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Inhaled beclomethasone in the treatment of early COVID-19: a double-blind, placebo-controlled, randomised, hospital-based trial in Sri Lanka

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ABSTRACT

Objectives To study if early initiation of inhaled beclomethasone 1200 mcg in patients with asymptomatic, mild or moderate COVID-19 reduces disease progression to severe COVID-19.

Design Double-blinded, parallel-groups, randomised, placebo-controlled trial.

Setting A hospital-based study in Sri Lanka.

Participants Adults with asymptomatic, mild or moderate COVID-19, presenting within the first 7 days of symptom onset or laboratory diagnosis of COVID-19, admitted to a COVID-19 intermediate treatment centre in Sri Lanka between July and November 2021.

Interventions All participants received inhaled beclomethasone 600 mcg or placebo two times per day, for 10 days from onset of symptoms/COVID-19 test becoming positive if asymptomatic or until reaching primary endpoint, whichever is earlier.

Primary outcome measure Progression of asymptomatic, mild or moderate COVID-19 to severe COVID-19.

Secondary outcome measures The number of days with a temperature of 38°C or more and the time to self-reported clinical recovery.

Results A total of 385 participants were randomised to receive beclomethasone(n=193) or placebo(n=192) stratified by age (≤60 or >60 years) and sex. One participant from each arm withdrew from the study. All participants were included in final analysis. Primary outcome occurred in 24 participants in the beclomethasone group and 26 participants in the placebo group (RR 0.90 ; p=0.763). The median time for self-reported clinical recovery in all participants was 5 days (95% CI 3 to 7) in the beclomethasone group and 5 days (95% CI 3 to 8) in the placebo group (p=0.5). The median time for self-reported clinical recovery in patients with moderate COVID-19 was 5 days (95% CI 3 to 7) in the beclomethasone group and 6 days (95% CI 4 to 9) in the placebo group (p=0.05). There were no adverse events.

Conclusions Early initiation of inhaled beclomethasone in patients with asymptomatic, mild or moderate COVID-19 did not reduce disease progression to severe COVID-19.

Trial registration number Sri Lanka Clinical Trials Registry; SLCTR/2021/017.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is a randomised double-blind adequately powered placebo-controlled trial.
⇒ This study brings evidence from low-middle-income countries and South Asians.
⇒ Patients were recruited irrespective of having symptoms or not.
⇒ Patients were recruited irrespective of their risk of developing complications.
⇒ Patients were randomised irrespective of their vaccination status.

INTRODUCTION

The majority of COVID-19 studies have focused on investigating and treating patients with severe COVID-19 admitted to hospital.[1] However, the majority of patients with COVID-19 are managed outside of hospital settings. It is a self-limiting disease in the majority but causes death in a small proportion of patients.[2] As it becomes necessary to prepare for a chronic global endemicity, especially with virus mutation, widely available, affordable interventions to reduce disease progression from early COVID-19 to severe COVID-19 are needed.

The role of corticosteroids in COVID-19 of varies with disease severity is as well as changing with the mode of administration. The Randomised evaluation of COVID-19 therapy (RECOVERY) trial showed that systemic dexamethasone is an effective treatment in treating patients with severe COVID-19 needing respiratory support[3] and has been incorporated into COVID-19 treatment guidelines. A recent study showed that high-dose dexamethasone, 20 mg daily, did not result in better clinical outcomes and was probably associated with higher 28-day mortality in patients on high-flow oxygen or

non-invasive ventilation, compared with dexamethasone 6 mg daily.[4] However, the benefit of inhaled corticosteroids in all patients presenting with early COVID-19, irrespective of the risk of COVID-19 complications, is still not fully understood. The Steroids in COVID-19 (STOIC) trial showed that early administration of inhaled budesonide in patients diagnosed with COVID-19 in the community reduced the likelihood of needing urgent medical care and the time to recovery.[5] Thereafter the Platform Randomized Trial of Treatments in the Community for Epidemic and Pandemic Illnesses (PRINCIPLE) trial showed that inhaled budesonide in early COVID-19 improved the time to recovery in people with COVID-19 in the community who are at higher risk of complications.[6] Another study published in August 2021 showed that ciclesonide inhalation shortened the duration of SARS-CoV-2 viral shedding in patients with mild-to-moderate COVID-19.[7] However, the CONTAIN trial showed that the combination of inhaled and intranasal ciclesonide did not show a statistically significant increase in the resolution of symptoms among healthy young adults with COVID-19 presenting with prominent respiratory symptoms.[7 8] Clemency *et al,* Lee *et al* and Duvignaud *et al* also reported ciclesonide did not reduce the time to alleviation of all COVID-19-related symptoms even though it led to fewer subsequent emergency department visits or hospital admissions for reasons related to COVID-19.[9–11] The European Medicines Agency's COVID-19 task force has concluded that there is currently insufficient evidence that inhaled corticosteroids are beneficial for patients with COVID-19.[12] However, a Cochrane review in May 2022 observed, with moderate-certainty, that inhaled corticosteroids probably reduce the combined endpoint of admission to hospital or death and increase the resolution of all initial symptoms at day 14, in people with COVID-19 and mild symptoms who can use inhaler devices. They further state that the observed low-certainty evidence for corticosteroids make little to no difference in all-cause mortality up to day 30 and may decrease the duration to symptom resolution with inhaled corticosteroids (ICS) early in the disease. Most data for the review had come from studies done in high-income settings using budesonide and ciclesonide before vaccination roll-outs and the lack of evidence concerning quality of life assessments, serious adverse events, and people with asymptomatic infection was noted in their review.[13] A further meta-analysis drew attention to the need to identify available, affordable and effective oral or inhaled medications that can be used early in the disease to prevent COVID-19 hospitalisation. This meta-analysis further noted that there is promising evidence for inhaled corticosteroids, particularly in older adults but additional placebo-controlled randomised trials to minimise bias and to obtain more accurate estimates of effect size are needed.[10] Moreover, the latest review of ICS in December 2022 highlighted the need for further development of treatments for COVID-19 to improve outcomes for patients globally, despite the successful rollout of vaccination programmes and developed medicines.[14] Most medicines, with the exception of dexamethasone, approved for COVID-19 treatment are expensive and not freely available widely. The only available, FDA-approved oral treatment for early COVID-19, 'Paxlovid (nirmatrelvir copackaged with ritonavir)' is not freely available in most low-middle-income countries like Sri Lanka. In addition, Paxlovid is approved only for the treatment of mild-to-moderate COVID-19 in adults who are at high risk for progression to severe COVID-19.

Therefore, we studied if early initiation of beclomethasone in patients with asymptomatic, mild or moderate COVID-19, irrespective of their risk of progression to severe COVID-19, reduces disease progression to severe COVID-19, in a randomised, double-blind placebo-controlled trial.

METHODS AND ANALYSIS

Study design and setting

We conducted a randomised, placebo-controlled, double-blind, parallel-group, clinical trial in Base Hospital Kandana, a semiurban, residential, intermediate treatment centre (ITC) for COVID-19, 14 km north of Colombo, the capital of Sri Lanka. The trial was conducted at a time Sri Lanka experienced its worst outbreak of COVID-19 in terms both of the number of patients and the number of deaths.[15 16] The dominant COVID-19 variant during the study period was the Delta variant (21I and 21J).[17] Throughout the period of this study, national policy mandated admission of any person positive for COVID-19 (with a positive SARS-CoV PCR or an antigen test) to a dedicated COVID-19 ITC where they were kept for minimum of 10 days from the day of first symptom onset or, if asymptomatic, from the date the COVID-19 test became positive, to avoid spread of the disease in the community. Positive case contact tracing was done even if asymptomatic to reduce the spread of the disease. This practice enabled our trial to achieve a very high study participant completion rate. The presence of self-reported symptoms had no effect on the duration of treatment with trial medicines.

Study objectives

Is early initiation of inhaled beclomethasone 600 mcg, two times per day in patients with asymptomatic, mild or moderate COVID-19 effective in reducing disease progression to severe COVID-19?

Study population and eligibility criteria

Inclusion criteria

All patients, 18 years of age and above, within the first 7 days of a proven COVID-19 infection who presented with asymptomatic, mild or moderate COVID-19.

Exclusion criteria

The patients with the following criteria were excluded: those who,

1. Withheld consent.
2. Used inhaled or systemic glucocorticoids within the last 14 days had a contraindication to beclomethasone.
3. Were unable to use inhalation devices without assistance.
4. Were suffering from psychiatric illnesses and lacked the insight to partake fully in the study.

COVID-19 severity was classified according to COVID-19 treatment guidelines of the National Institute of Health.[18]

Definition of asymptomatic disease—Individuals who have no symptoms that are consistent with COVID-19.

Definition of mild disease—Individuals who have any of the various signs and symptoms of COVID-19 but who do not have symptoms suggestive of lower respiratory tract infection or abnormal chest imaging.

Definition of moderate disease—Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an oxygen saturation (SpO_2) ≥94% on room air at sea level.

Definition of severe disease—Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an SpO_2 <94% on room air at sea level.

Sample size

At the initiation of the study in May 2021, we assumed that the prevalence of severe COVID-19, our primary endpoint, was 10%[19] in our population and we determined a reduction to 2.5% for the intervention to be clinically significant. The sample size was calculated for binary outcomes in two group comparisons with a power of 80% to demonstrate a difference between event rates of 2.5% and 10% in the treatment and placebo arms at a level of significance of 0.05 and was rounded to 190 per arm to allow for a 10% dropout rate.[20]

Randomisation

Patients were randomised to receive beclomethasone or the placebo in addition to usual care, stratified by participant age (≤60 years or >60 years) and sex. The randomisation was done using an online random sequence generator by the trial statistician, and allocation was done through block randomisation in a 1:1 ratio, with blocks of four participants in a block.

Blinding

Study participant recruitment and daily follow-up were carried out by four medically qualified research assistants. The study participants and research assistants who recruited patients to the study as well as the healthcare staff who provided care to the patients at the ITC were all blinded to the study trial drug administered. Double blinding of treatment allocated was achieved by preparing 512 (128×four groups according to age and sex, active and placebo) medication packages according to the above randomisation plan by an independent third person at a remote facility before starting the trial, leaving both investigators and participants blinded. The randomisation code was held securely at a location remote to the study investigators. Each trial pack contained medicines for 14 days, a dry powder inhaler, and a pen to fill questionnaires.

Interventions

The active intervention arm received inhaled beclomethasone 600 mcg (one 400 mcg and one 200 mcg capsule) per inhalation, two times per day, via a dry powder inhaler, in addition to routine care. The no-intervention arm received a matching placebo inhaled via a dry powder inhaler two times per day, in addition to the routine care given at state sector hospitals. Both beclomethasone and the placebo treatments were continued until patients reached the primary endpoint or for 10 days from the onset of symptoms/COVID-19 test becoming positive in asymptomatic individuals whichever is early. Routine care included supportive therapy, antipyrectics(paracetamol), antihistamines, vitamin C and salbutamol metered-dose inhalers used as needed as per the country's practice at the time the study was conducted.

The trial medication (beclomethasone) and the placebo capsules were identical in appearance. The embossed serial number on each card of dry powder capsules varied by one digit (of 13) between active and placebo. Neither the research assistants nor the patients knew which digit represented active drug or the placebo.

Implementation

Eligible patients admitted to the trial facility were recruited after obtaining written informed consent. Patients with exclusion criteria were excluded. Consecutive eligible patients were recruited under the four strata and a trial identifier (ID) was given by pretrained research assistants (medical graduates). Study subjects were issued with the prelabelled and packed medication pack matching their trial ID number by the research assistants. The research assistants were blind to the medication inside the pack supplied. Patients were followed up daily by the research assistants at the ITC.

The study facility had a working station for health staff to interview patients in a semiprivate area. This workstation was sealed off from the patients' area with a transparent plastic sheet. Participants were interviewed daily by research assistants across this using a microphone system. There was a small flap devised to transfer small items between the two areas.

The disease severity of the patients was documented at the admission to the trial facility by a single specialist physician who was blinded to the trial interventions. This specialist physician was responsible for the medical care of all the patients admitted to the trial facility. Patients' symptoms, signs and chest X-rays when available were used to categorise patients into different disease severities according to COVID-19 treatment guidelines of the National Institute of Health.[18] All patients were daily reviewed by the responsible specialist and his medical team. Any patient progressing to the severe disease was

removed from the trial and was started on supplemental O_2 therapy and oral or intravenous dexamethasone according to the management guidelines and was transferred to a higher-tier healthcare facility if ventilatory support is needed.

On day 0, at randomisation, the research assistants dispensed a trial medications pack demonstrated the use of the inhaler with a short mobile phone video clip and provided participants with two symptom diaries; the Common Cold Questionnaire[21] and the InFLUenza Patient-Reported Outcome Questionnaire.[22] Each day participants were reminded to take the prescribed trial medication and to complete the symptom diaries daily until discharge from the facility (ie, 10 days from the day of first symptoms onset or COVID-19 testing becomes positive in asymptomatic patients) or reaching primary endpoint, whichever occurred first. They were reminded daily to complete the symptom diaries which included questions on systemic symptoms like fever, appetite, myalgia, headache and symptoms related to eyes, nose, throat and chest. All participants were interviewed in person daily using a proforma until discharge from the facility or reaching the primary endpoint by the same research assistants who were medical graduates. Daily patient interviews concentrated on both respiratory system related and systemic symptoms of COVID-19, perceived beclomethasone dry power inhalation related side effects like oral candidiasis, dry throat/cough, hoarse voice, gastritis, acute changes in vision suggestive of glaucoma, any evidence of secondary infections diagnosed to be secondary to intervention by the treating specialist physician, allergic reactions and any new symptoms. Participants were asked if they felt they had recovered from the illness at daily interviews. The day participants felt they had recovered from COVID-19 was recorded as the day of self-reported recovery. Measures of SpO_2, temperature and medications were collected daily from the medical record. Possible drug-related side effects were reconfirmed by cross-checking with medical records. On day 28 following discharge from the facility or reaching the primary endpoint, all participants were contacted over the phone to gather information regarding short-term outcome of the illness: complete recovery, partial recovery or death. Complete recovery was defined as having no symptoms related to COVID-19 at day 28 and partial recovery was defined as having recovered from the acute illness but having some remaining symptoms related to COVID-19 by day 28. The cause of death given in the death certificate was used to identify if the death was a direct COVID-19 death or an unrelated death.

Outcomes

Primary endpoint

The primary endpoint was the progression of asymptomatic, mild or moderate COVID-19 to severe COVID-19. Severe disease was defined as, having SpO_2 <94% on room air at sea level according to the COVID-19 Treatment Guidelines by the NIH.[18]

Secondary endpoints

1. Number of days with a temperature of 38°C or more
2. Time to self-reported clinical recovery in days
3. Short-term clinical outcome at 28 days

Statistical analysis

The distribution of data was visually assessed using histograms. Descriptive statistics were calculated separately for the two groups; means of normally distributed variables were compared using t-test, asymmetrically distributed data were compared using Mann-Whitney U test and categorical variables were compared using the χ^2 test.

The probability of recovery between the intervention and no-intervention groups was studied using the Z test. The ratios of outcomes in the beclomethasone versus placebo group were studied using the χ^2 test. Post hoc subgroup analyses for primary/secondary outcome achievements stratified by the disease severity (asymptomatic, mild and moderate disease), age (more or less than 60 years) and the number of COVID-19 vaccine doses received (none, one or two) were done using the χ^2 test. Time to self-reported clinical recovery between the two groups was compared using Kaplan-Meier survival analysis with the log-rank test censoring at 28 days. All tests were done at a 5%, two-sided significance level and all comparative outcomes are presented as summary statistics with 95% CIs and reported per Consolidated Standards of Reporting Trials (CONSORT) guidelines. The primary outcome was analysed for the intention-to-treat (ITT) population. Less than 1% of data was determined as missing. IBM SPSS V.28.0 software was used for data management and analyses.

Patient and public involvement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

RESULTS

Between 13 July and 25 October 2021, 647 participants were screened and 385 were found eligible (figure 1). All 385 eligible participants consented and were included in the study and were allocated interventions. Adherence to medications was checked daily and was satisfactory. Two participants withdrew from the study, one due to dry cough and one absconded from the ITC. When unblinded, 193 were on beclomethasone and 192 were on placebo and all were assessed for the primary endpoint in the ITT analysis. Figure 1 shows the trial profile and table 1 shows the baseline characteristics of the two study groups. The two groups were not different including the percentage vaccinated (vaccinated with one dose—p 0.163, vaccinated with two doses—p 0.391).

The median duration of symptoms before randomisation of the beclomethasone arm and the placebo arm were 3.7±1.9 days and 3.9±1.9 days, respectively.

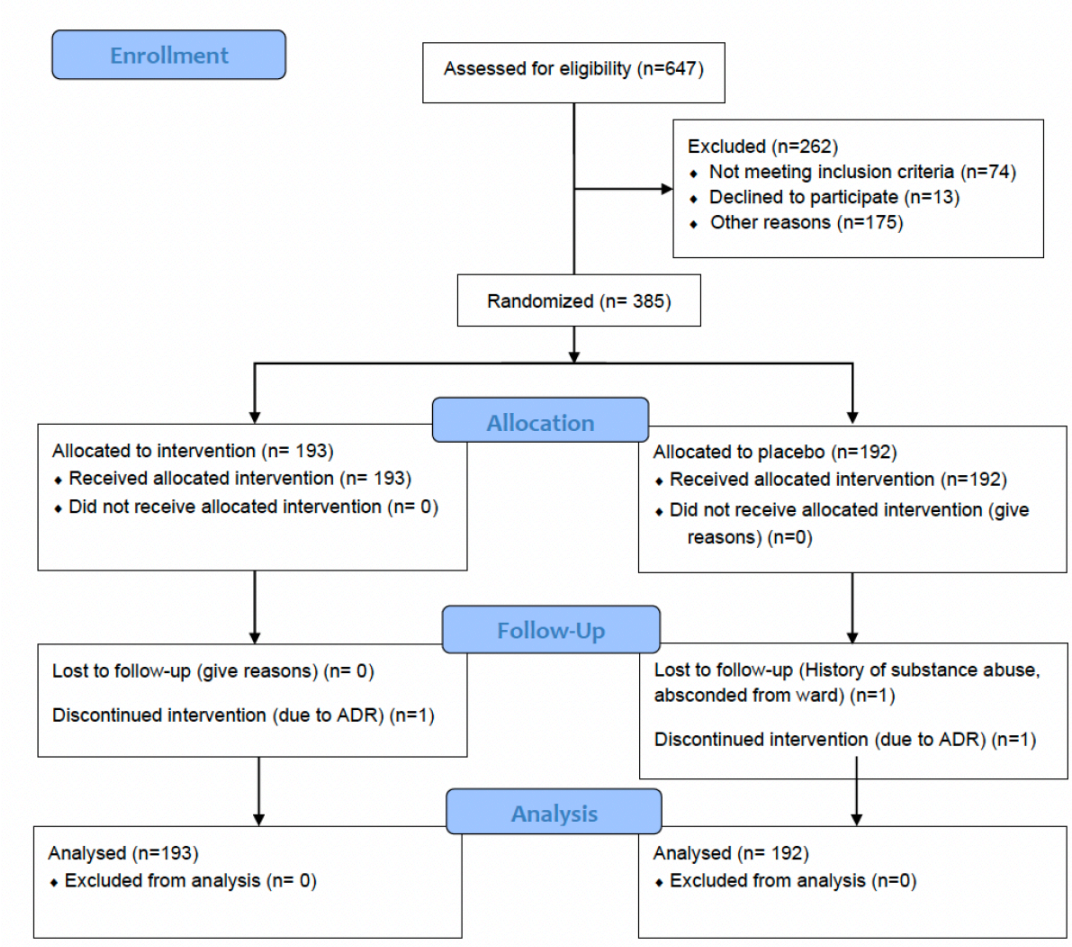

Figure 1 Trial profile. ADR, adverse drug reaction.

Primary endpoint achievement in the ITT population is shown in table 2. For the ITT population, the primary outcome occurred in 24 participants in the beclomethasone group and 26 participants in the placebo group (RR 0.90, 95% CI: 0.50 to 1.63; p=0.8) (table 2). Patients who achieved primary outcomes had received trial medications for a median of 2.5 days (IQR 1–4). In stratified analysis, of the participants who were unvaccinated for COVID-19, 11 (15.9%) in the beclomethasone group versus 15 (19.2%) in the placebo group reached primary endpoints (RR 0.80, 95% CI: 0.34 to 1.88; p=0.7). Subgroup analyses were carried out to study the primary outcome achievement in the participants according to COVID-19 severity at recruitment and there was none found. The proportion of patients reaching primary outcomes was not different when patients were stratified into two age groups; less than 60 years and 60 or more years.

Secondary outcome achievement in the ITT study population is shown in table 3. The median time to self-reported clinical recovery was 5 days (95% CI 3 to 7) in the beclomethasone group and 5 days (95% CI 3 to 8) in the placebo group (p=0.5). However, in stratified analysis, self-reported clinical recovery was 1 day shorter in patients with moderate COVID-19 treated with beclomethasone compared with placebo (p=0.05).

There were no deaths during the intervention phase of the study (table 3). Following completion of the study/reaching the endpoint, two deaths were reported by the day 28 closure of the study: one participant in the beclomethasone group died 20 days after discharge of a myocardial infarction and one participant in the placebo group died of COVID-19 pneumonia 2 days after transferring to a higher-tier healthcare facility. There was no difference in the short-term outcome of the patients in the two groups (p=0.8) (table 3).

Time to self-reported clinical recovery of the ITT population using data censoring at 28 days is shown in figure 2 and it did not show a significant difference between the two groups (log-rank test p=0.4).

The short course (maximum 10 days) of inhaled dry power beclomethasone was well tolerated with none having oral candidiasis, hoarse voice, gastritis, glaucoma, secondary infections or allergic reactions. Two participants, one each from the intervention group and the non-intervention group discontinued trial medication due to a dry cough which resolved spontaneously within 2–3 days.

DISCUSSION

Our study adds to the evidence that early initiation of inhaled beclomethasone in patients with asymptomatic,

Table 1 Baseline characteristics of the intention-to-treat population

	Beclomethasone arm (N=193)	Placebo arm (N=192)
Mean age, SD (years)	51.8 (17.3)	51.1 (18.6)
Sex, female, n (%)	99 (51.3%)	99 (51.9%)
Body mass index, mean (SD) kg/m^2	24.8 (5.2)	24.1 (5.4)
Medical history, n (%)		
Cardiovascular diseases	4 (2.1%)	1 (0.5%)
Diabetes mellitus	65 (33.7%)	66 (34.4%)
Hypertension	62 (32.1%)	62 (32.3%)
Past or current history of asthma	9 (4.7%)	7 (3.6%)
Other chronic respiratory conditions	0 (0.0%)	0 (0.0%)
Treatment with ACEI, n (%)	23 (11.9%)	26 (13.5%)
Vaccinated with one dose against COVID-19, n (%)	124 (64.2%)	113 (58.9%)
Vaccinated with two doses against COVID-19, n (%)	74 (38.8%)	70 (36.5%)
Duration of symptoms before admission		
Mean, (SD) days	3.7 (1.9)	3.9 (1.9)
COVID-19 severity on admission, n (%)		
Asymptomatic disease	13 (6.7%)	12 (6.3%)
Mild disease	122 (63.2%)	123 (64.1%)
Moderate disease	58 (30.1%)	57 (29.7%)
Prevalence of different symptoms on admission, n (%)		
Cough	115 (59.6%)	123 (64.1%)
Fever	109 (56.5%)	112 (58.3%)
Sore throat	67 (34.7%)	71 (37.0%)
Fatigue	60 (31.1%)	75 (39.1%)
Loss of sense of smell or taste	60 (31.1%)	89 (46.4%)
Breathlessness	59 (30.6%)	58 (30.2%)
Myalgia	58 (30.1%)	66 (34.4%)
Gastrointestinal symptoms	36 (18.7%)	37 (19.3%)
Loss of appetite	34 (17.6%)	29 (15.1%)
Chest pain or tightness	23 (11.9%)	34 (17.7%)
Highest temperature on admission, mean, (SD) °C	37 (17.4)	98.4 (17.4)
Lowest O_2 saturation on admission, mean, (SD) %	98.3 (1.1)	98.3 (1.2)

ACEI, ACE inhibitors.

mild or moderate COVID-19 did not reduce disease progression to severe COVID-19 in a double-blind, placebo-controlled clinical trial. However, we observed that self-reported clinical recovery was 1 day shorter in patients with moderate COVID-19.

The PRINCIPLE trial has shown that ICS in early COVID-19 reduced the time to recovery in individuals at high risk of COVID-19 complications. They further observed that there was no significant difference in the rate of hospitalisation or deaths with this treatment.[23] PRINCIPLE trial only recruited individuals at high risk of COVID-19 complications; that is, of 65 years or older or 50 years or older with comorbidities. We studied ICS in early COVID-19 in patients at all risk categories, that is, low and high risk of COVID-19 complications, and we found that this did not reduce the disease progression to severe disease but observed a reduction in the time to clinical recovery only in the patients presenting with moderate COVID-19. The RECOVERY trial showed that systemic dexamethasone offered a survival benefit in those who were receiving either invasive mechanical ventilation or oxygen alone at randomisation but offered no benefit, and possible harm, in those with less severe disease.[24] Adding to this, our study has shown that inhaled beclomethasone in patients with less severe disease did not receive any benefit. We did not observe any worsening of the outcome.

The STOIC trial showed that early administration of inhaled budesonide in individuals presenting with symptomatic COVID-19 reduced the likelihood of needing

Table 2 Primary endpoint achievement

	Beclomethasone arm* (N=193)	Placebo arm† (N=192)	P value
Primary endpoint achievement in the total population			
Primary endpoint achieved (n=193*, 192†)	24	26	0.8
Primary endpoint achievement in subpopulations			
Subpopulations on the severity of COVID-19 on admission			
Asymptomatic (n=13*, 12†)	0	1	0.5‡
Mild disease (n=122*, 123†)	16	18	0.7§
Moderately disease (n=58*, 57†)	8	7	0.8§
Subpopulations on age			
Less than 60 years (n=114*, 113†)	7	8	0.8‡
60 years or more (n=79*, 78†)	17	18	0.9‡
Subpopulations on the number of COVID-19 vaccines received before contracting COVID-19			
Zero doses (n=71*, 78†)	11	15	0.7‡
One dose (n=48*, 44†)	4	7	0.3‡
Two doses (n=74*, 70†)	9	4	0.3‡

*Beclomethasone arm.
†Placebo arm.
‡Fisher's exact test.
§Pearson's χ^2 test.
ICU, intensive care unit; n, sample size.

urgent medical care and reduced time to recovery after early COVID-19.[5] This differs from our main findings but is in line with our secondary endpoints where we also observed a reduction in time to self-reported recovery in patients presenting with moderate symptoms. There were some important differences between the STOIC and our study. STOIC was an unblinded study conducted in the community and used budesonide 1600 mcg daily while our study was a hospital-based, double-blind, placebo-controlled study, and we used beclomethasone 1200 mcg daily. The STOIC study restricted enrolment to symptomatic individuals. In contrast, we recruited all who tested positive for COVID-19 irrespective of their symptoms, as the aim of our intervention was to prevent individuals diagnosed with COVID-19 from progressing to severe disease by initiating ICS early. This may have contributed to the difference we observed in our primary endpoints. The majority of our patients were asymptomatic or mildly symptomatic. However, in the moderately symptomatic patients, we observed 1 day difference in self-reported time to recovery, in agreement with STOIC trial findings. The STOIC trial used budesonide and we used beclomethasone, both were ICS's. ICS exert a 'class effect' as anti-inflammatory agents. Comparison between ICS depends on a number of factors and from studies largely focused on asthma, bioequivalence between products and formulations has been determined by estimation of in vivo clinical effects rather than in vitro drug-receptor activity.[25 26] A range of studies have determined the bioequivalence ratio between beclomethasone and budesonide of 1:1.25–2.[25–27] Accordingly, for a daily dose of 1600 mcg dry powder budesonide, an equivalent daily dose of beclomethasone lies between 800 and 1200 mcg of which we used the higher concentration. Accordingly it is unlikely that the difference we observed is due to the ICS type and the dose we used. Study participants of our trial were daily interviewed by the researchers and were reminded to use the inhaler. Moreover, since the participants were hospitalised, inhaler use was witnessed at each drug round by nurses, and this made compliance to medicine almost 100%. The STOIC, PRINCIPLE and the other phase III US study were carried out before the vaccination rollout and the emergence of newer variants of SARS-CoV-2.[13] In contrast, around 60% of our study population in the intervention arm and the control arm had received at least one dose of the COVID-19 vaccine at a time when the dominant COVID-19 variant was the delta variant. This may suggest that ICS prophylaxis is less effective in a largely vaccinated population. Finally, our primary endpoint was very specific and differs from that of the STOIC trial which included a composite outcome of urgent care visits and hospitalisation. This could have contributed to observed differences between our findings and the STOIC trial. Additionally, a potential bias was highlighted in STOIC, of unblinded providers being more likely to refer to urgent care when a patient was not on treatment.[10]

There were several strengths of our trial. This was a double-blind, placebo-controlled randomised study. We achieved the calculated sample size to detect the effect we were looking for. We recruited patients irrespective of symptoms as early intervention was the point at which we wanted to act. We ran the full course of the trial and had a very high completion rate. Our endpoints were objective and very specific to COVID-19.

Table 3 Secondary endpoint achievement

	Beclomethasone arm* (N=193)	Placebo arm** (N=192)	P value
Number of days with temperature 38°C or more, median (IQR) days			
In total population	0 (0–0)	0 (0–0)	0.5
In subpopulations stratified on the severity of the disease on admission			
Asymptomatic (n=13*, 12**)	0 (0–0)	0 (0–0)	1.0
Mild disease (n=122*, 123**)	0 (0–0)	0 (0–0)	0.6
Moderately disease (n=58*, 57**)	0 (0–0)	0 (0–1)	0.8
In subpopulations stratified on the age of the patient			
Less than 60 years (n=114*, 113**)	0 (0–0)	0 (0–0)	0.2
60 years or more (n=79*, 78**)	0 (0–0)	0 (0–0)	0.4
Time to self-reported clinical recovery, median (IQR) days			
In total population	5 (3–7)	5 (3–8)	0.5
In subpopulations stratified on the severity of the disease on admission			
Asymptomatic (n=13*, 12**)	0 (0–0)	0 (0–4)	0.4
Mild disease (n=122*, 123**)	5 (3–8)	5 (3–7)	0.9
Moderately disease (n=58*, 57**)	5 (3–7)	6 (4–9)	0.05
In subpopulations stratified on the age of the patient			
Less than 60 years (n=114*, 113**)	5 (3–6)	5 (3–8)	0.4
60 years or more (n=79*, 78**)	5 (3–10)	5 (3–10)	0.9
Short-term outcome by day 28† in the total population			0.8
Complete recovery, n (%)	150	149	
Partial recovery, n (%)	27	30	
Death, n (%)			
Direct COVID-19 death	0	1	
Indirect COVID-19 death	1	0	

*Beclomethasone arm, ** Placebo arm.
†Symptomatic patients at randomisation.

However, it should be noted, our study was a single-centre study confined to a South Asian population, and the COVID-19 variant we studied was mainly the Delta variant (21I and 21J) which may limit its generalisability. The exclusion of those taking any corticosteroids within the previous 14 days restricted the number of participants with chronic lung diseases being included in our study, which remains an area of interest for COVID-19 treatment. We did not stratify randomisation according to the vaccination status nor the severity of the symptoms at recruitment, to allow for secondary endpoints with adequate power in subgroups defined by more than one variable. Furthermore, our study setting does not represent a typical clinical setting for patients with COVID-19 at the time of reporting in 2023 as asymptomatic and mildly symptomatic patients are now being managed in the community.

In vitro studies suggest mechanisms by which ICS (and β_2-agonists) might act on lung cells to reduce exacerbations caused by common cold viruses. Budesonide and formoterol have been shown to reduce type 14 rhinovirus-induced proinflammatory cytokine release and inhibit viral RNA replication in human tracheal epithelial cells. Multiple studies have shown that ICS, in combination with long-acting β_2-agonists, is an effective treatment for reducing virus-induced asthma exacerbations. COVID-19 is a self-limiting, viral disease in the majority but causes death in a small proportion of patients, especially the elderly where comorbidities and/or impaired immunity coexist.[2] An overactive type I immune response with overproduction of proinflammatory cytokines is the main mechanism suggested for the progression to severe COVID-19 and needing respiratory support. This may explain why dexamethasone,[24] interleukin 6 receptor blockers[28] and kinase inhibitors[29] help to prevent the cytokine storm and death in severe COVID-19.[2] The relative paucity of cytokine response in less severe disease may explain why ICS is not beneficial in asymptomatic or mild COVID-19.

Our study showed that early initiation of ICS in an individual positive for COVID-19, irrespective of symptom profile, does not reduce the progression of the disease to severe disease. However, early initiation of ICS as in this study may have benefits at least in hastening clinical

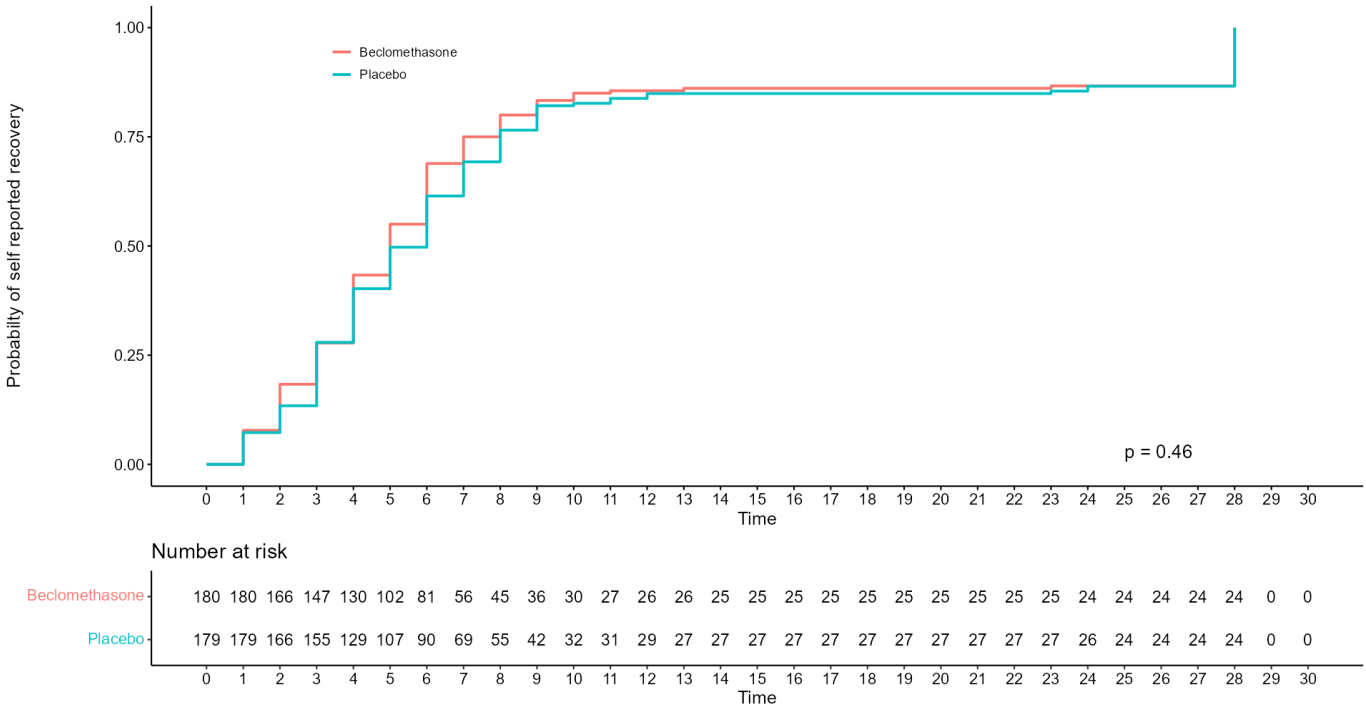

Figure 2 Time to self-reported clinical recovery of patients with symptomatic COVID-19 using data censoring at 28 days.

recovery in individuals presenting with moderate COVID-19, a finding also supported by the PRINCIPLE and STOIC trials. This warrants further study and confirmation, as ICS remains a low-cost, safe, simple and widely available therapeutic option, available to low-income and middle-income countries which may be of benefit to selected patients, especially with the SARS-CoV-2 virus continuously getting mutated and leading to a state of chronic endemicity.

CONCLUSION

Early initiation of inhaled beclomethasone in patients with asymptomatic, mild or moderate COVID-19 did not reduce disease progression to severe COVID-19. However, self-reported clinical recovery was 1 day shorter in patients with moderate COVID-19

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Competing interests None declared.

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Patient consent for publication Consent obtained directly from patient(s).

Ethics approval Ethical approval was obtained from the Ethics Review Committee, Faculty of Medicine, University of Kelaniya, Sri Lanka (P/59/06/2021) and the National Medicines Regulatory Authority (CT/P38/16/2021). The Clinical trial was registered at https://trialsearch.who.int/?TrialID=SLCTR/2021/017 (SLCTR/2021/017, 04 July 2021). Participants gave informed consent to participate in the study before taking part. All study procedures were performed in accordance with the relevant guidelines and regulations.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. All individual deidentified participant data (including data dictionaries) will be shared; Additional, related documents will be available (eg, study protocol, analysis plan, clinical study report, etc); Data will be shared with anyone on a reasonable request to the corresponding author and will be made available on the Faculty of Medicine, University of Kelaniya, Sri Lanka repository 5 years from the date of publication.

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