

Poor adherence with inhaled corticosteroids for asthma: can using a single inhaler containing budesonide and formoterol help?

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ABSTRACT

Background

Poor adherence with inhaled corticosteroids is an important problem in asthma management. Previous approaches to improving adherence have had limited success.

Aim

To determine whether treatment with a single inhaler containing a long-acting β_2 -agonist and a corticosteroid for maintenance treatment and symptom relief can overcome the problem of poor adherence with inhaled corticosteroids.

Design of study

Randomised, parallel group, open-label trial.

Setting

Forty-four general practices in Nottinghamshire.

Method

Participants who used less than 70% of their prescribed dose of inhaled corticosteroid and had poorly controlled asthma were randomised to budesonide 200 μg one puff twice daily plus their own short-acting β_2 -agonist as required (control group), or budesonide/formoterol 200/6 μg one puff once daily and as required (active group) for 6 months. The primary outcome was inhaled corticosteroid dose.

Results

Seventy-one participants (35 control, 36 active group) were randomised. Adherence with budesonide in the control group was approximately 60% of the prescribed dose. Participants in the active group used approximately 80% more budesonide than participants in the control group (448 versus 252 $\mu\text{g}/\text{day}$, mean difference 196 μg , 95% confidence interval 113 to 279; $P < 0.001$) and were less likely to withdraw from the study (3 versus 13; $P < 0.01$). No safety issues were identified.

Conclusion

Using a single inhaler for both maintenance treatment and symptom relief approximately doubled the dose of inhaled corticosteroid taken, suggesting this could be a useful strategy to overcome the problems related to poor adherence with inhaled corticosteroids.

Keywords

asthma; budesonide; formoterol; inhaled corticosteroids; patient-non-adherence.

INTRODUCTION

Poor adherence with inhaled corticosteroids is a major problem in asthma management,¹⁻³ occurring in 30–60% of patients.⁴⁻⁶ Reasons for poor adherence are numerous, but include a dislike of inhaled corticosteroids, lack of rapid symptom relief, and complicated treatment regimens.⁷⁻⁹

Because the β_2 -agonist formoterol has a rapid onset and long duration of action,¹⁰ it can be used for symptom relief and maintenance treatment.¹¹⁻¹³ When combined with budesonide in a single inhaler and used in this way it simplifies asthma treatment and provides a dose of inhaled corticosteroid with every dose of relief medication. Recent large multicentre studies show that this single-inhaler approach improves asthma control compared with a higher dose of inhaled corticosteroid,¹⁴⁻¹⁶ or an equivalent or higher dose of a combined long-acting β_2 -agonist and corticosteroid used for maintenance treatment only.¹⁶⁻¹⁹ The same approach may be particularly useful in patients who have poor adherence with inhaled corticosteroids because they would be

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unable to use a β_2 -agonist without taking an inhaled corticosteroid at the same time. For these patients the aim would be to increase the dose of inhaled corticosteroid taken.

This research was a pragmatic, parallel group, feasibility study to determine whether the underuse of inhaled corticosteroids by patients who are poorly adherent could be overcome by using a single inhaler containing budesonide and formoterol once daily and as required. The study had to be open-label as the specific focus of the study was to determine the effects of patients having only one inhaler, and a double-blind study would have required a double-dummy design and, therefore, two inhalers. Interventions during the study were limited to minimise the effect that being in the study had on patient adherence.

METHOD

Participants

General practices in Nottinghamshire were asked to participate if patient records had been stored for at least a year on an accessible database (Torex, EMIS or Micro Medic). Suitable patients were identified using a stepwise approach combining computerised general practice records and interviews (Figure 1).

The study recruited patients aged 18–70 years with a diagnosis of asthma and currently prescribed 400–1000 $\mu\text{g}/\text{day}$ of beclometasone dipropionate or equivalent. Participants had to have evidence of poor adherence, which was defined as having collected less than 70% of the expected number of prescriptions for inhaled corticosteroid in the year prior to the study. They also had to have evidence of poor asthma control which was defined as: having prescriptions for at least two courses of prednisolone or 10 canisters of short-acting β_2 -agonist in the year prior to the study; and taking four or more rescue puffs of β_2 -agonist for at least 4 days a week over the previous 4 weeks.

Exclusion criteria included the use of a long-acting β_2 -agonist, leukotriene antagonist, or oral corticosteroids in the previous 4 weeks, other significant medical problems, smoking history more than 20 pack years, pregnancy, or inadequate contraception in women of childbearing age.

Study design

This was a randomised, open-label, parallel group, 6-month study. An independent pharmacist used computer-generated random numbers to randomise each participant to one of two groups.

Control group. Participants were provided with one budesonide inhaler containing 100 doses with 200 μg budesonide per puff (Pulmicort Turbohaler®

200 μg , AstraZeneca), and were asked to take one puff twice daily and use their usual short-acting β_2 -agonist as required.

Active group. Participants were provided with one combined budesonide/formoterol inhaler containing 120 doses with 200 μg budesonide and 6 μg formoterol per puff (Symbicort Turbohaler® 200/6 μg , AstraZeneca). They were asked to take one puff once daily and as required, and to use no other inhaler.

Measurements

The Mini Asthma Quality of Life Questionnaire (MiniAQLQ),²⁰ and the Asthma Control Questionnaire (ACQ)²¹ were completed by participants. The MiniAQLQ score ranges from 1 to 7, with 1 indicating severely impaired asthma-related quality of life. The ACQ score ranges from 0 to 6, with 6 indicating severely uncontrolled asthma. Forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC) were measured with participants seated, as the best of three readings (MicroLab 3500 spirometer, Micro Medical).

Protocol

Participants were seen at their general practice for study visits. At the first visit participants completed baseline MiniAQLQ and ACQ, and underwent spirometry. Study medication was then given in exchange for the patients' usual asthma medication, with instructions on its correct use. Participants in the control group kept their usual short-acting β_2 -agonist.

Participants were asked to contact the study coordinator to arrange a visit when their study inhaler was nearly empty. At these visits a replacement study inhaler was provided and the number of doses remaining in the returned inhaler was counted. The two asthma questionnaires were completed, information about oral steroid use or visits to their GP for asthma-related problems since the last visit were

How this fits in

Poor adherence with inhaled corticosteroid is an important problem in asthma management. Previous approaches to improving adherence have had limited success. This study has shown that using a single inhaler for both maintenance treatment and symptom relief approximately doubled the dose of inhaled corticosteroid taken. This could be a useful strategy to overcome the problems associated with poor adherence with inhaled corticosteroids.

noted, and spirometry was performed. GP records were checked to corroborate the information provided by participants about unscheduled visits. A visit was arranged at 3 months if participants had not requested a new inhaler by that time, and a final visit was scheduled at 6 months. For safety reasons, participants in the active group were asked to contact the study investigator if they used 10 or more puffs of their study inhaler in 1 day.

Outcome measures

The primary outcome was the difference between the two groups in dose of inhaled budesonide during the 6-month study period. The total dose of budesonide taken by participants was calculated by subtracting the dose of budesonide remaining in the returned inhalers from the total dose of budesonide provided. Participants' average daily dose of budesonide was obtained by dividing the total dose taken by the number of days the participant was in the study.

Secondary outcomes included the difference between the two groups for change in MiniAQLQ and ACQ score, change in mean FEV₁, oral corticosteroid use, and participants' visits to the GP for asthma-related problems.

Power calculations were based on the assumption that a 25% difference in the inhaled corticosteroid dose would be clinically important. Assuming an average dose of inhaled budesonide of 45 mg (standard deviation [SD] 10 mg) over the 6 months in the control group, 50 patients in each group gave more than 90% power to detect a 25% difference in corticosteroid dose between the treatment groups. Due to difficulty in recruitment, only 71 participants were enrolled, but the study still had 90% power to detect this difference.

Analysis

All participants seen at least once after randomisation were included in the analysis. Daily dose of budesonide and change in FEV₁, MiniAQLQ, and ACQ scores were compared between groups by unpaired *t*-test. Average FEV₁ over the study period was calculated as the mean of all FEV₁ measurements obtained after the first visit. The number of participants who did not complete the study, and the number of participants visiting their GP or requiring oral steroids were compared using χ^2 test. Mean and 95% confidence intervals (CI) are given where appropriate.

RESULTS

Computerised records of 44 general practices were screened, from which 1961 potential participants with a diagnosis of asthma and evidence of poor

Figure 1. Flow chart showing stepwise participant selection and reasons for exclusions.

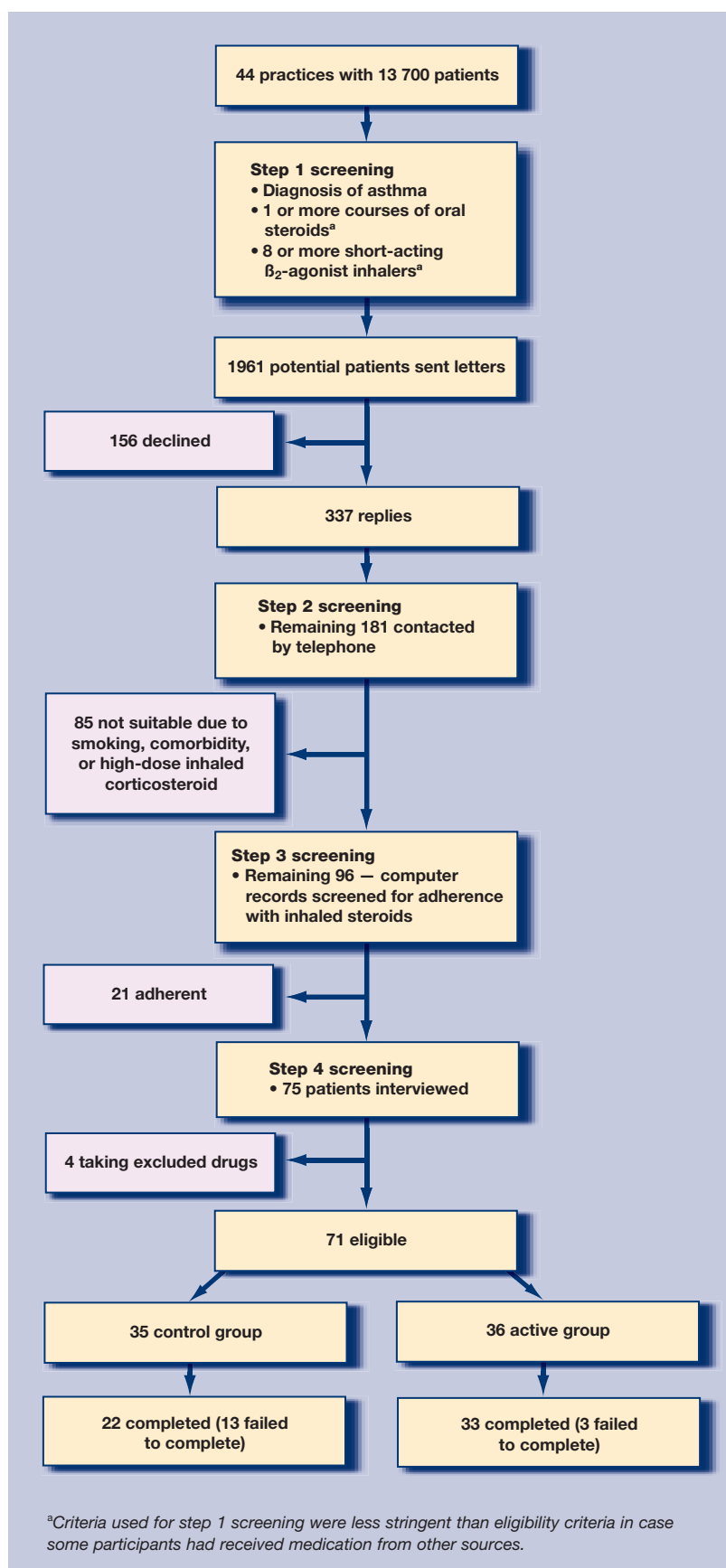


Table 1. Mean (SD) baseline data for control and active groups.

	Control group	Active group
Participants, <i>n</i>	35	36
Age, years	40.3 (12.3)	40.3 (12.8)
Sex, male/female	15/20	17/19
Duration of asthma, years	22.6 (14)	23.1 (12)
Daily dose of ICS prescribed, µg ^{a,b}	565 (254)	611 (222)
Daily dose of ICS used, µg ^{b,c}	272 (185)	283 (152)
Adherence with ICS, % ^b	45.4 (16.6)	45.6 (17)
Prednisolone courses, <i>n</i> ^b	1.17 (1)	1.0 (0.9)
Canisters of short-acting β ₂ -agonist, <i>n</i> ^b	10.2 (5.3)	12.4 (4.9)
FEV1, litres	2.65 (0.82)	2.9 (0.84)
FEV1 % predicted	82.3 (18.7)	88.1 (19.3)
GP visits for asthma, <i>n</i> ^b	2.4 (1.4)	1.4 (1.1)
Mini AQLQ score	4.7 (0.9)	4.9 (1.1)
ACQ score	2.11 (0.9)	1.82 (0.8)
Smokers (previous or current), <i>n</i>	15	15
Pack-years among smokers	9.5 (7)	6.7 (5)

ICS = inhaled corticosteroid. ^aDose of ICS equivalent to beclometasone delivered by a metered dose inhaler. ^bOver the year prior to the study. ^cEstimated dose of ICS taken from number of prescriptions collected.

asthma control were contacted by their GP on the researchers' behalf. A total of 181 patients were willing to participate and were screened further as

shown in Figure 1. Of these, 71 participants fulfilled the inclusion and exclusion criteria and were randomised into two reasonably well-matched groups: 35 in the control, and 36 in the active group (Table 1). Three participants from the active group and 13 from the control group withdrew from the study (*P* = 0.005). There were no outcome data for the 14 participants who failed to attend after their first visit. Of the five patients who could be contacted, reasons for discontinuing were worsening asthma (2 versus 0), difficulty in using the inhaler (1 versus 3), and sore throat (1 versus 0) in the control and active groups respectively; some participants gave more than one reason.

Budesonide use

The mean total dose of budesonide taken over the study period was 45.4 mg (SD = 17 mg) and 84.1 mg (SD = 35 mg) in the control and active groups respectively. The mean daily dose in the control and active groups was therefore 252 µg and 448 µg respectively, giving a mean difference of 196 µg (CI = 113 to 279; *P* < 0.001). The mean daily dose of budesonide ranged from 10 µg to 402 µg in the control group and from 143 µg to 915 µg in the active group (Figure 2).

Adherence with inhaled corticosteroid treatment, measured from GPs' electronic prescription records, was 43% in the year prior to the study. Adherence, measured from returned inhalers during the study, was 64% in the control group but could not be measured in the active group because participants used study medication as required.

MiniAQLQ and ACQ scores

Asthma-related quality of life and asthma control improved in both groups over the study period (Table 2). Mean increases in the MiniAQLQ score were 1.02 and 1.37 in the control and active groups respectively, giving a mean difference of 0.35 (95% CI = -0.3 to 1.0; *P* = 0.27). Similar trends were seen for each domain score. Mean ACQ score fell over the 6 months by 0.65 and 0.80 in the control and active groups respectively, giving a mean difference between groups of 0.15 (95% CI = -0.5 to 0.7; *P* = 0.62).

FEV1

The mean difference between baseline FEV1 and final FEV1 was 41 ml and 55 ml in the control and active group respectively. The mean change in FEV1 over the study period (difference between baseline FEV1 and average FEV1 for all subsequent study visits) was 52 ml and 46 ml in the control and active groups respectively (Appendix 1). Neither difference was significant. Average FEV1 was based on a

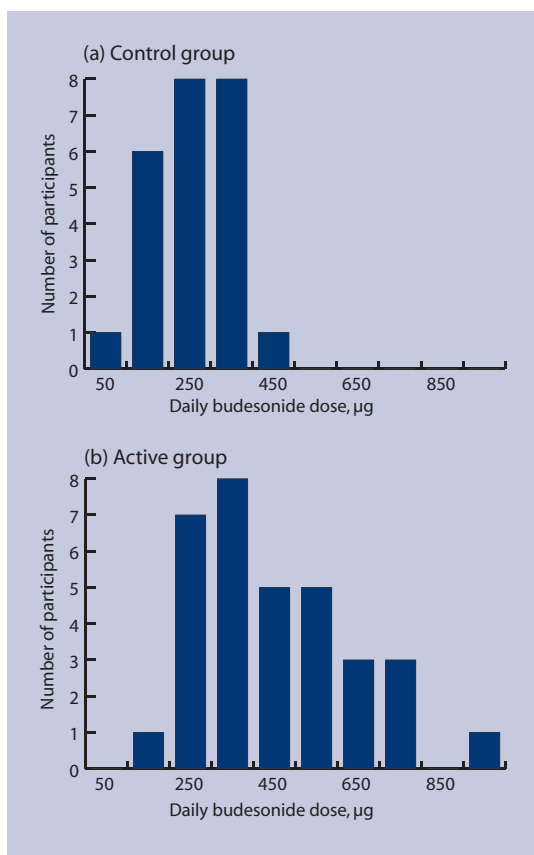


Figure 2. Range of mean daily budesonide dose during the 6-month study. (a) Control group; (b) active group.

Table 2. Secondary outcomes: mean values for participants who visited at least once after randomisation.

	Control group	Active group	Mean difference (95% CI)	P-value χ^2
MiniAQLQ score ^a				
Baseline	4.8	4.9		
Final	5.8	6.3		
Change	1.02	1.37	0.35 (-0.3 to 1)	P = 0.3
ACQ score ^a				
Baseline	1.9	1.8		
Final	1.25	1.0		
Change	-0.65	-0.80	0.15 (-0.5 to 0.7)	P = 0.6
FEV1 (L)				
Baseline	2.46	2.86		
Average	2.51	2.91		
Difference between baseline and average	0.05	0.05	0.01 (-0.2 to 0.2)	P = 0.9
Final	2.47	2.88		
Difference between baseline and final FEV1	0.04	0.05	0.01 (-0.2 to 0.2)	P = 0.9
Number of participants visiting GP/ total number of GP visits	6/12	5/6		P = 0.27
Number of participants prescribed oral steroids/ total number of oral steroid courses	3/6	4/6		P = 0.63

^aIncrease in the MiniAQLQ score and a reduction in the ACQ score denotes improved asthma control. MiniAQLQ = Mini Asthma Quality of Life Questionnaire. ACQ = Asthma Control Questionnaire. FEV1 = Forced expiratory volume in 1 second.

median of two and three visits in the control and active groups respectively.

Safety

No participant from the active group reported using 10 or more puffs a day of their study inhaler. During the study there were no hospital admissions, but six participants from the control group made a total of 12 visits to their GP for asthma-related problems, compared to five participants in the active group who had six visits. Three participants from the control group required a total of six courses of prednisolone for asthma-related problems compared to four participants and six courses in the active group. None of these differences was significant.

DISCUSSION

Summary of main findings

Participants in the control group used approximately 60% of the prescribed dose of inhaled budesonide over 6 months. Providing a single inhaler containing budesonide and formoterol for both maintenance and symptom relief almost doubled the dose of budesonide taken, thereby overcoming the problem of poor adherence seen in the control group. More participants from the active group completed the study, suggesting a preference for the single-inhaler approach.

Comparison with existing literature

Using a single inhaler containing budesonide and formoterol for maintenance and symptom relief is a

new approach to managing asthma, and comparisons with conventional treatment are encouraging. To date, this approach has reduced exacerbations when compared with a higher dose of inhaled corticosteroid,¹⁴⁻¹⁶ or an equivalent or higher dose of a combined long-acting β_2 -agonist and corticosteroid used for maintenance treatment only.¹⁶⁻¹⁹ As in most studies, patients known to have poor adherence to inhaled corticosteroid treatment were excluded from participating in these studies, and reported adherence rates during the studies were high, ranging from 85-99%.

Poor adherence with inhaled corticosteroids is a major problem in asthma management. It has been identified in 30% to 60% of patients,⁴⁻⁶ and is associated with poor asthma control,² and increased mortality.²² Although some studies have shown that patient education can improve adherence with inhaled corticosteroids, these interventions have been labour intensive, and their implementation has had limited success overall.²³ The present study found that using a single inhaler containing budesonide and formoterol for both maintenance and relief helped to overcome this problem because participants were unable to use their relief medication without inhaling a dose of budesonide.

Designing a study that does not affect adherence in the control group is difficult, because participation in any study is likely to influence behaviour and increase adherence, especially if there are regular study visits. The apparent increase in adherence in the control group (from 43% pre-study to 64%

during the study) suggests that this may have occurred to some extent in the present study, despite attempts to minimise interventions. Nevertheless, the mean daily dose in the control group was still only 252 µg (64% of the prescribed dose), compared to 448 µg for patients in the active group. Considering the evidence for poor asthma control prior to the study, a mean daily dose of 448 µg would seem more appropriate than 252 µg, and is approximately the dose prescribed in the control group. Inhaled corticosteroid dose was chosen as the primary endpoint at this stage because clinical outcomes would have required a much larger study, and patients who rely on relief medication could have been at risk of over-treatment with the formoterol and budesonide combination. No evidence of this was found: no participant reported taking 10 or more puffs in one day, and only one patient averaged more than 800 µg budesonide a day.

Strengths and the limitations of the study

Strengths of the study include the focus on patients with poor adherence and the pragmatic design. The pragmatic approach makes the study relevant to routine clinical practice but did impose some constraints on the study design. Researchers chose to compare the single inhaler approach with twice-daily budesonide, rather than budesonide and formoterol, because the study aimed to evaluate the single inhaler approach with the treatment that most poorly-adherent patients in primary care in the UK are using.

The open-label design was essential because the intervention studied was the use of one inhaler, and a double-blind study would have required participants to use two inhalers. To reduce the effect of the study on adherence in the control group, outcome measures, such as FEV₁, were measured opportunistically rather than at predetermined study visits. This meant that the study reflected usual clinical practice, but also that visits occurred at different times of day and, regardless of prior bronchodilator use, reduced the ability to detect differences in secondary outcomes, particularly FEV₁.

Implications for future research and clinical practice

Poor adherence with inhaled corticosteroids is common, and a major determinant of asthma morbidity. This pragmatic study demonstrates that it can be overcome by using a single inhaler for maintenance and symptom relief. A larger study to evaluate this approach on clinically important outcomes, such as exacerbations in patients with poor adherence is now required.

Funding body

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Ethical approval

Nottingham City Hospital ethics committee approved the study, and all participants provided written informed consent

Competing interests

The study was conceived, designed, executed, analysed, and written up in Nottingham and was supported by a non-conditional grant from AstraZeneca which included Milind P Sovani's salary. Christopher I Whale, Janet Osborne, Sue Cooper, and Kevin Mortimer have no conflict of interest. Tommy Ekström is employed by AstraZeneca. Anne E Tattersfield has received honoraria from AstraZeneca for speaking at meetings. Timothy W Harrison has received honoraria from AstraZeneca for speaking at meetings and attending advisory groups

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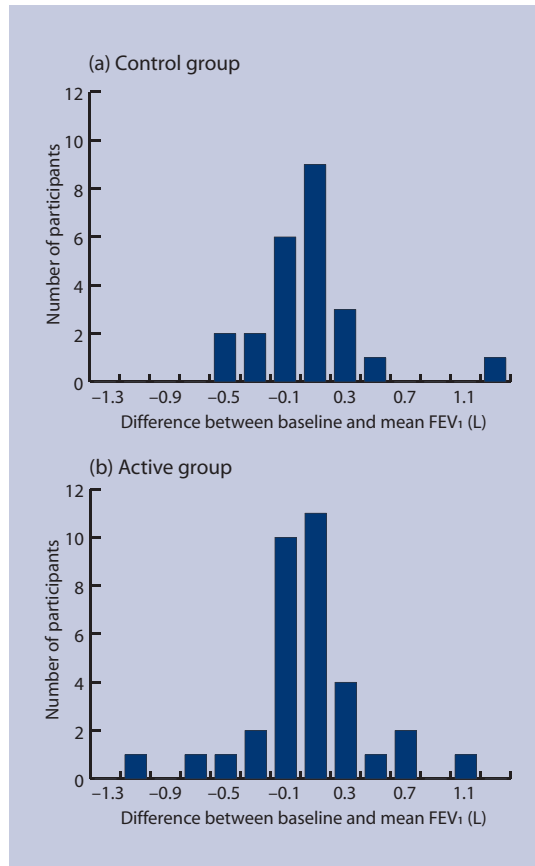
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Appendix 1. Mean change in Forced expiratory volume in 1 second (FEV₁) over the 6-month study period. (a) Control group; (b) active group.