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Original article

The Impact of Low-Cost Antibiotic Cotrimoxazole in Patients With COVID-19

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A B S T R A C T

The global pandemic Coronavirus Disease 19 (COVID-19) is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). Many patients with life-threatening illness due to COVID-19 die from hypoxic respiratory failure, which appears to be related to a cytokine storm syndrome leading to Acute Respiratory Distress Syndrome (ARDS). While steroids have some demonstrated benefits, supportive care remains the mainstay of treatment. However, in the absence of vaccines and proven treatments, during this current pandemic, we are considering repurposing currently available medications; one of the first is cotrimoxazole (CTX), which was one of the earliest medications for treating and preventing opportunistic infections caused by the human immunodeficiency virus (HIV), among other things. Cotrimoxazole in combination with folic acid is inexpensive, familiar to the public, and generally well tolerated, and treats secondary infections. Low cost and a good safety profile can make it an ideal candidate for the treatment of COVID-19 in a low-resource country like Libya. Here we report our observations with cotrimoxazole added to standard therapy in patients with severe COVID-19. Prospective data were gathered from consecutive newly diagnosed patients who presented to the Msallatah Isolation Center (Corona Center), Msallatah, Libya, between June and September of 2021 with critical COVID-19 on non-invasive ventilation and receiving standard therapy (ST) along with 480 mg oral cotrimoxazole (CTX). The first four days served as a control period during which patients with critical COVID-19 received only standard treatment. After a 4-day control period during which the patients received ST alone, nine patients (mean age ± SEM 40.5 ± 10.5 years, 66.66 percent male) were identified because they received CTX in addition to ST. We found that patients with critical COVID-19 who received CTX in addition to ST experienced significantly better outcomes, such as lower in-hospital mortality (0%), higher blood levels of D-Dimer (3735±579.9 mg/L versus 444.82±182.14 mg/L, $p<0.05$), and improvements in respiratory rate (36.42±3.9 mg/L versus 25.6±2.9 mg/L, $p<0.05$) and CRP at the fourth day of the experiment (142.12±34.7 mg/L versus 72.4±19.26 mg/L, $p<0.05$). These results demonstrate the beneficial effects of using cotrimoxazole in patients with severe COVID-19; it could help to reduce the need for respiratory support for thousands of patients, saving valuable lives and decreasing the burden on the healthcare system in countries with limited resources. The mechanism of action of cotrimoxazole in this situation is not clear; however, these outcomes may be due to the antibiotic activity and/or the anti-cytokine effects of cotrimoxazole. Further trials are needed to test our observations.

Introduction

Coronavirus Disease 19 (COVID-19) is a worldwide pandemic and a major global health concern, which is caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2). WHO reports state that by December 23, 2021, there were 537,4744 confirmed deaths out of 276,436,619 confirmed cases. In Libya, the mortality and morbidity rates have rapidly increased to reach over 383,445 confirmed cases, with over 5,626 deaths reported, by December 23rd, 2021 [1]. There are few effective treatments for people with severe disease, even though the illness often resolves on its own. According to recent studies, subgroups of patients with severe COVID-19 have persistent fevers, blood cytopenias, and a 50% chance of developing cytokine storm syndrome (CSS), a condition where the immune system overreacts to the virus[2, 3]. This "cytokine storm" causes T-lymphocyte, monocyte, and neutrophil activation, which results in respiratory failure and acute respiratory distress syndrome (ARDS), necessitating oxygen therapy and ventilatory support, and is linked to increased mortality [4].

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When host cells sustain mitochondrial damage, formyl peptides, also referred to as Damage-Associated Molecular Patterns, stimulate the formyl peptide receptors (FPRs), which may lead to neutrophil recruitment to the lung and the cytokine storm. Located on the exterior of neutrophils and monocytes, FPRs can trigger cytokine activation by releasing intracellular and extracellular reactive oxygen species (ROS) when activated. Significant hypoxaemia results from the blocking of the alveolar capillary bed caused by Neutrophil Extracellular Traps (NETs), which are also stimulated by it [5, 6]. Moreover, secondary bacterial infections are often seen in patients with viral pneumonia, with *Staphylococcus aureus* being the commonest pathogen in Influenza A and influencing prognosis. *Stenotrophomonas maltophilia* and MRSA (*methicillin-resistant Staphylococcus aureus*) are commonly seen in ventilated patients with SARS [7].

There is currently no effective antiviral therapy for SARS-CoV-2, and supportive care is the mainstay of therapy. As a result, we are still searching for a better therapeutic agent that will help in treating COVID-19 cases in terms of mortality, morbidity, oxygen requirement, and length of stay in the hospital.

Co-trimoxazole (composed of Trimethoprim and Sulfamethoxazole in a ratio of 1:5, respectively) is a sulfur-containing anti-folate bactericidal drug that is indicated for the treatment of hospital-acquired pneumonia in the UK. Moreover, it has been used for over 60 years for various indications, esp. respiratory tract infections. It is effective against a number of microorganisms, including *Methicillin-sensitive Staphylococcus Aureus* (MSSA), *Klebsiella pneumoniae, Methicillin-resistant Staphylococcus Aureus* (MRSA), *Haemophilus influenzae B,* and *Stenotrophomonas maltophilia* [8]. It is also known to have immunomodulatory and anti-inflammatory properties that may help to prevent progression to the critical phase and cytokine storm syndrome in severe COVID-19 patients. The medical literature contains case reports describing clinical recovery after the Middle East Respiratory Syndrome (MERS) with acute respiratory distress following the use of cotrimoxazole [8, 9]. It acts rapidly when given in high doses due to its better bioavailability and lung penetration. [8, 9]. Low cost and a good safety profile can make it an ideal candidate for the treatment of COVID-19 in a low-resource country like Libya. Here we report our observations with cotrimoxazole added to standard therapy in patients with severe COVID-19.

Methods

Subjects and settings

The present work was conducted in the Msallata Corona isolation center (Msallata city, Libya) in collaboration with the Faculty of Pharmacy, Elmergib University (Alkhoms city, Libya). Twenty-five patients were enrolled in this study; sixteen subjects were excluded because they did not match the inclusion criteria. Only nine eligible subjects completed this study (aged 30-51 years; 3 females and 6 males). The inclusion criteria were: Age > 18 years, diagnosed COVID-19 patients confirmed by chest examination findings of bilateral crackles on auscultation or chest x-ray showing bilateral infiltrates, RT-PCR, oxygen saturation <90% on air at rest, and C-Reactive Protein (CRP) > 50mg/L. The patients were excluded if they had multi-organ failure, severe liver disease, Acute Kidney Injury (GFR< 15), drug allergy/intolerance to cotrimoxazole, or pregnancy. Patients were followed up from 15 th July 2021 to 15th August 2021 until they were discharged, died, or the census date of 15th August 2021. Patients admitted with confirmed COVID-19 were commenced on standard therapy (ST), including antibiotics (tazobactam, clarithromycin, or azithromycin), dexamethasone, low molecular weight heparin, paracetamol, supplemental oxygen therapy, intravenous fluids, antiviral drugs (Ramdesivir), and other investigational therapies based on WHO guidelines[10, 11].

Study Protocol

Subjects continued taking their standard treatment during the study without any intended changes. Cotrimoxazol tablets (CTX; 80mg of trimethoprim and 400mg sulphamethoxazole-Bactrim®; Hoffman-La Roche, Basel, Switzerland; B.N: X4914B04) in the dose 480 mg twice/day were supplemented in a single blind manner to the test group for seven days. Participants were subjected to daily examination and observation during the study period. The baseline examination included: chest x-ray, RT-PCR, D-dimer, C-reactive protein, complete blood count (CBC), Blood oxygen saturation, and respiratory rate. The primary outcome measure was (% of patients who died after enrollment within the time frame of 14 days). The secondary outcome measures were (SpO2- saturation of oxygen in %, respiratory rate per minute, C-reactive Protein (CRP) level in mg/litre.

Statistical Analysis

Statistical analyses were conducted using GraphPad Prism Software (version 6). Continuous data are presented using mean ± SEMs. Comparisons between before and after CTX administration of continuous data were made using the t-test for parametric and Mann-Whitney U-test/Wilcoxon signed rank test for non-parametric data. A p-value of < 0.05 was considered to be significant.

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Results

Although the patients took the standard COVID-19 medication, CRP peaked at day zero of this study. Cotriomxazol produced a pronounced effect on CRP, where CRP was highly sensitive to cotriomxazol addition to the standard treatment regimen of the patients, where CRP decreased dramatically in the presence of cotriomxazol ($P < 0.05$), as shown in Figure 1.

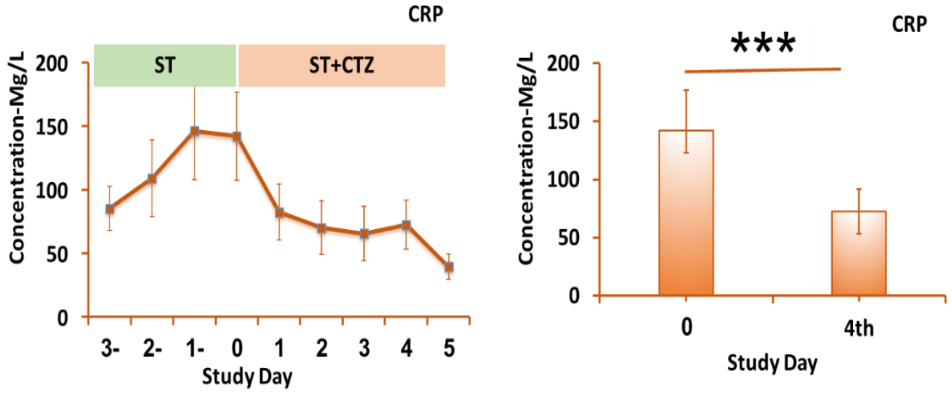

Figure 1. Effect of cotrimoxazole on CRP levels of COVID-19 patients. These data are represented as the mean CRP concentration before and after CTX administration, plotted against study days, along with the standard error of the mean (n = 9). ST: standard treatment; CTX: cotrimoxazol

A high WBC count (leukocytosis) is usually a sign that the body is fighting an infection, and the same is true in COVID-19. In this study, there was no significant difference in WBC count before and after adding CTX to the standard treatment of COVID-19 patients (Figure 2).

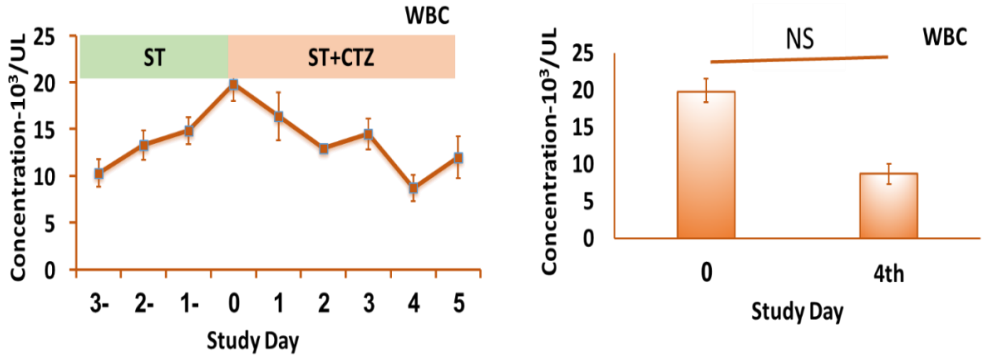

Figure 2. Effect of cotrimoxazole on WBC count levels of COVID-19 patients. These data are represented as the mean WBC concentration before and after CTX administration, plotted against study days, along with the standard error of the mean (n = 9). N S: non-significant

SpO_2 (oxygen saturation) is a measure of the amount of oxygen-carrying hemoglobin in the blood relative to the amount of hemoglobin not carrying oxygen. Patients receiving cotrimoxazol showed a dramatic increase in their oxygen saturation compared with the standard treatment-only period ($P < 0.05$), as shown in (Figure 3).

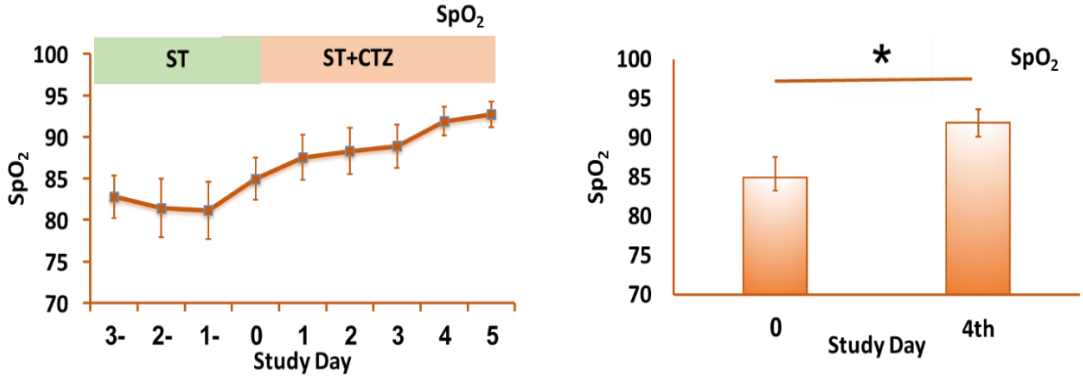

Figure 3. Effect of cotrimoxazole on SpO2 levels of COVID-19 patients. These data are represented as the mean SpO2 concentration before and after CTX administration, plotted against study days, along with the standard error of the mean (n = 9).

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Next, we have examined the effect of the respiratory rate (how many breaths per minute?). (Figure 4) showed the change in respiratory rate before and after the addition of cotrimoxazole to the standard treatment. The statistical test was performed between baseline (ST treatment only) and the other period (ST treatment + cotrimoxazol), where the respiratory rate showed a significant decrease in the respiratory rate after cotrimoxazol tablet administration ($P < 0.05$). patients with added CTX showed a significant improvement in their respiratory rates that was not seen in standard therapy alone.

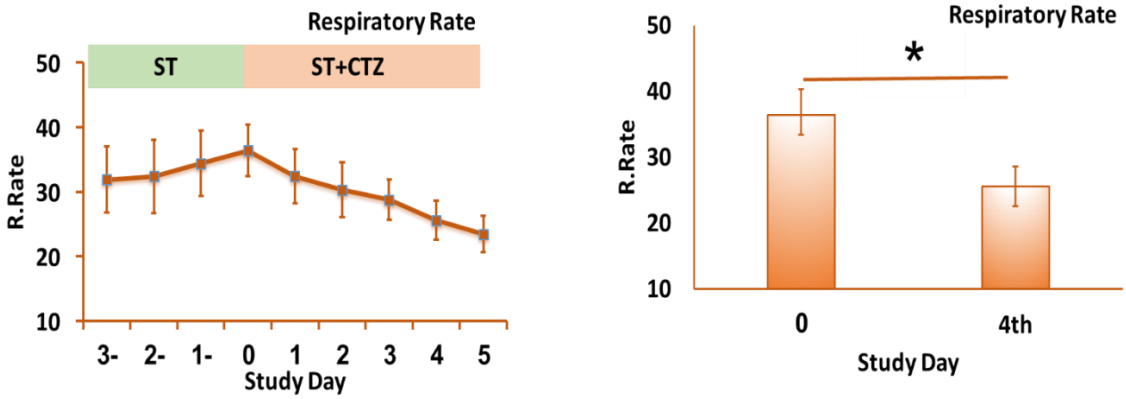

Figure 4. Effect of cotrimoxazole on the respiratory rate of COVID-19 patients. These data are represented as the mean respiratory rate before and after CTX administration, plotted against study days, along with the standard error of the mean (n = 9).

Next, we have analyzed the impact of cotrimoxazole on D-dimer blood concentrations. D-Dimer levels exhibited a notable decline following two days of cotrimoxazole tablet administration ($P < 0.05$). On day 4, patients demonstrated a statistically significant reduction in D-dimer levels in comparison to day 0 of this study, as shown in (Figure 5).

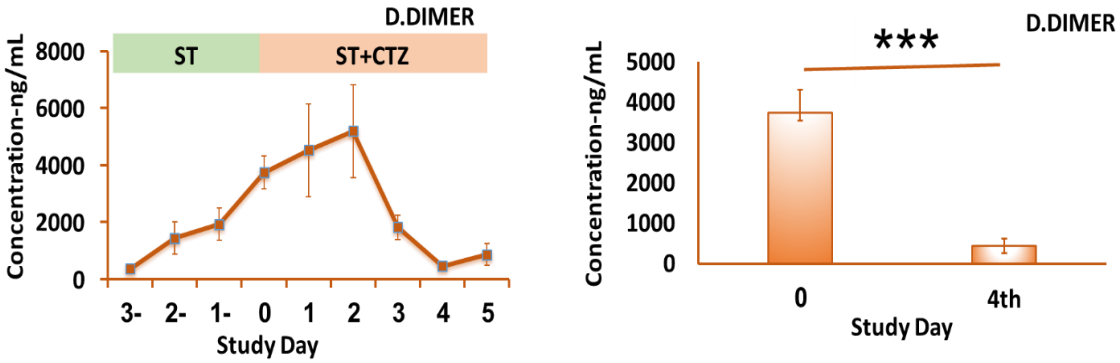

Figure 5: Effect of cotrimoxazole on D-Dimer levels of COVID-19 patients. These data are represented as the mean D-Dimer levels before and after CTX administration, plotted against study days, along with the standard error of the mean (n = 9).

Discussion

In COVID-19, only twenty percent of infected individuals become severely ill, and only 2–5% of patients die, but eighty percent of infected individuals are asymptomatic or show only mild symptoms[12-14]. Although the exact mechanism of ARDS in COVID-19 patients is not fully understood, the excessive production of pro-inflammatory cytokines is considered to be one of the major contributing factors[14-16].

The severe form of the disease frequently progresses to a critical situation known as ARDS, which is triggered by an exaggerated immune response to the virus, manifesting as cytokine storm syndrome (CSS). Lung cells are especially susceptible to this virus due to their high expression of the “lock” protein that SARS-CoV-2 utilizes for entry. The death of a significant number of lung cells in an individual leads to the respiratory issues commonly linked with COVID-19[17, 18].

Early recognition of a cytokine storm in COVID-19 patients is essential for optimizing recovery, enabling treatment with various biological agents aimed at lowering cytokine levels. Meta-analyses reveal distinct patterns that differentiate between patients with severe disease and those without. Indicators that may predict severe or fatal cases include "lymphopenia, thrombocytopenia, and elevated levels of ferritin, D-dimer, aspartate aminotransferase, lactate dehydrogenase, C-reactive protein, neutrophils, procalcitonin, and creatinine," alongside interleukin-6 (IL-6). Ferritin and IL-6 are considered potential immunological biomarkers for severe and fatal cases of COVID-19. Ferritin and C-reactive protein might serve as effective

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screening tools for the early identification of systemic inflammatory response syndrome in COVID-19 cases [19]. As a result, we were searching for a better therapeutic agent that could help in treating COVID-19 cases in terms of mortality, morbidity, oxygen requirement, and length of stay in the hospital. Therefore, this study primarily focuses on pharmacological interventions in patients with COVID-19. We have compared the characteristics and clinical outcomes in patients who received normal doses of CTX in addition to ST with the period of treatment where the same patients received standard treatment only.

One can ask why we choose to try Cotrimoxazole? Cotrimoxazole is an inexpensive drug licensed for use in respiratory infections with a good safety profile. It has a rapid onset of action with excellent bioavailability and lung penetration. They are generally available worldwide and may have benefits in preventing acute lung injury in this pandemic [20].

In this study, cotrimoxazole produced a pronounced effect on CRP, where CRP decreased dramatically in the presence of cotrimoxazole. Moreover, patients receiving cotrimoxazole showed a dramatic increase in their oxygen saturation compared with the standard treatment-only period ($P < 0.05$). Patient's received CTX tablets showed a significant improvement in their respiratory rates that was not seen in standard therapy alone. D-dimer is a fibrin degradation product, a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis. D-dimer levels are used as a predictive biomarker for the blood disorder, as in the coagulation disorders associated with COVID-19 infection[21] A fourfold increase in the protein is an indicator of poor prognosis in people hospitalized with COVID-19 [22, 23]. in this study, D-dimer levels showed a sharp decrease after only two days of cotrimoxazole tablet administration ($P < 0.05$). At day 4, patients showed a significant reduction in D-dimer levels compared to day 0 of this study. It is worth noting that no deaths were recorded during the study period among the people participating in this study.

A possible mechanism of action for cotrimoxazole is that it inhibits the formyl peptide receptors (FPRs) located on the surface of neutrophils and monocytes. Activation of FPRs can induce cytokine activation through the release of reactive oxygen species (ROS) both intracellularly and extracellularly. It also promotes the development of Neutrophil Extracellular Traps (NETs) that obstruct the alveolar capillary network, resulting in substantial hypoxaemia. Co-trimoxazole can inhibit the FPRs and decrease the migration of neutrophils to the lung and NETosis. Additionally, sulphamethaxazole restrains neutrophil activation by blocking Phorbol 12-myristate 13-acetate (PMA) stimulation, which in turn prevents Protein Kinase C activation and diminishes inflammation [5, 24]. This offers a possible explanation for the observed clinical benefit by reducing neutrophil, monocyte, and lymphocyte activation, leading to a reduction in the risk of ARDS [24-26].

Another suggested explanation of the role of cotrimoxazol in fighting COVID-19 is that the ability of cotrimoxazol to modulate pro-inflammatory cytokines involved in the innate immune response. Among the key pro-inflammatory cytokines in the innate immune response are IL-1, TNF-α, and IL-6. The primary sources of these cytokines during the innate immune response are tissue macrophages, mast cells, as well as endothelial and epithelial cells. A "cytokine storm" occurs due to a sudden spike in the levels of several pro-inflammatory cytokines, including IL-6, IL-1, TNF-α, and interferon. This surge in cytokines triggers the migration of various immune cells, such as macrophages, neutrophils, and T cells, from the bloodstream to the infection site, leading to destructive damage to human tissues. This destruction is caused by the disruption of interactions between endothelial cells, impaired vascular barriers, capillary damage, diffuse alveolar injury, multiorgan failure, and potentially death. One of the effects of the cytokine storm is lung injury, which can develop into acute lung injury or more severe acute respiratory distress syndrome (ARDS).[27]. Research indicates that patients with severe illness often exhibit elevated levels of pro-inflammatory cytokines, including interleukin (IL)-6, in contrast to those with moderate illness. Furthermore, an increased concentration of these cytokines suggests a worse prognosis for individuals with COVID-19 [28]. Inconsistent evidence suggests that cotrimoxazole may have anti-inflammatory properties, but conclusive data are lacking. We therefore have to test the hypothesis that cotrimoxazole reduces systemic inflammation in future work.

Conclusion

Cotrimoxazole administration has shown a significant reduction in mortality, clearly improved COVID-19 patients. This might be due to its antimicrobial properties or having immunomodulatory and anti-inflammatory properties, and could be considered as a potential treatment option for cytokine storm syndrome-mediated severe COVID-19. If our observation is confirmed by other large-scale studies, then hundreds of thousands of lives could be potentially saved worldwide by the use of this inexpensive, widely available, and safe drug. In addition, reducing hospital stay and use of ventilators could potentially reduce the overwhelming pressure upon the healthcare resources of developing nations.

Conflict of interest. Nil

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