

Inhaled Corticosteroids for Outpatients with Covid-19: A Meta-Analysis

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Abstract: The role of inhaled corticosteroids for outpatient COVID-19 is evolving. We meta-analyzed reported clinical trials and estimated probability of any effect and number needed to treat of 50 or 20 for symptom resolution by day 14 [100%, 99.8%, 93.1%] and hospitalization [88.6%, 72.7%, 26.3%] respectively.

Introduction:

Inhaled corticosteroids, in particular budesonide, have received substantial interest as inexpensive and safe treatments for non-hospitalized patients presenting with symptomatic SARS-CoV-2 infections following two open label randomized controlled trials (RCTs). STOIC (Steroids in COVID-19) [1], an RCT in outpatients diagnosed with COVID-19 (n=146), reported budesonide was effective at improving time to recovery and reducing the composite outcome of urgent care, emergency room visits, and hospitalization. Shortly thereafter, the PRINCIPLE trial (Platform Randomized Trial of Treatments in the Community for Epidemic and Pandemic Illnesses) [2] replicated the findings for time to recovery in a much larger population (n=1719 concurrent) and detected a reduction in hospitalization, primarily in older adults. However, both STOIC and PRINCIPLE were open label. Previous work has demonstrated that, with respect to respiratory symptoms, inhaled medications can have substantial placebo effects [3]. By contrast, both the recent CONTAIN trial (Inhaled Ciclesonide for the Treatment of COVID-19 in Non-hospitalized Adults) [4] and an industry-sponsored ciclesonide trial (Covis Pharma) [5] were placebo-controlled and failed to demonstrate a benefit in time to recovery with conflicting findings on hospitalizations. To best inform clinical practice, we conducted a meta-analysis of these trials to contextualize the totality of the data available on the use of inhaled corticosteroids for the treatment of symptomatic outpatients with COVID-19.

Methods:

We used the secondary outcome result of complete resolution of symptoms by Day 14 which was conserved between all four completed and reported inhaled corticosteroid randomized controlled trials: STOIC [1], PRINCIPLE [2], CONTAIN [4], and Covis Pharma [5]. We also compared the outcome of hospitalization; for STOIC, only the composite data was reported. Using STATA version 17 and the metan command, we performed a random effects meta-analysis for these outcomes. Analyses were stratified by the presence or absence of placebo control with a pooled overall effect estimate. With the estimates for risk ratio and the accompanying 95% confidence interval, we calculated the probability of any benefit ($RR > 1$ for symptom resolution, $RR < 1$ for hospitalization) as well as for a 5% (NNT of 20) and 2% (NNT 50) absolute difference based on the overall pooled control event rates by integrating the area under the probability density curves [6].

Results:

The four trials included a total of 2317 analyzed patients and are summarized in Table 1. The average age in patients enrolled in the STOIC, CONTAIN and Covis Pharma studies were similar ranging from 37 to 45, whereas the average age of patients in the PRINCIPLE trial was much higher at 64. The pooled relative risk and 95% confidence intervals for complete symptom resolution by day 14 and hospitalization are also reported in Table 1 and visualized in Supplemental Figures 1 and 2. As hypothesized, the effect size for symptomatic improvement

was larger in the open-label trials (RR 1.39; 95%CI 1.22-1.58) than in the placebo-controlled studies (RR 1.15; 95%CI 0.95-1.38). However, even the placebo-controlled studies suggest a 92.5% probability of any benefit and a 78.1% probability of an NNT \leq 50. Whereas the open label studies individually suggest a high probability of reduction in hospitalization (RR 0.44; 95%CI 0.12-1.70; 88.9% probability of any effect), the placebo-controlled estimate was more modest (RR 0.90; 95% CI 0.22-3.71; 55.5% probability of any effect).

Discussion:

This is the first meta-analysis of the four completed and reported trials of outpatient inhaled corticosteroid COVID-19 treatment. Our results support the use of inhaled corticosteroids (ciclesonide or budesonide) for the resolution of symptoms at day 14 of treatment. While there is demonstrably a placebo effect, the probability of an objective effect remains high in the placebo-controlled subgroup at 92.5% probability for any effect and 78.1% probability of an NNT of 50 or less. Overall, inclusive of any additional placebo effect, there is a 93.1% chance that the NNT is 20 or less. With respect to hospitalization, the effect is less clear for all comers; there is a large influence of the PRINCIPLE trial which included a much older population compared to the other trials, combined with lack of distinction between urgent care visits and hospitalization in STOIC. While the statistical test for heterogeneity in PRINCIPLE was not significant, there was a notable and plausible difference in the subgroup of patients older than age 65 (aOR 0.60; 95%CI 0.40-0.90) when compared to younger participants (aOR 1.03; 95%CI 0.59-1.80). Overall, the probability of a clinically significant effect on hospitalization (NNT \leq 50) was only 72.7% but this may also be an underestimate of the benefit if the treated population is older than 65 or has more comorbidities and a higher associated risk of deterioration.

Our analysis is limited by the granularity of the available data. An individual patient meta-analysis accounting for age and comorbidities might produce more accurate estimates, particularly in subgroups or in time to event analyses which could have increased power. Additionally, approximately two-thirds of the data is open label and subject to the placebo effect with respect to symptom reporting. There is also potentially bias in urgent care or emergency room utilization due to unblinded providers being less likely to refer to urgent care when the patient was on treatment, and/or a difference in care-seeking behavior for participants who were not receiving a treatment. Additionally, these trials were performed in different waves of the global COVID-19 pandemic. Patients and providers may have been more likely to refer patients to the emergency department early in the pandemic when less was known about the natural history of the disease. If additional placebo-controlled trials become available, it will be important to update this meta-analysis. The strength of our analysis is that we have used all the available data in combination with a probabilistic presentation allowing for determination of a variety of clinically relevant effect sizes. Inhaled corticosteroids are widely available, inexpensive in most jurisdictions, have few reported severe side effects and are likely beneficial based on the total evidence to date.

Overall, there is an ongoing need to identify effective oral or inhaled medications that can be used early in the disease to prevent COVID-19 hospitalization. It is unknown whether improving complete symptom resolution will have any meaningful impact on long term outcomes and the prevention of chronic symptoms that are now commonly reported. With respect to reduction in hospitalization, there is promise for inhaled corticosteroids, particularly in older adults; however, additional placebo controlled randomized trial evidence should still be sought to minimize bias and obtain more accurate estimates of effect size.

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Conflicts of Interest

NE, TCL, SB, ND, AKC and EGM were co-investigators on the CONTAIN trial.

CRedit author statement

Conceptualization - TCL, EGM; Methodology - TCL, EGM; Validation - TCL; Formal Analysis - TCL; Investigation - All authors; Resources - TCL; Data Curation - TCL, NE, EGM; Writing - Original Draft - TCL, ÉBC, RH, EGM; Writing - Review and Editing - All authors; Visualization TCL, EGM

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Table 1 - Trial descriptions and Meta-Analysis Results

Study	Primary Outcome	Number of Patients	Time to enrollment	Average Age	Male (%)	Comorbidities
CONTAIN (Placebo control)	Resolution of cough, dyspnea, and fever by day 7	203	≤6 days of symptoms	37	46.3%	20.2% overall 5.9% Hypertension 2.5% Diabetes 0.5% Coronary artery disease
Covis Pharma (Placebo control)	Time to alleviation of all symptoms	400	≤72h of test	43	44.8%	22% Hypertension 7.5% Diabetes
STOIC (Open label)	Covid-19 urgent care visits	139	≤7d of symptoms	45	42.4%	Median of 1 8.4% Coronary artery disease 5% Diabetes
PRINCIPLE (Open label)	Covid-19 related hospitalization or death	1719 (concurrent)	≤14d of symptoms	64	48.5%	80% (median of 1) 43-46% hypertension 20-23% Diabetes 15-17% Coronary artery Disease
Analysis	Pooled Risk Ratio		Probability Any Benefit	Probability NNT ≤50		Probability NNT ≤20
Symptom Free by Day 14 - Overall	1.29 (1.14-1.47)		100%	99.8%		93.1%
Placebo-controlled	1.15 (0.95-1.38)		92.5%	78.1%		42.6%
Open label	1.39 (1.22-1.58)		100%	100%		99.3%
Hospitalization – Overall	0.64 (0.31-1.29)		88.6%	72.7%		26.3%
Placebo-controlled	0.90 (0.22-3.71)		55.5%	43.3%		21.5%
Open label	0.44 (0.12-1.70)		88.9%	81.5%		58.2%