BRIEF REPORT

A feasibility randomized controlled superiority trial of fluticasone-vilanterol once daily use for the treatment of mild asthma in adults [version 1; peer review: awaiting peer review]

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Abstract

Background: The objective of this pilot study is to assess feasibility (recruitment and retention rates) of conducting a definitive randomized controlled trial (RCT) to investigate the effectiveness of fluticasone-vilanterol (Long-acting beta agonist+ Inhaled corticosteroids; LABA+ICS) in the management of mild asthma in adults, compared with usual care.

Methods: In this 8-month parallel two-arm pilot trial we randomly assigned 18 patients with mild asthma in a 1:1 ratio to the treatment (n=10) or usual care (n=8) arms. The treatment group received daily LABA+ICS therapy while the usual care group continued as required SABA or SABA+ICS combination. The main outcome measures were descriptors of study feasibility. Secondary outcomes were asthma control score, quality of life, and the number of asthma exacerbations.

Results: The baseline characteristics of participants did not differ significantly across the two arms at the start of the trial. Because of slow recruitment and limited funding, the study didn't meet our recruitment target but did successfully meet our retention criteria. At 32 weeks, analysis indicated significant improvement in asthma control scores in the intervention arm (1.31 vs 2.91; 95% CI [0.72, 2.44]; P-value=0.003), but no significant differences were noted in quality-of-life scores (P-value=0.197). There were no significant differences in post-intervention asthma control mean score (P-value=0.361) or QoL mean score (P-value=0.337) between the two arms after adjustment for pre-intervention scores.

Conclusions: This pilot RCT indicates that a definitive RCT is feasible in a primary health care setting. We recommend increasing the recruitment rate by relaxing eligibility criteria, extending the timeline, and increasing the number of sites for recruitment.
ClinicalTrials.gov registration: NCT04265105 (11/02/2020)

Keywords
Asthma, Thoracic Medicine, Respiratory Medicine, Public Health, General Medicine, Feasibility Trial.

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Author roles: Jassim G: Conceptualization, Data Curation, Formal Analysis, Funding Acquisition, Investigation, Methodology, Project Administration, Resources, Software, Supervision, Validation, Visualization, Writing – Review & Editing; Morcos M: Data Curation, Formal Analysis, Investigation, Methodology, Project Administration, Software, Writing – Original Draft Preparation, Writing – Review & Editing; O’Connell M: Conceptualization, Methodology, Validation, Writing – Review & Editing; Cunningham W: Conceptualization, Funding Acquisition, Investigation, Supervision, Visualization, Writing – Review & Editing

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Introduction

Asthma, a chronic condition characterized by inflammation of the airways, is a serious burden to global health. Asthma-related mortality cost $81.9 billion dollars in 2013 in the United States alone.1 Despite advanced treatments, the prevalence of asthma continues to increase.2 It is hypothesized that mortality may not be due to the severity of asthma, but rather to suboptimal control of the disease.3 Current asthma management focuses on reducing airway inflammation through the administration of inhaled corticosteroids (ICS) in combination with either short- or long-acting beta agonists (SABA or LABA, respectively).4

Traditionally, a LABA+ICS combined treatment is used when SABA and ICS are insufficient to achieve asthma control. In 2019, the Novel START, and PRACTICAL trials have both considered the substitution of SABA+ICS with budesonide-formoterol (LABA+ICS) for symptom relief in cases of mild asthma. The START trial concluded that the LABA+ICS regimen was superior to SABA (albuterol) alone for the prevention of asthma exacerbations.5 Similarly, the PRACTICAL trial compared the budesonide-formoterol (LABA+ICS) combination with budesonide-terbutaline (SABA+ICS), confirming that LABA+ICS regimen was more effective at preventing severe exacerbations than SABA+ICS combination.6 Furthermore, research indicates that replacing SABAs with LABAs could halve the risk of asthma exacerbations.6

The current recommendation of using LABA+ICS therapy for symptomatic asthma compared to usual asthma care in Bahrain has yet to be researched.

The objective of this pilot study is to explore the areas of uncertainty that need to be addressed before a definitive RCT can take place, to consider recruitment, randomization, intervention, retention, and acceptability, and to investigate the superiority of effectiveness of fluticasone-vilanterol (LABA+ICS) in the management of mild asthma in adults compared with usual care.

Methods

Trial design

This is a pilot parallel two arm randomized open-label controlled study conducted in a primary health care center in Bahrain.

Ethical considerations

The protocol was designed by the investigators and approved by various ethics committees including Kingdom of Bahrain Ministry of Health on 23/06/2020, number AURS/184/202; Royal College of Surgeons in Ireland – Bahrain (RCSI Bahrain) on 09/11/2021, number NCT04265105; and National Health Regulatory Authority of Bahrain on 16/09/2021. The trial is registered in https://clinicaltrials.gov/ (registration number NCT04265105) on 11th February 2020.

We used the CONSORT checklist when writing our report (Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomized trials).16 Written informed consent was obtained from all the patients before commencement of trial. The clinical trial unit at RCSI Bahrain had overall responsibility for the conduct of the trial, data management, and safety monitoring. The first author had full access to the trial data and ensured the accuracy and completeness of the data and the fidelity of the trial to the protocol.

Participants

The main inclusion criteria were patients between the ages of 21 and 75 years with a diagnosis of mild asthma attending the participating primary health care center in Bahrain, being managed with usual care (short-acting beta agonists (SABA) or SABA and ICS combination) and no other asthma medications.

Mild asthma, often termed mild intermittent or mild persistent asthma, is defined by the GINA management strategy as patients who meet the criteria for step 1 and step 2 treatment strategies.7

- Step 1: As-needed low-dose ICS-formoterol or albuterol
- Step 2: Daily low-dose ICS plus as-needed SABA, or as-needed low-dose ICS-formoterol

Exclusion criteria were use of LABA documented by medical record or self-reported, leukotriene receptor agonist, theophylline, anticholinergic agent, oral corticosteroids or cromone for regular maintenance therapy in 3 months before entry to the trial [nasal corticosteroid was permitted], medical record or self-reported diagnosis of COPD, bronchiectasis,
interstitial lung disease, lung cancer or significant other respiratory disease, history of admission to the ICU with life-threatening asthma at any time, 20 pack-year smoking history, pregnancy or breastfeeding at the time of enrolment, congestive heart failure, unstable coronary artery disease, atrial fibrillation or other clinically significant heart disease, any known or suspected contraindication or allergy to the Investigational Medical Products and currently enrolled in other clinical trials.

Randomization and treatment
Recruitment was done by physicians who were blinded to the allocation of the treatment and control groups. The research coordinator allocated patients to either arm using randomizer.com. The research coordinator who is independent of the project, was aware of the allocation of the patients 1:1 to the control vs treatment group. The intervention arm received fluticasone furoate/vilanterol, Relvar Ellipta (100 μg/25 μg inhalation powder (30 doses) once daily use. The control arm received usual care which is albuterol (Ventolin, GlaxoSmithKline), 100 μg, two inhalations from a pressurized metered-dose inhaler as needed for symptom relief with or without Fluticasone propionate (Flixotide Evohaler) 125 μg two inhalations from a pressurized metered-dose inhaler.

Procedure
Participants were approached by their physicians who then referred them to the research coordinator. Outcome was assessed at two intervals: Baseline week 0 at randomization (during a health center visit) and at 32 weeks (8 months) (via phone call) (Figure 1).

Primary outcome measures
The feasibility of this pilot study was assessed by evaluation of recruitment, randomization, intervention, retention, and acceptability.

![Figure 1. CONSORT flow diagram.](image-url)
Secondary outcome measures
We investigated patients’ experience of asthma, including their quality of life, asthma control, and the incidence of exacerbations.

The Asthma Quality of Life Questionnaire (AQLQ-S) consists of 32 questions that assess the quality of life of asthma patients, scored on a 7-point scale ranging from 1 (all of the time) to 7 (none of the time). Higher scores indicate better quality of life.

The Asthma Control Questionnaire (6 items) (ACQ-6): consists of 6 questions that assess asthma symptoms in the previous week, scored on a 7-point scale that ranges from 0 (no symptoms) to 6 (very severe symptoms) in which a 0.5-unit change represents the minimal clinically important difference. Higher scores indicate worse asthma control.

We investigated asthma exacerbations which we defined as worsening asthma that resulted in one or more of the following: an urgent medical care consultation (e.g., a primary care visit, an emergency department [ED] visit, or hospital admission); a prescription of systemic glucocorticoids for any duration, or an episode of high β₂-agonist use, which was defined as more than 16 puffs of albuterol or more than 8 puffs of budesonide–formoterol over the course of 24 hours.

Statistical analysis
Statistical analysis was an intention-to-treat superiority analysis. Descriptive analysis used frequencies and percentages for categorical variables, mean, standard deviation (SD) and median for continuous variables. The treatment effect was measured using the mean difference between study arms scores at baseline and 32 weeks. We used SPSS statistical software version 28.0.0.0 for analyses.

Results
Patients were enrolled during January 2022 from a primary health care center in Bahrain. At this time, 367 patients were assessed for eligibility in the trial, 281 didn’t meet the inclusion criteria and 68 patients declined participation in the trial so in total 18 took part. A flow chart of participant recruitment is presented in Figure 1.

Characteristics of participants at baseline
A total of 18 patients were recruited and randomized into the intervention (n=10) and usual care (n=8) groups and randomly allocated to intervention and control groups. No participants withdrew from the trial. The mean (SD) age of the patients was 40.40 (17.32) years old among the intervention group and 54.88 (17.92) in the control group. Half of the participants were male in the intervention arm and 75% in the control arm. All recruited patients had mild asthma with a baseline mean asthma control score of 2.91 for the intervention and 3.26 among control groups. The mean quality of life score was 4.56 was for the intervention group, and 5.08 for the control group. There were no statistically significant differences at baseline between the intervention and control groups in age (p-value=0.102), sex (p-value=0.367), asthma control (p-value 0.547) and quality of life scores (p-value=0.861) (Table 1).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention Fluticasone-Vilanterol once daily use N=10</th>
<th>Control standard of care (SABA:ICS) N=8</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>(40.40±17.32)</td>
<td>(54.88±17.92)</td>
<td>0.102</td>
</tr>
<tr>
<td>Sex</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>5 (50%)</td>
<td>6 (75%)</td>
<td>0.367</td>
</tr>
<tr>
<td>Female</td>
<td>5 (50%)</td>
<td>2 (25%)</td>
<td></td>
</tr>
<tr>
<td>Asthma control score*</td>
<td>(2.91±0.89)</td>
<td>(3.26±1.52)</td>
<td>0.547</td>
</tr>
<tr>
<td>Quality of life score**</td>
<td>(4.56±1.26)</td>
<td>(5.08±1.05)</td>
<td>0.861</td>
</tr>
</tbody>
</table>

*The asthma control questionnaire consists of 6 questions that assess asthma symptoms in the previous week, each of which is scored on a 7-point scale that ranges from 0 (no symptoms) to 6 (very severe symptoms) in which a 0.5-unit change represents the minimal clinically important difference. Higher score indicates worse asthma control.

**The quality-of-life questionnaire consists of 32 questions that assess the quality of life of asthma patients. The questions were scored on a 7-point scale that ranges from 1 (all the time) to 7 (none of the time). Higher score indicates better quality of life.
Primary outcome - feasibility of the trial
This feasibility trial was designed with the intention of recruiting 100 participants – 50 allocated to treatment regimen of Fluticasone – Vilanterol (ICS + LABA) and 50 allocated to the control group of ICS + SABA. We were only able to recruit 18 participants in total. This was due to factors including strict inclusion criteria and hesitancy of participation in experimental studies. However, the retention rate was 100% despite an 8-month timeline and 3 different outcome assessments: asthma control score, QoL score, and exacerbation survey.

Secondary outcomes
The mean asthma control score in the fluticasone-vilanterol intervention group was significantly lower after 8 months compared to the baseline, indicating better control of asthma (mean difference: 1.58; 95% confidence interval [CI], 0.72 to 2.44, p=0.003). Additionally, quality-of-life mean scores were higher in the intervention group after 8 months compared to the baseline, indicating better quality of life, but this difference was not statistically significant (mean difference: -0.75; 95% confidence interval [CI], -1.98 to -0.48, p=0.197) (Table 2). In the control group, asthma control and the quality-of-life scores were both lower at 8 months (32 weeks) than at baseline which indicates better asthma control but worse quality of life. However, neither were statistically significant (Table 2).

Table 2. Comparison between pre and post mean asthma control and quality of life scores within intervention and control groups.

<table>
<thead>
<tr>
<th></th>
<th>Mean score±SD</th>
<th>Mean difference±SD</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intervention group:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma control score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline score</td>
<td>2.90±0.94</td>
<td>1.58±1.12</td>
<td>[0.72, 2.44]</td>
<td>0.003</td>
</tr>
<tr>
<td>32 weeks score</td>
<td>1.31±0.93</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline score</td>
<td>4.56±1.25</td>
<td>-0.75±1.61</td>
<td>[-1.98, -0.48]</td>
<td>0.197</td>
</tr>
<tr>
<td>32 weeks score</td>
<td>5.31±1.09</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Control group:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthma control score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline score</td>
<td>3.25±1.63</td>
<td>1.495±2.26</td>
<td>[-0.59, -3.50]</td>
<td>0.130</td>
</tr>
<tr>
<td>32 weeks score</td>
<td>1.76±0.99</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quality of life score</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline score</td>
<td>5.07±1.04</td>
<td>0.191±0.95</td>
<td>[-0.69, -1.07]</td>
<td>0.613</td>
</tr>
<tr>
<td>32 weeks score</td>
<td>4.88±1.06</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Table 3 shows that there was no statistical difference in post-intervention asthma control mean score (p-value=0.361) or QoL mean score (p-value=0.337) between the two arms after adjustment for pre-intervention scores.

Table 3. ANCOVA result of the differences in post-intervention mean scores across both arms after adjustment for pre-intervention scores.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Intervention Fluticasone-Vilanterol once daily use</th>
<th>Control standard of care (SABA±ICS)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
</tr>
<tr>
<td>Asthma control score*</td>
<td>1.31</td>
<td>0.93</td>
<td>10</td>
</tr>
<tr>
<td>Asthma QoL score**</td>
<td>5.31</td>
<td>1.09</td>
<td>10</td>
</tr>
</tbody>
</table>

*R Squared=0.071 (Adjusted R Squared=-0.072).
**R Squared=0.110 (Adjusted R Squared=0.027).
Asthma exacerbations were assessed at 32 weeks (8 months) in both arms and showed insignificant differences across the two arms: We asked, “did you visit the hospital or the emergency department for asthma or SOB from the beginning of the study?” (p value=0.64), “did you need to use cortisone tablets from the beginning of the study?” (p value=0.41), “did you need to use Ventolin more than 16 times a day from the beginning of the study?” (p value=0.55), “did you need to use inhaler more than 8 times a day since the beginning of the study?” (p value=0.16), “did you need to use nebulizer more than 3 times a day since the beginning of the study?” (p value=0.55).

**Adverse events**
No serious adverse events were recorded.

**Discussion**
This study investigated whether an RCT of the effectiveness of Fluticasone-Vilanterol (LABA + ICS) in comparison to control (SABA+ICS) for the treatment of mild asthma was an appropriate trial design, and was feasible with respect to retention, patient acceptability of intervention and outcome measures, and adherence to protocol, however we struggled with recruitment in the specified timeframe and allocated funding for the research coordinator at the clinical site.

We attempted to recruit 50 participants in each arm within a specified timeframe of 12 months, but the trial was terminated prematurely at 8 months as it was taking longer than expected to recruit patients and the allocated funding had ended. This finding is relevant to future grant allocations, particularly for similar research in primary health care settings. The retention criteria were met successfully – all 18 patients completed the follow-up for the trial, indicating that patients were committed to the trial for its duration.

There are several progression criteria worth amending for a future completed randomized controlled trial including relaxation of eligibility criteria, extension of the timeline to 24 months, increasing the number of recruitment sites, training of research coordinators and securing funding.

As with previous research in this field, our results indicated that the intervention group, receiving Fluticasone-Vilanterol, had enhanced asthma control scores clinically and statistically, indicating better control and management of asthma. We believe this is an important finding given the small sample size, suggesting a powerful effect of the intervention.

Currently, the trend in medical practice is shifting to utilizing more ICS in the treatment of mild asthma rather than SABAs. Many studies have shown the benefit of this approach, and a recent meta-analysis concluded that replacing SABA with fast-acting LABA+ICS reliever therapy results in reduction of risk of severe exacerbations by one-third and a 25% reduction in risk when compared with double the baseline maintenance ICS/LABA and SABA treatment.

Our results are consistent with the START, PRACTICAL, and SMART trials and support the international move to ICS+LABAs for the treatment of mild asthma as a more effective intervention than SABAs alone. However, in the aforementioned trials, ICS was combined with Formoterol and the combination was used as a reliever in patients with mild asthma because of Formoterol’s fast acting bronchodilator properties, whereas in our study, we combined ICS with another LABA (Vilanterol) and the combination was used as a controller (daily maintenance dose) in patients with mild asthma.

GINA recommend two tracks for using the reliever in the management of asthma of all steps: Track1, using as needed ICS-Formoterol as a reliever (the preferred strategy) and Track2: using ICS whenever SABA is used as a reliever.

The British Thoracic Society (BTS)/Scottish Intercollegiate Guidelines Network (SIGN) guidelines appear to have taken a positive step by eliminating step 1 (SABA monotherapy) and instead using low dose ICS in patients with suspected or confirmed asthma.

In this pilot randomized clinical trial, patients were able to adhere to the new treatment of daily LABA+ICS treatment for the period of the trial. In addition, results support local efforts to update clinical treatment guidelines to match international recommendations for the treatment of mild asthma.

**Limitations and strengths**
Our trial has several limitations. It indicates that LABA+ICS treatment for mild asthma is feasible and safe with no negative impact on quality of life, but long-term safety and generalizability are not clear as there were only 18 participants recruited from one health center. Our study encountered challenges in recruitment due to the recent COVID-19 pandemic,
and research during the pandemic was difficult. Worldwide, many medical research activities including recruitment, visitations, and assessments stopped.\textsuperscript{14}

Further, patients with mild asthma tend to manage their condition at home and not present at health facilities where the trial recruitment took place. Additionally, this is one of few randomized controlled trials (RCTs) to be conducted in this part of the world where many patients may be reluctant to participate in experimental studies due to fear and unfamiliarity with this type of research.\textsuperscript{15} These factors resulted in the small sample of patients. Finally, this study investigated once daily dose of LABA+ICS and did not investigate the as needed protocol which could be the future direction of further research.

Our study has several strengths. This is one of the few interventional trials in this region where many patients are reluctant to participate in experimental studies for reasons discussed.\textsuperscript{15} Further, it is one of the few trials investigating the new shift in mild asthma treatment to update the existing treatment guidelines, and this trial has utilized structured validated questionnaires to test outcomes and establishes a baseline for future RCTs. Despite the small sample size, it is worth emphasizing that it demonstrated significant results favoring the intervention and this may impact future policy decisions and create a foundation for further study.

**Conclusion**

This pilot RCT indicates that a definitive RCT in a primary health care setting is feasible, in Bahrain. For such trials, we recommend optimizing the recruitment rate by relaxing eligibility criteria, extending timelines, and increasing the number of sites available for recruitment. Additionally, this pilot trial suggests that treatment with maintenance daily dose of ICS/LABA performs as well as or better than the standard SABA+ICS in the management of mild asthma.

**Data availability**

**Underlying data**

Dryad: The underlying data for ‘A feasibility randomized controlled superiority trial of fluticasone-vilanterol once daily use for the treatment of mild asthma in adults’, https://doi.org/10.5061/dryad.bnzs7h4gq.\textsuperscript{16}

**Reporting guidelines**

Dryad: CONSORT checklist for ‘A feasibility randomized controlled superiority trial of fluticasone-vilanterol once daily use for the treatment of mild asthma in adults’, https://doi.org/10.5061/dryad.bnzs7h4gq.\textsuperscript{16}

Data are available under the terms of the Creative Commons Zero “No rights reserved” data waiver (CC0 1.0 Public domain dedication).

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**Dr. Majd Al Khoury**, Research Department at Royal College of Surgeons in Ireland-Bahrain

**References**


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