Double blind randomised controlled trial of two different breathing techniques in the management of asthma

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Methods

Subjects

The study was described to potential subjects as comparing two breathing techniques potentially of use for people with asthma. The complete exclusion criteria were as follows: use of long-acting beta-agonists, current smoking or >10 pack-year smoking history, unstable asthma defined as requiring out of hours medical care or night waking more than once per week, asthma exacerbation or respiratory infection in previous 4♣weeks, oral corticosteroids in previous 4♣weeks, pregnancy or planned pregnancy, substantial limitation of shoulders or thoracic spine, complete nasal obstruction, prior tuition in Buteyko (established by indirect questioning).

Study design

Randomisation numbers were issued sequentially on a site-by-site basis, and the randomisation code remained concealed until the final analyses. Subjects learned and practised their exercises by video instruction (details under ‘Interventions’ and Table 1). Videos, identified by unique codes, were packaged and issued by Clinical Supplies, GlaxoSmithKline, Melbourne.

Table 1 Forced oscillation technique results: comparison between groups

Outcome measure	Baseline		Difference at week 12•: end stable ICS dose (95% CI)	Difference at week 28•: end ICS reduction (95% CI)	Comparison between groups (p-value)		
	Group A	Group B			Base	Wk 12	Wk 28
Forced Oscillation Technique: inspiratory capacity (l)*	2.13 (0.71)	2.47 (0.63)	–0.13 (–0.55 to 0.28) *[Missing: A:3, B:5]* Ratios at wk 12• (95%CI of ratio)	–0.14 (–0.51 to 0.23) *[Missing: A:1, B:3]* Ratios at wk 28• (95% CI of ratio)	0.10 Comparison between groups (p-value)	0.52	0.44
Forced Oscillation Technique: PreDI mean Rrs ($cmH_2O/l/s$)^,*	4.81 (1.63)	5.03 (1.48)	0.92 (0.71 to 1.22) *[Missing: A:3, B:5]*	0.92 (0.71 to 1.20) *[Missing: A:1, B:3]*	0.73	0.58	0.54
Forced Oscillation Technique: PostDI mean Rrs ($cmH_2O/l/s$)^,†	4.89 (1.55)	5.39 (1.64)	1.00 (0.75 to 1.34) *[Missing: A:6, B:6]*	0.90 (0.67 to 1.22) *[Missing: A:2, B:3]*	0.52	0.98	0.50
Forced Oscillation Technique: No. breaths/minute^	10.44 (1.37)	9.13 (1.38)	1.13 (0.94 to 1.37)	1.12 (0.91 to 1.36)	0.18	0.19	0.28

*Mean respiratory system resistance, Pre-Deep Inspiration

†Mean respiratory system resistance, Post-Deep Inspiration

In addition, to reviewing the subjects' exercises, the unblinded research assistant was also used to maintain blinding and safety. Subjects were reminded at each visit to avoid saying anything that would unblind study staff.

The criteria for ICS reduction at weeks 16 and 22 were: FEV_1 >70% baseline and >50% predicted, and Response Dose Ratio [RDR] mannitol ≤2×RDR mannitol at previous visit. There were three periods, each of two-weeks duration, in which subjects performed spirometry twice daily: prior to randomisation (weeks −2–0), after the first 12♣weeks on stable ICS (weeks 12–14), and at the end of the ICS down-titration period (weeks 28–30). Weeks 14–16 served to "wash-out" any potential effects of PEF monitoring before the first ICS down-titration visit.

Forced oscillation technique (FOT)

The custom built forced oscillation device (described previously by Salome *et al*[1]) delivered an oscillation frequency of 6♣Hz, and measured flow and pressure at the mouth during tidal breathing. Measurements of respiratory system resistance (Rrs) were made during approximately 1♣minute of tidal breathing, followed by a slow deep inspiration to total lung capacity (TLC) and a passive exhalation back to tidal breathing for approximately another minute. Subjects wore a nose clip and were instructed not to hold their breath at TLC. The resulting pressure and flow signals were measured and processed using custom software to calculate the Rrs, and provided six measurements of Rrs per second. The custom software automatically excluded erroneous and extreme Rrs values, which may occur if the glottis closes or the seal around the mouthpiece is lost during testing. Mean Rrs pre- and post-deep inspiration was calculated by the software as the mean of all Rrs measurements during the corresponding period of tidal breathing. Inspiratory capacity and respiratory rate were calculated by the software using the volume trace from the FOT device.

CO_2-ROB measurement

A device was designed and constructed in-house to assess route of breathing and end-tidal CO_2. The device was designed to measure the end tidal CO_2 concentration from the nose and mouth separately, as well as whether the subject was breathing primarily through the nose, the mouth or

both (mixed). A key element of the device design was to minimise its obtrusiveness, so as not to influence the subject's usual pattern of breathing. Therefore, use of a mask or insertion of prongs into the nasal cavity would have been undesirable. To the same end, subjects were not informed about the purpose of the device, and the recordings were made whilst the subject was distracted by completing the study questionnaires.

The device consisted of a headset, with a flexible arm holding two probes. The probes were positioned in front of the mouth and the nares respectively, as close as possible without touching the face. A thin, transparent sheet of plastic was positioned between the probes to minimise mixing of airflow. Thermistors were used to detect the airflow from the mouth and nose, and a continuous on-screen display allowed identification of any problems with positioning of the device. CO_2 was sampled continuously from the nose and mouth probes, and analysed in a CO_2 analyser (Datex Normocap CO_2 monitor). The output from the CO_2 analyser and the output from the amplification circuit for the thermistors were recorded directly on a computer via an analogue to digital conversion. Recordings were made for a minimum of two minutes, and twenty measurements were made per second. The device was calibrated with respect to CO_2 prior to each use.

Reliability testing was performed by five repeated measures of end tidal CO_2 on a single subject on the same day. After each measurement, the headset was removed and repositioned to simulate the use of the device on clinical trial subjects. The median end tidal CO_2 results fell within 0.3% (approximately 2♣mmHg; 0.3♣kPa) of each other.

Analysis was carried out by an investigator blinded to the subject's treatment allocation. Customised software allowed the data to be visualised as a continuous trace for quality control selection. For CO_2 analysis, a minimum threshold of 3% was selected to identify expiratory flow, based on the normal predicted values for exhaled breath in adults,[2] and the potential dilution of CO_2 between the nose/mouth and the intake port. CO_2 concentration was recorded as the median of the peak values, excluding data which lay below the threshold and data from incomplete or fragmented breaths. Route of breathing was determined from thermistor traces, being recorded as

predominantly nasal if ≥50% of breaths were from the nose and <40% of breaths were from the mouth, predominantly mouth if ≥50% breaths were from the mouth and <40% of breaths were from the nose. Subjects were classified as having mixed route of breathing when the proportion of nasal and mouth readings were both between 40–50%.

Some technical difficulties were experienced during the use of this device, which reduced the proportion of subjects with full data. Numbers of data points for each variable are indicated in Tables 3.[2, 3] The most common problems related to fragility of the headset construction, and the finding that some results which appeared acceptable during the recording phase were found to be below the CO_2 threshold.

End tidal CO_2 results from the custom-built device, which sampled exhaled breath outside the nares, were not expected to be identical with results from other methods such as mainstream/sidestream capnography. For comparison, we recorded end tidal CO_2 measurements for 20 normal (non-asthmatic, non-smoking) adults, using the same equipment and methodology as in the clinical trial. The median end tidal CO_2 value for these subjects was 4.86% (36.9♣mmHg; 4.92♣kPa), approximately 1% higher than for our asthmatic subjects (Table 3, 3.77–4.14%, n=42). Previous studies,[3, 4] have also demonstrated lower end tidal CO_2 in general asthmatic populations than non-asthmatic populations. These results suggest that our asthmatic patients were not characterised by hyperventilation to any greater extent than other, non-selected, asthmatics.

Table 3 Peak flow periods compared with non-peak flow periods

Outcome measure	**Week 12**	**Week 14**	**p-value**	**Week 28**	**Week 30**	**p-value**
AQLQ – Total§§§§,*	A:26 B:25	A:26 B:25		A:23 B:25	A:23 B:25	
Group A	0.81 (0.56–1.06)	0.78 (0.55–1.02)	0.7316	0.47 (0.32–0.63)	0.49 (0.31–0.66)	0.8145
Group B	0.56 (0.38–0.73)	0.41 (0.30–0.53)	0.0240	0.44 (0.27–0.61)	0.41 (0.26–0.57)	0.6606
Day Symp.Intensity Score*****,#	A:21 B:22	A:21 B:22		A:18 B:19	A:18 B:19	
Group A	2.00 (1.00–2.00)	1.00 (1.00–2.00)	0.0781	1.00 (1.00–2.00)	1.00 (1.00–2.00)	0.6250
Group B	1.50 (1.00–1.63)	1.00 (1.00–2.00)	0.1309	1.00 (1.00–2.00)	1.00 (1.00–2.00)	0.5625
NightSymp.IntensityScore†††††,#	A:23 B:19	A:23 B:19		A:19 B:19	A:19 B:19	
Group A	1.50 (1.00–2.00)	1.00 (1.00–2.00)	0.2754	1.00 (1.00–1.75)	1.00 (1.00–1.00)	0.3750
Group B	1.00 (1.00–1.75)	1.00 (1.00–1.00)	0.3125	1.00 (1.00–1.25)	1.00 (1.00–1.00)	0.3750
Proportion Symp.FreeDays‡‡‡‡‡,*	A:23 B:23	A:23 B:23		A:19 B:20	A:19 B:20	
Group A	22.97 (9.94–36.00)	34.29 (21.13–47.44)	0.0919	32.43 (17.04–47.82)	45.08 (28.40–61.77)	0.1025
Group B	23.89 (10.69–37.09)	35.40 (22.46–48.35)	0.0956	32.38 (18.29–46.48)	39.48 (25.17–53.78)	0.1889
Reliever Use (puffs/day)§§§§§,*	A:23 B:23	A:23 B:23		A:19 B:20	A:19 B:20	
Group A	1.41 (0.61–2.20)	1.00 (0.38–1.61)	0.0651	0.73 (0.24–1.22)	0.78 (0.22–1.34)	0.7274

Outcome measure	Week 12	Week 14	p-value	Week 28	Week 30	p-value
Group B	1.07 (0.32–1.81)	1.00 (0.43–1.57)	0.8104	1.06 (0.30–1.82)	1.23 (0.48–1.98)	0.4841
Reliever Free Days (%)******,#	A:23 B:23	A:23 B:23		A:19 B:20	A:19 B:20	
Group A	56.73 (37.91–75.54)	59.16 (40.66–77.67)	0.5126	72.61 (54.80–90.42)	72.31 (55.42–89.19)	0.9445
Group B	68.30 (51.08–85.53)	62.89 (45.31–80.46)	0.3223	68.81 (48.62–89.00)	62.69 (42.60–82.78)	0.2287
ACQ-7††††††,*	A:25 B:24	A:25 B:24		A:23 B:25	A:23 B:25	
Group A	1.32 (1.01–1.63)	1.19 (0.91–1.47)	0.3726	1.05 (0.78–1.32)	1.01 (0.77–1.26)	0.6825
Group B	1.19 (0.85–1.53)	1.04 (0.88–1.19)	0.1630	1.05 (0.81–1.28)	1.05 (0.72–1.38)	0.9676
Pt. Global Assessment‡‡‡‡‡‡,*	A:26 B:24	A:26 B:24		A:23 B:25	A:23 B:25	
Group A	66.42 (56.50–76.35)	67.62 (60.18–75.05)	0.8098	71.70 (61.19–82.20)	76.65 (68.76–84.55)	0.1103
Group B	72.71 (63.39–82.03)	78.50 (71.57–85.43)	0.1678	75.72 (66.55–84.89)	76.36 (70.87–81.85)	0.8813
Phys. Global Assessment§§§§§§,*	A:26 B:25	A:26 B:25		A:23 B:25	A:23 B:25	
Group A	67.19 (59.42–74.97)	70.81 (64.30–77.32)	0.0967	71.78 (66.10–77.46)	73.70 (68.29–79.11)	0.3652
Group B	66.64 (60.13–73.15)	68.12 (62.58–73.66)	0.5892	72.60 (67.18–78.02)	70.68 (65.46–75.90)	0.4876
Lung Function (FEV_1 % Pr)*	A:25 B:24	A:25 B:24		A:23 B:25	A:23 B:25	
Group A	79.97 (73.70–86.25)	80.12 (74.44–85.81)	0.9091	78.01 (71.24–84.79)	77.89 (71.15–84.63)	0.8898
Group B	71.88 (66.49–77.28)	73.28 (68.49–78.08)	0.4785	75.76 (70.61–80.91)	74.76 (69.56–79.96)	0.4591

Outcome measure	Week 12	Week 14	p-value	Week 28	Week 30	p-value
Lung Function (FVC % Pr)*	A:25 B:24	A:25 B:24		A:23 B:25	A:23 B:25	
Group A	101.43 (94.72–108.13)	101.01 (95.84–106.18)	0.8275	98.65 (92.07–105.23)	99.02 (92.74–105.29)	0.7867
Group B	92.30 (87.03–97.58)	94.10 (88.87–99.32)	0.2598	95.44 (90.15–100.73)	95.54 (90.14–100.93)	0.9613
RDR Mannitol^	A:9 B:9	A:9 B:9		A:9 B:9	A:9 B:9	
Group A	0.23 (0.15–0.35)	0.24 (0.14–0.42)	0.7322	0.21 (0.13–0.33)	0.22 (0.14–0.39)	0.5431
Group B	0.23 (0.16–0.35)	0.22 (0.15–0.31)	0.4947	0.23 (0.13–0.37)	0.20 (0.14–0.27)	0.3554
FOT: PreDI Mean Rrs*******,^	A:25 B:24	A:25 B:24		A:23 B:22	A:23 B:22	
Group A	4.68 (3.85–5.67)	4.49 (3.72–5.41)	0.9255	4.36 (3.61–5.26)	4.30 (3.48–5.30)	0.4736
Group B	5.04 (4.13–6.14)	5.06 (4.27–5.99)	0.8398	4.74 (3.94–5.70)	4.98 (4.07–6.10)	0.2202
FOT: PostDI MeanRrs†††††††,^	A:22 B:23	A:22 B:23		A:22 B:20	A:22 B:20	
Group A	5.00 (4.05–6.17)	4.18 (3.28–5.38)	0.0903	4.40 (3.47–5.57)	4.75 (3.72–6.06)	0.0927
Group B	4.98 (4.03–6.16)	5.34 (4.07–6.99)	0.5621	4.84 (4.01–5.82)	5.77 (4.57–7.29)	0.0009
FOT: Inspiratory Capacity*	A:25 B:24	A:25 B:24		A:23 B:22	A:23 B:22	
Group A	2.16 (1.84–2.48)	2.13 (1.87–2.40)	0.5194	2.08 (1.79–2.36)	2.15 (1.85–2.44)	0.3086

Outcome measure	Week 12	Week 14	p-value	Week 28	Week 30	p-value
Group B	2.30 (2.02–2.57)	2.24 (1.96–2.52)	0.9197	2.25 (2.01–2.50)	2.20 (1.91–2.49)	0.5085
FOT: No. breaths/min^	A:25 B:24	A:25 B:24		A:23 B:22	A:23 B:22	
Group A	11.47 (9.67–13.26)	11.89 (9.75–14.04)	0.1621	11.25 (9.33–13.16)	10.85 (8.69–13.01)	0.2626
Group B	9.96 (8.67–11.25)	9.65 (8.26–11.04)	0.3124	9.78 (8.71–10.86)	10.45 (8.79–12.11)	0.9046
End Tidal CO_2#	A:17 B:20	A:17 B:20		A:12 B:12	A:12 B:12	
Group A	3.58 (3.51–4.52)	3.91 (3.67–4.50)	0.8311	3.81 (3.40–4.41)	3.73 (3.58–3.79)	0.4688
Group B	4.02 (3.45–5.17)	3.37 (3.20–3.61)	0.1055	3.54 (3.23–3.87)	3.53 (3.18–3.95)	0.5781
Route of Breathing (% Nasal)	A:13 B:15	A:13 B:15		A:8 B:11	A:8 B:11	
Group A	8/13 (61.5)	11/13 (84.6)	0.0833	8/8 (100.0)	5/8 (62.5)	0.0833
Group B	12/15 (80.0)	7/15 (46.7)	0.0253	5/11 (45.5)	7/11 (63.6)	0.1573

*: Mean (95% CI); # : Median (IQR); ^: Geometric mean (95% CI).

§§§§: Asthma Quality of Life Questionnaire score[5], Range (best – worst): 0–5

*****: Recorded using electronic diary spirometers

†††††: Recorded using electronic diary spirometers

‡‡‡‡‡: Calculated based on data recorded on electronic diary spirometers

§§§§§: Recorded using electronic diary spirometers

******: Calculated based on data recorded on electronic diary spirometers

††††††: Asthma Control Questionnaire score[6] using the complete questionnaire – questions 1 to 7, score (best – worst): 0–6

‡‡‡‡‡‡: Measured on a Visual Analogue Scale from 0 (worst) to 100 (best)

§§§§§§: Measured on a Visual Analogue Scale from 0 (worst) to 100 (best)

*******: Mean Respiratory system resistance, Pre-deep inspiration

†††††††: Mean Respiratory system resistance, Post-deep inspiration

Mannitol challenge

Airway responsiveness to mannitol was assessed at all visits except Week –2, unless FEV_1% was 50–65% predicted (in which case it was at the Investigator's discretion), <50% predicted, or the subject had experienced an adverse event attributed to mannitol or withheld consent. Subjects who withheld consent did so as they reported finding repeated mannitol challenges unpleasant. This was particularly the case for subjects with only mild AHR, who required high doses, and as a result reported that this was associated with productive cough, unpleasant taste, throat irritation and a slow resolution of these symptoms (typically 24–48♣hours).

At week 12, 16 subjects in group A and 13 in group B consented to a mannitol challenge. At week 28, 13 subjects in each group did so.

The mannitol challenge was performed at the Investigator's discretion when FEV_1 was 50–65% predicted. Patients who did not have a mannitol challenge were still eligible for ICS reduction at the blinded Investigator's discretion, provided they were clinically stable and met the other dose reduction criteria. The response dose ratio (RDR) is an index of responsiveness, which expresses the percentage fall in FEV_1 as a proportion of the dose required to produce that fall. The greater the RDR value, the greater the airway hyperresponsiveness as a large percentage fall in FEV_1 has been achieved with a small quantity of mannitol.

The eight (Group A:5, Group B:3) adverse events attributed to mannitol included: delayed onset of chest tightness persisting for approximately 24♣hours despite normal or improved FEV_1 post-reliever administration at the end of the challenge, vomiting, migraine, and intense irritation of the throat and/or nasal passages for approximately 24♣hours post-challenge.

Patient and physician global assessment

Patient Global Assessments were completed after the ACQ and AQLQ, but prior to any other testing or staff input, in response to the prompt "Please mark on the line to indicate how well controlled you feel your asthma has been over the last two weeks." (visual analogue score, 0–100, anchored with "Very poorly controlled" and "Very well controlled"). No information was given to

subjects about the meaning of the words “asthma control”. The Physician Global Assessment was completed ≤1♣week after the visit, with the physician instructed to take into account the spirometry, ACQ, AQLQ, Patient Global Assessment, and electronic diary data. The physician assessment was likewise recorded on a visual analogue score, 0–100, anchored with “Very poorly controlled” and “Very well controlled”, in response to the prompt “Place a mark on the line to indicate how well controlled you feel this subject’s asthma has been over the past two weeks.” No further information was provided about the definition of asthma control. The Physician Global Assessments at one site were completed by one physician, and at the other site, by one of two physicians.

Symptom free and reliever free days

Symptom free and reliever free days were calculated from the electronic data recorded using electronic diary spirometers (AM2, Erich Jaeger GmbH, Hoechberg, Germany).

Handling of missing data

Missing data were handled according to the following rules, stipulated in the protocol:

- A. Data for all subjects who were randomised into the study were analysed at week 12. For subjects who withdrew between randomisation (week 0) and week 12, the last valid observation was carried forward to week 12.
- B. At week 28, all subjects who were still participating in the study at week 13 were analysed.

Thus, for subjects still participating in the study who did not provide data at week 12 or week 28, data for these subjects were not analysed. A sensitivity analysis was conducted for the primary outcome variables and for RDR mannitol (last available observation carried forward for subjects still participating in the study in addition to carrying forward for discontinued subjects; and no data carried forward for any subject), which confirmed that the conclusions for these outcomes remained unchanged.

Results

Table 2 Primary and secondary outcome measures: comparison within groups

				Comparison within groups (p-value)		
Outcome Measure	**Baseline**	**Week 12**	**Week 28**	Base Vs Wk 12	Base Vs Wk 28	Wk 12 Vs Wk 28
AQLQ – total‡,*	A:28 B:29	A:25 B:27	A:23 B:25			
Group A	0.77(0.57–0.96)	0.80 (0.52–1.07)	0.60(0.39–0.81)	0.4922	0.4602	0.0143
Group B	0.54(0.43–0.65)	0.52 (0.34–0.70)	0.44(0.27–0.62)	0.7691	0.0773	0.1817
Day Symp. Intensity Score§,#	A:27 B:29	A:26 B:26	A:23 B:22			
Group A	2.00 (1.00–3.00)	2.00(1.13–2.25)	1.00(1.00–2.00)	0.3804	0.3054	0.0674
Group B	2.00(1.00–3.00)	1.75(1.00–2.00)	1.00(1.00–2.00)	0.0910	0.0256	0.0781
Night Symp. Intensity Score**,#	A:28 B:29	A:26 B:26	A:23 B:21			
Group A	2.00(1.00–2.00)	1.00(1.00–2.00)	1.00(1.00–1.50)	0.9217	0.3054	0.2188
Group B	2.00(1.00–2.00)	1.00(1.00–1.25)	1.00(1.00–1.00)	0.0023	0.0005	0.5625
Proportion Symp. Free Days††,*	A:28 B:29	A:26 B:27	A:23 B:22			
Group A	23.51(13.10–33.91)	19.57 (10.40–28.74)	27.90 (16.26–39.54)	0.3695	0.7319	0.0333
Group B	22.07(10.49–33.66)	21.07 (12.09–30.05)	34.06 (22.18–45.94)	0.5146	0.0291	0.0509

				Comparison within groups (p-value)		
				Base Vs	Base Vs	Wk 12 Vs
Outcome Measure	**Baseline**	**Week 12**	**Week 28**	Wk 12	Wk 28	Wk 28
Reliever Use (puffs/day)‡‡,*	A:28 B:29	A:26 B:27	A:23 B:22			
Group A	2.94 (2.09–3.79)	1.57(0.81–2.32)	1.12(0.41–1.83)	0.0002	<0.0001	0.1493
Group B	3.09 (2.22–3.95)	1.22 (0.58–1.86)	1.30(0.39–2.22)	<0.0001	0.0022	0.8819
Reliever Free Days (%)§§,#	A:28 B:29	A:26 B:27	A:23 B:22			
Group A	6.67 (0.00–42.42)	53.49 (33.83–83.61)	73.75 (61.23–93.54)	0.001	0.0003	0.2979
Group B	8.33 (0.00–41.67)	55.26 (15.63–83.97)	85.24 (46.51–93.47)	0.0001	0.0002	0.7615
ACQ-7***,*	A:28 B:29	A:27 B:29	A:23 B:25			
Group A	1.46(1.22–1.70)	1.34(1.03–1.65)	1.08(0.80–1.37)	0.4851	0.0056	0.0831
Group B	1.37(1.16–1.58)	1.09(0.82–1.36)	1.05(0.77–1.32)	0.0324	0.0014	0.3216
ACQ-6†††,*	A:28 B:29	A:27 B:29	A:23 B:25			
Group A	1.30(1.04–1.57)	1.14(0.80–1.49)	0.85(0.56–1.15)	0.3946	0.0021	0.0570
Group B	1.16 (0.95–1.37)	0.78(0.51–1.05)	0.73(0.39–1.06)	0.0049	0.0018	0.5644
ACQ-5‡‡‡,*	A:28 B:29	A:27 B:29	A:23 B:25			

				Comparison within groups (p-value)		
				Base Vs	Base Vs	Wk 12 Vs
Outcome Measure	**Baseline**	**Week 12**	**Week 28**	Wk 12	Wk 28	Wk 28
Group A	1.26(0.98–1.54)	1.19(0.83–1.54)	0.88(0.58–1.18)	0.7925	0.0100	0.0655
Group B	1.10(0.89–1.31)	0.79(0.50–1.09)	0.74(0.40–1.08)	0.0365	0.0091	0.5243
Patient Global Assessment§§§,*	A:28 B:29	A:28 B:28	A:23 B:25			
Group A	61.32(51.67–70.97)	67.32(57.68–76.97)	70.89(61.50–80.27)	0.2941	0.1822	0.4401
Group B	66.17(58.28–74.07)	73.54(65.22–81.85)	75.72(66.78–84.66)	0.1269	0.0353	0.5646
Physician Global Assessment****,*	A:28 B:29	A:28 B:29	A:23 B:25			
Group A	61.43(55.56–67.30)	67.57(60.67–74.47)	70.23(64.47–75.99)	0.0733	0.0159	0.3066
Group B	62.31(56.27–68.36)	68.72(62.45–74.99)	72.60(66.81–78.39)	0.0467	0.0004	0.0098
Lung Function (FEV_1 % Pr)*	A:28 B:29	A:28 B:29	A:23 B:25			
Group A	80.78(74.52–87.03)	79.69(73.39–85.99)	78.80(71.73–85.87)	0.3857	0.0633	0.4379
Group B	78.93(72.48–85.38)	75.96(68.85–83.07)	75.76(68.93–82.59)	0.0359	0.8555	0.1097
Lung Function (FVC % Pr)*	A:28 B:29	A:28 B:29	A: 23 B:25			

				Comparison within groups (p-value)		
				Base Vs	Base Vs	Wk 12 Vs
Outcome Measure	**Baseline**	**Week 12**	**Week 28**	Wk 12	Wk 28	Wk 28
Group A	103.09(95.64–110.54)	100.59(93.98–107.21)	99.47(92.63–106.31)	0.2654	0.0274	0.3039
Group B	101.55(94.70–108.40)	96.90(89.26–104.54)	95.44(89.20–101.68)	0.0154	0.2641	0.1076
RDR Mannitol^	A:26 B:22	A:16 B:13	A:13 B:13			
Group A	0.02(–0.07–0.39)	0.14(0.06–0.24)	0.08(0.02–0.17)	0.4514	0.0329	0.0805
Group B	0.18(0.09–0.29)	0.10(0.04–0.18)	0.14(0.06–0.26)	0.5257	0.3268	0.2248
FOT: PreDI Mean Rrs††††,^	A:21 B:22	A:25 B:24	A:22 B:22			
Group A	4.81(3.85–6.00)	4.68(3.85–5.67)	4.37(3.59–5.33)	0.6063	0.5775	0.5932
Group B	5.03(4.23–5.99)	5.04(4.13–6.14)	4.74(3.94–5.70)	0.7323	0.3968	0.3689
FOT: PostDI Mean Rrs‡‡‡‡,^	A:19 B: 21	A:22 B:23	A:21 B:22			
Group A	4.90(3.95–6.05)	5.00(4.05–6.17)	4.37(3.41–5.60)	0.8570	0.0747	0.4944
Group B	5.39(4.30–6.76)	4.98(4.03–6.16)	4.84(4.02–5.83)	0.6347	0.3074	0.6798
FOT: Inspiratory Capacity*	A: 21 B:22	A:25 B:24	A:22 B:22			
Group A	2.13(1.80–2.45)	2.16(1.84–2.48)	2.11(1.82–2.40)	0.7132	0.5089	0.8187

				Comparison within groups (p-value)		
				Base Vs	Base Vs	Wk 12 Vs
Outcome Measure	**Baseline**	**Week 12**	**Week 28**	Wk 12	Wk 28	Wk 28
Group B	2.47(2.19–2.75)	2.30(2.02–2.57)	2.25(2.01–2.50)	0.6840	0.8507	0.9032
FOT: No. Breaths/minute^	A:21 B:22	A:25 B:24	A:22 B:22			
Group A	10.44(9.06–12.03)	10.79(9.34–12.47)	10.58(8.91–12.56)	0.2617	0.3791	0.8715
Group B	9.13(7.91–10.55)	9.52(8.35–10.85)	9.49(8.46–10.64)	0.9630	0.7799	0.9801
End tidal CO_2#	A:20 B:22	A:17 B:20	A:12 B:11			
Group A	4.14(3.46–5.20)	3.58(3.43–4.16)	3.81(3.33–4.51)	0.3394	0.2754	0.5469
Group B	3.77(3.46–5.26)	4.02(3.46–5.15)	3.54(3.04–4.33)	0.8900	0.4131	0.1309
Route of breathing (Nasal)						
Group A	16/20 (80%)	14/19 (73.68%)	14/14 (100%)	Cochrane Q Test Statistic: p=0.3679		
Group B	13/23 (56.52%)	14/21 (66.67%)	7/17(41.18%)	Cochrane Q Test Statistic: p=0.5134		

*Mean (95% CI); #Median (IQR); ^Geometric mean (95% CI)

‡Asthma Quality of Life Questionnaire score[5], Range (best-worst): 0–4

§Recorded using electronic diary spirometers

**Recorded using electronic diary spirometers

††Calculated based on data recorded on electronic diary spirometers

‡‡Recorded using electronic diary spirometers

§§Calculated based on data recorded on electronic diary spirometers

***Asthma Control Questionnaire score[6] using the complete questionnaire – questions 1 to 7, Range (best - worst): 0–6

†††Questions 1 to 6 only: lung function data removed

‡‡‡Questions 1 to 5 only: lung function and reliever use data removed

§§§Measured on a Visual Analogue Scale from 0 (worst) to 100 (best)

****Measured on a Visual Analogue Scale from 0 (worst) to 100 (best)

††††Mean respiratory system resistance, Pre-Deep Inspiration

‡‡‡‡Mean respiratory system resistance, Post-Deep Inspiration

Table 4 Control arm interventions in previous studies

Intervention	**Instruction re reliever use**	**Study**
Asthma education alone	Not specified	Thomas *et al*[7]
Asthma education + relaxation technique	Not specified	McHugh *et al*[8]
Asthma education + relaxation technique + abdominal breathing exercises not involving hypoventilation	Use only when symptomatic	Bowler *et al*[3]
Placebo 'Pink City Lung Exerciser' device	Use only when symptomatic	Cooper *et al*[9]
Video entitled 'Nature's Landscapes' consisting of scenery with background classical music	"None of the investigators provided encouragement or guidance for patients to reduce their asthma medication."	Opat *et al*[10]
Physical exercises with normal aerobic respiratory patterns	No instruction provided	Girodo *et al*[11]
Control patients effectively 'wait listed' i.e. continued on their pre-study treatment regimen without intervention	No instruction provided	Nagarathna and Nagendra[12], Girodo *et al*[11], Vedanthan *et al*[13], Fluge *et al* (from [14])

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