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ORIGINAL ARTICLE

MANAGEMENT BASED ON EXHALED NITRIC OXIDE LEVELS ADJUSTED FOR ATOPY REDUCES ASTHMA EXACERBATIONS IN CHILDREN: A DUAL CENTRE RANDOMISED CONTROLLED TRIAL

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Asthma management in children based on FeNO: RCT

Abstract

While several randomised control trials (RCTs) have evaluated the use of fractional exhaled nitric oxide (FeNO) to improve asthma outcomes, none used FeNO cut-offs adjusted for atopy, a determinant of FeNO levels. In a dual centre RCT, we assessed whether a treatment strategy based on FeNO levels, adjusted for atopy, reduces asthma exacerbations compared with the symptoms-based management (controls).

Children with asthma from hospital clinics of two hospitals were randomly allocated to receive an *a-priori* determined treatment hierarchy based on symptoms or FeNO levels. There was a 2-week run-in period and they were then reviewed ten times over 12-months. The primary outcome was the number of children with exacerbations over 12-months.

Sixty-three children were randomised (FeNO=31, controls=32); 55 (86%) completed the study. Although we did achieve our planned sample size, significantly fewer children in the FeNO group (6 of 27) had an asthma exacerbation compared to controls (15 of 28), p=0.021; number to treat for benefit=4 (95%CI 3-24). There was no difference between groups for any secondary outcomes (quality of life, symptoms, FEV_1). The final daily inhaled corticosteroids (ICS) dose was significantly (p=0.037) higher in the FeNO group (median 400µg, IQR 250-600) compared to the controls (200, IQR100-400).

Taking atopy into account when using FeNO to tailor asthma medications is likely beneficial in reducing the number of children with severe exacerbations at the expense of increased ICS use. However, the strategy is unlikely beneficial for improving asthma control. A larger study is required to confirm or refute our findings.

Key Words: FeNO, asthma, pediatrics, atopy.

Introduction

Asthma is one of the most common chronic disease in children, accounting for 12[1] to 21[2] % of hospitalisations worldwide.[3] Preventing exacerbations, particularly severe exacerbations and hospitalisations, is one goal of good asthma management. The second component in asthma management is monitoring of asthma control (by subjective and objective measures).[4-6] Subjective measures usually involve a series of questions used for clinical assessment, diary cards and quality of life (QoL) questionnaires. Traditional objective methods include peak flow, spirometry and degree of airway hyper-responsiveness.[7] Newer, and arguably more sensitive, methods include measurement of airway inflammation such as airway cellularity in induced sputum or fractional exhaled nitric oxide (FeNO).[8]

Induced sputum has been shown to be beneficial in adults[9] but is relatively labour intensive and has limited availability, particularly in children. In contrast, FeNO is easily measured in children and confers some advantage over sputum eosinophils.[7] Thus its universal use has been advocated by some.[10] However, our Cochrane review found that the role of utilising exhaled nitric oxide to tailor the dose of inhaled corticosteroids cannot be routinely recommended for clinical practice at this stage and its role in monitoring asthma remains uncertain.[11]

There are 7 published[12-18] randomised controlled trials (4 children/adolescents and 3 adults) that have assessed whether adjustment of asthma treatment in accordance to FeNO levels is superior to 'usual management'. None of the 4 paediatric studies[13-15,17] used asthma exacerbations as the primary outcome, while three adult papers did.[12,16,18] Meta-analysis revealed there was no significant difference in exacerbations between the FeNO group compared to controls.[11] In adults, the daily dose of inhaled corticosteroids (ICS) at end of study was decreased in the FeNO group compared to controls (mean difference -450 µg

(95%CI -677, -223; p<0.0001). However in children, adjusting medications according to FeNO levels resulted in a significant increase of mean daily ICS dose (mean difference 140 µg, 95%CI 29, 251; p=0.014).

Thus, controversy remains of the benefit or otherwise on the benefits of use of FeNO for routine asthma management.[19] Further, the appropriate FeNO cut-off remains elusive despite recent recommendations.[20] FeNO levels are dependent on atopy[21,22] and none of the RCTs have considered atopic status in FeNO levels when medications were adjusted. We conducted a dual-centre RCT with 3 unique features; exacerbation was our primary outcome, atopy was considered in the FeNO strategy when medications were tailored and lastly, only FeNO levels were used (discounting symptoms) in the FeNO strategy group.

Our aim was to determine if adjustment of asthma medications based on FeNO levels (compared to management based on clinical symptoms) reduces severe exacerbations in children with asthma. We also examined the effect on two asthma control measures (diary card and QoL). We hypothesised that a childhood asthma management strategy based on FeNO and atopy status reduces exacerbations requiring rescue oral corticosteroids and/or hospitalisations.

Methods

Subjects

Inclusion criteria: Children aged >4 years with persistent asthma,[4] prescribed anti-inflammatory asthma treatment, and receiving their care primarily through our clinical service at Royal Children's Hospital, Brisbane or Prince of Wales Hospital, Hong Kong. We excluded children who had underlying cardio-respiratory illness such as bronchiectasis or tracheomalacia, inability to take ICS or long acting beta-2-agonists (LABA) or had previous poor adherence to medications (as documented in clinic notes).

The study was approved by the ethics committee at Royal Children's Hospital, Brisbane and Prince of Wales Hospital, Hong Kong. Informed and written consent was obtained from all parents of participants. The trial is registered with the Australia New Zealand Clinical Trials Registry (ACTRN012605000321640)

Protocol

Children and their parents were approached when they attended a routine clinic visit. After consent and recruitment, we recorded the child's demographics, run-in measurements and their technique of taking their medications checked by an asthma educator-nurse (HP and CA). A 2-week run-in period was undertaken to ensure stability. During this period, the children were maintained on their current treatment. If they were unstable (based on clinician review and diary cards) their medications were adjusted by their treating physician and a further run-in period was undertaken. At the end of the run-in, the child was randomised and initial measurements were obtained. These were spirometry, asthma QoL[23,24], FeNO, skin prick test and commencement of asthma symptom diary[25].

The children were randomised (stratified by age [<6 or ≥ 6 years] and site [Brisbane or Hong Kong]) to one of two strategies (a) management based on clinical symptoms (control group) or (b) management based on FeNO levels (FeNO group). Randomisation was done by an independent individual off-site through computer generation sequence list in permuted random blocks of 4 to 6. Allocation was fully concealed using opaque covers.

Patients were followed up for 12-months, with monthly visits for the first 4 months and every 2 months thereafter. Children attended at the same time of day on each occasion. At each visit we assessed patients with FeNO, spirometry before and after 400ug inhaled salbutamol, the Paediatric Asthma Caregiver QoL Questionnaire (PACQLQ)[24] and Paediatric Asthma QoL Questionnaire (PAQLQ)[23] (in children aged ≥7 years), symptom diary cards[25] and review by paediatric respiratory physician. FeNO measurements were performed before spirometry. All investigations were standardised. Decisions to adjust therapy (in accordance to hierarchy of medication treatment) were made by investigators who were blinded to the participant's FeNO if randomised to clinical symptoms group or symptoms scores if randomised to FeNO group. The asthma management strategy was not revealed to the children and parents. Adherence was monitored by checking their medications (supplied for the entire study period). Cumulative doses of ICS for each child was calculated based on the child's daily dose over the study period and expressed per child-year.

Hierarchy of medication treatment

The hierarchy (Table 1) was modified from the Australian National Asthma Council guidelines[4] and GINA guidelines.[5] In the control group treatment decisions were made on symptoms as recorded on the asthma symptom diary card. Control was considered inadequate and treatment increased if scores increased by ≥15% since the previous visit. Treatment was stepped down if the child's scores totalled < 10 in recent week. Reasons for using these cuts

offs are described below. In the FeNO group, adjustment of treatment was based on FeNO level and atopic status. If FeNO was elevated, therapy was stepped up according to the predetermined hierarchy of management (Table 1). If FeNO was low for 2 consecutive visits, medications were stepped down. Elevated FeNO was defined (based on a cohort study[26] in Perth, Australia) as ≥10ppb in children with no positive skin prick test (SPT), ≥12ppb in children with one positive SPT, and ≥20ppb in children with ≥2 positive SPT.

Details of methods

Allergens used for SPT in Brisbane were Alternaria mould, cat hair, cockroach mix, dust mite DPT, couch grass, and grass mix #7 (Hollister-Stier, WA, USA). Negative (diluents) and positive (histamine) controls were also used. The allergens used in Hong Kong were Dermatophagoides pteronyssinus and Dermatophagoides farinae house dust mites, cat and dog dander, mixed American and German cockroaches, mixed ragweed, grass pollens, and tree pollens, and mixed moulds (*Penicillium notatum, Alternaria tenuis, Aspergillus fumigatus, and Hormodendrum cladosporioides*). Atopy was defined as wheal ≥3mm larger than the negative control and larger than the histamine.

FeNO was measured with a chemiluminescence analyser (Sievers NOA 280i, Colorado, USA) with children exhaling at 0.05L/second for >4 seconds in order to obtain a stable NO value for > 2 seconds, in accordance to ATS/ERS guidelines.[27] Exhalations were repeated until three measurements were within 5% of the mean. Spirometry was performed using ATS criteria and % predicted based on local age and sex matched reference values in Hong Kong[28] and Eigen[29] from Australian data (Hibbert[30] (children ≥8 years) in Brisbane.

As multiple clinicians were involved in the on-going clinical care of the children, it was necessary to standardise clinical management. Thus, we utilised a validated daily diary

asthma card.[25] The diary (completed every day) consisted of 4 questions (Table 2) with a 6-point scale, with a score of 6 reflecting worse symptoms. To obtain the composite scale, the score per question is averaged thus providing a score of 0-6 per day. The asthma scores were quantified by entering the numerical answer into a spreadsheet and average obtained for the previous month. The cut offs used for altering medications are based on the following: Santanello et al's paper[31] had described that children had well controlled asthma if their scores per day was <1/day (mean 0.56, SD 0.67) per week. For the week's total score taking 1.96 times the SD, the upper limit equates to 9.2/week. Hence we considered children were well controlled if their total weekly score was <10. Our previous paper[32] on asthma had also similar results with respect to the scores when well. For the 15% change representing instability, this was based on 1.96 times the standard deviation of the median change in the children with unstable asthma, as described by the authors of the asthma diary scale in their paper for discriminant validity between stable and unstable children.[31]

Outcome measures

The primary outcome (stated *a-priori* in our trial registration) was number of children with severe exacerbation defined as respiratory events requiring a course of oral corticosteroids with or without hospitalisation. Exacerbation treatment was determined by the primary paediatrician or respiratory physician that was blinded to the child's allocated group. In accordance to as ATS guidelines[33] (that was not available at time of study design), requirement for oral corticosteroids or hospitalisation represents a severe exacerbation. Secondary outcomes were: FEV_1 %predicted, asthma QoL, symptom scores and dose of ICS at end of study. ICS dose was expressed as budesonide-equivalent dose, with fluticasone considered twice the dose of budesonide.

Statistical analysis

Sample size was calculated based on Green et al[9] study, which was the only study available at the time the study commenced. In Green et al's[9] study the reduction in exacerbation in sputum-managed group was 31% less than the control arm (109 exacerbations in 26 subjects). To obtain a 30% reduction in exacerbations in the FeNO group compared to controls (3 per person year), a sample size of 43 per group was required for 90.5% power at 0.05 significance level. We planned to recalculate sample size based on findings on the first 60 children recruited. However, as the first preliminary analysis showed a difference between groups, the study was terminated prior to reaching the sample size.

Descriptive statistics were used to summarise the demographic characteristics of the patients. Data that had a normal distribution were described using means and SD; medians and inter-quartile ranges (IQR) were used otherwise. Fisher's exact tests were employed for categorical data. Kruskal-Wallis analyses were used for group comparisons. Two-tailed p values of < 0.05 were considered significant. All statistical calculations were analysed using SPSS Version 13. Intention to treat analyses was used, and children who dropped out were assumed to have no exacerbations.

Results

We recruited 65 children between February 2006 to April 2008; of whom 63 were randomised. Two children were not randomised; one child could not be stabilised during the run-in despite 3 visits, and one withdrew due to family circumstances. Of the 63 children who were randomised, only 2 children required adjustment of their medications during the run-in period to stabilise their asthma and therefore the 2-week run-in was repeated. By chance, both were randomised to the FeNO arm. During the follow-up period, 8 children withdrew (4 from each arm), leaving 27 children in FeNO management group and 28 in clinical symptom group (Figure 1). No participant withdrew because of poor asthma control. The two groups were well matched at baseline (Table 3) for demographic and clinical features, other than symptom score that was significantly higher in the controls.

Exacerbations

None of the children were hospitalised during the study period. Compared to the control group, significantly less children in the FeNO group had ≥1 exacerbation over the study period (6 children in FeNO group versus 15 in controls, p=0.017) (Figure 2). The number needed to treat (NNT) to prevent one child from having any exacerbation in 12 months was 4 (95%CI 3, 24). However, although the rate of exacerbations was lower in the FeNO group (0.39 per person-year) compared to controls (0.78 per person-year), the difference did not reach statistical significance (p=0.102). When the groups were sub-analysed into those with ≥2 exacerbations per year, we also found no significant difference between the groups (3 children in FeNO group versus 5 children in control group, p=0.251).

Other outcome measures

Asthma QoL scores, FEV_1 %predicted and FeNO values were not significantly different between the groups at the end of, or at any time point of the study (p range from 0.08 to

0.829) (figure 3). Asthma diary scores were also similar between the groups (p value range 0.06 to 0.928). Asthma symptom scores at final visit were: FeNO group (median 0, IQR 0, 8.75) and controls (median 2.5, IQR 0, 17.25, p=0.394).

Inhaled corticosteroid (ICS) dose

At end of study (12-months), the final daily ICS dose was significantly (p=0.037) higher in the FeNO group (median 400 µg, IQR 250, 600) compared to the control group (median 200 µg, IQR100, 400). However, when the difference between final and baseline dose was considered, there was no difference (p=0.139) between the groups (FeNO group: median 0, IQR (-175, 100); control group: median of -200, (IQR -300, 100). With respect to the cumulative dose per child-year, the total median dose was significantly higher in the FeNO group (168,000µg, IQR 93,000, 210,000) compared to the control group (105,000µg, IQR 73,500, 156,000), p=0.016.

Discussion

Our dual centre RCT evaluated an asthma management strategy based on FeNO (with atopy considered) compared to usual treatment (controls, based on asthma guidelines). We found that significantly fewer children in the FeNO group had severe asthma exacerbations compared to children managed by symptom control (diary). However, while the exacerbation rate was lower in the FeNO group (compared to controls), this did not reach statistical significance (which is likely related to the lack of power). Children in the FeNO group had significantly higher ICS use (daily dose by the end of the 12 months and accumulative dose) compared to the control group, but the difference between end and start of trial was not significantly different between groups. Also asthma control factors (asthma and cough diary scores, QoL) were similar between groups.

While there are now several published RCTs[13-15,17] that evaluated whether using FeNO to adjust asthma medications is superior to using symptoms alone, our study has 3 features that likely accounts (at least in part) for our different results differ from previous published RCTs in children/adolescent. These features are (a) our study is the sole study that adjusted FeNO cut-offs based on atopy, (b) none of the previous paediatric studies used asthma exacerbations as the primary outcome, and (c) the FeNO strategy only utilised FeNO levels to adjust treatment.

There are 4 published RCTs in children that have evaluated the benefit of a FeNO-based strategy in adjusting medications for asthma.[13-15,17] None had shown any significant benefit of using FeNO compared to controls with respect to exacerbations but none of the studies used exacerbation as their primary end-point, used FeNO levels solely in intervention arm or adjusted according to atopy status. In contrast, the adult-based studies[12,16,18] used exacerbations as their primary outcome, but none showed any benefit in reducing asthma

exacerbation. Also, none of these adult studies adjusted FeNO based on atopy. De Jongste et al[15] assessed daily FeNO telemonitoring in 151 children with atopic asthma over 30 weeks with treatment (adjusted every 3 weeks). Both control and FeNO groups showed an increase in symptom-free days, improvement of FEV_1 and QoL, and a reduction in ICS dose, with no significant difference between the groups. Fritsch et al[13] concluded that therapy aimed at lowering FeNO in 47 children with asthma, improved parameters of small airway function but was did not improve clinical markers of asthma control. At the end of the study (6 months) children in the FeNO group had higher median daily doses of ICS in comparison to the control group (316 µg versus 241 µg) but reported as not significant.[13] Pijnenburg et al[17] showed that titrating steroids based on FeNO levels in children did not result in higher steroid doses and improves airway hyper-responsiveness and markers of airway inflammation, but there was no difference in exacerbations or asthma symptoms between groups. In Szefler et al's study[14] (n=546 adolescents), the mean number of days with asthma symptoms (primary outcome), pulmonary function and asthma exacerbations also did not differ between the groups. Participants in the FeNO group received higher doses of ICS (difference 119 µgm per day, 95%CI 49 to 189) than controls. All but one study[17] reported no difference in FeNO levels between the groups at end point. Pijnenburg et al[17] reported no change from baseline in the FeNO group, but the symptom group had an increase of 32% from baseline levels.

Our study is the first RCT on FeNO-based asthma management evaluation that have considered the presence or severity of atopy in their algorithm of management. Our FeNO cut-off levels were adjusted in accordance to severity of atopy defined on SPT. We speculate that this is one of the reasons why our study showed a benefit compared to the others which did not show a difference in exacerbations between groups. Raised FeNO in children has been associated with atopy with or without respiratory symptoms.[21,22] FeNO values in people with atopy can be as high as 54ppb compared to non-atopic people even in the absence of any

disease.[34] However our inclusion criteria was different as not all the children in our study was atopic whereas 'Atopic asthma' was an inclusion criterion for Pijnenburg et al[17] as defined as RAST class 2 or higher for at least one airborne allergen ever. Similarly all children in Fritsch et al[13] and de Jongste[15] had an inclusion criteria of positive skin prick test or RAST. Szefler et al[14] attended to skin prick tests with 88% testing positive to at least 1 of 15 allergens. Of the adult studies, Shaw and colleagues[16] reported that some of their participants were atopic (62% in FeNO group, 70% in control group). Powell and colleagues[18] also reported participants being atopic (75.2% in FeNO group, 76.2% in control group). Whereas Smith et al[12] did not describe whether their subjects were atopic or not. The cut-offs we used for adjustment was low but this was intended in the context that children already on ICS would have low FeNO levels and we were guided by the sole paper that reported FeNO levels and atopy in children at the time our study commenced. It could be argued that adjustment for age, gender, size and ethnicity should also be taken into account. However we considered this unnecessary as it would have been not feasible to adjust for so many factors. Further age and ethnicity are lesser predictors for FeNO levels (compared to atopy)[35] and our study was a RCT and groups were well matched (table 3).

In our study, children in the FeNO group had significantly higher ICS doses than controls. This is similar to 2 other published paediatric studies[13,14] but dissimilar to two others.[15,17] Although, there was no significant difference between groups for ICS dose in the Pijnenburg et al[17] study, children in that study had a high mean daily dose of ICS at the final visit (FeNO group= 935µg (SD 656); control group= 910 µg (SD 678)). The cumulative dose of ICS at end of study was also significantly higher in the FeNO group.

The cut offs of FeNO utilised for stepping up or down therapy also differed among previous published studies (ranging from 15 to 30 ppb). Recently published ATS guidelines[20] suggests

that FeNO levels in children <20ppb is less likely to respond to corticosteroids (CS) and levels >35ppb in children will be responsive to CS. These guidelines also recommend that cut points are utilised rather than reference values.[20] Furthermore, in the RCT's conducted to date the algorithms used are not based on ASthma TReatment ALgorithm (ASTRAL) studies.[36] Jacinto et al[37] conducted a systematic review examining the reference/normative values and individual factors effecting FeNO levels. They concluded that the formulation of reference values should be "based on a preset physiological model with endogenous and stable factors".[37]

We used a cut-off that was very low as, when our protocol was designed in 2005, there was little data to guide and we based our cut off values on the only data available in large healthy Australian cohort.[21] Despite this limitation, we believe that the concept of atopy adjustment for FeNO levels is important given that our study was dual-centred with significant differences found between the two treatment strategies. Recently, "personal best" has been suggested as the cut-off point[38] but defining this level may not be straight forward.

Current asthma guidelines differ with respect to steps in therapy and none of the current guidelines currently recommend using FeNO. In designing our hierarchy of treatment we considered feasibility, the Australian approach and health system (at the time the study was designed). Thus the steps used in our study are neither aligned to steps in the BTS or USA guidelines.[5,6] Also, we used a validated symptom score diary to assure a consistent interpretation of symptoms ie. to semi-objectively quantify asthma symptoms as opposed to true 'usual care'. The change of scores to up and down-tailor medications is beyond the realms of 'usual care' but arguably our method was more robust as usual care would be difficult to define when several physicians across 2 centres were involved in the care of the children. Further use of a symptom scoring system allowed blinding of the physician.

Nevertheless, our 'control' strategy did not represent 'placebo' as the children were still actively managed. This possibly dilutes the effect of the utility of using FeNO.

Further to the above, our study has several additional limitations. Firstly, we ceased recruitment after 2.3 years for feasibility reasons, before reaching our planned sample size, as preliminary analysis had shown a difference between the groups. This is a major limitation as we did not pre-specify stopping rules in our trial register. We did not perform post-hoc power analyses for equivalence for the outcomes where there were no difference between groups, in line with current recommendations on post hoc analyses.[39]

Secondly, although the children, parents and physician were unaware of the group allocation, the authors (HP & CA) who performed the FeNO measurements and calculated the scores from the parents' dairy cards were not blinded. Thirdly, we did not ask the parents or children after the trial which group they thought they were in, so we were unable to test participant masking. Fourthly, although the randomisation sequence was externally generated and different block sizes were used, there is small chance of selection bias in our study. Routinely in practice decisions regarding treatment are certainly more complex than our simple algorithm, consequently our study did not compare 'usual care'.

Despite the favourable results in number of patients experiencing asthma exacerbations in the 12 month follow-up period, the other asthma outcomes measured that reflect asthma control asthma QoL and symptoms) showed no difference between groups. A decrease in exacerbation rates from baseline in both groups could be possibly explained by the Hawthorne effect. The discordance between asthma control and exacerbations is increasingly appreciated.[40,41] While exacerbations are an important outcome, arguably subjective measures of asthma control are also important. Thus, although our findings demonstrate that monitoring

FeNO is useful in reducing exacerbations, it is likely not beneficial in all children. It is possible that it is most beneficial to children who have frequent exacerbations. The non beneficial effect on asthma control is consistent in all published paediatric studies to date.[13-15,17]

In spite of the limitations of our study, we believe that our study is important as this is the first RCT on FeNO that has taken atopy status into account. We conclude that taking atopy into account when using FeNO to tailor asthma medications is likely beneficial in reducing the number of children with severe exacerbations. This occurred at the expense of significantly higher ICS doses. However, the strategy is unlikely beneficial for improving asthma control and a larger study that addresses the limitations presented above, is required to confirm or refute our findings.

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Figures

Figure 1: Consort Flow chart

Figure 2: Cumulative asthma exacerbations in Clinical Symptoms group (controls) and FeNO group.

Graph shows FeNO group had smaller cumulative number of asthma exacerbations over study period when compared to clinical symptoms group.

Figure 3: FeNO in ppb of the two groups during the study period.

Figure shows FeNO levels in ppb (median, IQR) over the study period between the 2 strategies (Run-in measurement is prior to commencing run-in period and initial measurement after run-in). There was no statistical significance between the groups at each time point.

Figure 4: FEV_1 % predicted pre-bronchodilator in the two groups during the study period. There was no statistical significance between the groups at each time point.

Figure 5: Asthma Quality of Life scores in the two groups during the study period. There was no statistical significance between the groups at each time point.