Repeated dose budesonide/formoterol compared to salbutamol in adult asthma: a randomised crossover trial

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The comparative bronchodilator responses of repeated administration of salbutamol 200 µg and budesonide/formoterol 200/6 µg differed depending on the time of measurement; salbutamol caused greater systemic β_2-agonist, cardiovascular and adverse effects https://bit.ly/3KqWcDm

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Abstract

Background Our objective was to determine the comparative bronchodilator, systemic β_2-agonist, cardiovascular and adverse effects of salbutamol 200 µg and budesonide/formoterol 200/6 µg when taken repeatedly in stable asthma.

Methods This open-label, crossover, single-centre, controlled trial randomised adults with asthma to different orders of two treatment regimens: salbutamol 200 µg *via* metered-dose inhaler at 0, 30, 60 and 90 min, then salbutamol 2.5 mg *via* nebuliser at 120, 140, 160 and 420 min; or budesonide/formoterol 200/6 µg one actuation *via* Turbuhaler at 0, 30, 60 and 90 min, then two actuations at 120, 140, 160 and 420 min. The primary outcome measure was forced expiratory volume in 1 s (FEV_1) after 180 min. Secondary outcomes included repeat measures of FEV_1, serum potassium, heart rate and adverse events

Results Of 39 patients randomised, two withdrew due to adverse events (QT_{CF} prolongation and T-wave abnormalities) after the first intervention with salbutamol. The mean±SD change from baseline FEV_1 180 min after randomisation for salbutamol and budesonide/formoterol regimens was 0.71±0.46 L (n=38) and 0.58±0.45 L (n=37), respectively, with a mean±SD paired difference of −0.10±0.40 L (n=37) and a model-based estimated difference of −0.12 (95% CI −0.25–0.02) L (p=0.088). In the main secondary analysis, salbutamol resulted in significantly greater FEV_1 from 30 to 240 min, but lesser FEV_1 at 360 and 420 min. Salbutamol resulted in a significantly lower serum potassium, and a higher heart rate and number of adverse events.

Conclusions The comparative bronchodilator responses of repeated administration of salbutamol 200 µg and budesonide/formoterol 200/6 µg differed depending on the time of measurement. Salbutamol caused greater systemic β_2-agonist and cardiovascular effects and more adverse events.

Introduction

The Global Initiative for Asthma recommends that combination inhaled corticosteroid (ICS)/formoterol is the preferred reliever to short-acting β_2-agonist (SABA), for adults and adolescents with any severity of asthma [1, 2]. This is based on evidence that budesonide/formoterol reliever alone reduces the relative risk of severe exacerbations by at least 60% compared to SABA reliever therapy in mild asthma [3, 4], by 15% compared to maintenance budesonide plus SABA reliever [5] and by about one-third in patients taking maintenance ICS/long-acting β_2-agonist (LABA) [6, 7]. This reduction in severe exacerbation risk is seen with self-administered use by patients in the long-term treatment of asthma in the community setting. In contrast, the relative bronchodilator and anti-inflammatory effects of the repeated administration of budesonide/formoterol compared to SABAs, as may occur in the emergency department (ED) setting, are uncertain. This is an important issue as repeated dosing of ICS in acute severe asthma is associated with a substantive improvement in lung function [8] and a reduced risk of hospital admission [9].

The doses of budesonide/formoterol *versus* salbutamol (or terbutaline) used as reliever therapy in community-based trials have been 200/6 µg *versus* 200 µg (or 500 µg) [3–7]. This trial compares bronchodilation following repeated administration of budesonide/formoterol compared to salbutamol in this dose ratio of 200/6 µg:200 µg in adults with stable asthma and moderate-to-severe airflow obstruction. The primary objective was to compare the magnitude of bronchodilation after 180 min of initiation of the two treatments. Our hypothesis was that budesonide/formoterol would have superior bronchodilator efficacy than salbutamol due to the additional genomic and nongenomic effects of repeated doses of ICS [10–12].

Materials and methods

Study design and participants

This was an investigator-led, open-label, crossover, single-centre, randomised controlled trial comparing salbutamol with budesonide/formoterol conducted at the Medical Research Institute of New Zealand (Wellington, New Zealand). The trial was run in accordance with Good Clinical Practice guidelines and the Declaration of Helsinki, and was approved by the Northern B Health and Disability Ethics Committee (19/NTB/83) and registered with the Australian New Zealand Clinical Trials Registry (ACTRN12619001083189). Adults with asthma aged 16–65 years, with forced expiratory volume in 1 s (FEV_1) 40–70% predicted and bronchodilator reversibility with FEV_1 ⩾12% and >200 mL, were recruited. Details of inclusion and exclusion criteria are given in supplementary table S1. Written informed consent was obtained from all participants. Participants were required to withhold their SABA inhalers for 6 h, LABA inhalers for 24 h and ultra-LABA inhalers for 48 h prior to each visit.

Procedures

Participants attended an initial screening visit to determine eligibility and then returned on a different day for randomisation and the first intervention regimen, followed by reattendance for the second intervention regimen after a minimum washout period of 1 week. The schedule of assessments and tests is shown in figure 1; further details of testing procedures can be found in the supplementary material.

Intervention regimens

The bronchodilator regimens (figure 1) were based on the doses of salbutamol self-administered by patients in the community prior to a hospital presentation [13] and guideline recommendations for the use of salbutamol in the ED [14].

The salbutamol regimen was salbutamol (Ventolin 100 µg CFC-free metered-dose inhaler; GlaxoSmithKline, Brentford, UK) two actuations *via* a spacer at 0, 30, 60 and 90 min, followed by salbutamol (Asthalin 2.5 mg per nebule; Rex Medical, Auckland, New Zealand) nebulised, one nebule at 15 $L \cdot min^{-1}$ at 120, 140, 160 and 420 min. The budesonide/formoterol regimen was budesonide/formoterol (Symbicort Turbuhaler 200 µg budesonide and 6 µg formoterol; AstraZeneca, Cambridge, UK) one actuation at 0, 30, 60 and 90 min, followed by Symbicort Turbuhaler 200/6 µg, two actuations at 120, 140, 160 and 420 min. In addition, at the 8-h time-point (480 min), participants randomised to the salbutamol regimen received 12 actuations of budesonide (Pulmicort Turbuhaler 200 µg; AstraZeneca) to ensure that they received the same ICS dose on study days with no differential carry-over effects between randomised intervention regimens.

Outcomes

The primary outcome measure was FEV_1 after 180 min. Secondary outcome measures were FEV_1, exhaled nitric oxide fraction (F_{ENO}) and modified Borg dyspnoea scale score at 30, 60, 90, 120, 150, 210, 240, 300, 360, 420 and 480 min, and serum potassium, blood eosinophil levels, heart rate and QT_{CF} (corrected QT interval using Fridericia's formula) at 180 and 480 min.

Sample size

Based on the previous crossover study [15], the estimated paired standard deviation for this study was an FEV_1 of 0.43 L. A sample size of 39 had 90% power to detect a minimally clinical important difference in FEV_1 of 0.23 L [16], with a two-sided α of 0.05. Assuming a dropout rate of 10%, 44 participants were required. A re-estimation of the sample size was done at a planned interim analysis after 15 participants had been randomised. The paired difference change in FEV_1 from baseline for the two treatments was 0.20 (95% CI −0.015–0.41) L. The standard deviation for the paired difference in FEV_1 was 0.38 (95% CI 0.28–0.61) L. Based on the point estimate for the standard deviation, it was calculated that 32 participants would be needed for 90% power to detect a difference in FEV_1 of 0.23 L. We therefore continued with the original sample size of 39 participants without consideration of dropouts.

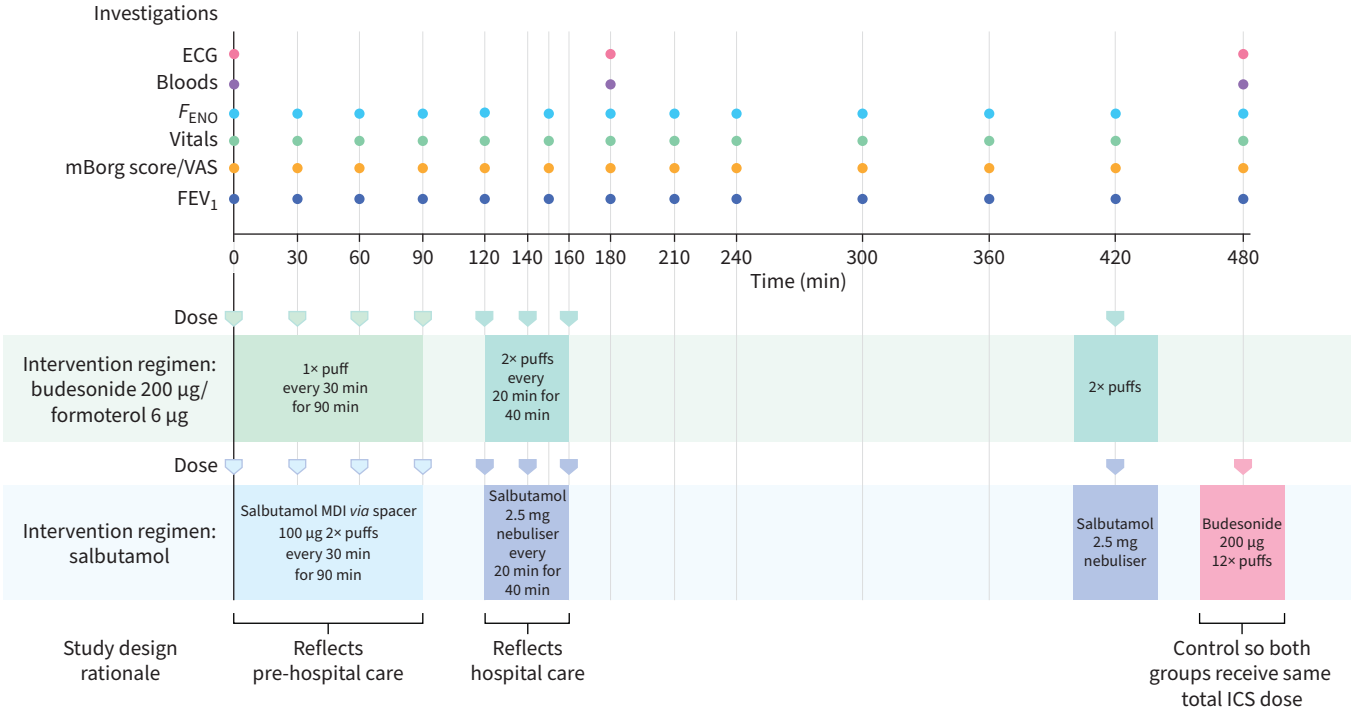

FIGURE 1 Investigation and dosing schedule. F_{ENO}: exhaled nitric oxide fraction: mBorg: modified Borg; VAS: visual analogue scale; FEV_1: forced expiratory volume in 1 s; MDI: metered-dose inhaler; ICS: inhaled corticosteroid.

Randomisation

Participants were randomised 1:1 to different orders of the intervention regimens in an AB–BA crossover design. The randomisation method involved a computer-generated sequence supplied by the study statistician, independent of the investigators. The sequence was uploaded into the Research Electronic Data Capture (REDCap; www.project-redcap.org) system by an individual who was otherwise uninvolved in study processes. REDCap concealed the allocations until after randomisation. Investigators enrolled participants and both were not masked to group assignment.

Statistical methods

For the primary analysis of FEV_1 after 180 min, a mixed linear model was used with fixed effects for baseline FEV_1, order of treatments and treatment, and a random effect based on the participant with an unstructured variance–covariance matrix. For the sensitivity analyses, all measurement times were used, denoted as a "full" mixed linear model. In these models an overall p-value tests the hypothesis that the difference between treatments is different at the different measurement times, which is a time-by-treatment interaction. The "full" models can also estimate comparisons of treatments at each time-point, with associated p-values of differences between treatments within each measurement time. The estimates of treatment differences within each time period from the "full" mixed model may differ from simpler analyses because more data is used in their estimation.

The analysis of serum potassium, blood eosinophil count, heart rate and QT_{CF} used the same models as for the $\log_e$ F_{ENO} and Borg score. F_{ENO} had a strongly skewed distribution and was analysed on the log-transformed scale. The exponent of the difference in logarithms is interpreted as the ratio of geometric means. McNemar's test for paired contingency tables and an appropriate estimate of the difference in paired proportions was used to assess for the difference in proportion of participants with adverse events.

SAS version 9.4 (SAS Institute, Cary, NC, USA) was used except for the analysis of adverse events where version 12.4 was used. Further details of statistical methods are available in the supplementary material.

Results

There were 39 participants recruited between 2 October 2019 and 1 November 2020 (figure 2). The trial was paused from 23 March 2020 to 8 June 2020 in accordance with the New Zealand government's

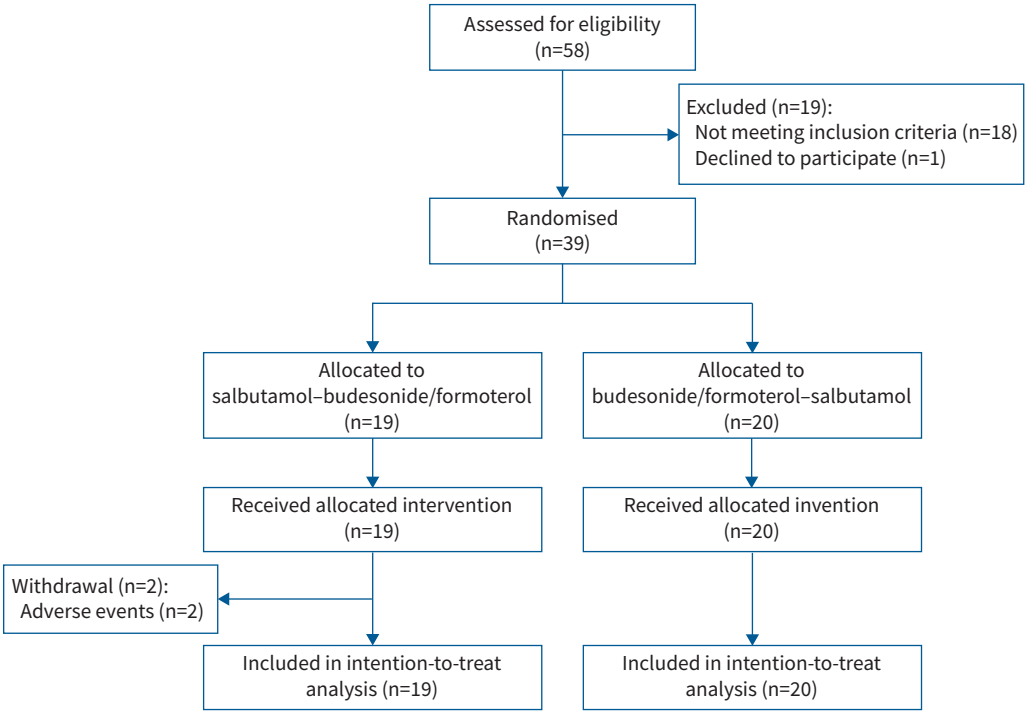

FIGURE 2 CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

coronavirus disease 2019 (COVID-19) response. Two participants were withdrawn during the first intervention regimen due to adverse events (QT_{CF} prolongation and T-wave abnormalities) following administration of salbutamol. All participants were included in the intention-to-treat analysis. Baseline characteristics are shown in table 1. At baseline, participants had mean±SD FEV_1 60.7±9.1% predicted and F_{ENO} 44.6±48.4 ppb.

In the primary analysis, the mean±SD change from baseline FEV_1 180 min after randomisation for salbutamol and budesonide/formoterol regimens was 0.71±0.46 L (n=38) and 0.58±0.45 L (n=37), respectively, with a mean±SD paired difference of −0.10±0.40 L (n=37) and a model-based estimated difference of −0.12 (95% CI −0.25–0.02) L (p=0.088). A box plot of FEV_1 change from baseline is shown in figure 3, and FEV_1 at each time-point for the salbutamol and budesonide/formoterol interventions is shown in figure 4. In the secondary analysis, using all measurement times in a "full" mixed linear model, there was evidence that the differences in FEV_1 between treatments depended on the time of measurement ($p_{interaction}$<0.001) (table 2). The estimates and p-values in table 2 are derived from the individual treatment comparisons within time from the 'full' mixed linear model and differ from the simpler analyses as they incorporate the full data.

There was no evidence that F_{ENO} in the two intervention regimens was different at the different time-points (figure 5). When averaged over all time-points, F_{ENO} was lower in the salbutamol group compared to the budesonide/formoterol group (ratio of geometric means 1.04, 95% CI 1.02–1.06; p<0.001). There was no evidence of a difference in Borg score between treatments (supplementary figure S1).

Serum potassium was lower in the salbutamol intervention at both time-points (table 3). In a model without a time-by-treatment interaction term, the mean serum potassium over both time-points was lower in the salbutamol intervention (point estimate of difference 0.21 (95% CI 0.13–0.28) $mmol \cdot L^{-1}$; p<0.001).

Blood eosinophil count was higher in the budesonide/formoterol regimen after 180 min (estimate 0.065 (95% CI 0.022–0.11)$\times 10^9$ L^{-1}; p<0.004), but not after 480 min (−0.02 (95% CI −0.06–0.024)$\times 10^9$ L^{-1}; p=0.36). There was strong evidence of time-by-treatment interaction (p=0.007).

Heart rate was lower in the budesonide/formoterol regimen and the size of the difference depended on time: −10 (95% CI −12.6– −7.4) $beats \cdot min^{-1}$; p<0.001 after 180 min; and −4 (95% CI −6.5– −1.4)

TABLE 1 Baseline characteristics of the study population (n=39)

Age (years)	46.0±14.3
Sex	
Female	20 (51.3)
Male	19 (48.7)
Ethnicity[#]	
European	33 (84.6)
Māori	3 (7.7)
Pacific Peoples	1 (2.6)
Asian	2 (5.1)
Smoking status	
Ex-smoker	11 (28.2)
Never-smoker	28 (71.8)
Pack-years	1.4±2.4
Age at asthma diagnosis (years)	10.9±11.1
Medication use	
Patient-reported use of SABA-only at enrolment	5 (12.9)
Patient-reported use of ICS+SABA at enrolment	8 (20.5)
Patient use of ICS/LABA-only at enrolment	10 (25.6)
Patient use of ICS/LABA+SABA at enrolment	16 (41.0)
Lung function	
FEV_1 (L)	2.06±0.67
FEV_1 (% pred)	60.7±9.1
F_{ENO} (ppb)	44.6±48.4
$\log_e F_{ENO}$ (ppb)	3.40±0.85
Modified Borg dyspnoea scale score	1.9±1.3
Serum potassium (mmol·L^{-1})	4.5±0.37
Blood eosinophils (×10^9 L^{-1})	0.34±0.22
Resting heart rate (beats·min^{-1})	69.7±11.8
QT_{CF} (ms)	415.1±18.1

Data are presented as mean±SD or n (%). SABA: short-acting β_2-agonist; ICS: inhaled corticosteroid; LABA: long-acting β_2-agonist; FEV_1: forced expiratory volume in 1 s; F_{ENO}: exhaled nitric oxide fraction. [#]: prioritised ethnicity using Level 1 codes [17].

beats·min^{-1}; p=0.003 after 480 min. The QT_{CF} was shorter in the budesonide/formoterol regimen with no evidence of a time-by-treatment interaction: −4.4 (95% CI −7.9– −0.1) ms (p=0.013).

There were 79 adverse events in total with no serious adverse events (supplementary table S8). There were significantly more adverse events during the salbutamol regimen compared to the budesonide/formoterol

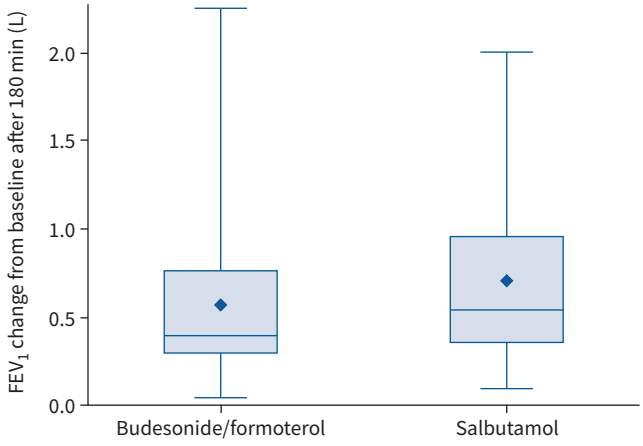

FIGURE 3 Box plot of forced expiratory volume in 1 s (FEV_1) change from baseline after 180 min. The diamond symbol indicates the mean, the horizontal lines are the 25th, 50th (median) and 75th percentiles, and the whiskers are from the minimum to maximum values.

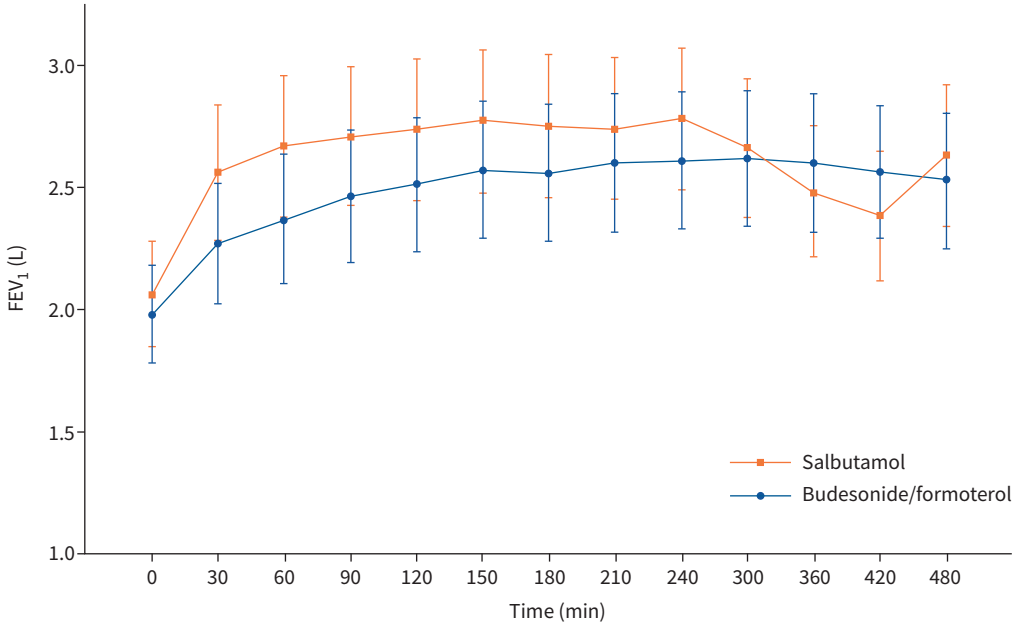

FIGURE 4 Time course of forced expiratory volume in 1 s (FEV_1) for budesonide/formoterol and salbutamol.

regimen (estimated difference in paired proportions 37.8, 95% CI 22.2–53.5; p<0.001). There were significantly higher proportions of tremor and light-headedness in the salbutamol regimen compared to the budesonide/formoterol regimen (estimated difference in paired proportions 37.8, 95% CI 22.1–53.5; p<0.001; and 18.9, 95% CI 6.3–31.5; p=0.003, respectively).

Discussion

This randomised controlled trial showed that there was no significant difference in the magnitude of bronchodilation between repeated doses of budesonide/formoterol 200/6 µg and salbutamol 200 µg at the primary outcome time-point of 180 min. In the secondary analysis, however, there were significant differences between treatments depending on the time of measurement, with salbutamol resulting in a greater magnitude of bronchodilation over the first 4 h, and budesonide/formoterol achieving a greater magnitude of bronchodilation at 360 and 420 min. Salbutamol resulted in a greater fall in serum potassium, a systemic β_2-agonist effect [18], consistent with a lesser β_2-agonist effect for budesonide/formoterol 200/6 µg compared to salbutamol 200 µg. Also consistent with these findings, salbutamol resulted in a higher heart rate and greater prolongation of QT_{CF}, and adverse effects occurred more frequently. This study was not designed to determine dose equivalence of the two treatments but to compare bronchodilation and adverse effects at commonly used doses.

TABLE 2 Secondary analyses of forced expiratory volume in 1 s comparison at all time-points

Time (min)	Budesonide/formoterol minus salbutamol difference (95% CI) (L)	p-value
30	−0.22 (−0.29– −0.15)	<0.001
60	−0.22 (−0.29– −0.15)	<0.001
90	−0.18 (−0.25– −0.11)	<0.001
120	−0.16 (−0.23– −0.09)	<0.001
150	−0.13 (−0.20– −0.06)	<0.001
180	−0.15 (−0.22– −0.07)	<0.001
210	−0.10 (−0.17– −0.03)	0.004
240	−0.13 (−0.20– −0.06)	<0.001
300	0.0 (−0.07–0.07)	0.96
360	0.16 (0.09–0.23)	<0.001
420	0.16 (0.09–0.23)	<0.001
480	−0.06 (−0.13–0.01)	0.11

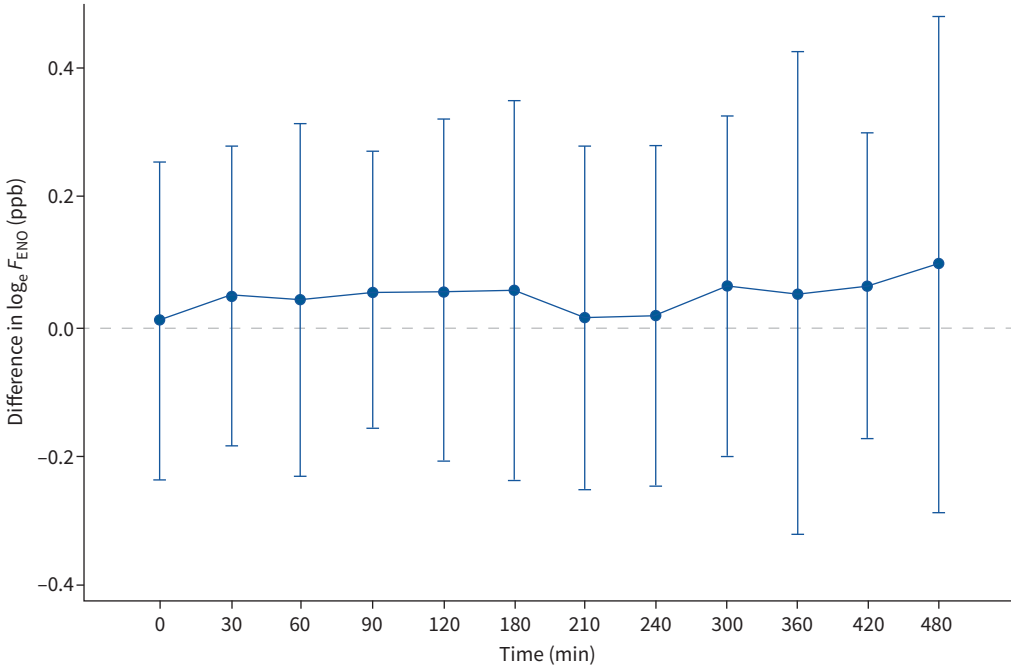

FIGURE 5 Time course for difference in $\log_e$ exhaled nitric oxide fraction (F_{ENO}) over time (budesonide/formoterol minus salbutamol).

Previous studies reporting differences between formoterol and salbutamol at the dose ratio used in our study are difficult to interpret because those studies do not report differences in point estimates and confidence intervals for differences in FEV_1, and all have different time-points for primary evaluation. In a study of acute presentations to the ED [19], in which formoterol 6 µg×4 and salbutamol 200 µg×4 were taken three times over 1 h, the primary measurement time was 75 min, and although the actual FEV_1 at this time was not reported, the changes from baseline FEV_1 of 37% and 28%, respectively, are consistent with changes from baseline of 0.39 and 0.30 L; a difference of 0.09 L favouring the formoterol group. In another ED study [20], in which budesonide/formoterol 400/12 µg×2 and salbutamol 100 µg×8 were taken twice 5 min apart, and the primary outcome was area under the curve normalised for time to 90 min, the measures were 1.38 and 1.52 L, respectively, consistent with a difference of 0.135 L, favouring the salbutamol arm. Finally, in a third ED study [21], in which formoterol 6 µg×4 and salbutamol 200 µg×4 were taken twice 30 min apart, the primary measurement time was FEV_1 after 45 min; however, the results were reported as percentage change from baseline FEV_1 and the point estimate for this favoured salbutamol, although the confidence intervals were wide and included the pre-specified clinically important difference to detect.

There are a number of methodological issues relevant to the interpretation of the findings. First, the study was open-label and so this introduced potential bias. Second, we used a model of adults with moderate-to-severe reversible airflow obstruction in an outpatient clinic situation, rather than the acute asthma setting in the ED. This had the potential advantage of allowing for a crossover study design and preventing confounding due to β_2-agonist self-administration and/or systemic corticosteroid treatment prior to the administration of the randomised treatments in the ED setting. However, this means that the findings are not necessarily generalisable to patients presenting to the ED with a severe exacerbation.

TABLE 3 Analysis of serum potassium

Time (min)	Budesonide/formoterol minus salbutamol difference (95% CI) ($mmol \cdot L^{-1}$)	p-value
180	0.26 (0.16–0.37)	<0.001
480	0.15 (0.05–0.25)	0.004

The salbutamol dosing schedule was consistent with the New Zealand adult asthma guideline recommendations [14]. The corresponding budesonide/formoterol doses were based on the 200/6 µg *versus* salbutamol 200 µg therapeutic dose ratio used in the community clinical trials, and the 6:1 dose bronchodilator equivalence between nebuliser and metered-dose inhaler with spacer administration [22], to account for the lack of a nebuliser product for budesonide/formoterol. This also meant that the study could not be blinded, which has the potential to introduce bias.

We chose FEV_1 after 180 min as the primary outcome measure as this time-point corresponded to the end of the intensive bronchodilator regimen, at which stage a decision would be made in clinical practice as to whether to discharge or admit the patient to hospital. The repeated measures of FEV_1 over the 8-h time period allowed an assessment of the time course, during which we observed that the differences between treatments depended on the time of measurement. The greatest difference in FEV_1 occurred during the first 60 min, with FEV_1 following salbutamol being 0.22 L greater, close to our pre-specified difference to detect of 0.23 L [16]. FEV_1 remained around 0.10–0.18 L higher with salbutamol until 240 min, 80 min after the end of the intensive cumulative dosing period. FEV_1 was 0.16 L higher with budesonide/formoterol at 360 and 420 min, an effect presumably due to the longer duration of action of formoterol [23, 24]. These differences suggest that whereas salbutamol may lead to greater efficacy in the acute ED setting, when used in these comparative doses, the more prolonged bronchodilation with budesonide/formoterol may contribute to its greater efficacy with self-administration in the community setting [25]. Many statistical tests have been carried out, so conclusions based on the secondary and sensitivity analyses should be viewed with caution as they are not adjusted for potential type I error inflation.

The finding that serum potassium with salbutamol was 0.26 and 0.15 $mmol \cdot L^{-1}$ lower at 180 and 480 min, respectively, demonstrates that budesonide/formoterol 200/6 µg has lesser systemic β_2-agonist effect than salbutamol 200 µg. This is consistent with the finding of a nonsignificant 0.26 *versus* 0.16 $mmol \cdot L^{-1}$ mean fall in serum potassium over 180 min with salbutamol 200 µg×8 *versus* budesonide/formoterol 200/6 µg×8, respectively, in severe asthma [20], and the nonsignificant 0.06 $mmol \cdot L^{-1}$ greater fall between 45 and 240 min with salbutamol 200 µg×8 *versus* formoterol 6 µg×8, in another ED study [21], but not the third ED study [19] in which the mean minimum serum potassium with formoterol 6 µg×12 was lower than salbutamol 200 µg×12 (3.2 *versus* 3.5 $mmol \cdot L^{-1}$, respectively).

To broaden assessment, heart rate and QT_{CF} interval were measured, representing cardiovascular β_1/β_2 and cardiac electrophysiological β_2 effects. We observed that repeated doses of salbutamol 200 µg caused a greater increase in heart rate and QT_{CF} interval prolongation than budesonide/formoterol 200/6 µg, changes which increase the risk of ventricular arrhythmias [26]. The clinical relevance of the differences is borne out by the observation that tremor and light-headedness occurred more frequently with salbutamol, and the requirement for two patients to be withdrawn due to adverse effects including QT_{CF} prolongation and T-wave abnormalities.

F_{ENO} was measured to assess potential acute airways anti-inflammatory effects, following the demonstration that in stable asthma, budesonide 2400 µg reduced sputum eosinophils at 6 h, an effect which was associated with a reduction in bronchial hyperresponsiveness [27]. In contrast to these findings, we observed no reduction in F_{ENO} with budesonide/formoterol, despite a budesonide dose of 2000 µg over 3 h. When averaged over time, F_{ENO} was slightly greater with the budesonide/formoterol intervention, a finding most likely due to chance. The mean baseline F_{ENO} of the participants was 45 ppb, and it remains to be determined whether adults presenting with a severe exacerbation and a higher F_{ENO} might obtain anti-inflammatory effects with the repeated use of budesonide/formoterol. The other potential benefit with the ICS component of budesonide/formoterol is the acute nongenomic vasoconstrictor effects within the airways, considered to be responsible for the substantive improvement in lung function with the repeated use of ICS in the ED treatment of exacerbations [8–12]. It is possible that these effects may have contributed to the bronchodilator response observed with the repeated use of budesonide/formoterol in this study.

Blood eosinophil count in our study was higher in the budesonide/formoterol regimen after 180 min, which is likely a chance finding unrelated to the systemic absorption of budesonide. A previous study demonstrated that the peak plasma concentration of budesonide was achieved 5–10 min after a single dose administration of 1200 µg of budesonide *via* Turbuhaler in moderate-to-severe asthma [28]. In another study, peak plasma concentration was achieved within 20 min of administration of 1600 µg of budesonide *via* Turbuhaler in mild-to-moderate asthma [29]. The effect of repeated, cumulative dosing of budesonide over an 8-h period on plasma concentrations is unknown; however, our observation of a time-by-treatment interaction with blood eosinophil levels may be due to the accumulation of plasma concentration of budesonide over the dosing period.

The findings have two main clinical implications. The first, answering the main question addressed in this study, is that the use of budesonide/formoterol according to this cumulative dosing regimen does not result in superior bronchodilation compared to salbutamol and may in fact result in lesser bronchodilation over the first 4 h, the time period over which clinical decisions regarding admission to hospital are made.

The second relates to the as-needed use of these medications as reliever therapy in the long-term treatment of asthma. The use of budesonide/formoterol 200/6 µg one actuation as-needed reduces the risk of severe exacerbations compared to salbutamol 100 µg×2 (or equivalent terbutaline dose), when either taken alone or together with ICS/LABA maintenance therapy [5–7, 25]. The results of this study suggest that this greater efficacy with budesonide/formoterol is achieved despite a lesser acute although more prolonged bronchodilator response, suggesting that the ICS component of reliever therapy, titrated according to changes in symptoms, is the key component contribution to this efficacy. Arguably the clinical relevance of differences in bronchodilator efficacy in the community setting is a moot point, as the patient can simply take an additional dose if needed to relieve symptoms. The nature of as-required relief is that patients use as much as necessary and the real-life use of these inhalers leads to different patterns of use [3, 4, 30]. However, it is pertinent to remember that asthma mortality epidemics [31–33] have been associated with high-dose preparations of β_2-agonist and that the relatively lower β_2-agonist dose may have a potential safety advantage, as suggested by our findings.

In conclusion, these findings inform the comparative efficacy of repeated administration of budesonide/formoterol with salbutamol in the acute exacerbation setting and provide insight into the greater efficacy of budesonide/formoterol reliever therapy in reducing severe exacerbation risk with long-term use.

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This trial was prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR) with identifier number ACTRN12619001083189. Individual participant data that underlie the results reported in this article, after de-identification (text, tables, figures and appendices), will be available 1 year after publication until a minimum of 5 years after publication. Data will be available to researchers who provide a methodologically sound proposal that has been approved by the study steering committee to achieve the aims outlined in the approved proposal. Data can be obtained through a signed data access agreement. The agreement can be obtained by e-mailing the Principal Investigator: richard.beasley@mrinz.ac.nz. The study protocol is available publicly on the ANZCTR website.

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