RESEARCH ARTICLE

Comparison between the effects of two treatment regimens from GINA guidelines step 3 on quality of life and inflammatory biomarkers of pediatric asthmatic patients: an observational study [version 1; peer review: awaiting peer review]

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Abstract

Background: Asthma is a complicated condition characterized by chronic airway inflammation and airflow restriction, resulting in various respiratory symptoms such as shortness of breath, wheezing, coughing, and chest tightness. The research intended to evaluate and compare the clinical outcomes of two interchangeable treatment regimens administered to a group of Iraqi asthmatic children.
Methods: This observational clinical study was conducted on a sample of pediatric Iraqi asthmatic patients in the central pediatric hospital in Baghdad. The study enrolled asthmatic children with moderate persistent asthma, who a specialized physician had diagnosed. Patients had been allocated to two groups to receive either medium doses of beclomethasone inhaler (80 µg twice a day) for group one, or low doses (40 µg twice a day) plus montelukast chewable tablets (5 mg once daily) for group two. This study used the Child Health Survey–child version (CHS–child version) to investigate the quality of life of included patients. Also, this study investigated the inflammatory blood markers; (eosinophils and prostaglandin D2).
Results: This research included 63 patients ranging in age from 7 to 11 years, with a slight male preponderance: group one patients (n=30) and group two patients (n=33). Compared with baseline levels, the study groups had considerably higher quality of life scores at the first follow-up visit (P<0.05). After that, the two groups' scores were non-significantly higher at the second follow-up visit compared with the first follow-up visit (P>0.05). Both groups significantly improved inflammatory biomarkers at the first follow-up visit (P <0.05). The second follow-up visit revealed further improvement in both groups.

Open Peer Review

Approval Status *AWAITING PEER REVIEW*

Any reports and responses or comments on the article can be found at the end of the article.

Conclusion: This research found that both groups generated substantial improvements in study parameters compared with baseline values and that the second group, which included a beclomethasone inhaler with montelukast, was associated with the highest degree of improvement in terms of quality-of-life ratings.

Keywords
moderate asthma, montelukast, children health survey, prostaglandin D2, eosinophils.

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Introduction

Asthma is a complicated disease characterized by a range of respiratory symptoms and chronic airway inflammation; airflow restriction produces respiratory symptoms such as shortness of breath, wheezing, coughing, and chest tightness.[1] In Iraq, asthma is prevalent among children, with an incidence of 15.8%.[2] Numerous physiological, inflammatory, and structural factors contributed to the development of this disorder.[3] International recommendations for controlling chronic asthma in children suggest inhaled corticosteroids (ICSs) as the recommended medication, with leukotriene receptor antagonists (LTRAs) as an alternative. Montelukast (MLK) is the first LTRA licensed for use in young asthmatic children by the Food and Drug Administration.[4] Eosinophils play an essential role in the pathophysiology of asthma, and it is implicated in airway epithelial damage and airway wall remodeling.[5] It has been known that arachidonic acid's most prevalent cyclooxygenase metabolite is prostaglandin D2 (PGD2). It is a mast cell activation marker in asthma.[6]

Children with asthma are driven to adjust their lifestyle to prevent difficulties or exacerbations, which significantly impacts their behavioral and social health.[7] Despite the emergence of efficient and safe medication, asthma substantially affects a child's health-related quality of life (HRQoL). Quality of life (QoL) is a term that refers to an individual's self-well-being. This phrase refers to people's contentment with significant areas of their lives, such as their physical and mental well-being, social connections, and personal activities.[8] Many established forms of study have focused on how asthma impacts the quality of life. Research conducted in Nigeria revealed that almost a quarter of the children visiting asthma clinics had mental well-being concerns in addition to the interference of asthma with everyday activities.[9] Much research in the Arab world has found that the psychological components of asthma significantly negatively influence the quality of life of children.[10] In Iraq, it is critical to investigate the consequences of asthma on patients' quality of life, yet there is currently a shortage of such research. As a result, our goal is to assess the effects of a medium dosage inhaled corticosteroid alone with a low-dose inhalation corticosteroid combination with oral montelukast on quality of life and inflammatory biomarkers in pediatric asthma patients.

Methods

Ethical approval

On January 2, 2022, the scientific and ethical committee reviewed and approved the project proposal presented to the College of Pharmacy, University of Baghdad, which defines the aims of the present study in addition to the anticipated procedures for data collection (ethics board approval code: 2283). Furthermore, clearance was acquired from the Iraqi Ministry of Health (ethical board approval code: 302) on 16th January 2022. The investigator informed each participant and first-degree relative about the goal of the investigation and got verbal and written consent to participate in the research. The patients were not provided any incentives.

Study design

The present investigation was an observational, prospective study on children with asthma who had previously received a diagnosis.

Setting

This study was performed at a single facility, with patients invited from the Central Hospital of Pediatrics in Baghdad between January 5th and May 30th, 2022.

Sample size

G*Power (RRID: SCR 013726) version 3.1.9.7 has been used to calculate the number of participants. With a 95% confidence interval, 90% power, a two-tailed alpha of 0.05, and an effect size of 0.42, the following output parameters were obtained: With a non-centrally parameter of 3.6733, a critical t=1.999, and Df=61, the sample size required to be at least 63 cases.

Eligibility criteria

The study's inclusion criteria were[1]: patient age range 7–11 years,[2] newly diagnosed moderate persistent asthma as diagnosed by a specialist physician.

Exclusion criteria

The study's exclusion criteria were[1]: patients did not provide their consent to participate,[2] significant comorbid cardiac or respiratory disease,[3] concurrent respiratory tract infection, and[4] acute exacerbation of asthma that requires systemic corticosteroids.

Bias
To get the desired conclusion, the ideal study population is well-defined, accessible, highly reliable, and reasonable. To avoid bias, participants were recruited so that children with hearing, speech, or cognitive problems that restrict topic knowledge were excluded. We also used familiar words to avoid misunderstandings.

The questionnaires
The researcher investigated patients' quality of life using the Child Health Survey–child version (CHS–child version); the original model is in English.[11] To Eliminate Communication Barriers, The investigators translated the CHS–child version questionnaire. The translation was evaluated by three clinical pharmacy specialists from the College of Pharmacy at the University of Baghdad. The responses to the questionnaire were obtained *via* a direct interview with the patient. The participants answered all questions with parental assistance; the recall period lasted two weeks.

Laboratory and clinical examination
A specialized physician performed clinical evaluations to confirm the diagnosis and was responsible for ordering periodic blood samples for follow-up. At the same time, the researcher utilized the gathered blood samples for investigation.

Measuring eosinophil
In a certified laboratory, a specific stain (hematoxylin and eosin) allows eosinophils added to a blood sample to be seen and counted on a handheld cell counter called a hemocytometer. The absolute eosinophil count was computed by multiplying the proportion of eosinophils by the white blood cell count after five minutes of incubation.

Measuring prostaglandin D2 (PGD2)
Human prostaglandin D2 (PGD2) ELISA Kit supplied by Shanghai YL Biotec Co., Ltd with Catalog No.: YLA1432HU, Lot No.: YL4669261616 was used throughout the research procedure. The steps required to complete the test were summarized as follows: preparing all reagents, samples, and standards. Add prepared pieces, bars, and ELISA solutions, and allow them to react at 37°C for 60 minutes. The plate was washed five times, and then we added Chromogen Solution A and Solution B and incubated for 10 minutes at 37°C for color development. Stop solution was added and the optical density measurement was read within ten minutes before the final calculation was completed.

Follow-up
A baseline visit was performed to recruit suitable patients for the study, and the pediatrician was in charge of patient diagnosis and grouping. After the physician confirmed the diagnosis, each patient was randomly assigned to a research group and performed baseline testing. The patient's second appointment was four weeks after the first visit, and the patient's third appointment was four weeks after the second visit. The baseline tests were repeated over these three sessions.

Statistical analysis
The IBM SPSS Statistics (RRID: SCR 016479) version 27 software for Microsoft Windows was employed throughout the statistical analysis. Descriptive statistics were used to describe the participants' demographic details and disease characteristics (means, standards deviations, frequencies, and percentages). The differential analyses were performed using parametric tests since the continuous variables were normally distributed. During each visit, the researcher used an independent t-test to compare the means of the two groups. *P*-values less than 0.05 were considered statistically significant.

Results
The researcher evaluated 152 individuals for this study; 51 patients did not meet the study criteria and were eliminated, while 101 pediatric patients met the standards and were thus included. Following that, 38 patients failed to attend follow-up sessions, and the researcher discarded their findings, whereas 63 patients finished the study, as shown in Figure 1. In group one, the mean age is 9 ± 1.01 years, whereas, in group two, it is 9 ± 1.19 years. The mean value of the baseline child's health survey score (CHS score) is 52 ± 3 in group one and 56 ± 3 in group two. In group one, the mean baseline plasma level of prostaglandin D2 (PGD2) is 1.21 ± 0.5 ng/L, while in group two, it is 1.10 ± 0.5 ng/L, the mean baseline plasma eosinophil count (Eosinophil) in group one is $0.57\ 0.79\times10^9$/L.

In contrast, in group two, it is $0.54\ 0.073\times10^9$/L as shown in Table 1. There was a significant difference between the two groups in QoL score improvement at the first follow-up visit (*P*-value <0.001), whereas group two patients demonstrated a more remarkable improvement in QoL score, and there was no difference between the two groups at the second follow-up visit (*P*-value=0.8). It was found that there is a significant difference in QoL between the second follow-up visit and baseline visit in both groups; whereases group two patients showed a more substantial improvement in QoL scores

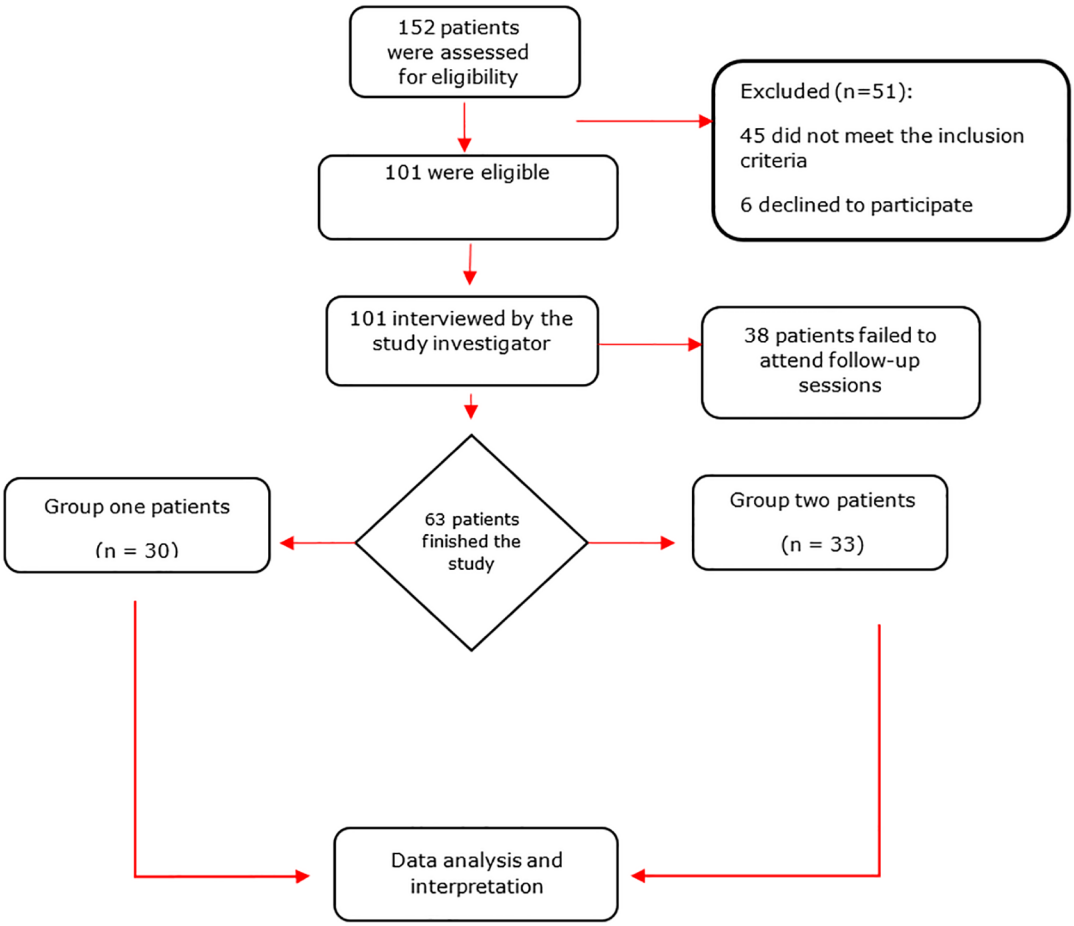

Figure 1. Study participants' flowchart.

Table 1. Baseline sociodemographic and clinical parameters.

Parameter	Group 1	Group 2	*P-Value
Age (years)±SD	9±1.01	9±1.19	0.52
CHS score±SD	52±3	56±3	0.06
PGD2 ng/L±SD	1.21±0.5	1.1±0.5	0.065
Eosinophil/L±SD	$0.57\pm0.079\times10^9$	$0.54\pm0.073\times10^9$	0.273

*Independent samples T-test, CHS=child health survey, PGD2=prostaglandin-D2, SD=standard deviation.

(*P*-value =0.019), compared with group one (*P*-value=0.025), and a significant difference between the two groups in the total change in QoL scores (*P*-value=0.04), as presented in Table 2. Both groups showed a substantial decrease in PGD2 level in the first follow-up visit; there was a significant difference between the two groups in PGD2 decrement in the first follow-up visit (*P*-value=0.03). In contrast, group two patients showed a more substantial decrease and a non-significant difference between the two groups in the second follow-up visit, (*P*-value=0.15), as illustrated in Table 3. Both groups showed a non-significant decrease in eosinophil count in the first follow-up visit. It was found that there is a significant difference in eosinophil count between the second follow-up visit and baseline visit in group one, (*P*-value=0.01). In contrast, group two patients showed a non-significant difference (*P*-value=0.07). And a significant difference between the two groups in the total change in eosinophil count (*P*-value=0.04) Table 4.

Table 2. Effect of studied regimens on QoL scores.

QoL Score	Group 1	Group 2	*P*-value**
Baseline±SD	52±3	56±3	0.06
1st follow-up (4 weeks)±SD	59±3.0	69±4	0.00***
2nd follow-up (8 weeks)±SD	60±2	69±3	0.8
P-value*	0.025****	0.019****	0.04*****

*Paired T-test, **Independent samples T-test, QoL=quality of life, SD=standard deviation, ***significant difference between first follow-up and baseline visit, ****considerable difference between the second follow-up visit and the baseline visit, *****significant difference between group one and group two total change.

Table 3. Effect of studied regimens on PGD2.

PGD2 ng/L	Group 1	Group 2	*P*-value**
Baseline±SD	1.21±0.5	1.1±0.5	0.065
1st follow-up (4 weeks)±SD	1.19±0.8***	1.05±0.5***	0.03******
2nd follow-up (8 weeks)±SD	1.01±0.3****	1.03±0.98	0.15
P-value*	0.00*****	0.07	0.7

*Paired T-test, **Independent samples T-test, PGD2=prostaglandin-D2, SD=standard deviation, ***Significant difference between first follow-up and baseline visit, ****Significant difference between second and first follow-up visit, *****Significant difference between second follow up visit and baseline visit, ******significant difference between the two groups in the first follow up visit.

Table 4. Effect of studied regimens on blood eosinophil levels.

Eosinophil/L	Group 1	Group 2	*P*-value**
Baseline±SD	$0.57\pm0.079\times10^9$	$0.54\pm0.073\times10^9$	0.07
1st follow-up (4 weeks)±SD	$0.49\pm0.049\times10^9$	$0.51\pm0.065\times10^9$	0.05
2nd follow-up (8 weeks)±SD	$0.48\pm0.05\times10^9$	$0.51\pm0.05\times10^9$	0.09
P-value*	0.01***	0.07	0.04 ****

*Paired T-test, **Independent samples T-test, ***significant difference between second follow-up visit and baseline visit, ****considerable difference between second follow-up visit and baseline visit, SD=standard deviation.

Discussion

Asthma is a prevalent pediatric lower respiratory inflammatory disorder.[12,13] The clinical practice focuses on asthma exacerbation and disease control. The Global Strategy for Asthma Management and Prevention, released by GINA and redefined in 2021, has contradicting guidance and diverse conclusions on asthma definition and management.[14] There is considerable interest regarding asthmatic patients' symptom management and the possibility of poor consequences in clinical practice. As a result, it is not unexpected that various recommendations are available to help health care practitioners manage asthma in children and adults.[15,16] Children with chronic asthma are more likely than healthy children to have poorer quality of life and psychological symptoms, which are both connected to disease activity and symptom management.[17,18] Compared to children with well-controlled asthma, children with non-controlled asthma had a worse QoL.[19,20] Hospitalization represents the direct burden of asthma. Indirect costs, such as school-related losses, are more significant among younger patients. Intangible costs are associated with decreased quality of life, physical activity limits, and academic performance.[21] This study showed that the second regimen's quality of life score has improved overall compared to the first regimen, which may be attributable to the dual regimen's lower corticosteroid dosage, fewer side effects, and a higher likelihood of the child playing and engaging in typical activities as a result of these factors.

Routine QoL evaluation is recommended for asthmatic children and an electronic form formulation that clinical pharmacists in hospitals may use to measure the quality of life of asthmatic patients with varying degrees of severity and other age groups.[22,23] Many biomarker studies have been conducted in recent years, despite the lack of clear findings. Furthermore, their clinical usefulness is unclear. It is well known that there is no such ideal biomarker. In everyday clinical practice, however, it would be preferable to have a universal, inexpensive, and non-invasive test capable of

predicting which children will develop asthma in the future, diagnosing asthma, monitoring treatment adherence, offering assistance during follow-up, and even predicting long-term progression.[24–26] This study shows a slight dominance of the male gender in asthma, which agrees with the previous Chinese study results. According to earlier cross-sectional research on asthma prevalence in China, the nationwide prevalence of asthma in male and female children was 3.51% and 2.29 %, respectively.[27] New biomarkers for asthma are discussed in this study. In addition to the conventional biomarker eosinophils, this research demonstrates the utility of using the novel blood biomarker PGD2 as a follow-up marker to assess illness progression. Both treatment regimens show an overall improvement in inflammatory biomarkers. There was no discernible difference between the first and second groups in the readings from the first and second follow-up visits. This study revealed a substantial difference across study groups in the fourth week of the follow-up. This is in line with prior research on asthmatic patients, which showed a significant difference between study groups between the fourth and eighth weeks of the trial.[1]

Limitations

There are a few possible limitations that should be considered when evaluating this research results. The small patient group was the first concern that sprang to mind, partly because of the restriction of the 7–11 years age range. A kind of difficult communication to deliver the question to this age group. Thirdly, only one center was used to select candidates. Finally, because our patients may not generally be typical of Iraqi patients, it is critical to repeat this research with larger sample size. Finally, another limitation is that the data are reported at a certain period and does not take into account changes in participants' lived experiences regarding medicine use and adherence over time.

Conclusion

In evaluating patients' health status, quality of life evaluation is just as significant as quantitative indicators, particularly for children. Relying on biomarkers, the second group is not statistically different from the first group but is different based on the quality-of-life score; overall improvement in the quality-of-life score in the dual regimen is better than in the first regimen.

Data availability

Underlying data

Zenodo: QoL Scores, prostaglandin-D2, and eosinophil levels at baseline and follow-up period. https://doi.org/10.5281/zenodo.6977308.[28]

This project contains the following underlying data:

- Article's data.xlsx (QoL Scores, prostaglandin-D2, and eosinophil levels at baseline and follow-up period)

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