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RESEARCH ARTICLE

High dose cotrimoxazole treatment in patients with severe COVID-19: A randomised controlled trial

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ABSTRACT

Background: Cotrimoxazole for severe COVID-19 may have a better prognosis because of its antibacterial, immunomodulatory, and anti-inflammatory activities. We examined the efficacy of high-dose cotrimoxazole therapy in terms of duration of hospital stays and reduction in mortality in severe COVID-19 infections.

Methods: From May to November 2021, we conducted a double blind randomised controlled trial with two parallel groups in the COVID units of Bangabandhu Sheikh Mujib Medical University and Anwar Khan Modern Medical College Hospital, Dhaka. One group received standard therapy in addition to an oral dose of 960 mg of cotrimoxazole twice daily for 7 days (intervention group), while the other group received standard treatment and a placebo (standard group). Pre-protocol analysis was done.

Results: A total of 188 patients were enrolled, but 166 completed the study. Of them, 93 were in the intervention group and 73 were in standard group. The mean ages of the groups were similar (intervention, 56.2 and standard, 59.2 years) (*P*=0.10). The mortality at 28 days between groups was also similar (11.8% in the intervention group and 15.0% in the standard group) (*P*=0.56). The hospital stay was 13.7 days for the intervention group and 13.5 days for the standard group (*P*=0.86). However, the reduction in C-reactive protein was statistically significant in the intervention group, with a mean decline of 23.6 mg/L (95% confidence interval, 0.5–46.7 mg/L).

Conclusion: High-dose cotrimoxazole did not benefit in shortening in-hospital stay or reducing mortality at day 28 in patients with severe COVID-19. However, the decline in the C-reactive protein level was significant, necessitating further research.

Keywords: *cotrimoxazole, severe COVID, randomised controlled trial, Bangladesh*

INTRODUCTION

COVID-19 is primarily a respiratory infection characterised by fever, tiredness, muscle soreness, dry cough, and shortness of breath.[1] The host's inflammatory immune response is triggered by the release of interleukins (IL) and interferons, notably IL1, IL2, IL6, IL7, tumour necrosis factor-alpha interferon-gamma, and other cytokines when the virus causes the infected cells to rupture.[2]

The recruitment of cells like neutrophils and monocytes due to damage associated molecular patterns in the lungs leads to the release of more cytokines. Cytokine storms can cause widespread hyperinflammatory response, causing severe lung injury and, ultimately,

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HIGHLIGHTS

1. Cotrimoxazole has antibacterial, immunomodulatory, and anti-inflammatory activities. Several studies have claimed its benefits in treating COVID-19 patients.
2. In our series, the high dose of cotrimoxazole didn't yield benefits over shortening of in-hospital stay.
3. No reduction in terms of mortality at 28 days with high-dose cotrimoxazole therapy.

multiorgan failure.[3,4] Preventing cytokine storms, as well as avoiding further bacterial infections, is imperative to managing patients with severe COVID-19.[5]

Cotrimoxazole has been a widely used antibiotic in therapeutic settings for almost sixty years. Studies have shown that cotrimoxazole effectively blocks activity related to damage associated molecular patterns in the lungs, which ultimately disrupts the organisation of inflammatory cells and numerous cytokines such as IL-1, IL-2, IL-6, IL-8, and others.[6,7,8] Cotrimoxazole may be recognised as a better drug for improving COVID-19-associated pneumonia. It might prevent complications associated with it, as initial evidence was given from a few case reports,[5] showing its beneficial effects on clinical outcomes in COVID-19 patients.

Thus, high-dose cotrimoxazole is a candidate for further research because of its immunomodulatory activity, affordability, and good safety record. In this study, we examined the efficacy of high-dose cotrimoxazole therapy in severe COVID-19 infection in terms of reducing in-hospital stay and mortality by day 28.

METHODS

Trial design

This two-centre, placebo-controlled, randomised trial was conducted from May to September 2021 in the COVID units of Bangabandhu Sheikh Mujib Medical University (BSMMU) and Anwar Khan Modern Medical College Hospital, Dhaka. BSMMU's Ethical Review Board approved the protocol. It has been registered in the ClinicalTrials.gov. Informed written consent was obtained from the patients before enrolling in the study.

Study population and sample

The study included patients 18 or older who needed oxygen 5–15 L/min (administered using a face mask or non-rebreathing masks) to maintain a saturation level of >92%. The patients were either clinically suspected of having COVID-19 or confirmed positive cases through RT-PCR. Fever, respiratory symptoms, and radiological abnormalities indicated clinically suspected COVID-19. Patients with a glomerular filtration rate of less than 15 mL/min, liver failure, acute heart failure, pregnancy, patients with sulfur sensitivity, drug allergy, septic shock, acute respiratory distress syndrome, patients requiring high-flow nasal cannula (HFNC) ventilatory support were excluded.

Data from a COVID-19 study showed an in-hospital stay reduction of 25%, which is required to calculate the power of the trial.[9] Thus, we calculated 94 individuals needed for each group to detect a significant difference with a power >90% in each group.

Intervention

We randomly assigned the patients in a 1:1 ratio for either standard therapy with placebo or high-dose cotrimoxazole in addition to standard treatment. In addition to receiving standard medications, including antibiotics, patients in the study's experimental group were given oral tablets of high-dose cotrimoxazole (960 mg) consisting of 160 mg trimethoprim and 800 mg sulphamethoxazole. They were given twice daily for 7 days. Standard therapy and a placebo were given to patients in the control group per hospital guidelines. The standard therapies per institutional protocol are awake-prone positioning, corticosteroid therapy, nutritional support, antivirals, thrombo-prophylaxis, antibiotics for secondary bacterial infection, oxygen support, hydration, and antipyretics.

Masking

Eligible participants were centrally randomised to receive treatment with high-dose cotrimoxazole or matching placebo tablets. The active drug and placebo were procured from a single source (pharmaceutical company) with the same packaging, colour, and taste to ensure blinding. The randomisation list was masked to study participants, the sponsor, investigators, study

TABLE 1 **Baseline characteristics of the cotrimoxazole intervention and standard treatment (with placebo) groups at admission in two hospitals in Dhaka**

Characteristics	Number (%)		*P*
	Intervention (n=93)	Standard (n=73)	
	Number (%)		
Gender			
Male	64 (68.0)	54 (72.0)	0.47
Female	29 (31.2)	19 (20.4)	
Co-morbidities			
Diabetes mellitus	51 (54.8)	40 (54.8)	0.99
Hypertension	51 (54.8)	45 (61.6)	0.38
Ischaemic heart disease	11 (11.8)	14 (19.1)	0.19
Body mass index (kg/m2)			
<24.9	33 (35.4)	23 (31.5)	0.38
25-29.9	25 (26.8)	27 (36.9)	
≥30	35 (37.6)	23 (31.5)	
SpO2			
<90%	51 (54.8)	43 (58.9)	0.60
>90%	42 (45.1)	30 (41.0)	
Physical findings at baseline			
SpO2 (%)	94.9 (4.8)	95.1 (3.8)	0.23
Heart rate, beats per minute	88.5 (21)	87.0 (16.5)	0.27
Respiratory rate, breaths per minute	26.1 (4.8)	26.2 (5.5)	0.57
	Mean (SD)		
Laboratory findings at admission to hospital[a]			
Total count of WBC (per cmm)	9,453 (3,900)	9,810 (4,403)	0.47
Differential count			
Neutrophil (%)	77.2 (10.6)	77.2 (10.9)	0.53
Lymphocyte (%)	18.82 (10.9)	18.1 (10.7)	0.55
Platelet (per cmm)	2,40,000 (92,920)	2,32,000 (96,060)	0.39
Serum ferritin (ng/mL)	711.7 (732.1)	1012.7 (975.8)	0.46
Serum creatinine (mg/dL)	1.0 (0.4)	1.4 (1.5)	0.66
d-dimer (µg/mL)	0.8 (0.8)	1.7 (3.9)	0.68
C-reactive protein, mg/L	138.9 (81.8)	111.9 (66.7)	0.08

[a]10-15 missing values in each of these variables; SD, standard deviation

monitors, and laboratory personnel till decoding was done for statistical analysis. As all study participants had severe COVID-19 infection at baseline based on the criteria of U.S. Centers for Disease Control at the initiation of the study, randomisation was not stratified further.

After enrolment, the study drug or placebo was dispensed. Participants were followed up during their in -hospital stay until discharge or death. Research assistants contacted them by telephone on study days 7 and 28 to verify compliance and screen for progression to severe illness or other complications.

Data collection

The data was collected using a pre-designed case record form, which was thoroughly reviewed. The information obtained from the case record forms was decoded and safely kept on a secured site. Data on comorbidities, severity of sickness, clinical and laboratory examinations, and demographics were collected. CRP was sent at baseline and 48 hours after starting high-dose cotrimoxazole or placebo. Adverse events were collected throughout the study and monitored until the events were resolved.

Outcome measures

The primary outcome measure was the duration of hospitalisation, measured in days. The secondary outcomes were the assessment of oxygen needs, use of a high-flow nasal cannula, need for intensive care unit admission, need for ventilation, reduction of baseline C-reactive protein (CRP) levels, and death within 28 days.

Statistical analyses

Data are expressed as frequencies or percents for qualitative values and mean (standard deviation) for quantitative values with normal distribution. The two groups were compared using chi-square test for categorical variables, and Mann-Whitney U test for quantitative variables because there were deviations from normality. Mean difference in the CRP values (baseline — 28 days) were calculated and their 95% confidence intervals were obtained. The within group mean difference was compared using paired *t* test. $P<0.05$ was considered statistically significant. SPSS version 25 was the statistical software used for the analysis.

RESULTS

Baseline characteristics

We enrolled 188 RT-PCR-positive severe COVID-19 in-patients, but 166 completed the study. Their baseline characteristics are given in **TABLE 1**. The mean (standard deviation) age in the intervention group versus the standard therapy group was 56.2 (1.2) and 59.2 (1.5) years ($P=0.10$). The intervention group had a male representation of 68%, while 72% ($P=0.47$) in the standard arm. Vital signs and laboratory findings were

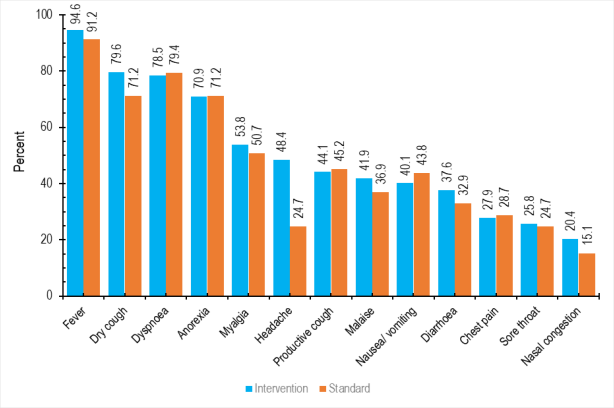

FIGURE 1 **Symptoms of the intervention and standard groups at admission**

similar between groups. The presenting symptoms were similar between groups (**FIGURE 1**). Twenty percent of the intervention and 18% of standard group received antibiotics other than cotrimoxazole (*P*=0.71).

Primary outcome

We couldn't find any significant improvement in terms of duration of hospital or intensive care unit stay in the intervention group (**TABLE 2**). The length of hospitalisation in the intervention group was 13.7 days, while in the standard group it was 13.5 days (*P*=0.86). On the other hand, duration in the intensive care unit stay was 14.5 days (n=8) for the intervention group and 9.1 days (n=7) for the standard control group (*P*=0.47).

Secondary outcomes

We couldn't find any significant improvement in death at 28 days or the need for oxygen in this trial. By day 28, there were 11 deaths out of 73 (15.0%) in the standard arm compared to 11 out of 93 (11.8%) patients in the intervention arm (*P*=0.56) (**TABLE 2**). At day 28, in the intervention group, 76 patients (81%) and in the standard group, 58 patients (79%) did not require oxygen (*P*=0.62). We also examined the changes in CRP levels. There was a statistically significant (*P*<0.001) mean decline at 48 hours in the intervention group, 23.6 mg/L. However, the decline in the standard group (7.2 mg/L) was not statistically significant (**TABLE 3**).

DISCUSSION

We compared the in-hospital stay, mortality rate, and decrease in the inflammatory marker CRP between patients who were administered high-dose cotrimoxazole in addition to standard therapies and patients who got standard treatment alone.

This study did not show any statistically significant difference in mortality, oxygen dependency or length of hospitalisation compared to baseline. The use of other antibiotics as a part of the standard treatment might have attenuated the effect of cotrimoxazole.

This result was inconsistent with the findings reported in the study by Quadery and colleagues, which showed an in-hospital mortality rate of 11%. The cotrimoxazole group outperformed the standard therapy group, which had a rate of 29% (*P*=0.02).[10] However, the cotrimoxazole group's recovery took 6 days, whereas it was 7 days in the standard group (*P*=0.50), which is consistent with the results of our study. One plausible explanation could be that it was a preliminary project analysis.

TABLE 2 **Outcome at 28 days of the intervention and standard groups[a]**

Outcomes	Intervention (n=93)	Standard (n=73)	*P*
Requirement of intensive care unit support[b]	8 (8.6)	7 (9.5)	0..52
Duration of hospital stay, median (Interquartile range)	13.7 (12.1-15.2)	13.5 (11.7-15.2)	0.86
Duration of intensive care unit stay, median (Interquartile range)	14.5 (0.1-28.9)	9.1 (1.7-16.5)	0.47
Discharge	74 (79.5)	55 (75.3)	0.74
Hospitalised- requiring no oxygen	2 (2.1)	3 (4.1)	0.51
Hospitalised with oxygen	6 (6.5)	3 (4.1)	0.62
Deaths	11 (11.8)	11 (15.0)	0.56

[a]Results are n (%) unless indicated otherwise; [b]8 for intervention and 7 for standard group.

TABLE 3 **Comparison of C-reactive protein (mg/L) at baseline and after 48 hours between the groups**

Groups	Mean (Standard deviation)		Mean difference (95% Confidence interval)
	At baseline	After 48 hours	
Intervention (n=93)	138.9 (81.8)	43.2 (43.3)	23.6 (0.5 to 46.7)
Standard (n=73)	111.9 (66.7)	50.4 (49.9)	7.2 (-21.8 to 7.4)

Varney *et al.* showed that there was improvement within 48 hours of treatment with cotrimoxazole in a retrospective analysis of 22 patients with severe COVID-19, as indicated by a decrease in CRP levels (P=0.002) and a reduction of oxygen requirements (P<0.001).[11] Although we found no significant change in oxygen requirements, a significant decline in the CRP levels was observed. This might be the reason for the low (but non-significant) proportion of mortality in the intervention group. However, our study was a double-masked, randomised, placebo-controlled trial with 166 participants, which is larger than many studies.[10, 11] The dose we used in the cotrimoxazole group also treated diseases like nocardiosis with an excellent safety profile.[9] In our study, we also encountered no significant adverse effects.

Our study has some limitations too. It did not include patients with severe acute respiratory distress syndrome requiring high-flow nasal canula ventilatory support and septic shock. We included only severe COVID-19 patients. Therefore we cannot comment if high-dose cotrimoxazole affects mild or moderate COVID-19 infections.

Conclusion

Findings in this study revealed no additional improvements in mortality at hospital and at 28 day, and the length of in-hospital stay when high-dose cotrimoxazole was given in addition to standard treatment in severe COVID-19 patients. There is lack of evidence of efficacy of high-dose cotrimoxazole therapy in severe COVID-19 patients. However, the decline in the CRP levels at 28 days deserves further work.

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Author contributions

Conception and design: SMA, HJ, TT. *Acquisition, analysis and interpretation of data:* SRQ, SMA, TT . *Manuscript drafting and critical revision:* CAS, HZ. *Approval of the final version of the manuscript:* SMA. *Guarantor of accuracy and integrity of the work:* SMA, HJ.

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Conflict of interest

We do not have any conflict of interest.

Ethical approval

Ethical approval of the protocol was obtained from Institutional Review Board of BSMMU (protocol id: BSMMU/2021/4098A; date: 03.05.2021).

Data availability statement

We confirm that the data supporting the findings of this study will be shared upon reasonable request.

Trial registration

Trial registration was taken from ClinicalTrials.gov, number NCT04884490.

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