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Comparison of treatments for Pediatric asthma; A systematic review

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Abstract

Background:

Asthma is an airway inflammatory illness of persistent nature. It is distinguished by mucus plugging wheezing episodes, cough and breath shortness. It is the most prevalent persistent respiratory illness of childhood. Poor control of asthma is linked with several consequences, including severe symptoms and life-threatening attacks. There are various pharmacological therapeutic options for the management of asthmatic children.

Aim:

To compare the outcomes of different pediatric asthma treatments by examining the research focused on this topic.

Methods:

Searching through the scientific databases and using many terms was done to obtain relevant studies. The exploration procedure focused on original pediatric studies written in English language and available for full text comparing different asthma treatment with inhaled corticosteroids.

Results:

Eight studies were the final number of research enrolled in this review. The extracted data was summarized under major titles. A total of 1360 children were included and several medications were reported, including short and long acting beta-agonists, omalizumab, montelukast and theophylline.

Conclusion:

Combination regimen of ICS with other asthmatic therapies seems to provide better control of asthma among the pediatric subjects compared to monotherapy. Furthermore, the combination therapy led to ICS dose reduction. The selection of

the best regimen is dependent on several factors that should be considered before the adoption of a definite therapeutic regimen.
Keywords: ICS, Pediatric, Medication, Comparison, Asthma.

Introduction:

Asthma is a persistent inflammatory illness of the airway; it is distinguished by persistent and acute bronchoconstriction, hyper-responsiveness of the airway, mucus plugging, and airway edema **[1]**. The asthmatic patient can also experience wheezing episodes, cough, and breath shortness **[2]**. There are various cells incorporated in asthma, such as eosinophils, mast cells, neutrophils, and other cells with their products **[1]**. Almost 14% of pediatrics around the globe complain of asthma, which makes it the most prevalent persistent respiratory illness of pediatrics **[3]**.

Poor control of asthma is linked with a frequency of adverse outcomes among pediatrics and families **[4]**. It was demonstrated that some patients may experience severe manifestations and life-threatening attacks in case of uncontrolled asthma **[5]**. For most cases, controller and reliever therapies provide suitable long-term management **[1]**. Most asthmatic pediatrics have mild to moderate condition and can be controlled by the avoidance of triggering agents and /or with adoption of medications such as inhaled corticosteroids (ICS), short-acting inhaled beta-receptor agonists (SABA), leukotriene receptor antagonists (LTRA) and the addition of long-acting beta-agonists (LABA) as required **[1]**.

ICS is considered as well—tolerated and effective in the prevention of exacerbation, improving pulmonary function and enabling rescue treatment usage and asthma management for children with chronic manifestations **[6]**. However, 2-5% of the pediatrics with asthma have uncontrolled condition, although they receive maximum therapy with conventional medications and may require additional biologic therapy **[7, 8]**.

Several highly efficient adjuvant treatments have been progressed for the treatment of severe asthma, encompassing monoclonal antibodies (MAbs) influencing type 2-inflammatory pathways. Such biological agents are now recommended as the first-line add-on therapy for the pediatrics **[9]**. Such biological therapies have been displayed to be well-tolerated and effective **[7]**. It was stated that administrating ICS and other asthmatic medications should be assessed through diverse phases based on symptoms‘ frequency **[1]**. So, this review was established to identify the outcomes of different pediatric asthma treatments in comparison to ICS.

Method and Search strategy:

The PRISMA statement **[10]** was the guidance while writing this review. Scientific databases were explored to obtain relevant research. The explored databases included PubMed, Scopus, Science Direct, and Google Scholar. There are several medications for pediatric asthma that represent huge heterogeneity in research; therefore, we focused on studies that reported a comparison of asthma treatment in comparison to ICS for pediatrics. Hence, the applied keywords for the search procedure included "ICS, Comparison, Montelukast, SABA, LABA, Biologic therapy, Outcomes, Improvements, Asthma, Pediatrics, and Children," which were used in different combinations to get all possible research.

Eligibility criteria:

All the titles we obtained were examined precisely to prevent missing significant research. The findings were refined to exclude duplicates and were further checked to select only original research. The English language was mandated for the inclusion of the articles, and all research designs were eligible. The remaining findings were

checked again to exclude all articles conducted on the adult population, and mixed studies included adults and the pediatric population. Due to the variations in the included age categories of children, the included articles were those enrolled subjects aged 1-18 years. Also, articles that didn't report ICS therapy and compared other regimens with ICS were excluded. The remaining articles were checked to include those available for full-text and reporting complete data. The illustration of the criteria of involvement is displayed in figure 1.

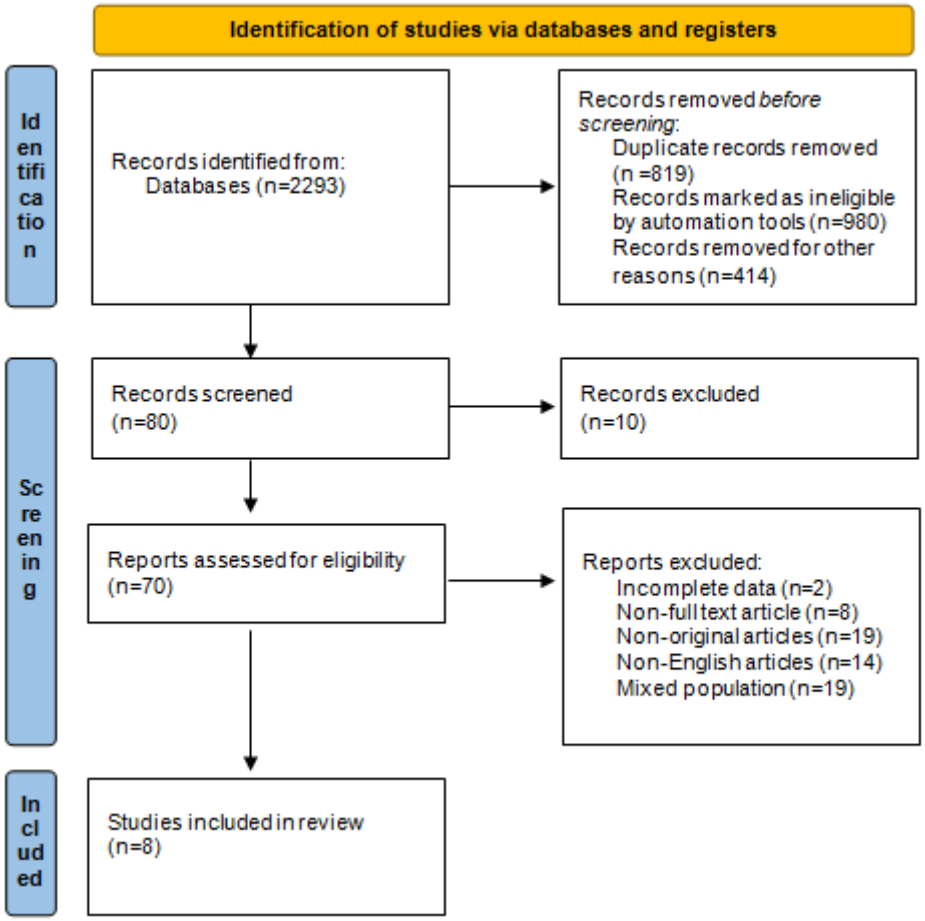

Fig1: Criteria of involvement

Data review and analysis:

The first phase involved reviewing of the abstracts to determine the data of concern for extraction. The next phase involved reviewing of each article and extraction of relevant data using an excel sheet. The data was then transferred to a pre-designed table to summarize the extracted data under major titles.

Results:

Based on the determined criteria, eight articles were enrolled **[11-18],** and they were published between 2004 and 2023 **(Table 1).** The various designs were found, and they included randomized trial **[11]**, retrospective **[12]**, prospective **[13, 18]**, prospective and observational **[14, 16]**, observational **[15]**, and randomized open-label **[17]**. There were four treatment regimens assessed in comparison to ICS, and they included SABA, LABA, omalizumab, and montelokast. The regimens were either compared to ICS, assessed alone, and compared as a combination with ICS or comibned with ICS and compared with ICS before combination. The patients‘ total number was 1360 cases with the age range of 1-17 years.

One study compared using SABA as required to the combination of regular SABA and ICS for subjects with mild chronic condition **[11]**. Two studies focused on LABA **[12]**; one study compared ICS alone with combination of ICS and LABA for severe chronic asthma **[12]**. The other study compared changing to medium dose ICS alone with ICS medium dose combined with LABA for cases with mild to severe condition **[13]**.
Two studies concerned with omalizumab, the studies compared ICS and omalizumab intervention to ICS alone before intervention **[14, 15];** one study enrolled uncontrolled severe asthma cases **[14]**, whereas the other study didn't specify the severity of the condition **[15].** The remaining three studies assessed montelukast **[16-18]**; one study compared montelukast with ICS and montelukast combination for uncontrolled asthma **[16]**. Another one compared two combinations; one involved montelukast and low-dose ICS, and the other combination was theophylline & low-dose ICS for asthmatic cases **[17]**. The last study encompassed three categories: those that received montelukast alone, the other category that received ICS twice, and the third one that received both agents **[18]**.
Regarding the outcomes of such assessed regimens; regarding SABA, using SABA alone as required or regularly in addition to ICS resulted in improvement of controlled asthma signs and lung functions significantly, with more potential improvement for the combination treatment for mild persistent asthma ($P<0.005$) **[11]**.
Regarding LABA, a combination of ICS and LABA resulted in significant improvement compared to ICS, including a significant reduction in recurrent exacerbation ($P<0.0001$) and a lower incidence of moderate to severe exacerbations ($P=0.0005$) for severe asthma **[12]**. The other study revealed considerable improvement in asthma control ($P<0.0001$), emergency visits, receiving oral steroids, unscheduled visits to physicians, wheezing, coughing, and missed school days ($P<0.001$); however, ICS and LABA combination was more prone to cause asthma control **[13]**.
The addition of omalizumab to the initial ICS treatment resulted in asthma control in all patients, significant reduction in exacerbation and full reduction in severe crises, no hospitalization recorded, reduction in the frequency of oral corticosteroids, salbutamol, reduced dose of ICS ($P=0.002$) **[14]**, ($P=0.0001$) **[15]**, no need for oral corticosteroids, and at long-term usage reduction of hospital admission and emergency visits **[15]**. However, one study reported no impact on pulmonary function, with two cases out of 17 having mild adverse reactions **[14]**, whereas the other study reported a significant improvement in lung function ($P=0.0001$) with no side effects **[15]**.
Montelukast monotherapy was more efficient compared to a combination regimen with ICS in achieving controlled asthma. However, both regimens led to remarkable and similar improvements in uncontrolled asthma and QOL of caregivers, but the additional benefit of montelukast in combination therapy was that it reduced ICS dosage **[16]**. For mild chronic asthma, montelukast resulted in wide improvements in airway blockage, daily symptoms, nocturnal awakenings, daily as-required beta agonist usage, frequency of exacerbation, and patients who experienced exacerbation. Such improvements were similar to those that resulted from ICS and a combination of montelukast and ICS **[18]**.
The comparison between low-dose ICS combined with either montelukast or theophylline displayed that the montelukast combination led to a potential increase in airflow in the morning and evening compared to theophylline. However, both groups displayed no variation regarding clinical and laboratory adverse outcomes. **[17]**.

Table 1: The extracted data

Author and Publication year	Study design	Regimen	Size and age	Results and main findings
Amir et al. 2023 [11]	RCT	*SABA alone as needed *SABA & ICS; SABA regularly and daily ICS	-N=80 with mild chronic asthma *40 in each group -Age:6-12 Y	*The control of asthma symptoms was improved in both categories significantly, with potential improvement in the SABA &ICS group (P<0.005). *Both categories had significant improvement in lung function following the interventions, with more improvement in the SABA& ICS group (P<0.005).
Alakeel et al 2022 [12]	Retrospective	*ICS *ICS& LABA	-N=586 severe chronic asthma *ICS=480 *ICS&LABA=106 -Age:1-17 Y	*Those who received ICS only experienced a considerable elevation in the number of recurrent exacerbation episodes compared to those in the combination regimen (P< 0.0001). *Moderate to severe exacerbations were considerably higher in the ICS alone (P= 0.0005).
Al-Turki et al 2020 [13]	Prospective	*All subjects were on low-ICSs dose at baseline. Subjects were either switched to medium-dose ICS or medium-dose ICS & LABA	-N=163 Asthma: *Mild=26 patients *Moderate=112 *Severe=25 *ICS=106 *LABA&ICS=57 -Age:5.6±3.6 Y	*The mean of the asthma Control Test improved (P < 0.0001) in both categories. *Emergency visits, oral steroids, and unscheduled visits to physicians for acute asthma markedly reduced (P < 0.001) in both categories. *Days/month with wheezing, nighttime cough, and missed school days remarkably reduced in both categories (P < 0.001). *Cases on ICS were less prone to achieve asthma control compared to the ICS+LABA category.
Giubergia et al 2019 [14]	Prospective, longitudinal & observational	*Omalizumab was injected subcutaneously with a dose relied on weight and IgE levels for patients on ICS.	-N= 17 uncontrolled severe asthma -Age= 11.5Y	*Controlling asthma occured in all patients (p = 0.00001) after omalizumab. *Exacerbations were lowered by 48.5 % (p = 0.009) and severe crises, by 100 % (p = 0.001). *None of the cases was hospitalized (p = 0.007). *The dose of ICS was lowered by 20 % (P=0.002).

				*Also, the frequency of subjects using continuous oral corticosteroids (p = 0.01), salbutamol (p = 0.001), and oral corticosteroids (p = 0.003) was reduced. *Pulmonary function was not impacted. *Two cases experienced mild adverse reactions.
Folque et al 2019 [15]	Observational	*Omalizumab dose-dependent on weight and IgE levels for patients on ICS	-N=48 -Age=5-17 Y	*ICS dose was reduced considerably at six months (P=0.0001) *After six months, nobody used oral corticosteroids. *Hospital admission rate and visits to the emergency for asthma exacerbation was potentially reduced in the third and fourth years of follow-up, respectively. *Improvement occurred in lung function (P=0.0001). *No adverse effects.
Berube et al 2014 [16]	Prospective observational	*Montelukast *Montelokast & ICS	-N=328uncontrolled asthma -Age:6.9±3.4 Y	*Controlled asthma was achieved by 75% in monotherapy and 70.9% in combination category at 12 weeks. *Significant improvements in uncontrolled asthma in the monotherapy category occurred compared to baseline (P <0.001), and the QOL of the caregiver was improved considerably compared to baseline (P< 0.001). *Also, significant improvements occurred in the combination category regarding uncontrolled asthma (P< 0.001) and caregiver QOL (P< 0.001). *After a 12-week montelukast add-on therapy, 22.6% of subjects lowered their ICS dosage.
Kondo et al 2006 [17]	Randomized open-label	*Montelukast & low-dose ICS *Theophylline & low-dose ICS	-N=75 asthmatic *Montelukast=39 *Theophylline=36 -Age:6-14 Y	*A significant increase in the morning (at 2 weeks P=0.04, at 4 weeks P= 0.01) and evening at 4 weeks (P=0.02) airflow was discovered in the montelukast compared with the theophylline category. *There was no considerable variance between both categories in incidences of clinical and laboratory adverse experiences.

Karaman et al 2004 [18]	Randomized prospective	*Montelukast once daily *ICS twice daily *Montelukast &ICS	-N=63 mild chronic asthma *Montelukast=20 *ICS=22 *Combined=21 -Age:8-14 Y	* Montelukast resulted in improvement in airway obstruction, daily symptoms, total daily as-needed beta-agonist use, nocturnal awakenings, proportions of days, and cases with asthma exacerbation. *Such beneficial impacts were similar to those caused by ICS and the combination. *There were no potential adverse impacts requiring treatment discontinuation.

RCT; Randomized controlled trial, SABA; Short-acting beta-agonist, ICS; Inhaled corticosteroid, LABA; Long-acting beta agonist, QOL; Quality of life.

Discussion:

The usage of pharmacological agents varies based on age, controlling symptoms, and the national guidelines used **[2]**. ICS is currently the principal therapy for asthma **[19]**. Hence, this work was carried out to identify the outcomes of different pediatric asthma treatments in comparison to ICS.

Classically, mild asthma was recommended to managed by as required SABA **[19]**. However, several exacerbations and mortalities have been reported among almost one-third of cases **[20, 21]**. In our analysis, the study focused on SABA revealed no adverse impacts of SABA and it resulted in similar outcomes to the combined SABA and ICS, but with more improvements noted for the combined regimen **[11]**.

For pediatrics aged 6-11 years, it was recommended by the GINA in the 2022 update to use low-dose ICS combined with SABA for intermittent asthma, whereas in mild chronic conditions, a daily low dose of ICS was recommended **[1, 22]**. This regimen was followed by the study in our analysis, whereas the age of the children was 6-12 years, and they had mild chronic conditions and were on daily ICS and regular SABA for the combined regimen. This combined regimen was superior to SABA alone and led to more improvements in lung function and symptoms of asthma **[11]**.

It was stated that the overuse of SABA is linked with an elevated risk of severe exacerbation and death **[23]**, which could be lowered by regularly treating low-dose ICS among one-half to two-thirds of patients **[24]**. In our analysis, the adoption of SABA didn't result in any adverse outcomes, and this may be related to the fact that this medication was given for a short duration of only eight weeks **[11]**.

ICS can also be combined with LABA as the first choice with proven efficacy **[25, 26]**. Previously, the use of LABA monotherapy has been linked with safety concerns **[27]**. However, in our analysis, the two studies concerned with LABA revealed that moderate to severe exacerbation and less control of asthma were associated with ICS alone, not the combined therapy with LABA. This reveals the potential role of LABA in combination with ICS to control and improve asthma outcomes **[12, 13]**.

Contrary to our findings, a previous review included 33 trials with 6381 pediatrics that revealed that adding LABA to ICS was not linked with a potential reduction in exacerbations requiring systemic steroids **[28]**. A meta-analysis adopted 35 RCTs with 12010 pediatrics deduced that ICS and LABA combined therapy was most efficient in preventing exacerbations **[29]**, which was in agreement with our findings but in contrast to the previous review **[28]**.

A meta-analysis of 29 trials deduced that uncontrolled children/teenagers on low-dose ICS should be changed to a medium-dose ICS+LABA to decrease the exacerbation risks and improve lung function **[30]**. One of the two studies in this review reported switching to medium dose ICS following low dose ICS for both ICS monotherapy and ICS and LABA combination **[13]**.

Regarding biological therapy, the selection of one agent was proposed to be based on the biomarkers and phenotype of asthma **[7]**. Omalizumab is the first available humanized MABs influencing IGE. It was approved for the management of moderate to severe allergic asthma, and it can be prescribed for pediatrics aged at least six years **[31, 32]**. However, among the studies in our work, only one of two studies related to omalizumab enrolled uncontrolled severe conditions **[14]**, whereas the other study didn’t reveal the severity of asthma. Also, one study enrolled children less than six years of age **[15]**. However, in comparison to ICS prior to omalizumab, the add-on olizumab resulted in significant improvements, including controlled condition in all cases, reduction of severe crisis and exacerbations, no need or reduced rate of hospitalization and emergency visits, reduction of dosage of ICS, oral corticosteroids,

and salbutamol with improvement in lung function reported in one study **[15]**, but the other study revealed no impact on pulmonary function **[14]**. Such findings indicate the potential beneficial impact of omalizumab in combination with ICS in improving and controlling asthma.

Similar to our findings in a systematic review, it was demonstrated that receiving omalizumab resulted in reduction of ICS dose, usage of oral corticosteroids and the requirement of additional rescue therapy compared to controls. Such outcomes further improved the QOL of the pediatrics and their families **[33]**. A previous analysis of enrolled studies with 2168 asthmatic pediatrics managed with omalizumab revealed that this agent was effective in decreasing the risk of exacerbation **[34]**.

Omalizumab is generally well-tolerated, and the major side impacts include local pain at the site of injection and local skin reactions with short resolution **[35, 36]**. In our analysis, side effects were reported in one study, and they occurred in two of 17 cases; they experienced mild adverse reactions **[14]**.

Despite the reduced effectiveness of LTRA compared with ICS, the daily LTRA may another choice for the management of asthma **[37]**. Montelukast is an LTRA, and it is an alternative therapeutic option to ICS. It acts by blocking cysteinyl leukotrienes, which are a class of pro-inflammatory mediators that reduce eosinophil migration, hypersecretion of mucous, and bronchoconstriction **[38]**. This agent is adopted either as a second-line monotherapy or as combined regimen with ICS; however, it can be implemented as a first-line therapy **[38]**.

Our findings regarding montelukast indicate that montelukast alone and combined with ICS resulted in similar significant improvements; however, montelukast monotherapy was more efficient compared to the combination. Nonetheless, the add-on of montelukast to ICS is beneficial in reducing the ICS dose.

A previous review included eight studies conducted on mild to moderate chronic asthmatic children aged 2-18 years and compared montelukast to ICS monotherapy. It was found that both regimens improved the symptoms; however, four studies revealed the superiority of ICS compared with montelukast, whereas the remaining four research displayed no variations between both agents **[38]**. One advantage of montelukast over ICS is the ease of its administration as it is taken once daily as oral medication compared with ICS, which is required as twice-daily inhaled agent and requires more cooperation from the child **[38]**.

Theophylline is an agent used for the management of asthma, commonly due to its ease of usage, good anti-inflammatory impacts and low cost **[39]**. In this work, montelukast combination with ICS was superior to that of theophylline with ICS **[17]**.

Conclusion:

There are various pharmacological treatments for asthmatic children. ICS, combined with other therapeutic agents, including SABA, LABA, and omalizumab, resulted in potential improvement in asthma control and symptoms among children. However, montelukast monotherapy seems to be better compared to combination therapy. The advantage of a combination of ICS with other therapeutic agents is that such combination results in a reduction in the ICS dosage used. There were no severe adverse effects reported and such agents seem to be safe. However, the ideal therapeutic regimen is dependent on several factors, such as the severity of the condition and symptoms, the age of the children, the guidelines of the region, and the availability of treatments in a specific region.

Limitations, Strengths, and Recommendations:

One of the limitations of this review is the inclusion of studies that enrolled subjects till the age of 17 years, and this is due to the variation of children's age definition in each study and the scarcity of pediatric studies focusing on asthma treatment and including children less than 14 years. Also, there were few studies for each medication, and this was due to the determined criteria. Another limitation is that we didn't compare different asthmatic treatments with each other, and we focused on ICS in comparison to other therapeutic agents for two reasons: first, ICS is majorly used as a treatment for pediatric asthma, and it is hard to compare between the various available asthmatic treatments due to the great heterogeneity of the studies, including heterogeneity of design, treatment regimen, and therapeutic agents, severity of the disease as well as outcomes. The strength of this work is that this is the first systematic analysis to highlight the current subject. Therefore, further studies that compare different agents and focus on children age not exceeding 12 years are required.

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