37.988	41.000
8	Man	48	37.098	38.902	41.000	41.000
9	Man	38	31.902	32.637	36.887	41.000
10	Man	42	26.410	26.379	34.316	33.590
11	male	45	20.801	19.793	41.000	39.863
12	male	45	18.348	18.004	41.000	40.238
13	male	57	14.980	15.645	25.234	24.199
14	male	50	19.035	20.066	41.000	41.000

Table 2: Case data statistics

Results

The statistical results presented in Table 3 reveal significant differences in the N gene ($t = -7.014$, $P < 0.001$) and ORF1ab gene ($t = -7.398$, $P < 0.001$). Moreover, the post-treatment values of the N gene and ORF1ab gene were notably higher than their respective pre-treatment values. This indicates that the co mbined treatment of Molnupiravir and Lianhua Qingwen was effective in the management of COVID-19.

	Pre-treatment		Post-treatment		*t*	*P*
	M	SD	M	SD		
N	24.175	6.044	37.138	4.614	− 7.014	0.000
ORF1ab	24.526	6.393	37.921	4.881	− 7.398	0.000

Table 3: Differential comparison of treatment effects before and after treatment

Discussion

Currently, the Omicron strain has replaced the Delta strain as the predominantly endemic strain[18, 19]. Although the Omicron strain is more transmissible than the Delta strain, its pathogenicity has diminished[20]. In our study, we observed that many cases infected with the Omicron strain did not exhibit significant clinical symptoms. Patients only displayed mild to moderate respiratory and systemic symptoms and did not develop hypoxia, shortness of breath, or other complications necessitating hospitalization. In our clinical laboratory, we employ PCR to detect SARS-CoV-2 viral load. Studies, such as the work of E. Pujadas and others have established an association between SARS-CoV-2 viral load and mortality[21]. Our research primarily focused on patients in the early stages of the disease when the virus was actively replicating, and our findings indicated that outpatient antiviral therapy could effectively halt disease progression, reducing hospitalization and mortality rates[22].

Molnupiravir, an oral antiviral drug has demonstrated efficacy in treating patients with early-stage, mild cases of COVID-19[23]. It recently completed Phase III clinical trials in late 2021 and was approved for use in late 2022. The UK was the first country to authorize the use of Molnupiravir[4]. Some researchers, like F. Kabinger et al., have noted that Molnupiravir's mechanism of action includes increasing the frequency of viral RNA mutations and impairing SARS-CoV-2 replication in both animal models and humans[24].

This aligns with our findings, as we observed a decline in Ct values of SARS-CoV-2 nucleic acid assay results after two courses of the drug, suggesting a reduction in viral load. Our findings supported the discontinuation of centralized isolation, as per the newly released "Diagnostic and Treatment Protocol for Novel Coronavirus Pneumonia (Trial 10th Edition).[13]"

Lianhua Qingwen is an innovative and patented herbal medicine with potential efficacy in treating respiratory diseases[6]. In COVID-19 treatment, Lianhua Qingwen has demonstrated favorable therapeutic effects with minimal adverse reactions[25]. It was included in the "New Coronavirus Pneumonia Diagnosis and Treatment Program (Trial Ninth Edition)" issued by the National Health Commission in March 2022 as a therapeutic drug for patients with medically observed, mild, and common forms of the disease[13-26]. Recent studies, such as those by Chen Chaowu[27], Tan Duxun[28], and Li Ya[29], have confirmed its effectiveness in improving clinical symptoms and reducing inflammation in patients. additionally, research by Liu M and others[30] suggests that combining Chinese and Western medicine is more effective in treating COVID-19 without increasing adverse effects.

Molnupiravir, as a ribonucleoside analog, can inhibit the replication of the coronavirus[31]. When combined with Lianhua Qingwen in our study, it effectively reduced viral load in patients, as evidenced by declining Ct values. However, as a drug that recently completed clinical phase III trials, its efficacy and potential side effects in treating COVID-19 require

further scientific investigation. Scholars, such as R. Dal-Ré, emphasize the importance of assessing the safety and efficacy of antiviral medications against the Omicron variant[32]. Furthermore, the active metabolite of Molnupiravir, β-d-n4-hydroxy cytidine, has been reported to be cytotoxic and mutagenic in mammalian cells[24-33]. The use of Molnupiravir has drawn significant attention, and more research is needed to comprehensively assess its efficacy and safety in combination therapy.

Limitation of the Study

Our study focuses on the limited research regarding the combined application of Molnupiravir and Lianhua Qingwen in integrative Chinese and Western medicine treatment for COVID-19, employing rigorous research design, implementation, and data analysis methods. It represents a unique and innovative contribution, filling a gap in the literature and providing insights into the combined treatment of COVID-19 using Molnupiravir and Lianhua Qingwen. While our study is preliminary and exploratory, aiming to lay the groundwork for future larger-scale research, it offers valuable insights for clinical practice.

Our research sheds light on COVID-19 treatment, particularly in the early stages of infection. The combined therapy of Molnupiravir and Lianhua Qingwen shows promising clinical benefits, contributing to epidemic control and patient well-being. However, further scientific validation is required to confirm the efficacy and safety of these treatments in clinical settings. Multi-center clinical trials should be strengthened to fully explore their potential in addressing the evolving landscape of COVID-19 and safeguarding global public health.

Conclusion

The potential of Molnupiravir in treating COVID-19 has attracted significant attention, with some promising research findings. However, further comprehensive scientific investigation is necessary to evaluate its efficacy and safety, particularly in combination therapy. Our study reinforces the promising performance of Molnupiravir in treating COVID-19 patients, aligning with prior research and offering valuable insights into reducing viral load, facilitating patient recovery, and enhancing the drug's clinical application. Similarly, Lianhua Qingwen, an innovative traditional Chinese medicine, has emerged as a promising tool in combating COVID-19, demonstrating efficacy in symptom improvement and modulating the body's response, particularly in early treatment. The growing recognition of the importance of integrating Chinese and Western medicine is evident among scholars, and our study provides a novel perspective, especially for early-stage infections. The combination therapy of Molnupiravir and Lianhua Qingwen presents potential clinical benefits and significantly contributes to epidemic control and patient well-being.

In this study, we have substantiated the efficacy of Molnupiravir and Lianhua Qingwen in effectively inhibiting the replication of SARS-CoV-2. This provides robust and compelling evidence of their effectiveness.

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